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(54) Title: GALNAC COMPOSITIONS FOR IMPROVING SIRNA BIOAVAILABILITY

(57) Abstract: Provided herein, are compositions comprising GalNAc moieties that may be conjugated to an oligonucleotide. The oligonucleotide may be a small interfering RNA or an antisense oligonucleotide. Also provided herein are methods of treatment that include administering the composition to a subject.

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GALNAC COMPOSITIONS FOR IMPROVING SIRNA BIOAVAILABILITY

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Application No. 63/320,431, filed March 16, 2022, U.S. Provisional Application No. 63/354,359, filed June 22, 2022, and U.S. Provisional Application No. 63/430,542, filed December 6, 2022, which applications are incorporated herein by reference.

INCORPORATION BY REFERENCE OF A SEQUENCE LISTING

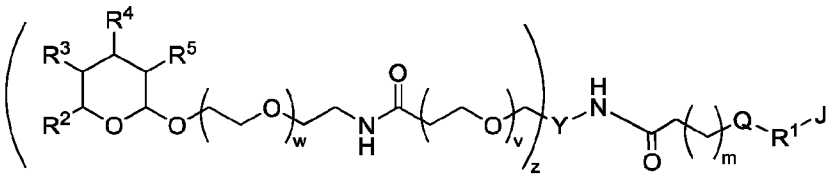
[0002] The present application is being filed along with a Sequence Listing in electronic format. The Sequence Listing is provided as a file entitled 54462-735601_PCT.xml, created March 13, 2023, which is 922,453 bytes in size. The information in the electronic format of the Sequence Listing is incorporated by reference in its entirety.

BACKGROUND

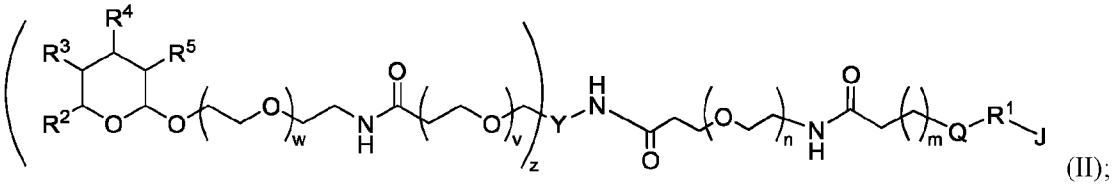
[0003] Cardiovascular, metabolic, and liver-related disorders are abundant, and may affect a wide variety of persons. Improved therapeutics are needed for treating these disorders.

SUMMARY

[0004] Disclosed herein is a compound represented by Formula (I) or (II):



(I), or



(II);

or a salt thereof, wherein

J is an oligonucleotide;

each w is independently selected from any value from 1 to 20;

each v is independently selected from any value from 1 to 20;

n is selected from any value from 1 to 20;

m is selected from any value from 1 to 20;

z is selected from any value from 1 to 3, wherein

if z is 3, Y is C

if z is 2, Y is CR^6, or

if z is 1, Y is $C(R^6)_2$;

Q is selected from:

C_{3-10} carbocycle optionally substituted with one or more substituents independently selected from halogen, -CN, -NO_2, -OR^7, -SR^7, -$N(R^7)_2$, -$C(O)R^7$, -$C(O)N(R^7)_2$, -$N(R^7)C(O)R^7$, -$N(R^7)C(O)N(R^7)_2$, -$OC(O)N(R^7)_2$, -$N(R^7)C(O)OR^7$, -$C(O)OR^7$, -$OC(O)R^7$, -$S(O)R^7$, and C_{1-6} alkyl, wherein the C_{1-6} alkyl, is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, -NO_2, and -NH_2;

R^1 is a linker selected from:

-O-, -S-, -$N(R^7)$-, -C(O)-, -$C(O)N(R^7)$-, -$N(R^7)C(O)$-, -$N(R^7)C(O)N(R^7)$-, -$OC(O)N(R^7)$-, -$N(R^7)C(O)O$-, -C(O)O-, -OC(O)-, -S(O)-, -$S(O)_2$-, -$OS(O)_2$-, -$OP(O)(OR^7)O$-, -$SP(O)(OR^7)O$-, -$OP(S)(OR^7)O$-, -$OP(O)(SR^7)O$-, -$OP(O)(OR^7)S$-, -$OP(O)(O^-)O$-, -$SP(O)(O^-)O$-, -$OP(S)(O^-)O$-, -$OP(O)(S^-)O$-, -$OP(O)(O^-)S$-, -$OP(O)(OR^7)NR^7$-, -$OP(O)(N(R^7)_2)NR^7$-, -$OP(OR^7)O$-, -$OP(N(R^7)_2)O$-, -$OP(OR^7)N(R^7)$-, and -$OPN(R^7)_2NR^7$-;

each R^2 is independently selected from:

C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, -OR^7, -SR^7, -$N(R^7)_2$, -$C(O)R^7$, -$C(O)N(R^7)_2$, -$N(R^7)C(O)R^7$, -$N(R^7)C(O)N(R^7)_2$, -$OC(O)N(R^7)_2$, -$N(R^7)C(O)OR^7$, -$C(O)OR^7$, -$OC(O)R^7$, and -$S(O)R^7$;

R^3 and R^4 are each independently selected from:

-OR^7, -SR^7, -$N(R^7)_2$, -$C(O)R^7$, -$C(O)N(R^7)_2$, -$N(R^7)C(O)R^7$, -$N(R^7)C(O)N(R^7)_2$, -$OC(O)N(R^7)_2$, -$N(R^7)C(O)OR^7$, -$C(O)OR^7$, -$OC(O)R^7$, and -$S(O)R^7$;

each R^5 is independently selected from:

-$OC(O)R^7$, -$OC(O)N(R^7)_2$, -$N(R^7)C(O)R^7$, -$N(R^7)C(O)N(R^7)_2$, -$N(R^7)C(O)OR^7$, -$C(O)R^7$, -$C(O)OR^7$, and -$C(O)N(R^7)_2$;

each R^6 is independently selected from:

hydrogen;

halogen, -CN, -NO_2, -OR^7, -SR^7, -$N(R^7)_2$, -$C(O)R^7$, -$C(O)N(R^7)_2$, -$N(R^7)C(O)R^7$, -$N(R^7)C(O)N(R^7)_2$, -$OC(O)N(R^7)_2$, -$N(R^7)C(O)OR^7$, -$C(O)OR^7$, -$OC(O)R^7$, and -$S(O)R^7$; and

C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, -CN, -NO_2, -OR^7, -SR^7, -$N(R^7)_2$, -$C(O)R^7$, -$C(O)N(R^7)_2$, -$N(R^7)C(O)R^7$, -$N(R^7)C(O)N(R^7)_2$, -$OC(O)N(R^7)_2$, -$N(R^7)C(O)OR^7$, -$C(O)OR^7$, -$OC(O)R^7$, and -$S(O)R^7$;

each R^7 is independently selected from:

hydrogen;

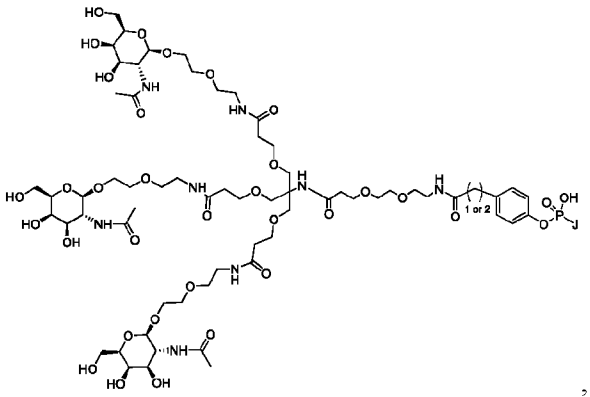
C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, -NO_2, -NH_2, =O, =S, -O-C_{1-6} alkyl, -S-C_{1-6} alkyl, -$N(C_{1-6}$ alkyl$)_2$, -$NH(C_{1-6}$ alkyl), C_{3-10} carbocycle, and 3- to 10-membered heterocycle; and

C_{3-10} carbocycle, and 3- to 10-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, -

NO_2, $-NH_2$, =O, =S, $-O-C_{1-6}$ alkyl, $-S-C_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)_2$, $-NH(C_{1-6}$ alkyl), C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, and C_{1-6} haloalkyl.

In some embodiments, each w is independently selected from any value from 1 to 10. In some embodiments, each w is independently selected from any value from 1 to 5. In some embodiments, each w is 1. In some embodiments, each v is independently selected from any value from 1 to 10. In some embodiments, each v is independently selected from any value from 1 to 5. In some embodiments, each v is 1. In some embodiments, n is selected from any value from 1 to 10. In some embodiments, n is selected from any value from 1 to 5. In some embodiments, n is 2. In some embodiments, m is selected from any value from 1 to 10. In some embodiments, m is selected from any value from 1 to 5. In some embodiments, m is selected from 1 and 2. In some embodiments, z is 3 and Y is C. In some embodiments, Q is selected from C_{5-6} carbocycle optionally substituted with one or more substituents independently selected from halogen, -CN, $-NO_2$, $-OR^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, $-C(O)N(R^7)_2$, $-N(R^7)C(O)R^7$, $-N(R^7)C(O)N(R^7)_2$, $-OC(O)N(R^7)_2$, $-N(R^7)C(O)OR^7$, $-C(O)OR^7$, $-OC(O)R^7$, and $-S(O)R^7$. In some embodiments, Q is selected from C_{5-6} carbocycle optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, $-NO_2$, and $-NH_2$. In some embodiments, Q is selected from phenyl and cyclohexyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, $-NO_2$, and $-NH_2$. In some embodiments, Q is selected from phenyl. In some embodiments, Q is selected from cyclohexyl. In some embodiments, R^1 is selected from $-OP(O)(OR^7)O-$, $-SP(O)(OR^7)O-$, $-OP(S)(OR^7)O-$, $-OP(O)(SR^7)O-$, $-OP(O)(OR^7)S-$, $-OP(O)(O^-)O-$, $-SP(O)(O^-)O-$, $-OP(S)(O^-)O-$, $-OP(O)(S^-)O-$, $-OP(O)(O^-)S-$, $-OP(O)(OR^7)NR^7-$, $-OP(O)(N(R^7)_2)NR^7-$, $-OP(OR^7)O-$, $-OP(N(R^7)_2)O-$, $-OP(OR^7)N(R^7)-$, and $-OPN(R^7)_2-NR^7$. In some embodiments, R^1 is selected from $-OP(O)(OR^7)O-$, $-SP(O)(OR^7)O-$, $-OP(S)(OR^7)O-$, $-OP(O)(SR^7)O-$, $-OP(O)(OR^7)S-$, $-OP(O)(O^-)O-$, $-SP(O)(O^-)O-$, $-OP(S)(O^-)O-$, $-OP(O)(S^-)O-$, $-OP(O)(O^-)S-$, and $-OP(OR^7)O-$. In some embodiments, R^1 is selected from $-OP(O)(OR^7)O-$, $-OP(S)(OR^7)O-$, $-OP(O)(O^-)O-$, $-OP(S)(O^-)O-$, $-OP(O)(S^-)O-$, and $-OP(OR^7)O-$. In some embodiments, R^1 is selected from $-OP(O)(OR^7)O-$ and $-OP(OR^7)O-$. In some embodiments, R^2 is selected from C_{1-3} alkyl substituted with one or more substituents independently selected from halogen, $-OR^7$, $-OC(O)R^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, and $-S(O)R^7$. In some embodiments, R^2 is selected from C_{1-3} alkyl substituted with one or more substituents independently selected from $-OR^7$, $-OC(O)R^7$, $-SR^7$, and $-N(R^7)_2$. In some embodiments, R^2 is selected from C_{1-3} alkyl substituted with one or more substituents independently selected from $-OR^7$ and $-OC(O)R^7$. In some embodiments, R^3 is selected from halogen, $-OR^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, $-OC(O)R^7$, and $-S(O)R^7$. In some embodiments, R^3 is selected from $-OR^7$ $-SR^7$, $-OC(O)R^7$, and $-N(R^7)_2$. In some embodiments, R^3 is selected from $-OR^7$ - and $-OC(O)R^7$. In some embodiments, R^4 is selected from halogen, $-OR^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, $-OC(O)R^7$, and $-S(O)R^7$. In some embodiments, R^4 is selected from $-OR^7$ $-SR^7$, $-OC(O)R^7$, and $-N(R^7)_2$. In some embodiments, R^4 is selected from $-OR^7$ - and $-OC(O)R^7$. In some embodiments, R^5 is selected from $-OC(O)R^7$, $-OC(O)N(R^7)_2$, $-N(R^7)C(O)R^7$, $-N(R^7)C(O)N(R^7)_2$, and $-N(R^7)C(O)OR^7$. In some embodiments, R^5 is selected from $-OC(O)R^7$ and $-N(R^7)C(O)R^7$. In some embodiments, each R^7 is independently selected from: hydrogen; and C_{1-6} alkyl optionally substituted with

one or more substituents independently selected from halogen, -CN, -OH, -SH, $-NO_2$, $-NH_2$, =O, =S, -O-C_{1-6} alkyl, -S-C_{1-6} alkyl, -N(C_{1-6} alkyl)$_2$, -NH(C_{1-6} alkyl), C_{3-10} carbocycle, or 3- to 10-membered heterocycle. In some embodiments, each R^7 is independently selected from C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, $-NO_2$, $-NH_2$, =O, =S, -O-C_{1-6} alkyl, -S-C_{1-6} alkyl, -N(C_{1-6} alkyl)$_2$, and -NH(C_{1-6} alkyl). In some embodiments, each R^7 is independently selected from C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, and -SH. In some embodiments, w is 1; v is 1; n is 2; m is 1 or 2; z is 3 and Y is C; Q is phenyl or cyclohexyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, $-NO_2$, $-NH_2$, and C_{1-3} alkyl; R^1 is selected from -OP(O)(OR^7)O-, -OP(S)(OR^7)O-, -OP(O)(O$^-$)O-, -OP(S)(O$^-$)O-, -OP(O)(S$^-$)O-, and -OP(OR^7)O-; R^2 is C_1 alkyl substituted with -OH or -OC(O)CH_3;
R^3 is -OH or -OC(O)CH_3; R^4 is -OH or -OC(O)CH_3; and R^5 is -NH(O)CH_3. In some embodiments, the compound comprises:



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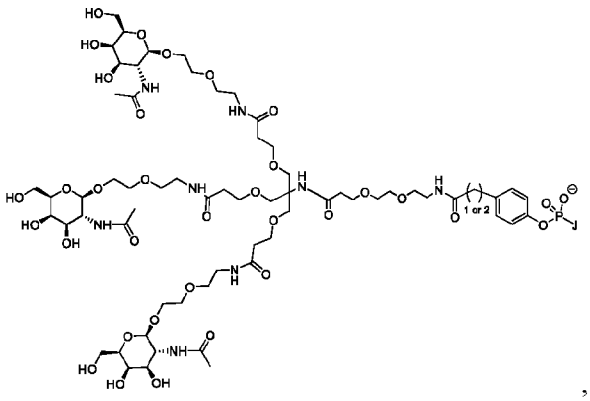

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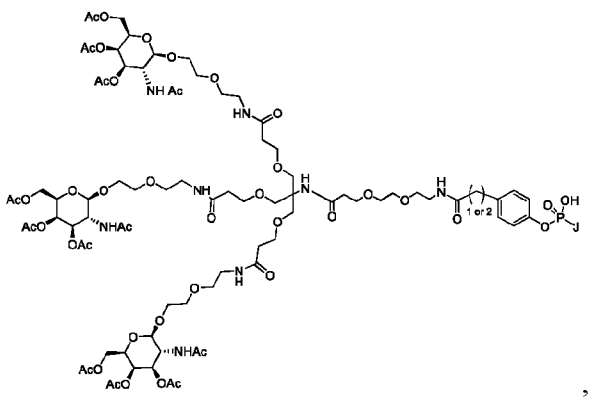

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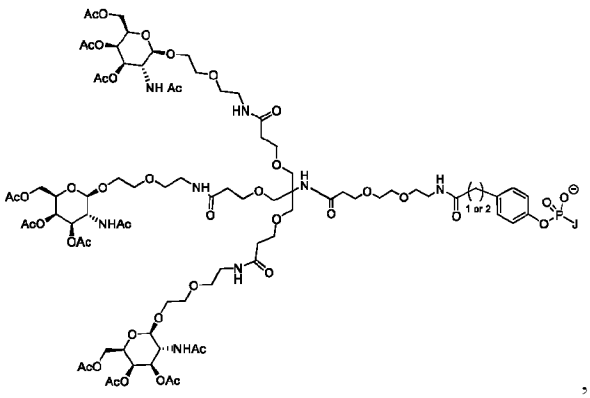

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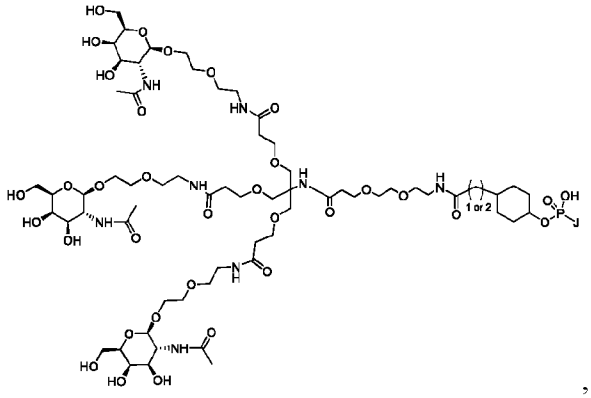

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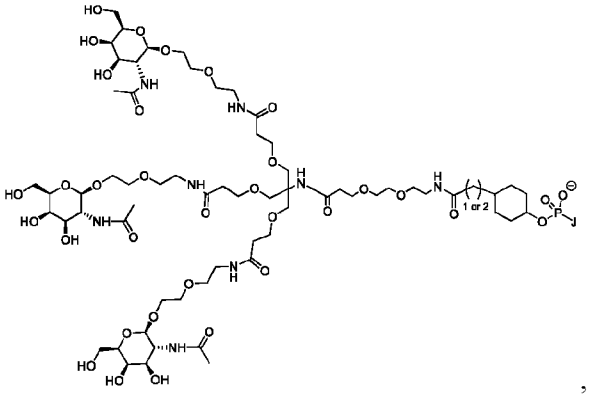

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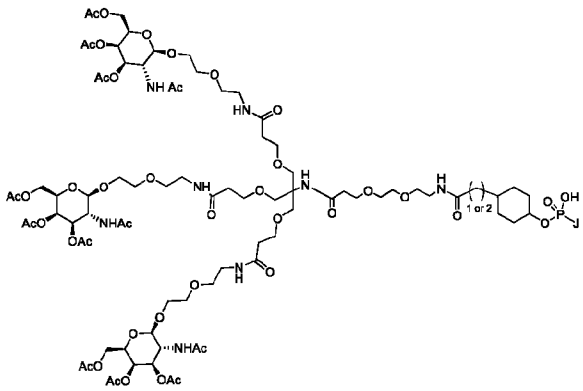

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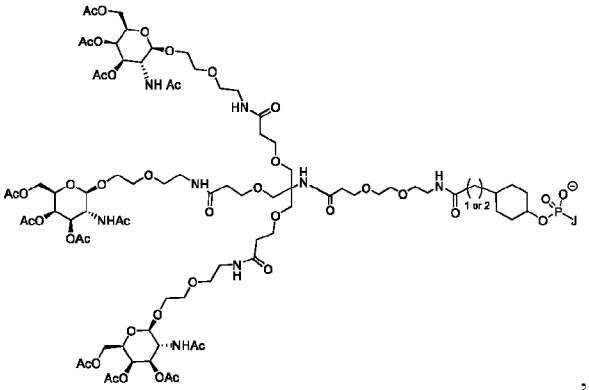

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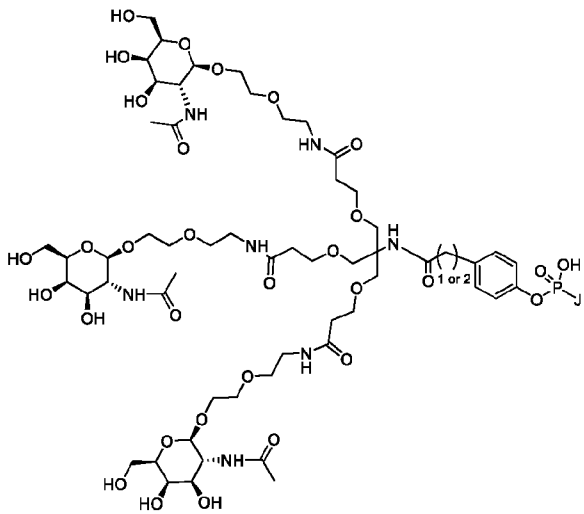

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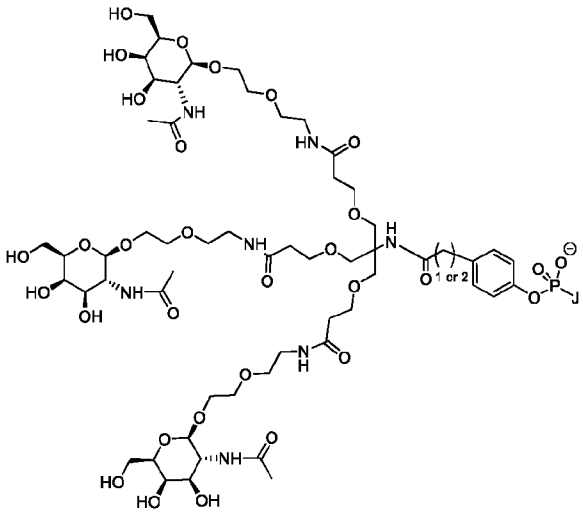

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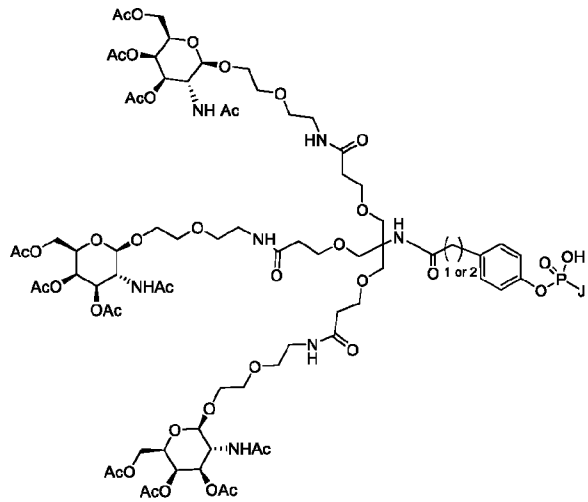

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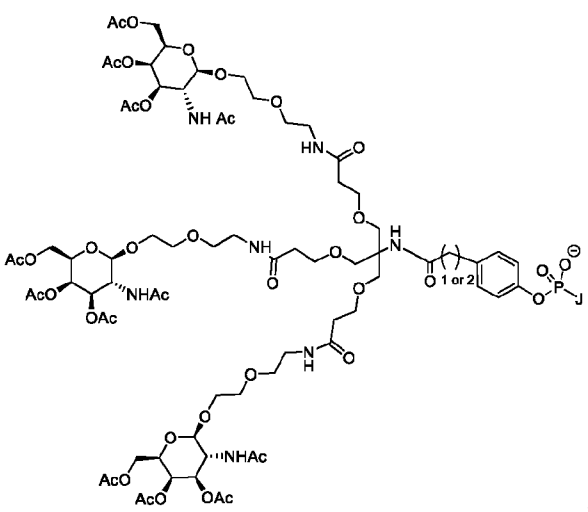
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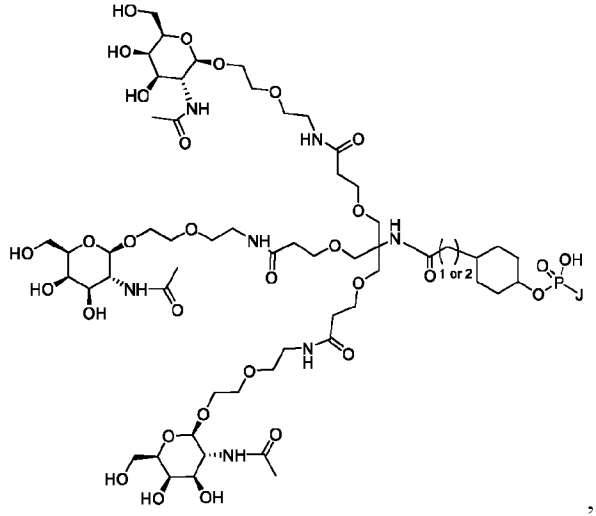
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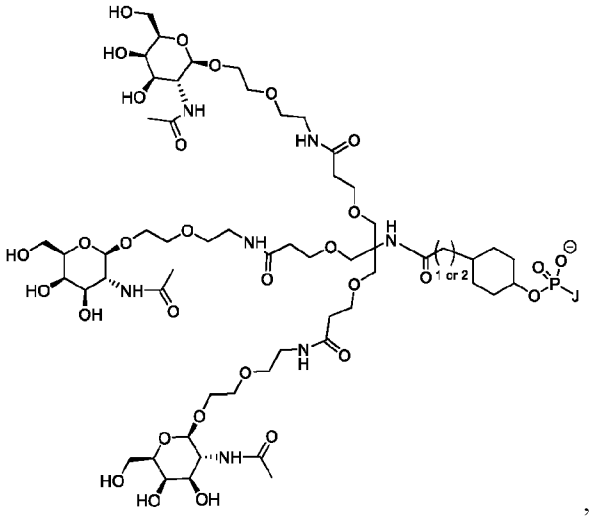
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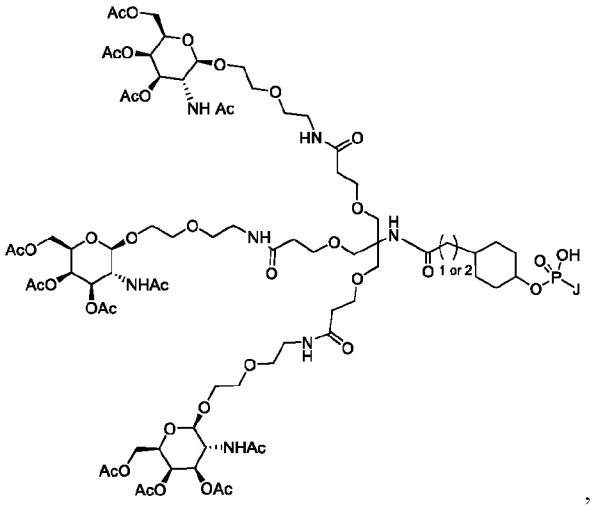
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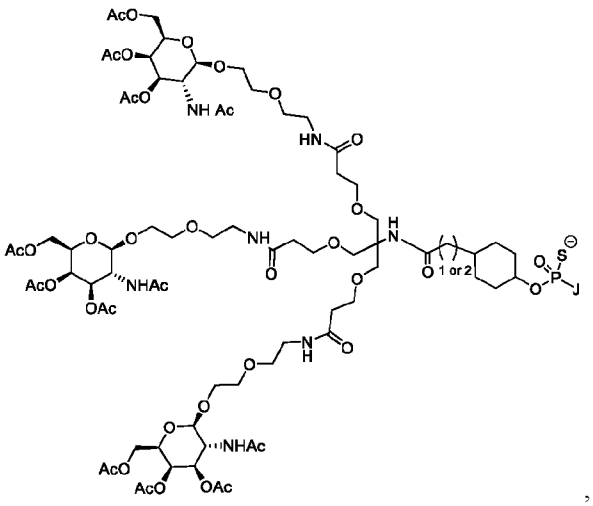
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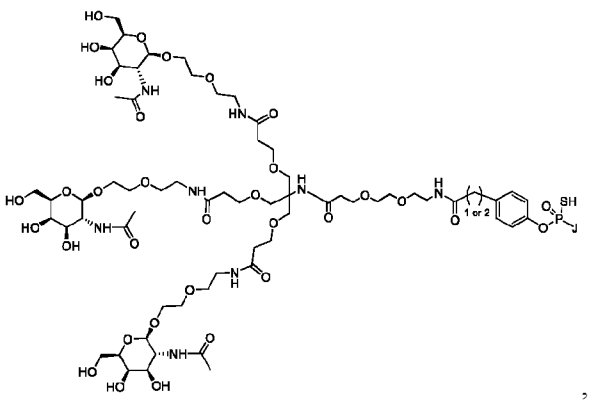
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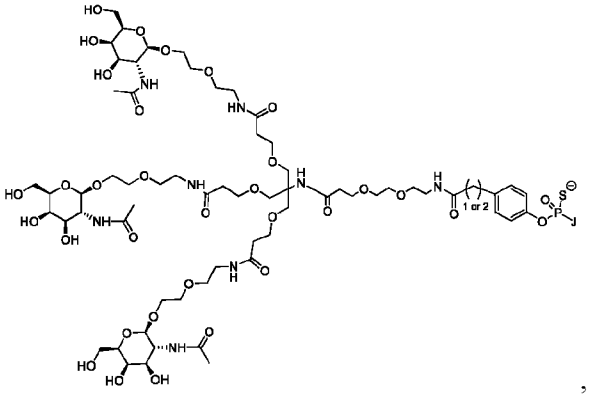

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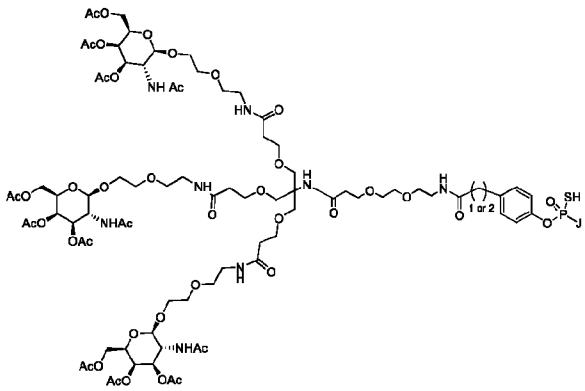

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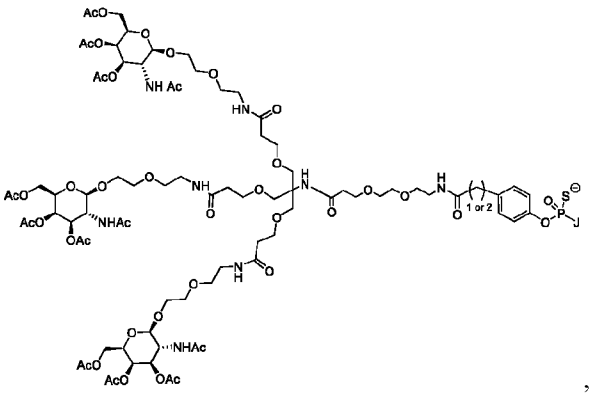

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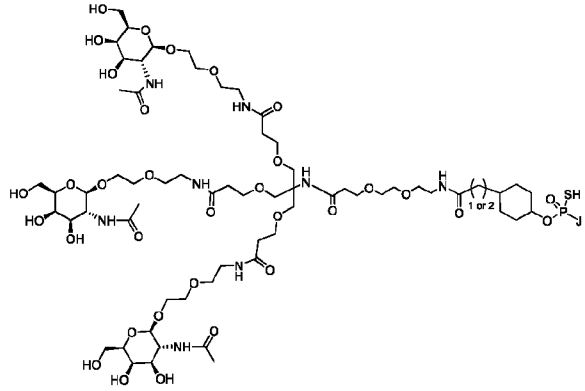

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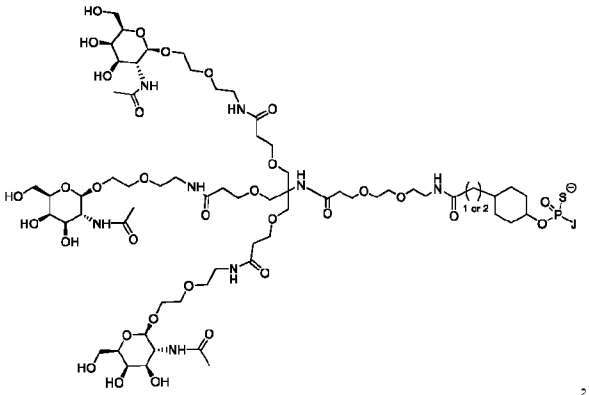

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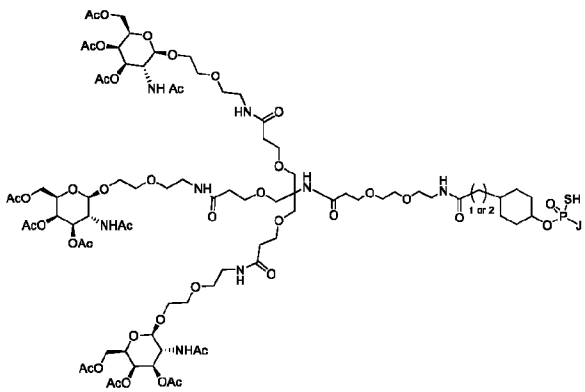

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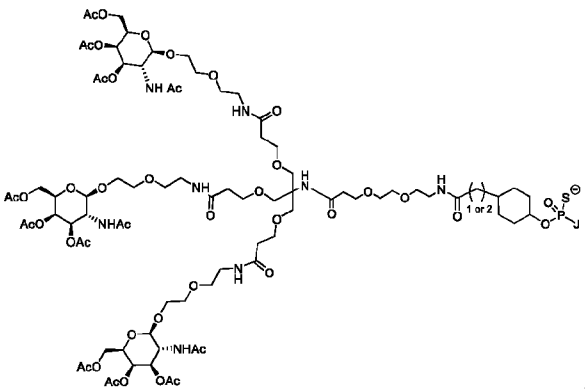

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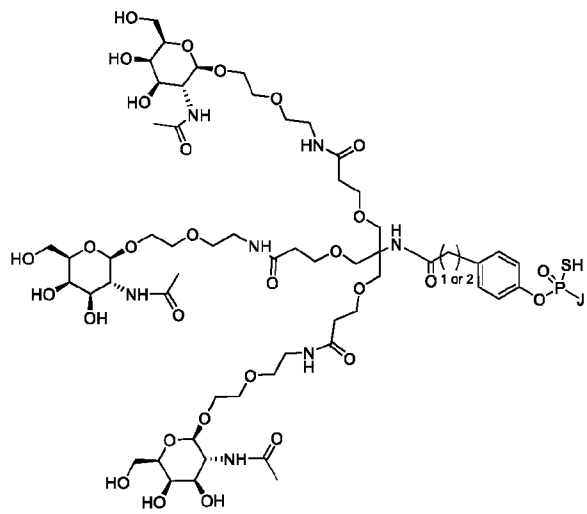

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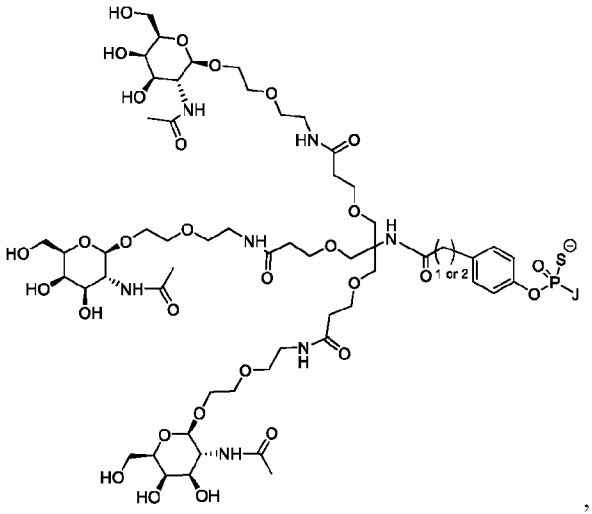

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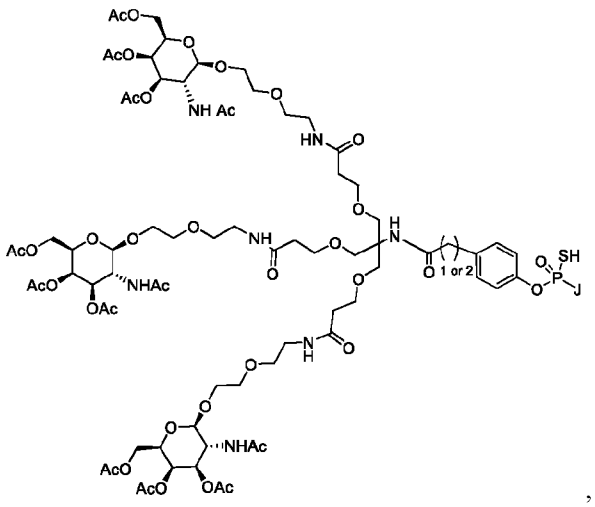

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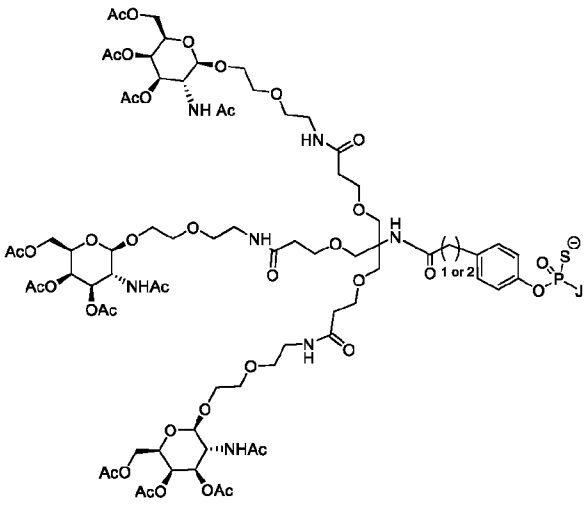

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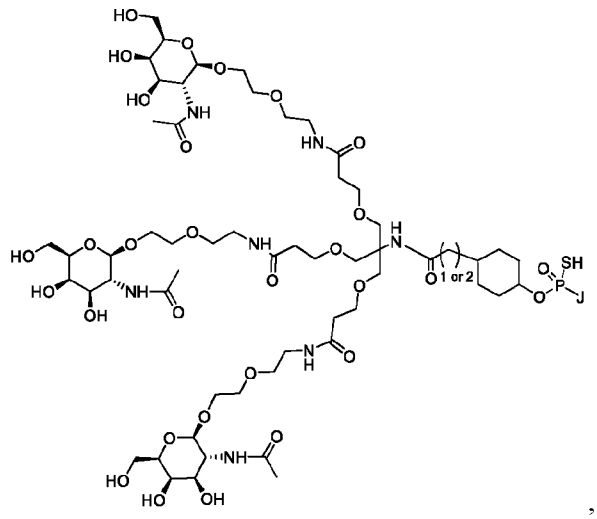

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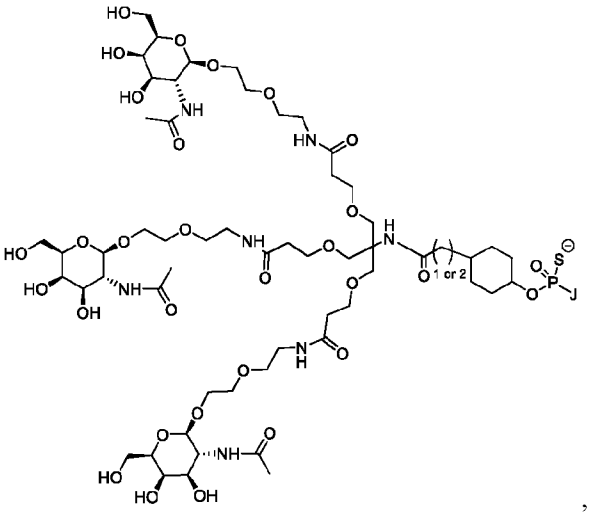
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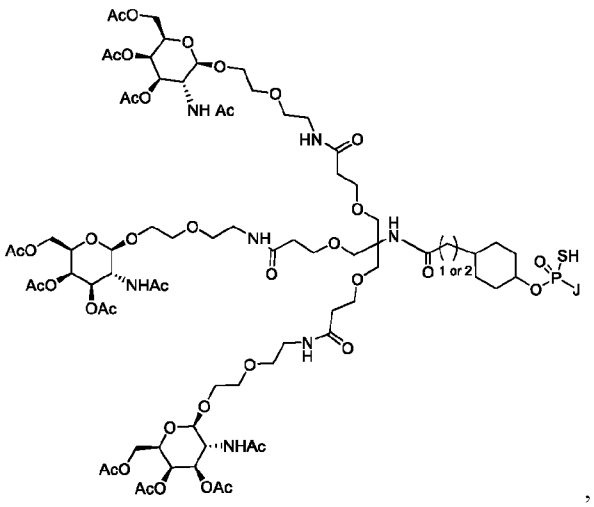
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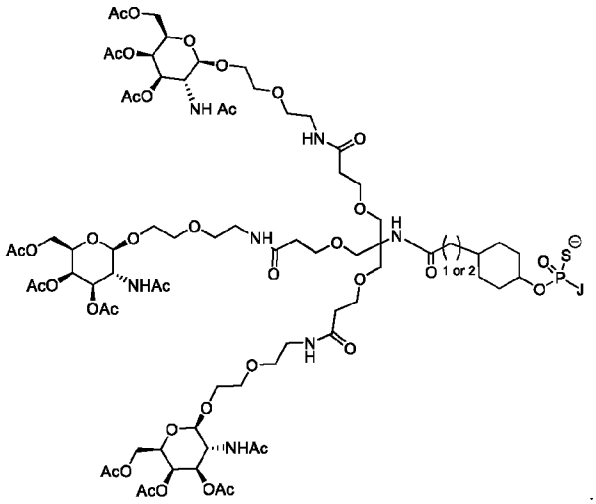

or .

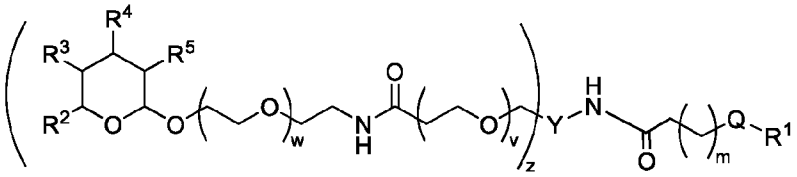
In some embodiments, the oligonucleotide (J) is attached at a 5' end or a 3' end of the oligonucleotide. In some embodiments, the oligonucleotide comprises DNA. In some embodiments, the oligonucleotide comprises RNA. In some embodiments, the oligonucleotide comprises one or more modified internucleoside linkages. In some embodiments, the one or more modified internucleoside linkages comprise alkylphosphonate, phosphorothioate, methylphosphonate, phosphorodithioate, alkylphosphonothioate, phosphoramidate, carbamate, carbonate, phosphate triester, acetamidate, or carboxymethyl ester, or a combination thereof. In some embodiments, the oligonucleotide comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 modified internucleoside linkages. In some embodiments, the oligonucleotide comprises one or more modified nucleosides. In some embodiments, the one or more modified nucleosides comprise a locked nucleic acid (LNA), hexitol nucleic acid (HLA), cyclohexene nucleic acid (CeNA), 2'- methoxyethyl, 2'-O-alkyl, 2'-O-allyl, 2'-O-allyl, 2'-fluoro, or 2'-deoxy, or a combination thereof. In some embodiments, the one or more modified nucleosides comprise a **2',4' constrained ethyl nucleoside, a 2'**-O-methyl nucleoside, 2'-deoxyfluoro nucleoside, 2'-O-N-methylacetamido (2'-O-NMA) nucleoside, a 2'-O- dimethylaminoethoxyethyl (2'-O-DMAEOE) nucleoside, 2'-O-aminopropyl (2'-O-AP) nucleoside, 2'-ara-F, **2'fluoro, or 2' O**-alkyl, or a combination thereof. In some embodiments, the oligonucleotide comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15,

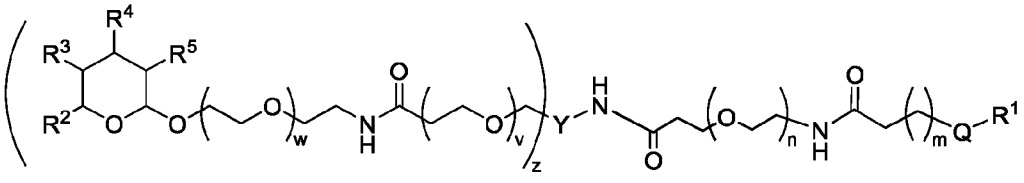
16, 17, 18, 19, 20, 21, or more modified nucleosides. In some embodiments, the oligonucleotide comprises a lipid attached at a 3' or 5' terminus of the oligonucleotide. In some embodiments, the lipid comprises cholesterol, myristoyl, palmitoyl, stearoyl, lithocholoyl, docosanoyl, docosahexaenoyl, myristyl, palmityl stearyl, or α-tocopherol, or a combination thereof. In some embodiments, the oligonucleotide comprises an arginine-glycine-aspartic acid (RGD) peptide attached at a 3' or 5' terminus of the oligonucleotide. In some embodiments, the RGD peptide comprises Cyclo(-Arg-Gly-Asp-D-Phe-Cys), Cyclo(-Arg-Gly-Asp-D-Phe-Lys), Cyclo(-Arg-Gly-Asp-D-Phe-azido), an amino benzoic acid derived RGD, or a combination thereof. In some embodiments, the oligonucleotide comprises a small interfering RNA (siRNA) comprising a sense strand and an antisense strand. In some embodiments, the sense strand is 12-30 nucleosides in length. In some embodiments, the antisense strand is 12-30 nucleosides in length. In some embodiments, the sense strand and the antisense strand form a double-stranded RNA duplex. In some embodiments, a first base pair of the double-stranded RNA duplex is an AU base pair. In some embodiments, the sense strand or the antisense strand comprises a 3' overhang. In some embodiments, the 3' overhang comprises 1, 2, or more nucleosides. In some embodiments, the sense strand comprises any one of modification patterns 1S to 6S, or 1S#2 to 6S#2. In some embodiments, the antisense strand comprises any one of modification patterns 1AS to 9AS. In some embodiments, the oligonucleotide comprises an antisense oligonucleotide (ASO). In some embodiments, the ASO is 12-30 nucleosides in length. In some embodiments, the ASO comprises modification pattern ASO1. In some embodiments, the compound binds to an asialoglycoprotein receptor. In some embodiments, the compound targets a hepatocyte.

[0005] Disclosed herein is a pharmaceutical composition comprising the compound of any one of the compounds described herein, and a pharmaceutically acceptable carrier, excipient, or diluent. In some embodiments, the pharmaceutical composition is sterile. In some embodiments, the pharmaceutical composition comprises a pharmaceutically acceptable carrier. In some embodiments, the pharmaceutically acceptable carrier comprises water, a buffer, or a saline solution. In some embodiments, the oligonucleotide targets a target mRNA and when administered to a subject in an effective amount decreases the target mRNA or a target protein by at least 10%.

[0006] Disclosed herein is a method of decreasing a target mRNA or target protein in a subject in need thereof, comprising administering an effective amount of the pharmaceutical composition of any one of the compounds described herein. In some embodiments, the effective amount decreases a measurement of the target mRNA or target protein in the subject, relative to a baseline target mRNA or target protein measurement. In some embodiments, the effective amount treats a disorder in the subject. In some embodiments, the effective amount decreases a measurement of a symptom or parameter related to the disorder in the subject, relative to a baseline symptom or parameter measurement. In some embodiments, the measurement of the symptom or the parameter related to the disorder in the subject is decreased for at least 10 days. In some embodiments, the measurement of the symptom or the parameter related to the disorder in the subject is decreased for at least 100 days. In some embodiments, the disorder comprises a metabolic disorder. In some embodiments, the disorder comprises a liver disorder.

[0007] Disclosed herein is a compound represented by Formula (A) or (B):


(A), or


(B);

or a salt thereof, wherein

each w is independently selected from any value from 1 to 20;

each v is independently selected from any value from 1 to 20;

n is selected from any value from 1 to 20;

m is selected from any value from 1 to 20;

z is selected from any value from 1 to 3, wherein

if z is 3, Y is C

if z is 2, Y is CR^6, or

if z is 1, Y is $C(R^6)_2$;

Q is selected from:

C_{3-10} carbocycle optionally substituted with one or more substituents independently selected from halogen, -CN, $-NO_2$, $-OR^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, $-C(O)N(R^7)_2$, $-N(R^7)C(O)R^7$, $-N(R^7)C(O)N(R^7)_2$, $-OC(O)N(R^7)_2$, $-N(R^7)C(O)OR^7$, $-C(O)OR^7$, $-OC(O)R^7$, $-S(O)R^7$, and C_{1-6} alkyl, wherein the C_{1-6} alkyl, is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, $-NO_2$, and $-NH_2$;

R^1 is selected from:

$-OR^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, $-C(O)N(R^7)_2$, $-N(R^7)C(O)R^7$, $-N(R^7)C(O)N(R^7)_2$, $-OC(O)N(R^7)_2$, $-N(R^7)C(O)OR^7$, $-C(O)OR^7$, $-OC(O)R^7$, $-S(O)R^7$, $-S(O)_2R^7$, $-OS(O)_2R^7$, $-OP(O)(OR^7)_2$, $-OP(S)(OR^7)_2$, $-SP(O)(OR^7)_2$, $-OP(O)(SR^7)(OR^7)$, $-OP(O)(OR^7)N(R^7)_2$, $-OP(S)(OR^7)N(R^7)_2$, $-SP(O)(OR^7)N(R^7)_2$, $-OP(O)(SR^7)N(R^7)_2$, $-OP(O)(N(R^7)_2)_2$, $-OP(S)(N(R^7)_2)_2$, $-SP(O)(N(R^7)_2)_2$, $-OP(OR^7)_2$, $-SP(OR^7)_2$, $-OP(OR^7)(SR^7)$,$-OP(OR^7)N(R^7)_2$, $-OP(SR^7)N(R^7)_2$, $-SP(OR^7)N(R^7)_2$, $-OP(N(R^7)_2)_2$, and $-SP(N(R^7)_2)_2$;

each R^2 is independently selected from:

C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, $-OR^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, $-C(O)N(R^7)_2$, $-N(R^7)C(O)R^7$, $-N(R^7)C(O)N(R^7)_2$, $-OC(O)N(R^7)_2$, $-N(R^7)C(O)OR^7$, $-C(O)OR^7$, $-OC(O)R^7$, and $-S(O)R^7$;

R^3 and R^4 are each independently selected from:

$-OR^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, $-C(O)N(R^7)_2$, $-N(R^7)C(O)R^7$, $-N(R^7)C(O)N(R^7)_2$, $-OC(O)N(R^7)_2$, $-N(R^7)C(O)OR^7$, $-C(O)OR^7$, $-OC(O)R^7$, and $-S(O)R^7$;

each R^5 is independently selected from:

$-OC(O)R^7$, $-OC(O)N(R^7)_2$, $-N(R^7)C(O)R^7$, $-N(R^7)C(O)N(R^7)_2$, $-N(R^7)C(O)OR^7$, $-C(O)R^7$, $-C(O)OR^7$, and $-C(O)N(R^7)_2$;

each R^6 is independently selected from:

hydrogen;

halogen, $-CN$, $-NO_2$, $-OR^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, $-C(O)N(R^7)_2$, $-N(R^7)C(O)R^7$, $-N(R^7)C(O)N(R^7)_2$, $-OC(O)N(R^7)_2$, $-N(R^7)C(O)OR^7$, $-C(O)OR^7$, $-OC(O)R^7$, and $-S(O)R^7$; and

C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, $-CN$, $-NO_2$, $-OR^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, $-C(O)N(R^7)_2$, $-N(R^7)C(O)R^7$, $-N(R^7)C(O)N(R^7)_2$, $-OC(O)N(R^7)_2$, $-N(R^7)C(O)OR^7$, $-C(O)OR^7$, $-OC(O)R^7$, and $-S(O)R^7$;

each R^7 is independently selected from:

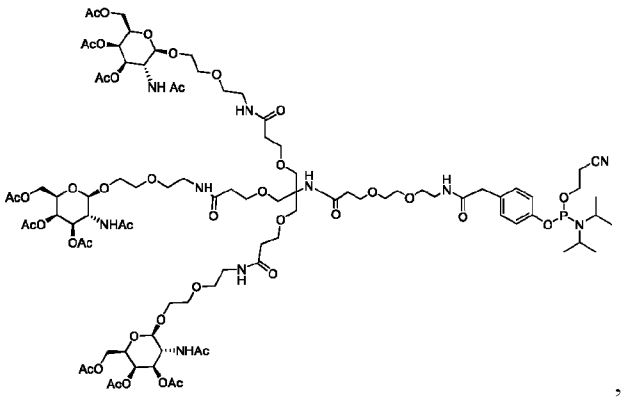
hydrogen;

C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, $-CN$, $-OH$, $-SH$, $-NO_2$, $-NH_2$, $=O$, $=S$, $-O-C_{1-6}$ alkyl, $-S-C_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)_2$, $-NH(C_{1-6}$ alkyl$)$, C_{3-10} carbocycle, and 3- to 10-membered heterocycle; and

C_{3-10} carbocycle, and 3- to 10-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, $-CN$, $-OH$, $-SH$, $-NO_2$, $-NH_2$, $=O$, $=S$, $-O-C_{1-6}$ alkyl, $-S-C_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)_2$, $-NH(C_{1-6}$ alkyl$)$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, and C_{1-6} haloalkyl.

In some embodiments, each w is independently selected from any value from 1 to 10. In some embodiments, each w is independently selected from any value from 1 to 5. In some embodiments, each w is 1. In some embodiments, each v is independently selected from any value from 1 to 10. In some embodiments, each v is independently selected from any value from 1 to 5. In some embodiments, each v is 1. In some embodiments, n is selected from any value from 1 to 10. In some embodiments, n is selected from any value from 1 to 5. In some embodiments, n is 2. In some embodiments, m is selected from any value from 1 to 10. In some embodiments, m is selected from any value from 1 to 5. In some embodiments, m is selected from 1 and 2. In some embodiments, z is 3 and Y is C. In some embodiments, Q is selected from C_{5-6} carbocycle optionally substituted with one or more substituents independently selected from halogen, $-CN$, $-NO_2$, $-OR^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, $-C(O)N(R^7)_2$, $-N(R^7)C(O)R^7$, $-N(R^7)C(O)N(R^7)_2$, $-OC(O)N(R^7)_2$, $-N(R^7)C(O)OR^7$, $-C(O)OR^7$, $-OC(O)R^7$, and $-S(O)R^7$. In some embodiments, Q is selected from C_{5-6} carbocycle optionally substituted with one or more substituents independently selected from halogen, $-CN$, $-OH$, $-SH$, $-NO_2$, and $-NH_2$. In some embodiments, Q is selected from phenyl and cyclohexyl, each of which is optionally substituted with one or more substituents independently selected from halogen, $-CN$, $-OH$, $-SH$, $-NO_2$, and $-NH_2$. In some embodiments, Q is selected from phenyl. In some embodiments, Q is selected from cyclohexyl. In some embodiments, R^1 is selected from $-OP(O)(OR^7)_2$, $-OP(O)(OR^7)N(R^7)_2$, $-OP(O)(N(R^7)_2)_2$, $-OP(OR^7)_2$, $-OP(OR^7)N(R^7)_2$, and $-OP((NR^7)_2)_2$. In some embodiments, R^1 is selected from $-OP(O)(OR^7)_2$ and $-$

$OP(OR^7)N(R^7)_2$. In some embodiments, R^1 is selected from $-OP(O)(OCH_2CH_3)OH$ and $-OP(OCH_2CH_2CN)N(CH(CH_3)_2)_2$. In some embodiments, R^1 is $-OP(OCH_2CH_2CN)N(CH(CH_3)_2)_2$. In some embodiments, R^2 is selected from C_{1-3} alkyl substituted with one or more substituents independently selected from halogen, $-OR^7$, $-OC(O)R^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, and $-S(O)R^7$. In some embodiments, R^2 is selected from C_{1-3} alkyl substituted with one or more substituents independently selected from $-OR^7$, $-OC(O)R^7$, $-SR^7$, and $-N(R^7)_2$. In some embodiments, R^2 is selected from C_{1-3} alkyl substituted with one or more substituents independently selected from $-OR^7$ and $-OC(O)R^7$. In some embodiments, R^3 is selected from halogen, $-OR^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, $-OC(O)R^7$, and $-S(O)R^7$. In some embodiments, R^3 is selected from $-OR^7$ $-SR^7$, $-OC(O)R^7$, and $-N(R^7)_2$. In some embodiments, R^3 is selected from $-OR^7$ - and $-OC(O)R^7$. In some embodiments, R^4 is selected from halogen, $-OR^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, $-OC(O)R^7$, and $-S(O)R^7$. In some embodiments, R^4 is selected from $-OR^7$ $-SR^7$, $-OC(O)R^7$, and $-N(R^7)_2$. In some embodiments, R^4 is selected from $-OR^7$ - and $-OC(O)R^7$. In some embodiments, R^5 is selected from $-OC(O)R^7$, $-OC(O)N(R^7)_2$, $-N(R^7)C(O)R^7$, $-N(R^7)C(O)N(R^7)_2$, and $-N(R^7)C(O)OR^7$. In some embodiments, R^5 is selected from $-OC(O)R^7$ and $-N(R^7)C(O)R^7$. In some embodiments, each R^7 is independently selected from: hydrogen; and C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, $-NO_2$, $-NH_2$, =O, =S, $-O-C_{1-6}$ alkyl, $-S-C_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)_2$, $-NH(C_{1-6}$ alkyl), C_{3-10} carbocycle, or 3- to 10-membered heterocycle. In some embodiments, each R^7 is independently selected from C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, $-NO_2$, $-NH_2$, =O, =S, $-O-C_{1-6}$ alkyl, $-S-C_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)_2$, and $-NH(C_{1-6}$ alkyl). In some embodiments, each R^7 is independently selected from C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, and -SH. In some embodiments, w is 1; v is 1; n is 2; m is 1 or 2; z is 3 and Y is C; Q is phenyl or cyclohexyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, $-NO_2$, $-NH_2$, and C_{1-3} alkyl; R^1 is selected from $-OP(O)(OR^7)_2$ and $-OP(OR^7)N(R^7)_2$; R^2 is C_1 alkyl substituted with -OH or $-OC(O)CH_3$; R^3 is -OH or $-OC(O)CH_3$; R^4 is -OH or $-OC(O)CH_3$; and R^5 is $-NH(O)CH_3$. In some embodiments, the compound comprises:



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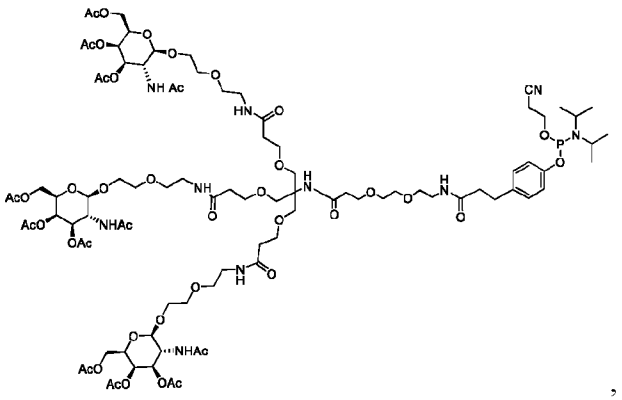

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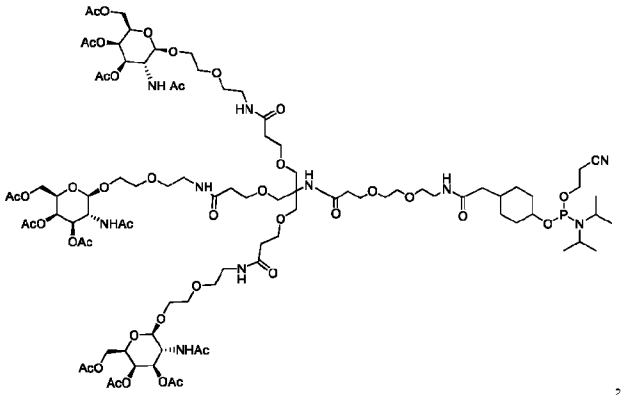

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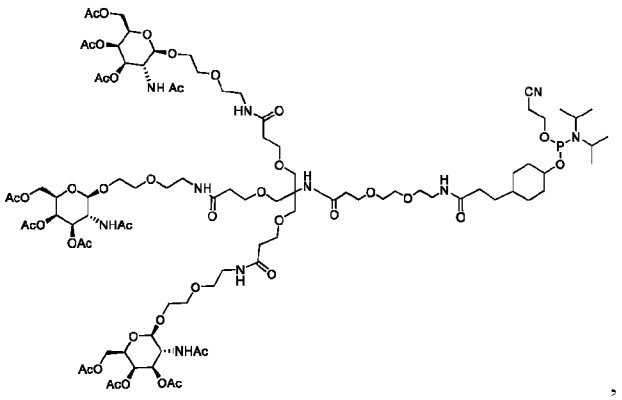

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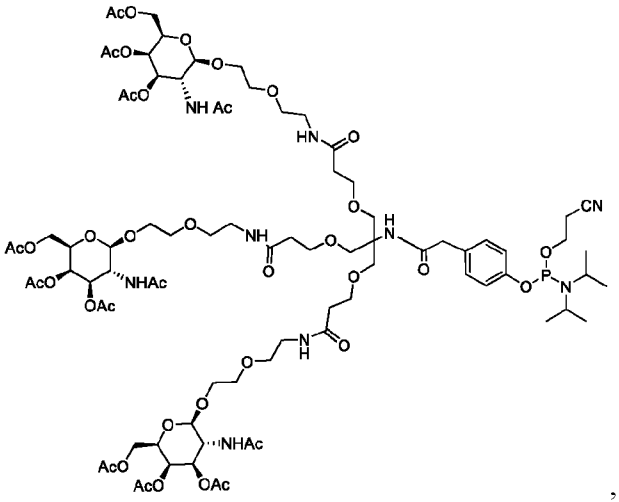

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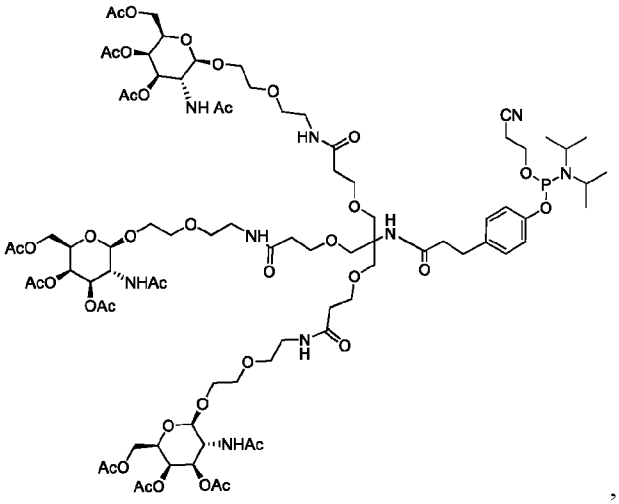

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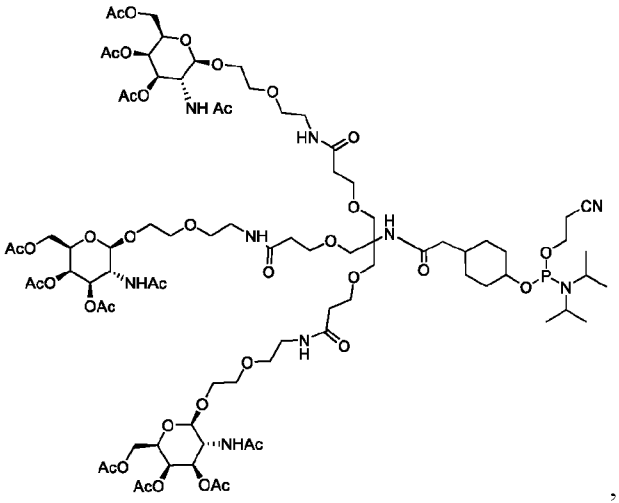

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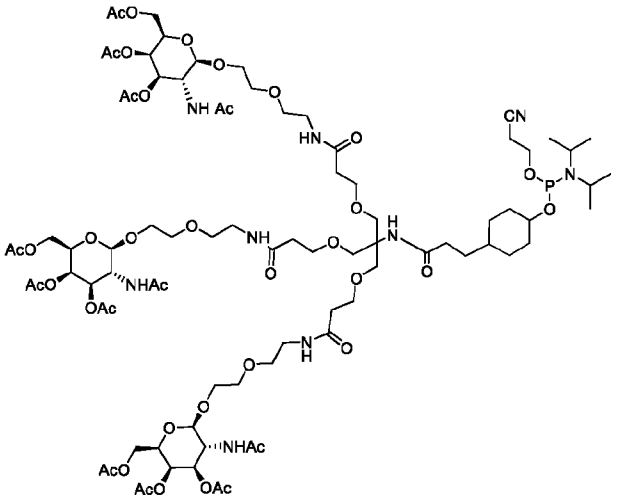

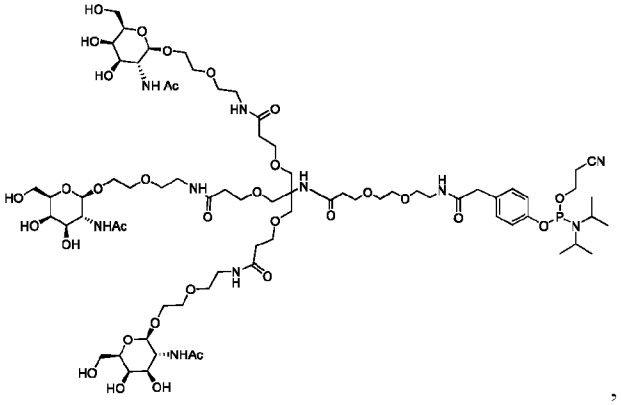

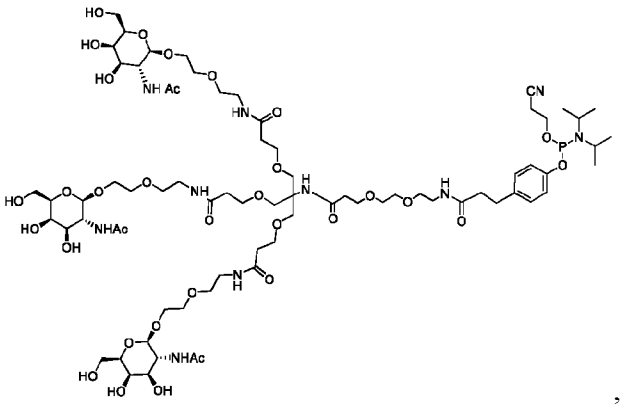

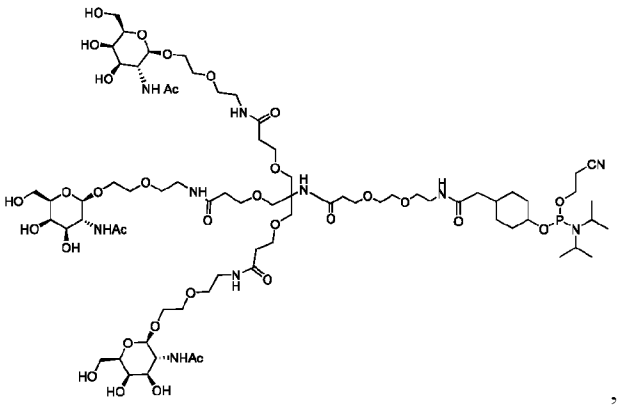

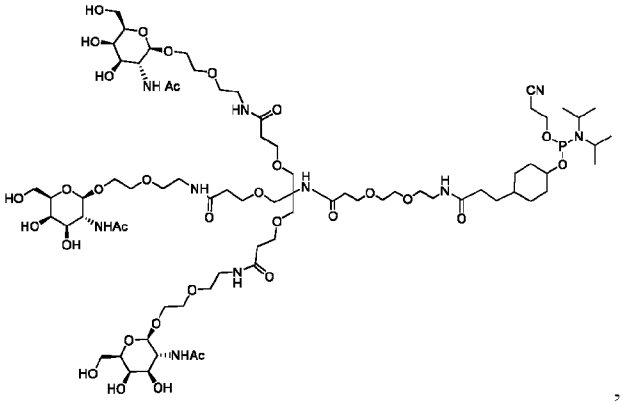

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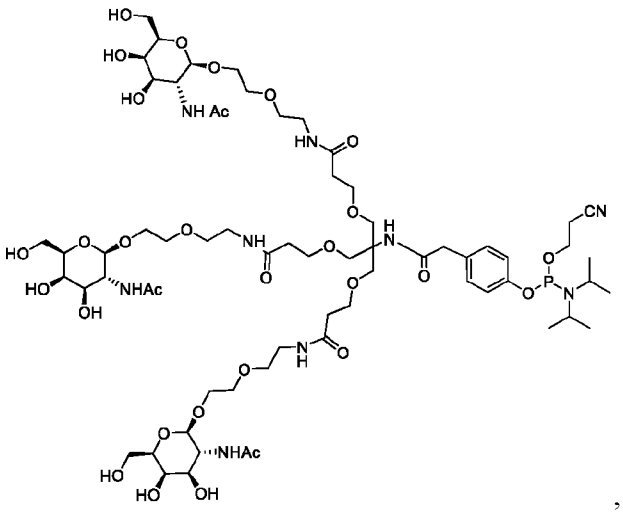

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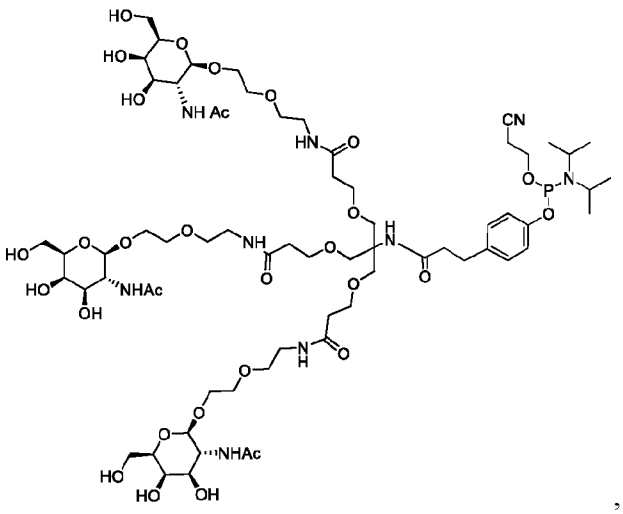

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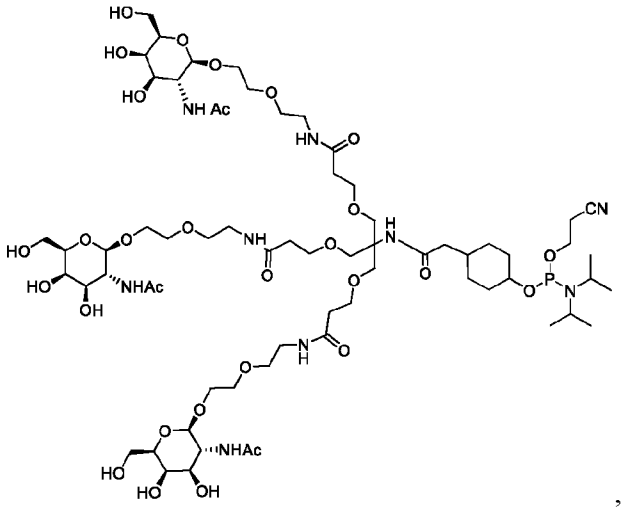

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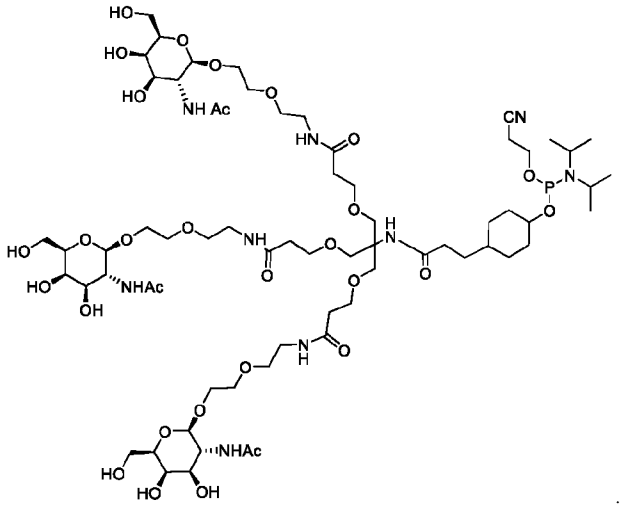

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DETAILED DESCRIPTION

[0008] N-Acetylgalactosamine (GalNAc), is an amino sugar derivative of galactose. GalNAc and GalNAc-containing moieties may bind lectins such as asialoglycoprotein receptors. These receptors may be included on hepatocytes. Thus, GalNAc may target an oligonucleotide to a hepatocyte or to the liver.

[0009] Provided herein, are GalNAc moieties. These GalNAc moieties may be conjugated to an oligonucleotide such as a small interfering RNA (siRNA) or antisense oligonucleotide (ASO). The oligonucleotide conjugated to the GalNAc moiety may be administered to a subject, targeted to a liver or hepatocyte, or used to treat a liver related disorder in the subject.

I. COMPOSITIONS

[0010] Provided herein, in some embodiments, are compositions comprising an oligonucleotide and an N-Acetylgalactosamine (GalNAc) moiety. In some embodiments, the composition comprises an oligonucleotide. The oligonucleotide may inhibit a target gene or oligonucleotide. The oligonucleotide may bind a target oligonucleotide. In some embodiments, the composition is used in a method described herein.

[0011] Provided herein, in some embodiments, are compounds comprising an oligonucleotide and a GalNAc moiety. In some embodiments, the compound comprises an oligonucleotide. The oligonucleotide may bind to a target oligonucleotide. In some embodiments, the compound is used in a method described herein. In some embodiments, the compound is included in a composition described herein.

[0012] The oligonucleotide of the compound or composition described herein may comprise a small interfering RNA (siRNA) or an antisense oligonucleotide (ASO).

[0013] Some embodiments include a composition comprising a GalNAc moiety, and an oligonucleotide that when administered to a subject in an effective amount decreases a target mRNA or protein level in a cell, fluid or tissue of the subject. Some embodiments include a composition comprising a GalNAc moiety, and an oligonucleotide that when administered to a subject in an effective amount decreases a target mRNA or protein level in liver tissue or in a hepatocyte. In some embodiments, the composition comprises a GalNAc moiety, and an oligonucleotide that when administered to a subject in an effective amount decreases levels of a target e.g. mRNA in a cell or tissue. In some embodiments, the cell is a hepatocyte. In some embodiments, the tissue is liver tissue. Some embodiments include a composition comprising a GalNAc moiety, and an oligonucleotide that when administered to a subject in an effective amount decreases a target mRNA level in liver tissue. Some embodiments include a composition comprising a GalNAc moiety, and an oligonucleotide that when administered to a subject in an effective amount decreases a target mRNA level in a hepatocyte.

[0014] In some embodiments, the decrease in the target oligonucleotide level is specific to a hepatocyte in relation to another cell type. In some embodiments, the decrease in the target RNA level is specific to a hepatocyte in relation to another cell type. In some embodiments, the decrease in the target mRNA level is specific to a hepatocyte in relation to another cell type. In some embodiments, the decrease in the target protein level is specific to a hepatocyte in relation to another cell type. In some embodiments, the decrease in the target oligonucleotide level is specific to liver tissue in relation to another tissue type. In some embodiments, the decrease in the target RNA level is specific to liver in relation to another tissue type. In some embodiments, the decrease in the target mRNA level is specific to liver in relation to another tissue type. In some embodiments, the decrease in the target protein level is specific to liver in relation to another tissue type.

[0015] In some embodiments, the composition comprises a GalNAc moiety, and an oligonucleotide that binds to a target oligonucleotide, which when administered to a subject in an effective amount decreases the target oligonucleotide levels in a cell or tissue. In some embodiments, the target oligonucleotide levels are decreased by about 2.5% or more, about 5% or more, or about 7.5% or more, as compared to prior to administration. In some embodiments, the target oligonucleotide levels are decreased by about 10% or more, as compared to prior to administration. In some embodiments, the target oligonucleotide levels are decreased by about 20% or more, about 30% or more, about 40% or more, about 50% or more, about 60% or more, about 70% or more, about 80% or more, about 90% or more, or about 100%, as compared to prior to administration. In some embodiments, the target oligonucleotide levels are decreased by no more than about 2.5%, no more than about 5%, or no more than about 7.5%, as compared to prior to

administration. In some embodiments, the target oligonucleotide levels are decreased by no more than about 10%, as compared to prior to administration. In some embodiments, the target oligonucleotide levels are decreased by no more than about 20%, no more than about 30%, no more than about 40%, no more than about 50%, no more than about 60%, no more than about 70%, no more than about 80%, no more than about 90%, or no more than about 100%, as compared to prior to administration. In some embodiments, the target oligonucleotide levels are decreased by 2.5%, 5%, 7.5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, or by a range defined by any of the two aforementioned percentages.

[0016] In some embodiments, the composition comprises a GalNAc moiety, and an oligonucleotide that binds to a target mRNA, which when administered to a subject in an effective amount decreases the target mRNA levels in a cell or tissue. In some embodiments, the target mRNA levels are decreased by about 2.5% or more, about 5% or more, or about 7.5% or more, as compared to prior to administration. In some embodiments, the target mRNA levels are decreased by about 10% or more, as compared to prior to administration. In some embodiments, the target mRNA levels are decreased by about 20% or more, about 30% or more, about 40% or more, about 50% or more, about 60% or more, about 70% or more, about 80% or more, about 90% or more, or about 100%, as compared to prior to administration. In some embodiments, the target mRNA levels are decreased by no more than about 2.5%, no more than about 5%, or no more than about 7.5%, as compared to prior to administration. In some embodiments, the target mRNA levels are decreased by no more than about 10%, as compared to prior to administration. In some embodiments, the target mRNA levels are decreased by no more than about 20%, no more than about 30%, no more than about 40%, no more than about 50%, no more than about 60%, no more than about 70%, no more than about 80%, no more than about 90%, or no more than about 100%, as compared to prior to administration. In some embodiments, the target mRNA levels are decreased by 2.5%, 5%, 7.5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, or by a range defined by any of the two aforementioned percentages.

[0017] In some embodiments, the composition comprises a GalNAc moiety, and an oligonucleotide that binds to an oligonucleotide encoding a target protein, which when the composition is administered to a subject in an effective amount decreases the target protein levels in a cell or tissue. In some embodiments, the cell is a hepatocyte. In some embodiments, the tissue is liver tissue. In some embodiments, the target protein levels are decreased by about 2.5% or more, about 5% or more, or about 7.5% or more, as compared to prior to administration. In some embodiments, the target protein levels are decreased by about 10% or more, as compared to prior to administration. In some embodiments, the target protein levels are decreased by about 20% or more, about 30% or more, about 40% or more, about 50% or more, about 60% or more, about 70% or more, about 80% or more, about 90% or more, or about 100%, as compared to prior to administration. In some embodiments, the target protein levels are decreased by no more than about 2.5%, no more than about 5%, or no more than about 7.5%, as compared to prior to administration. In some embodiments, the target protein levels are decreased by no more than about 10%, as compared to prior to administration. In some embodiments, the target protein levels are decreased by

no more than about 20%, no more than about 30%, no more than about 40%, no more than about 50%, no more than about 60%, no more than about 70%, no more than about 80%, no more than about 90%, or no more than about 100%, as compared to prior to administration. In some embodiments, the target protein levels are decreased by 2.5%, 5%, 7.5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, or by a range defined by any of the two aforementioned percentages.

[0018] In some embodiments, the composition comprises a GalNAc moiety, and an oligonucleotide that binds to a target oligonucleotide (e.g. mRNA) and when administered to a subject in an effective amount decreases an adverse phenotype (e.g. a symptom of a disorder associated with the target oligonucleotide). In some embodiments, the adverse phenotype is decreased by about 2.5% or more, about 5% or more, or about 7.5% or more, as compared to prior to administration. In some embodiments, the adverse phenotype is decreased by about 10% or more, as compared to prior to administration. In some embodiments, the adverse phenotype is decreased by about 20% or more, about 30% or more, about 40% or more, about 50% or more, about 60% or more, about 70% or more, about 80% or more, about 90% or more, or about 100%, as compared to prior to administration. In some embodiments, the adverse phenotype is decreased by no more than about 2.5%, no more than about 5%, or no more than about 7.5%, as compared to prior to administration. In some embodiments, the adverse phenotype is decreased by no more than about 10%, as compared to prior to administration. In some embodiments, the adverse phenotype is decreased by no more than about 20%, no more than about 30%, no more than about 40%, no more than about 50%, no more than about 60%, no more than about 70%, no more than about 80%, no more than about 90%, or no more than about 100%, as compared to prior to administration. In some embodiments, the adverse phenotype is decreased by 2.5%, 5%, 7.5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%, or by a range defined by any of the two aforementioned percentages.

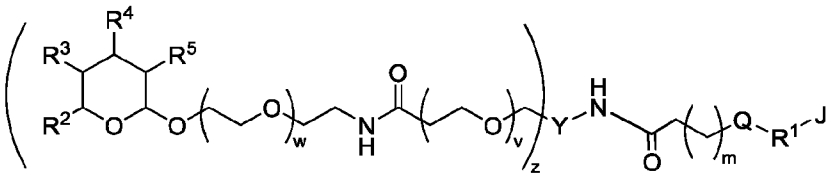
[0019] In some embodiments, the composition comprises a GalNAc moiety, and an oligonucleotide that binds to a target oligonucleotide (e.g. mRNA) and when administered to a subject in an effective amount increases a protective phenotype (e.g. protective against a disorder). In some embodiments, the protective phenotype is increased by about 2.5% or more, about 5% or more, or about 7.5% or more, as compared to prior to administration. In some embodiments, the protective phenotype is increased by about 10% or more, as compared to prior to administration. In some embodiments, the protective phenotype is increased by about 20% or more, about 30% or more, about 40% or more, about 50% or more, about 60% or more, about 70% or more, about 80% or more, about 90% or more, or about 100% or more, as compared to prior to administration. In some embodiments, the protective phenotype is increased by about 200% or more, about 300% or more, about 400% or more, about 500% or more, about 600% or more, about 700% or more, about 800% or more, about 900% or more, or about 1000% or more, as compared to prior to administration. In some embodiments, the protective phenotype is increased by no more than about 2.5%, no more than about 5%, or no more than about 7.5%, as compared to prior to administration. In some embodiments, the protective phenotype is increased by no more than about 10%, as compared to prior to

administration. In some embodiments, the protective phenotype is increased by no more than about 20%, no more than about 30%, no more than about 40%, no more than about 50%, no more than about 60%, no more than about 70%, no more than about 80%, no more than about 90%, or no more than about 100%, as compared to prior to administration. In some embodiments, the protective phenotype is increased by no more than about 200%, no more than about 300%, no more than about 400%, no more than about 500%, no more than about 600%, no more than about 700%, no more than about 800%, no more than about 900%, or no more than about 1000%, as compared to prior to administration. In some embodiments, the protective phenotype is increased by 2.5%, 5%, 7.5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, 150%, 200%, 250%, 300%, 400%, 500%, 600%, 700%, 800%, 900%, or 1000%, or by a range defined by any of the two aforementioned percentages.

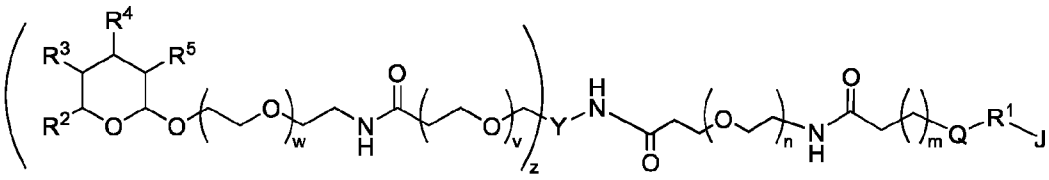
A. GalNAc moieties and compounds

[0020] Provided herein, in some embodiments, are compositions comprising a GalNAc moiety. Provided herein, in some embodiments, are compositions comprising a GalNAc moiety and an oligonucleotide. In some embodiments, a composition comprising GalNAc moiety and an oligonucleotide is described by a compound of Formula (I) or Formula (II). In some embodiments the oligonucleotide of Formula (I) or Formula (II), is J. In some embodiments the GalNAc moiety of Formula (I) or Formula (II) is the molecular moiety bound to J. The oligonucleotide may comprise a small interfering RNA (siRNA) or an antisense oligonucleotide (ASO).

[0021] Provided herein, in some embodiments, is a compound represented by Formula (I) or (II):



(I), or



(II);

or a salt thereof, wherein

J is an oligonucleotide;

each w is independently selected from any value from 1 to 20;

each v is independently selected from any value from 1 to 20;

n is selected from any value from 1 to 20;

m is selected from any value from 1 to 20;

z is selected from any value from 1 to 3, wherein

if z is 3, Y is C

if z is 2, Y is CR^6, or

if z is 1, Y is $C(R^6)_2$;

Q is selected from:

C_{3-10} carbocycle optionally substituted with one or more substituents independently selected from halogen, -CN, $-NO_2$, $-OR^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, $-C(O)N(R^7)_2$, $-N(R^7)C(O)R^7$, $-N(R^7)C(O)N(R^7)_2$, $-OC(O)N(R^7)_2$, $-N(R^7)C(O)OR^7$, $-C(O)OR^7$, $-OC(O)R^7$, $-S(O)R^7$, and C_{1-6} alkyl, wherein the C_{1-6} alkyl, is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, $-NO_2$, and $-NH_2$;

R^1 is a linker selected from:

-O-, -S-, $-N(R^7)-$, -C(O)-, $-C(O)N(R^7)-$, $-N(R^7)C(O)-$, $-N(R^7)C(O)N(R^7)-$, $-OC(O)N(R^7)-$, $-N(R^7)C(O)O-$, -C(O)O-, -OC(O)-, -S(O)-, $-S(O)_2-$, $-OS(O)_2-$, $-OP(O)(OR^7)O-$, $-SP(O)(OR^7)O-$, $-OP(S)(OR^7)O-$, $-OP(O)(SR^7)O-$, $-OP(O)(OR^7)S-$, $-OP(O)(O^-)O-$, $-SP(O)(O^-)O-$, $-OP(S)(O^-)O-$, $-OP(O)(S^-)O-$, $-OP(O)(O^-)S-$, $-OP(O)(OR^7)NR^7-$, $-OP(O)(N(R^7)_2)NR^7-$, $-OP(OR^7)O-$, $-OP(N(R^7)_2)O-$, $-OP(OR^7)N(R^7)-$, and $-OPN(R^7)_2NR^7-$;

each R^2 is independently selected from:

C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, $-OR^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, $-C(O)N(R^7)_2$, $-N(R^7)C(O)R^7$, $-N(R^7)C(O)N(R^7)_2$, $-OC(O)N(R^7)_2$, $-N(R^7)C(O)OR^7$, $-C(O)OR^7$, $-OC(O)R^7$, and $-S(O)R^7$;

R^3 and R^4 are each independently selected from:

$-OR^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, $-C(O)N(R^7)_2$, $-N(R^7)C(O)R^7$, $-N(R^7)C(O)N(R^7)_2$, $-OC(O)N(R^7)_2$, $-N(R^7)C(O)OR^7$, $-C(O)OR^7$, $-OC(O)R^7$, and $-S(O)R^7$;

each R^5 is independently selected from:

$-OC(O)R^7$, $-OC(O)N(R^7)_2$, $-N(R^7)C(O)R^7$, $-N(R^7)C(O)N(R^7)_2$, $-N(R^7)C(O)OR^7$, $-C(O)R^7$, $-C(O)OR^7$, and $-C(O)N(R^7)_2$;

each R^6 is independently selected from:

hydrogen;

halogen, -CN, $-NO_2$, $-OR^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, $-C(O)N(R^7)_2$, $-N(R^7)C(O)R^7$, $-N(R^7)C(O)N(R^7)_2$, $-OC(O)N(R^7)_2$, $-N(R^7)C(O)OR^7$, $-C(O)OR^7$, $-OC(O)R^7$, and $-S(O)R^7$; and

C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, -CN, $-NO_2$, $-OR^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, $-C(O)N(R^7)_2$, $-N(R^7)C(O)R^7$, $-N(R^7)C(O)N(R^7)_2$, $-OC(O)N(R^7)_2$, $-N(R^7)C(O)OR^7$, $-C(O)OR^7$, $-OC(O)R^7$, and $-S(O)R^7$;

each R^7 is independently selected from:

hydrogen;

C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, $-NO_2$, $-NH_2$, =O, =S, $-O-C_{1-6}$ alkyl, $-S-C_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)_2$, $-NH(C_{1-6}$ alkyl), C_{3-10} carbocycle, and 3- to 10-membered heterocycle; and

C_{3-10} carbocycle, and 3- to 10-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, -

NO_2, -NH_2, =O, =S, -O-C_{1-6} alkyl, -S-C_{1-6} alkyl, -N(C_{1-6} alkyl)$_2$, -NH(C_{1-6} alkyl), C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, and C_{1-6} haloalkyl.

[0022] In some embodiments, each w is independently selected from any value from 1 to 20. In some embodiments, each w is independently selected from any value from 1 to 15. In some embodiments, each w is independently selected from any value from 1 to 10. In some embodiments, each w is independently selected from any value from 1 to 5. In some embodiments, each w is independently selected from any value from 1 to 4. In some embodiments, each w is independently selected from any value from 1 to 3. In some embodiments, each w is independently selected from any value from 1 to 2. In some embodiments, each w is independently 1. In some embodiments, w is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20.

[0023] In some embodiments, each v is independently selected from any value from 1 to 20. In some embodiments, each v is independently selected from any value from 1 to 15. In some embodiments, each v is independently selected from any value from 1 to 10. In some embodiments, each v is independently selected from any value from 1 to 5. In some embodiments, each v is independently selected from any value from 1 to 4. In some embodiments, each v is independently selected from any value from 1 to 3. In some embodiments, each v is independently selected from any value from 1 to 2. In some embodiments, each v is independently 1. In some embodiments, v is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20.

[0024] In some embodiments, n is selected from any value from 1 to 20. In some embodiments, n is selected from any value from 1 to 15. In some embodiments, n is selected from any value from 1 to 10. In some embodiments, n is selected from any value from 1 to 9. In some embodiments, n is selected from any value from 1 to 8. In some embodiments, n is selected from any value from 1 to 7. In some embodiments, n is selected from any value from 1 to 6. In some embodiments, n is selected from any value from 1 to 5. In some embodiments, n is selected from any value from 1 to 4. In some embodiments, n is selected from any value from 2 to 4. In some embodiments, n is selected from any value from 1 to 3. In some embodiments, n is 2 or 3. In some embodiments, n is 3. In some embodiments, n is selected from any value from 1 to 2. In some embodiments, n is 2. In some embodiments, n is 1. In some embodiments, n is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20.

[0025] In some embodiments, m is selected from any value from 1 to 20. In some embodiments, m is selected from any value from 1 to 15. In some embodiments, m is selected from any value from 1 to 10. In some embodiments, m is selected from any value from 1 to 9. In some embodiments, m is selected from any value from 1 to 8. In some embodiments, m is selected from any value from 1 to 7. In some embodiments, m is selected from any value from 3 to 7. In some embodiments, m is selected from any value from 1 to 6. In some embodiments, m is selected from any value from 2 to 6. In some embodiments, m is selected from any value from 3 to 6. In some embodiments, m is selected from any value from 4 to 6. In some embodiments, m is 6. In some embodiments, m is selected from any value from 1 to 5. In some embodiments, m is selected from any value from 3 to 5. In some embodiments, m is 5. In some embodiments, m is 4 or 5. In some embodiments, m is selected from any value from 1 to 4. In some

embodiments, m is 4. In some embodiments, m is 3 or 4. In some embodiments, m is selected from any value from 2 to 4. In some embodiments, m is selected from any value from 1 to 3. In some embodiments, m is 3. In some embodiments, m is selected from any value from 1 to 2. In some embodiments, m is 2. In some embodiments, m is 1. In some embodiments, m is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20.

[0026] In some embodiments, z is selected from any value from 1 to 3. In some embodiments, z is 3 and Y is C. In some embodiments, z is 2 and Y is CR^6. In some embodiments, z is 1 and Y is $C(R^6)_2$.

[0027] In some embodiments, Q is selected from C_{3-10} carbocycle optionally substituted with one or more substituents independently selected from halogen, -CN, $-NO_2$, $-OR^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, $-C(O)N(R^7)_2$, $-N(R^7)C(O)R^7$, $-N(R^7)C(O)N(R^7)_2$, $-OC(O)N(R^7)_2$, $-N(R^7)C(O)OR^7$, $-C(O)OR^7$, $-OC(O)R^7$, $-S(O)R^7$, and C_{1-6} alkyl, wherein the C_{1-6} alkyl, is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, $-NO_2$, and $-NH_2$. In some embodiments, Q is selected from C_{3-6} carbocycle optionally substituted with one or more substituents independently selected from halogen, -CN, $-NO_2$, $-OR^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, $-C(O)N(R^7)_2$, $-N(R^7)C(O)R^7$, $-N(R^7)C(O)N(R^7)_2$, $-OC(O)N(R^7)_2$, $-N(R^7)C(O)OR^7$, $-C(O)OR^7$, $-OC(O)R^7$, $-S(O)R^7$, and C_{1-6} alkyl, wherein the C_{1-6} alkyl, is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, $-NO_2$, and $-NH_2$. In some embodiments, Q is selected from C_{5-6} carbocycle optionally substituted with one or more substituents independently selected from halogen, -CN, $-NO_2$, $-OR^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, $-C(O)N(R^7)_2$, $-N(R^7)C(O)R^7$, $-N(R^7)C(O)N(R^7)_2$, $-OC(O)N(R^7)_2$, $-N(R^7)C(O)OR^7$, $-C(O)OR^7$, $-OC(O)R^7$, and $-S(O)R^7$. In some embodiments, Q is selected from C_6 carbocycle optionally substituted with one or more substituents independently selected from halogen, -CN, $-NO_2$, $-OR^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, $-C(O)N(R^7)_2$, $-N(R^7)C(O)R^7$, $-N(R^7)C(O)N(R^7)_2$, $-OC(O)N(R^7)_2$, $-N(R^7)C(O)OR^7$, $-C(O)OR^7$, $-OC(O)R^7$, and $-S(O)R^7$. In some embodiments, Q is selected from C_5 carbocycle optionally substituted with one or more substituents independently selected from halogen, -CN, $-NO_2$, $-OR^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, $-C(O)N(R^7)_2$, $-N(R^7)C(O)R^7$, $-N(R^7)C(O)N(R^7)_2$, $-OC(O)N(R^7)_2$, $-N(R^7)C(O)OR^7$, $-C(O)OR^7$, $-OC(O)R^7$, and $-S(O)R^7$. In some embodiments, Q is selected from C_{5-6} carbocycle optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, $-NO_2$, and $-NH_2$. In some embodiments, Q is selected from phenyl, cyclohexyl, cyclopentadiene, and cyclopentyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, $-NO_2$, and $-NH_2$. In some embodiments, Q is selected from phenyl and cyclohexyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, $-NO_2$, and $-NH_2$. In some embodiments, Q is selected from phenyl and cyclohexyl. In some embodiments, Q is phenyl. In some embodiments, Q is cyclohexyl.

[0028] In some embodiments, R^1 is a linker selected from -O-, -S-, $-N(R^7)-$, -C(O)-, $-C(O)N(R^7)-$, $-N(R^7)C(O)-$, $-N(R^7)C(O)N(R^7)-$, $-OC(O)N(R^7)-$, $-N(R^7)C(O)O-$, -C(O)O-, -OC(O)-, -S(O)-, $-S(O)_2-$, $-OS(O)_2-$, $-OP(O)(OR^7)O-$, $-SP(O)(OR^7)O-$, $-OP(S)(OR^7)O-$, $-OP(O)(SR^7)O-$, $-OP(O)(OR^7)S-$, $-OP(O)(OR^7)NR^7-$, $-OP(O)(N(R^7)_2)NR^7-$, $-OP(OR^7)O-$, $-OP(N(R^7)_2)O-$, $-OP(OR^7)N(R^7)-$, and $-OPN(R^7)_2-NR^7--$. In some embodiments, R^1 is a linker selected from -O-, -S-, $-N(R^7)-$, -C(O)-, $-C(O)N(R^7)-$, -

$N(R^7)C(O)$-, -$N(R^7)C(O)N(R^7)$-, -$OC(O)N(R^7)$-, -$N(R^7)C(O)O$-, -$C(O)O$-, -$OC(O)$-, -$S(O)$-, -$S(O)_2$-, -$OS(O)_2$-, -$OP(O)(OR^7)O$-, -$SP(O)(OR^7)O$-, -$OP(S)(OR^7)O$-, -$OP(O)(SR^7)O$-, -$OP(O)(OR^7)S$-, -$OP(O)(O^-)O$-, -$SP(O)(O^-)O$-, -$OP(S)(O^-)O$-, -$OP(O)(S^-)O$-, -$OP(O)(O^-)S$-, -$OP(O)(OR^7)NR^7$-, -$OP(O)(N(R^7)_2)NR^7$-, -$OP(OR^7)O$-, -$OP(N(R^7)_2)O$-, -$OP(OR^7)N(R^7)$-, and -$OPN(R^7)_2NR^7$-. In some embodiments, R^1 is selected from -$OP(O)(OR^7)O$-, -$SP(O)(OR^7)O$-, -$OP(S)(OR^7)O$-, -$OP(O)(SR^7)O$-, -$OP(O)(OR^7)S$-, -$OP(O)(O^-)O$-, -$SP(O)(O^-)O$-, -$OP(S)(O^-)O$-, -$OP(O)(S^-)O$-, -$OP(O)(O^-)S$-, -$OP(O)(OR^7)NR^7$-, -$OP(O)(N(R^7)_2)NR^7$-, -$OP(OR^7)O$-, -$OP(N(R^7)_2)O$-, -$OP(OR^7)N(R^7)$-, and -$OPN(R^7)_2NR^7$. In some embodiments, R^1 is selected from -$OP(O)(OR^7)O$-, -$SP(O)(OR^7)O$-, -$OP(S)(OR^7)O$-, -$OP(O)(SR^7)O$-, -$OP(O)(OR^7)S$-, -$OP(O)(O^-)O$-, -$SP(O)(O^-)O$-, -$OP(S)(O^-)O$-, -$OP(O)(S^-)O$-, -$OP(O)(O^-)S$-, and -$OP(OR^7)O$-. In some embodiments, R^1 is selected from -$OP(O)(OR^7)O$-, -$OP(S)(OR^7)O$-, -$OP(O)(O^-)O$-, -$OP(S)(O^-)O$-, -$OP(O)(S^-)O$-, and -$OP(OR^7)O$-. In some embodiments, R^1 is selected from -$OP(O)(OR^7)O$- and -$OP(OR^7)O$-. In some embodiments, R^1 is a linker selected from -OP(O)(OH)O-, -SP(O)(OH)O-, -OP(S)(OH)O-, -OP(O)(SH)O-, -OP(O)(OH)S-, -$OP(O)(O^-)O$-, -$SP(O)(O^-)O$-, -$OP(S)(O^-)O$-, -$OP(O)(S^-)O$-, and -$OP(O)(O^-)S$-. In some embodiments, R^1 is a selected from -$OP(O)(OR^7)O$-, -$OP(O)(OR^7)NR^7$-, -$OP(O)(N(R^7)_2)NR^7$-, -$OP(OR^7)O$-, -$OP(N(R^7)_2)O$-, -$OP(OR^7)N(R^7)$-, and -$OPN(R^7)_2NR^7$-. In some embodiments, R^1 is selected from -S-, -S(O)-, -$S(O)_2$-, -$OS(O)_2$, -$SP(O)(OR^7)O$-, -$OP(S)(OR^7)O$-, -$OP(O)(SR^7)O$-, -$OP(O)(OR^7)S$-, -$SP(O)(O^-)O$-, -$OP(S)(O^-)O$-, -$OP(O)(S^-)O$-, and -$OP(O)(O^-)S$-. In some embodiments, R^1 is selected from -S-, -S(O)-, -$S(O)_2$-, -$OS(O)_2$, -$SP(O)(OR^7)O$-, -$OP(S)(OR^7)O$-, -$OP(O)(SR^7)O$-, and -$OP(O)(OR^7)S$-. In some embodiments, R^1 is selected from -$OP(S)(OR^7)O$-, -$OP(O)(SR^7)O$-, and -$OP(O)(OR^7)S$-. In some embodiments, R^1 is selected from -$OP(S)(OR^7)O$-, -$OP(O)(SR^7)O$-, -$OP(S)(O^-)O$-, and -$OP(O)(S^-)O$-. In some embodiments, R^1 is selected from -$OP(S)(OR^7)O$- and -$OP(O)(SR^7)O$-. In some embodiments, R^1 is selected from -$OP(O)(OR^7)O$-, -$OP(OR^7)N(R^7)$-, and -$OPN(R^7)_2O$-. In some embodiments, R^1 is -$OP(O)(OH)O$-, -$OP(O)(OCH_2CH_3)O$-, -$OP(OCH_2CH_2CN)N(CH(CH_3)_2)$-, or -$OPN(CH(CH_3)_2)_2O$-. In some embodiments, R^1 is selected from -OP(O)(OH)O- and $OP(O)(O^-)O$-. In some embodiments, R^1 comprises -O- or -S-. In some embodiments, R^1 comprises -O-. In some embodiments, R^1 comprises -S-. In some embodiments, R^1 is a linker selected from -O- or -S-. In some embodiments, R^1 is -O-. In some embodiments, R^1 is -S-.

[0029] In some embodiments, each R^2 is independently selected from C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, -OR^7, -SR^7, -$N(R^7)_2$, -$C(O)R^7$, -$C(O)N(R^7)_2$, -$N(R^7)C(O)R^7$, -$N(R^7)C(O)N(R^7)_2$, -$OC(O)N(R^7)_2$, -$N(R^7)C(O)OR^7$, -$C(O)OR^7$, -$OC(O)R^7$, and -$S(O)R^7$. In some embodiments, each R^2 is independently selected from C_{1-3} alkyl substituted with one or more substituents independently selected from halogen, -OR^7, -$OC(O)R^7$, -SR^7, -$N(R^7)_2$, -$C(O)R^7$, and -$S(O)R^7$. In some embodiments, each R^2 is independently selected from C_{1-3} alkyl substituted with one or more substituents independently selected from -OR^7, -$OC(O)R^7$, -SR^7, and -$N(R^7)_2$. In some embodiments, each R^2 is independently selected from C_1 alkyl substituted with one or more substituents independently selected from -OR^7 and -$OC(O)R^7$. In some embodiments, each R^2 is independently selected from -CH_2OH and -$CH_2OC(O)CH_3$.

[0030] In some embodiments, each R^3 is independently selected from $-OR^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, $-C(O)N(R^7)_2$, $-N(R^7)C(O)R^7$, $-N(R^7)C(O)N(R^7)_2$, $-OC(O)N(R^7)_2$, $-N(R^7)C(O)OR^7$, $-C(O)OR^7$, $-OC(O)R^7$, and $-S(O)R^7$. In some embodiments, each R^3 is independently selected from halogen, $-OR^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, $-OC(O)R^7$, and $-S(O)R^7$. In some embodiments, each R^3 is independently selected from $-OR^7$, $-OC(O)R^7$, $-SR^7$, and $-N(R^7)_2$. In some embodiments, each R^3 is independently selected from $-OR^7$ and $-OC(O)R^7$. In some embodiments, R^3 is independently selected from -OH and $-OC(O)CH_3$.

[0031] In some embodiments, each R^4 is independently selected from $-OR^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, $-C(O)N(R^7)_2$, $-N(R^7)C(O)R^7$, $-N(R^7)C(O)N(R^7)_2$, $-OC(O)N(R^7)_2$, $-N(R^7)C(O)OR^7$, $-C(O)OR^7$, $-OC(O)R^7$, and $-S(O)R^7$. In some embodiments, each R^4 is independently selected from halogen, $-OR^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, $-OC(O)R^7$, and $-S(O)R^7$. In some embodiments, each R^4 is independently selected from $-OR^7$, $-OC(O)R^7$, $-SR^7$, and $-N(R^7)_2$. In some embodiments, each R^4 is independently selected from $-OR^7$ and $-OC(O)R^7$. In some embodiments, R^4 is independently selected from -OH and $-OC(O)CH_3$.

[0032] In some embodiments, each R^5 is independently selected from-$OC(O)R^7$, $-OC(O)N(R^7)_2$, $-N(R^7)C(O)R^7$, $-N(R^7)C(O)N(R^7)_2$, $-N(R^7)C(O)OR^7$, $-C(O)R^7$, $-C(O)OR^7$, and $-C(O)N(R^7)_2$. In some embodiments, each R^5 is selected from $-OC(O)R^7$, $-OC(O)N(R^7)_2$, $-N(R^7)C(O)R^7$, $-N(R^7)C(O)N(R^7)_2$, and $-N(R^7)C(O)OR^7$. In some embodiments, each R^5 is independently selected from $-OC(O)R^7$ and $-N(R^7)C(O)R^7$. In some embodiments, each R^5 is independently selected from $-N(H)C(O)CH_3$.

[0033] In some embodiments, each R^6 is independently selected from hydrogen, halogen, -CN, $-OR^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, $-C(O)N(R^7)_2$, $-N(R^7)C(O)R^7$, $-N(R^7)C(O)N(R^7)_2$, $-OC(O)N(R^7)_2$, $-N(R^7)C(O)OR^7$, $-C(O)OR^7$, $-OC(O)R^7$, and $-S(O)R^7$; and C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, -CN, $-OR^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, $-C(O)N(R^7)_2$, $-N(R^7)C(O)R^7$, $-N(R^7)C(O)N(R^7)_2$, $-OC(O)N(R^7)_2$, $-N(R^7)C(O)OR^7$, $-C(O)OR^7$, $-OC(O)R^7$, and $-S(O)R^7$. In some embodiments, each R^6 is independently selected from hydrogen, halogen, -CN $-OR^7$, $-SR^7$, $-N(R^7)_2$, and C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, $-OR^7$, $-SR^7$, and $-N(R^7)_2$. In some embodiments, each R^6 is independently selected from hydrogen, halogen, -CN, -OH, -SH, and $-NH_2$.

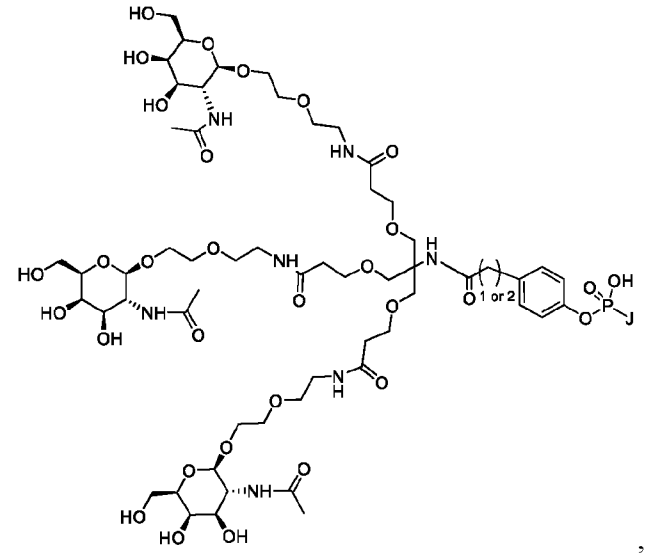
[0034] In some embodiments, each R^7 is independently selected from: hydrogen; C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, $-NO_2$, $-NH_2$, =O, =S, $-O-C_{1-6}$ alkyl, $-S-C_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)_2$, $-NH(C_{1-6}$ alkyl), C_{3-10} carbocycle, and 3- to 10-membered heterocycle; and C_{3-10} carbocycle, and 3- to 10-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, $-NO_2$, $-NH_2$, =O, =S, $-O-C_{1-6}$ alkyl, $-S-C_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)_2$, $-NH(C_{1-6}$ alkyl), C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, and C_{1-6} haloalkyl. In some embodiments, each R^7 is independently selected from: hydrogen; and C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, $-NO_2$, $-NH_2$, =O, =S, $-O-C_{1-6}$ alkyl, $-S-C_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)_2$, $-NH(C_{1-6}$ alkyl), C_{3-10} carbocycle, 3- to 10-membered heterocycle. In some embodiments, each R^7 is independently selected from C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen,

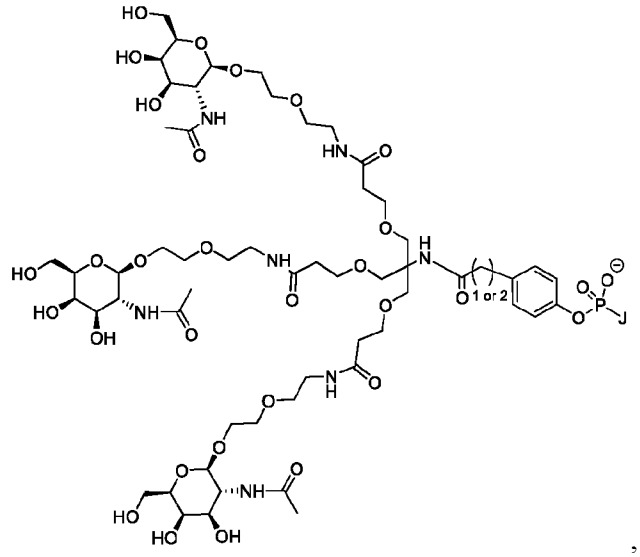
-CN, -OH, -SH, $-NO_2$, $-NH_2$, =O, =S, -O-C_{1-6} alkyl, -S-C_{1-6} alkyl, -N(C_{1-6} alkyl)$_2$, and -NH(C_{1-6} alkyl). In some embodiments, R^7 is independently selected from C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, and -SH. In some embodiments, each R^7 is independently selected from hydrogen. In some embodiments, each R^7 is independently selected from C_{1-3} alkyl optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, $-NO_2$, $-NH_2$, -O-C_{1-6} alkyl, -S-C_{1-6} alkyl, -N(C_{1-6} alkyl)$_2$, and -NH(C_{1-6} alkyl).

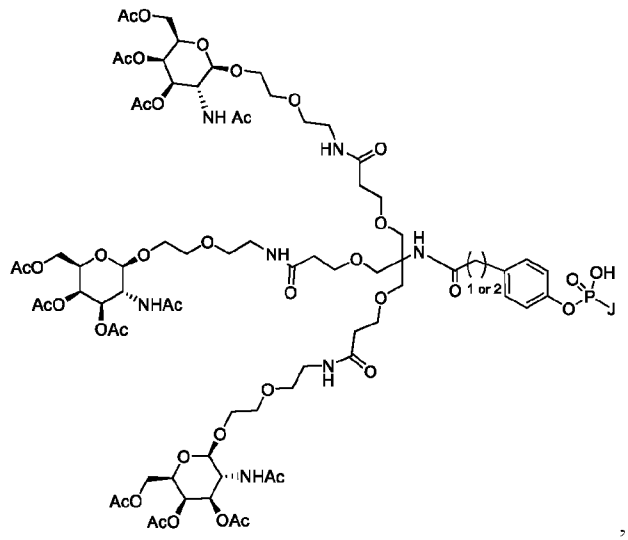
[0035] In some embodiments, w is 1; v is 1; n is 2; m is 1 or 2; z is 3 and Y is C; Q is phenyl or cyclohexyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, $-NO_2$, $-NH_2$, and C_{1-3} alkyl; R^1 is selected from -OP(O)(OR^7)O-, -OP(S)(OR^7)O-, -OP(O)(O^-)O-, -OP(S)(O^-)O-, -OP(O)(S^-)O-, and -OP(OR^7)O-; R^2 is C_1 alkyl substituted with -OH or $-OC(O)CH_3$; R^3 is -OH or $-OC(O)CH_3$; R^4 is -OH or $-OC(O)CH_3$; and R^5 is $-NH(O)CH_3$.

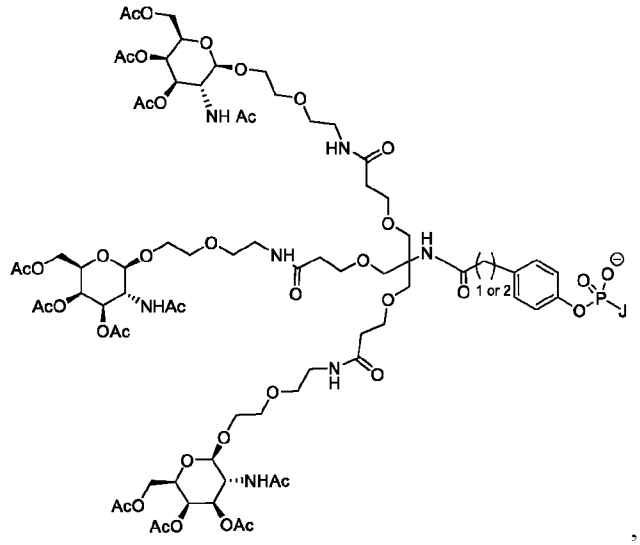
[0036] In some embodiments, w is 1; v is 1; n is 2; m is 1 or 2; z is 3 and Y is C; Q is phenyl or cyclohexyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, $-NO_2$, $-NH_2$, and C_{1-3} alkyl; R^1 is selected from -OP(O)(OH)O-, -OP(S)(OH)O-, -OP(O)(O^-)O-, -OP(S)(O^-)O-, -OP(O)(S^-)O-, and -OP(OH)O-; R^2 is C_1 alkyl substituted with -OH or $-OC(O)CH_3$; R^3 is -OH or $-OC(O)CH_3$; R^4 is -OH or $-OC(O)CH_3$; and R^5 is $-NH(O)CH_3$. In some embodiments, w is 1; v is 1; n is 2; m is 1 or 2; z is 3 and Y is C; Q is phenyl or cyclohexyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, $-NO_2$, $-NH_2$, and C_{1-3} alkyl; R^1 is selected from -OP(O)(OH)O-, -OP(S)(OH)O-, and -OP(OH)O-; R^2 is C_1 alkyl substituted with -OH or $-OC(O)CH_3$; R^3 is -OH or $-OC(O)CH_3$; R^4 is -OH or $-OC(O)CH_3$; and R^5 is $-NH(O)CH_3$.

[0037] In some embodiments, a compound of Formula (I) is selected from:









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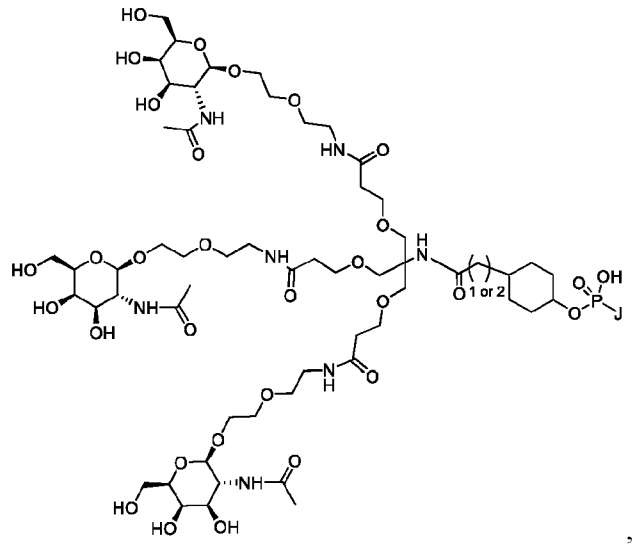

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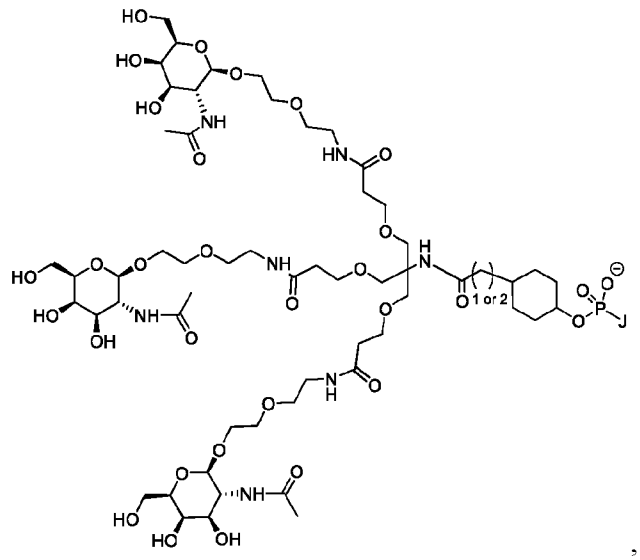

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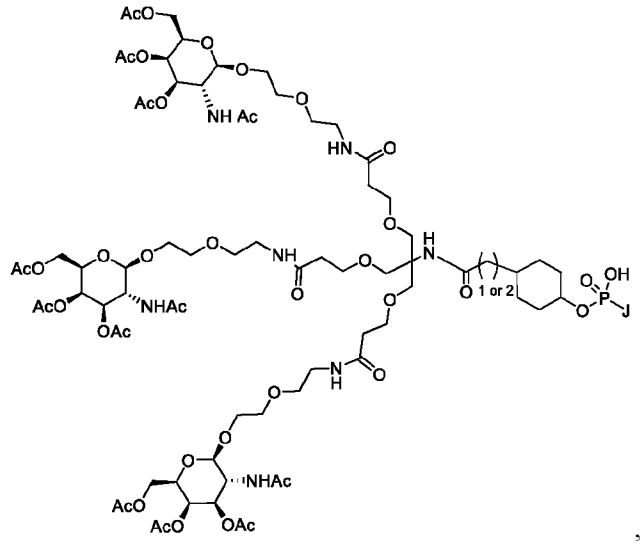

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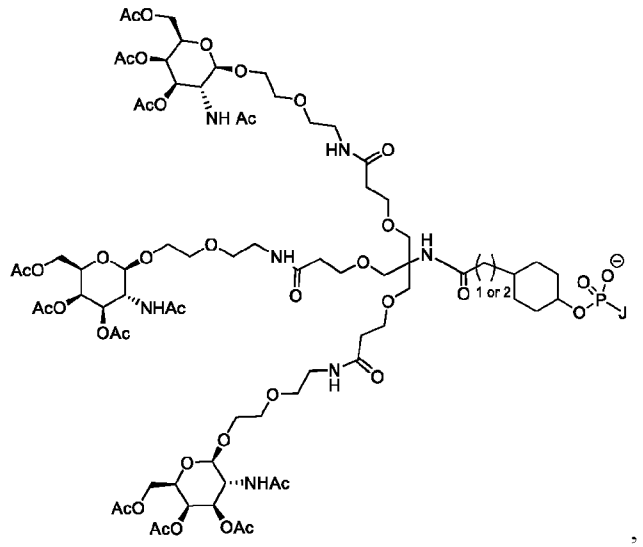

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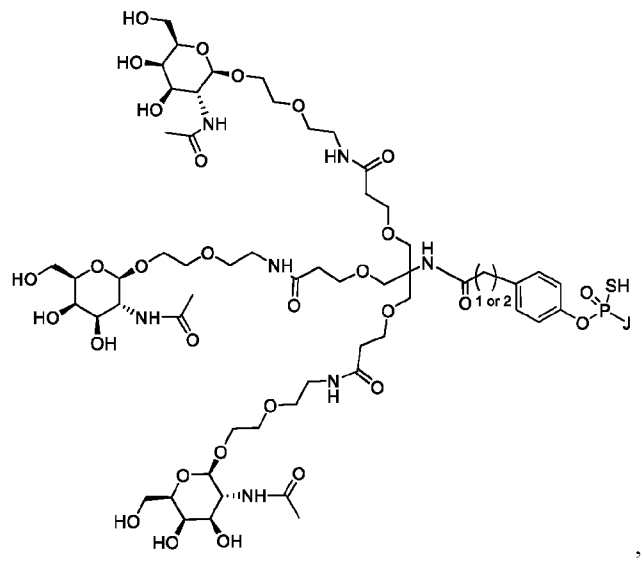

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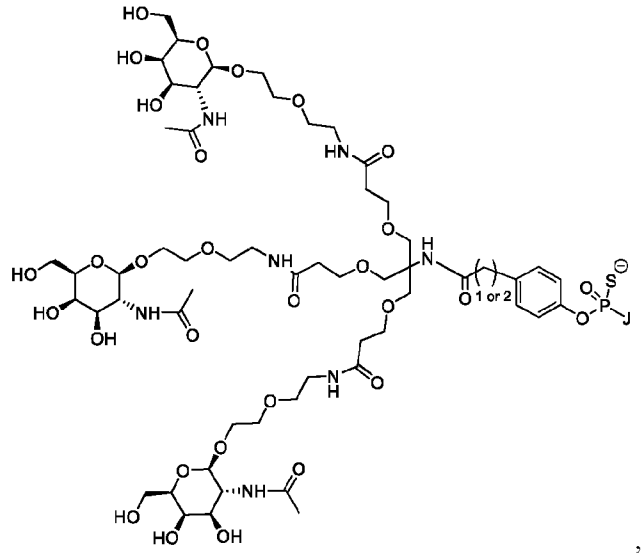

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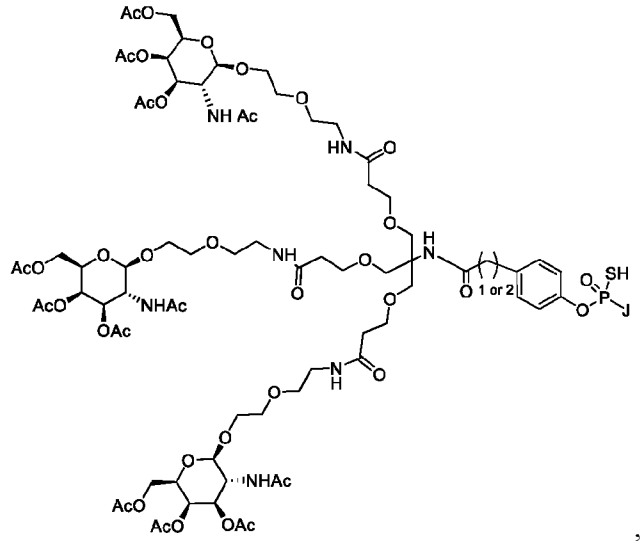

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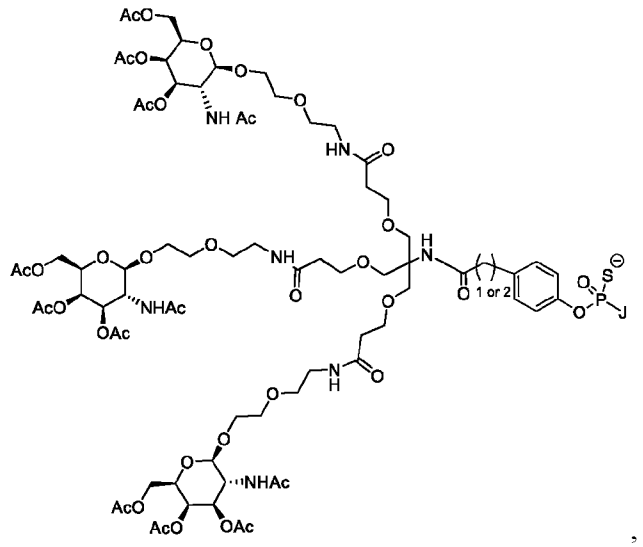

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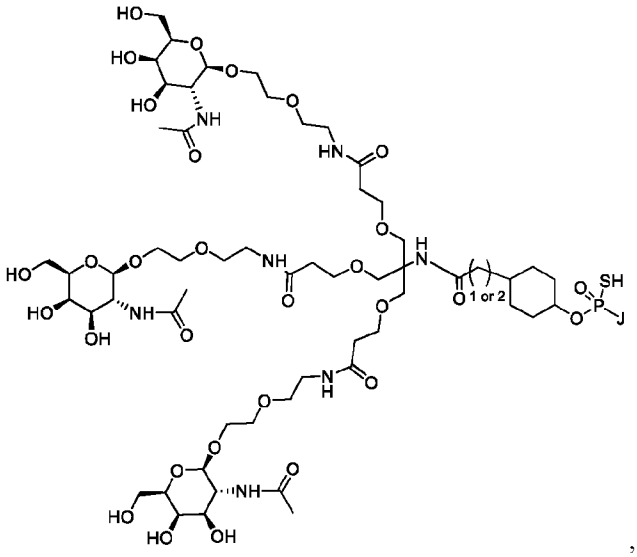

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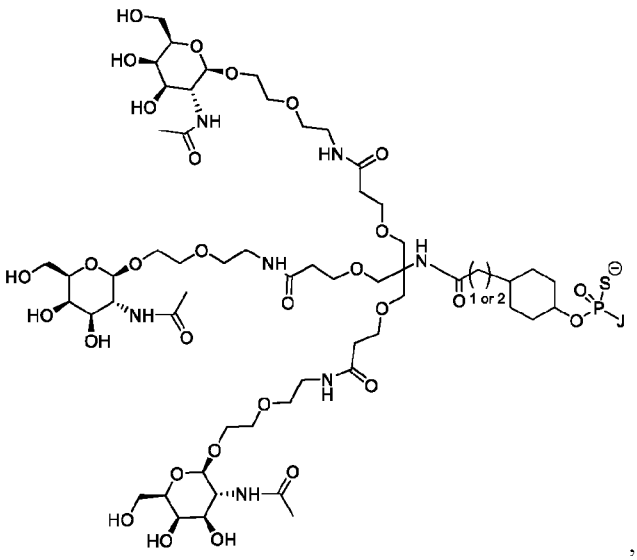

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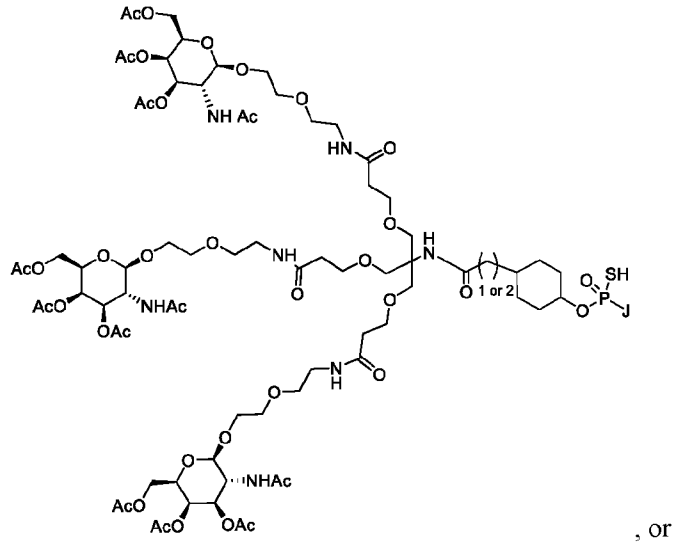

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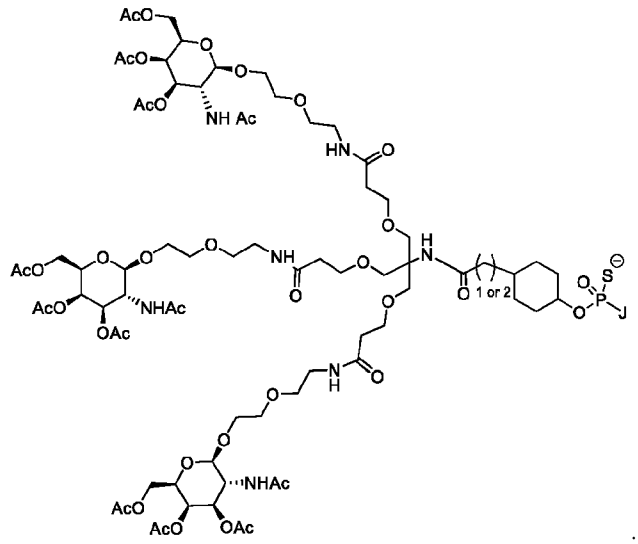

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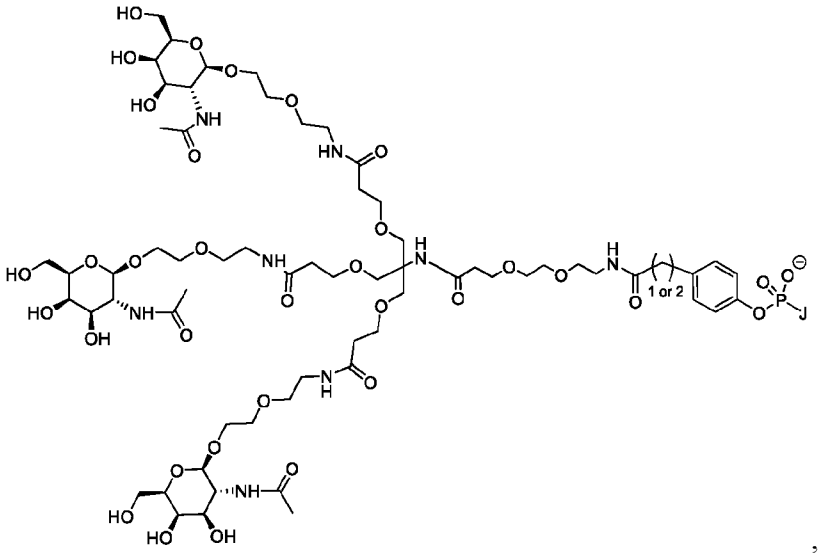
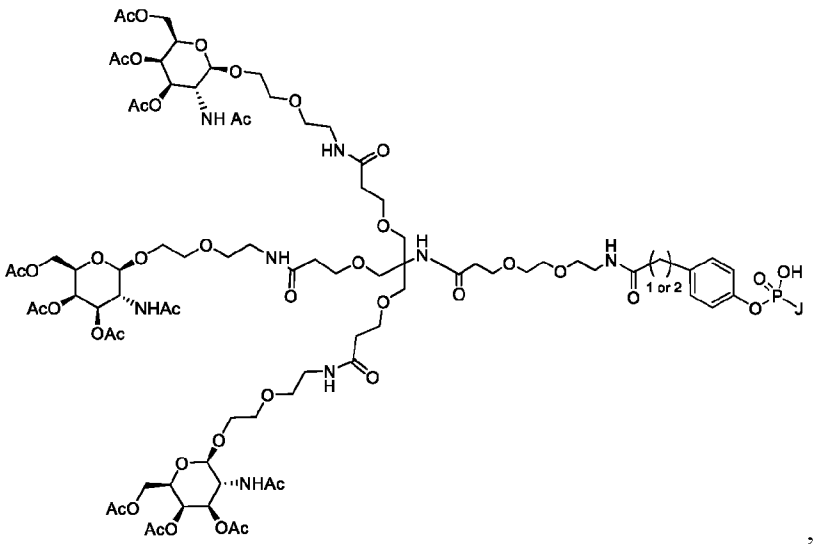
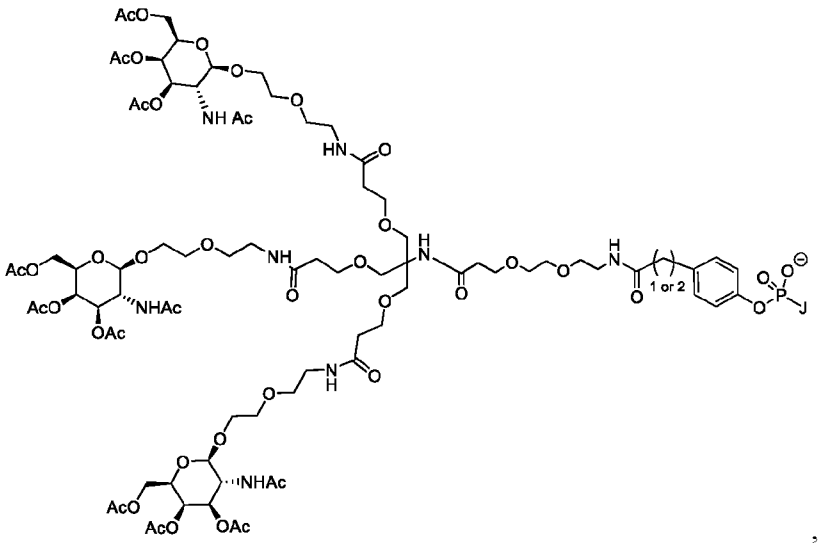
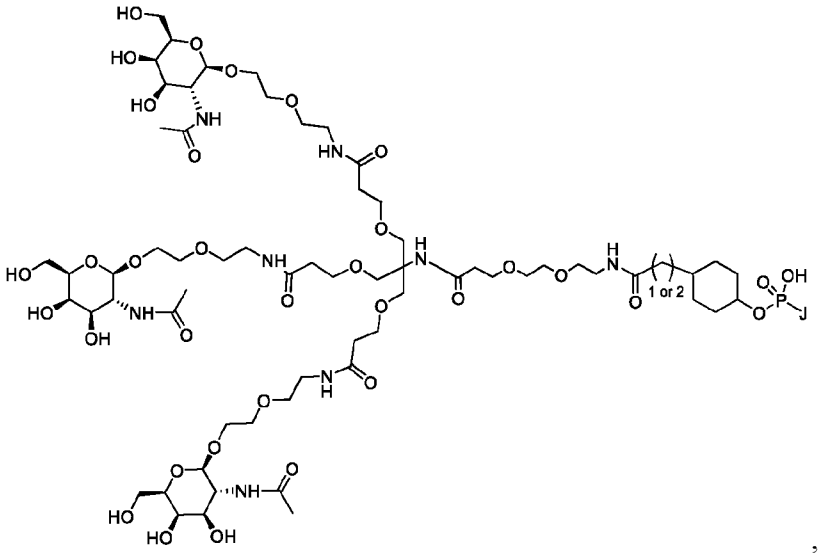
[0038] In some embodiments, a compound of Formula (II) is selected from:









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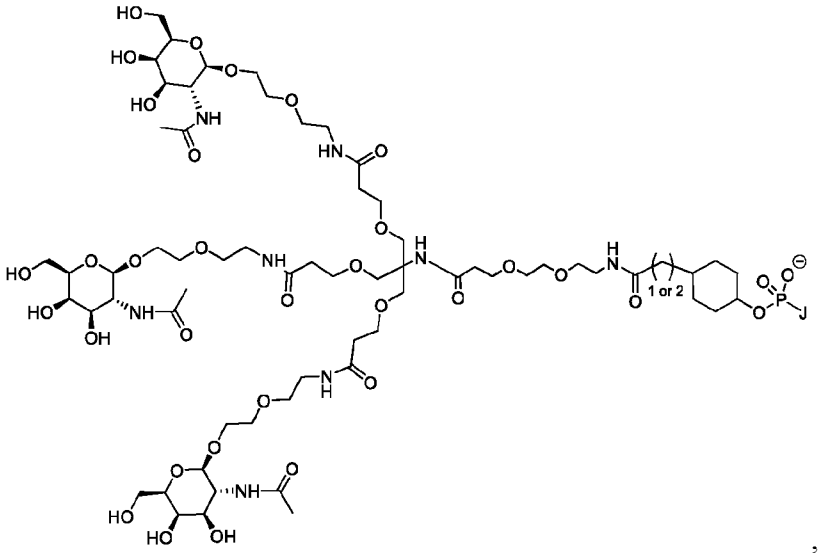

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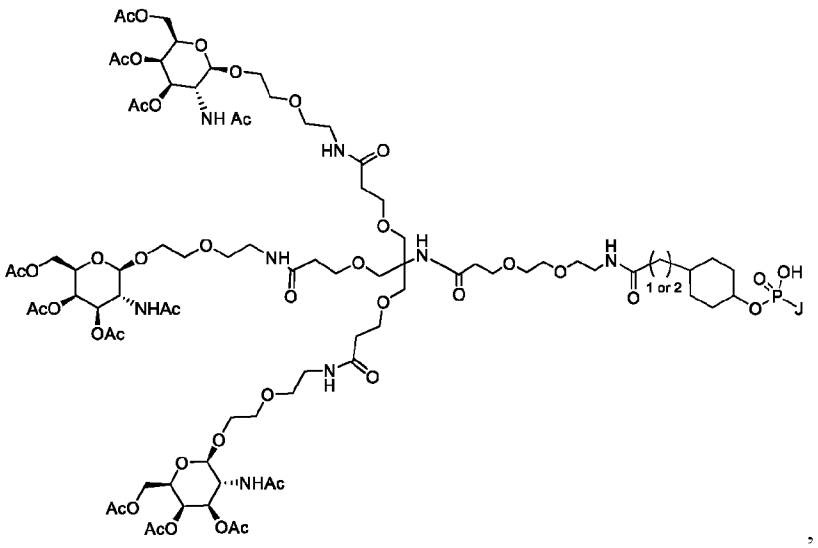

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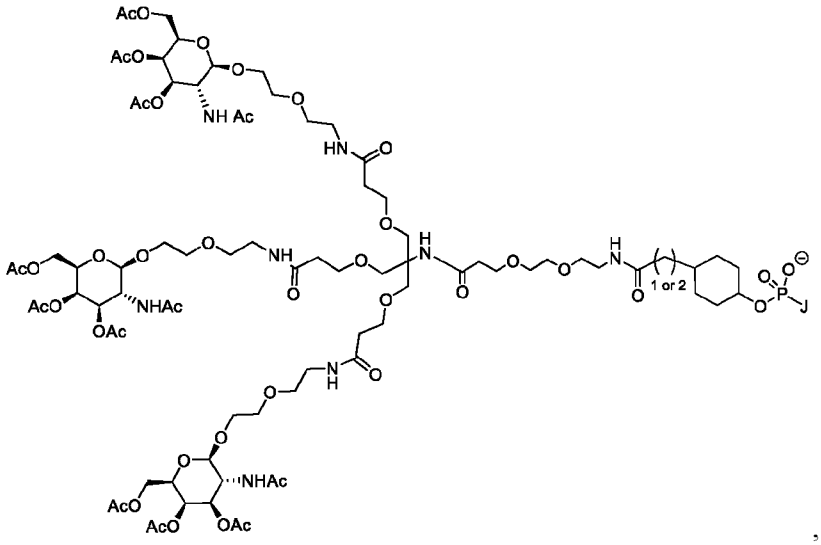

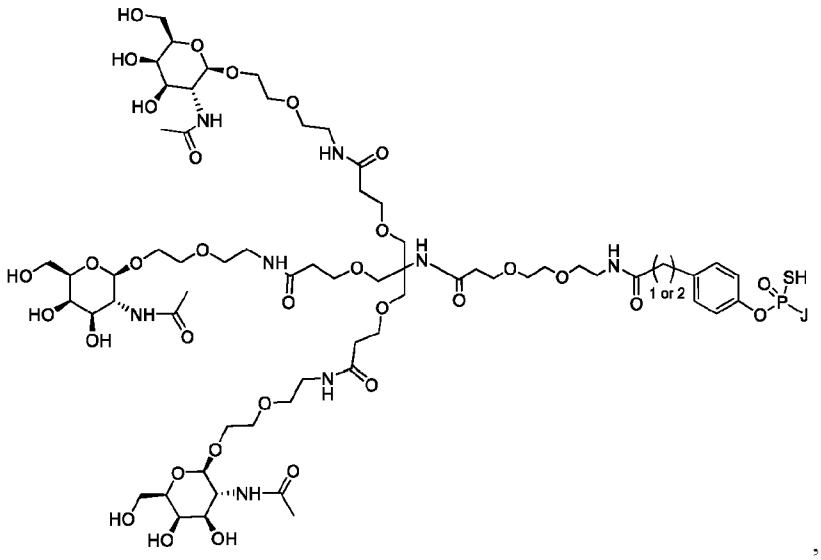

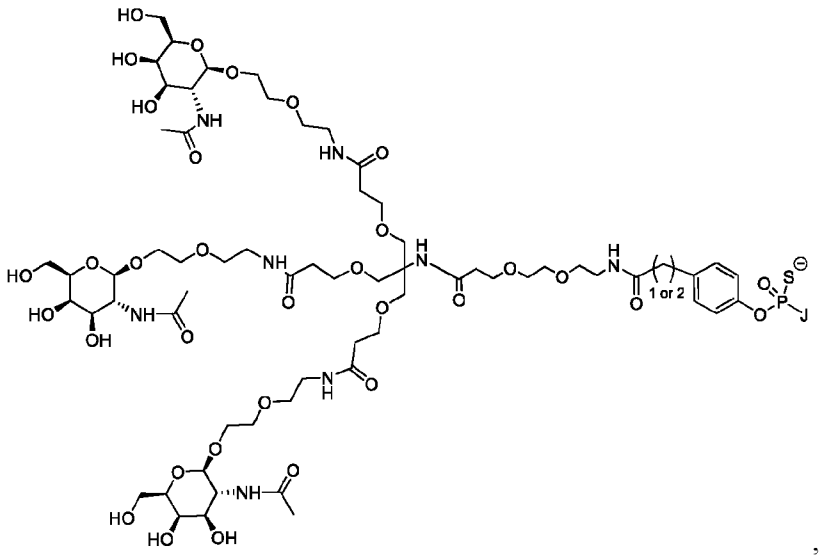

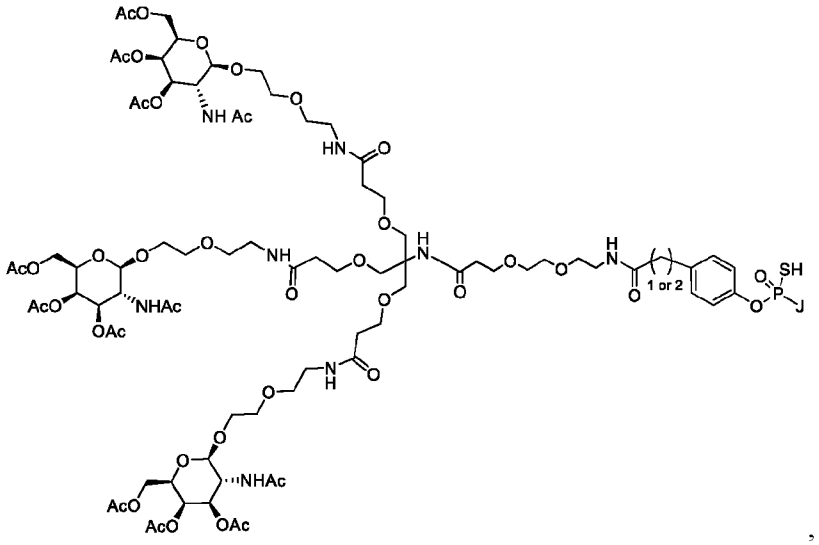

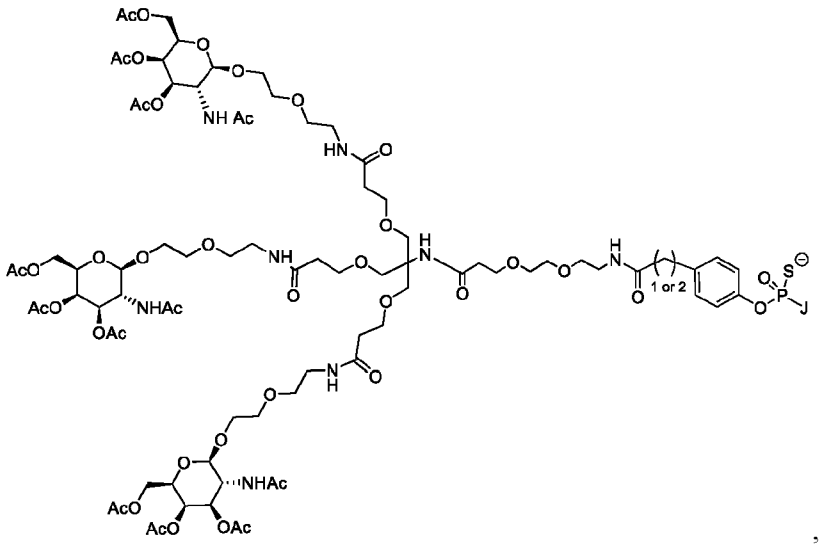

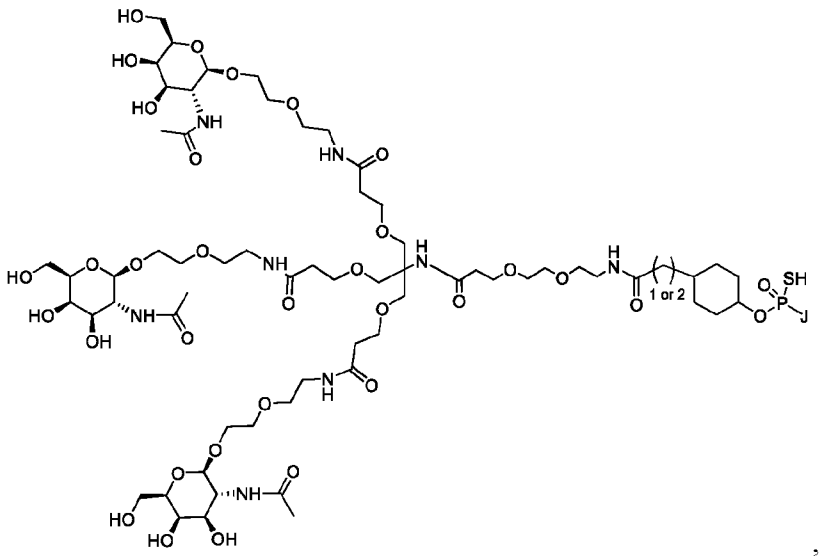

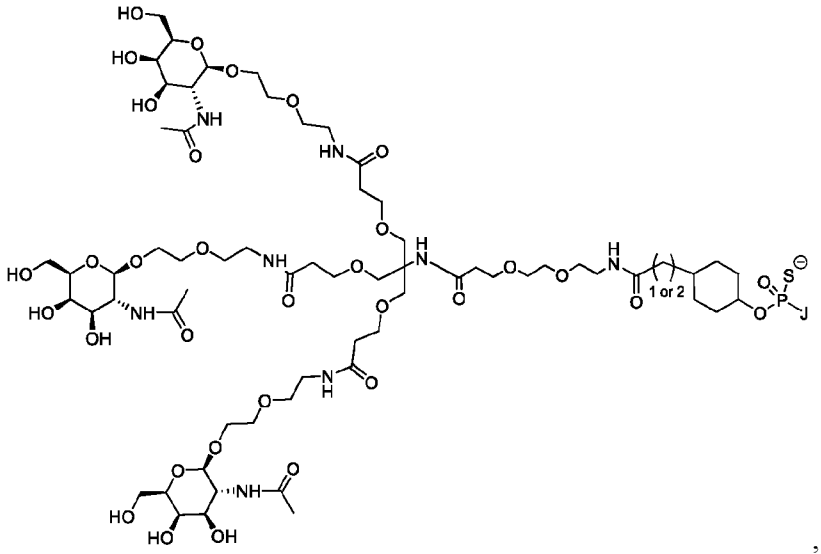

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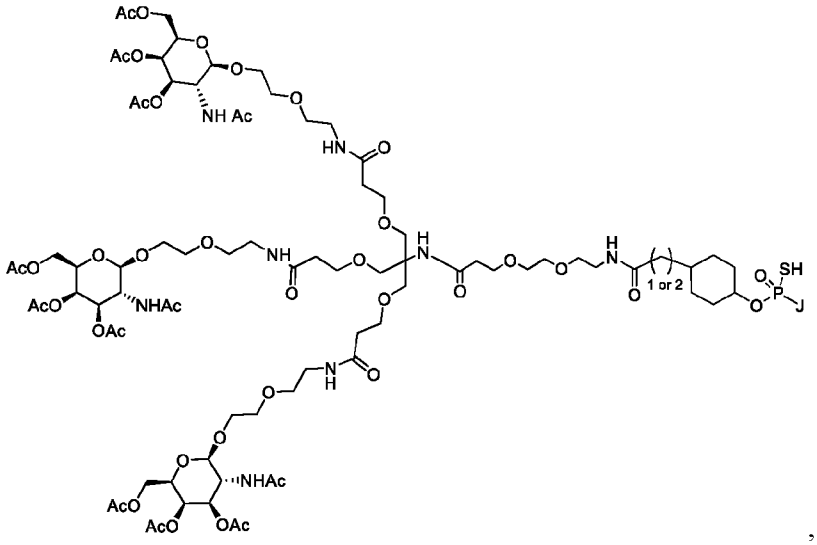

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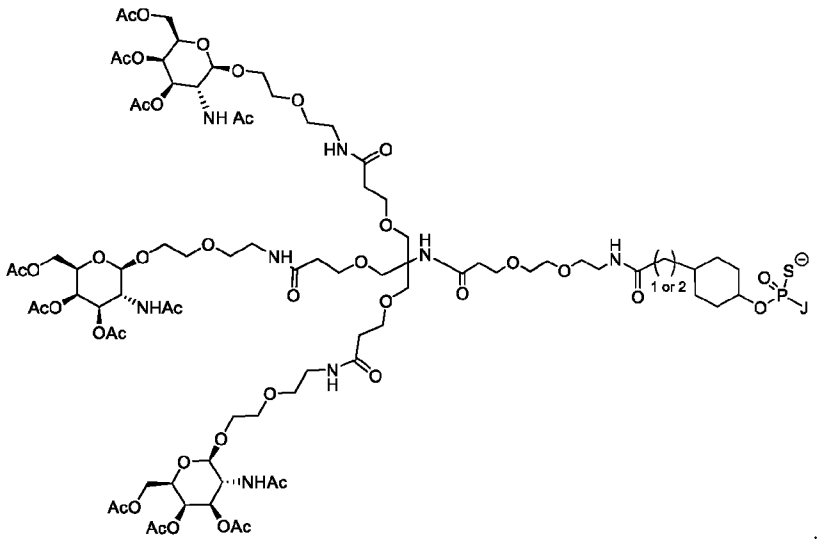

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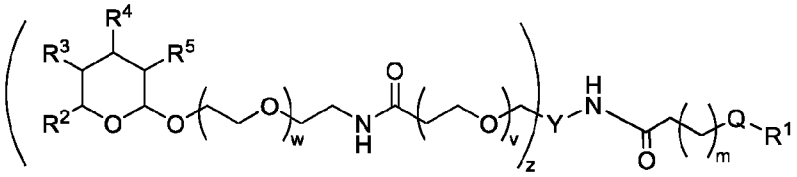
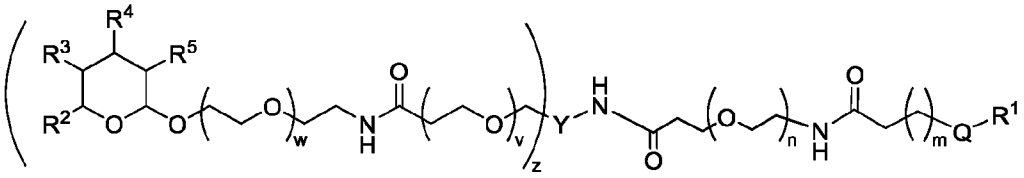
[0039] In some embodiments, the compound of Formula (I), (II), or (III) binds to a lectin. In some embodiments, the compound binds to an asialoglycoprotein receptor. In some embodiments, the

compound binds to a liver cell receptor. In some embodiments, the compound binds to a hepatocyte receptor. In some embodiments, the compound targets a liver cell.

[0040] Provided herein, in some embodiments, compositions described herein comprise a GalNAc compound. In some embodiments, a GalNAc compound describes a compound of Formula (A) or Formula (B):


(A), or


(B);

or a salt thereof, wherein

each w is independently selected from any value from 1 to 20;

each v is independently selected from any value from 1 to 20;

n is selected from any value from 1 to 20;

m is selected from any value from 1 to 20;

z is selected from any value from 1 to 3, wherein

if z is 3, Y is C

if z is 2, Y is CR^6, or

if z is 1, Y is $C(R^6)_2$;

Q is selected from:

C_{3-10} carbocycle optionally substituted with one or more substituents independently selected from halogen, -CN, $-NO_2$, $-OR^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, $-C(O)N(R^7)_2$, $-N(R^7)C(O)R^7$, $-N(R^7)C(O)N(R^7)_2$, $-OC(O)N(R^7)_2$, $-N(R^7)C(O)OR^7$, $-C(O)OR^7$, $-OC(O)R^7$, $-S(O)R^7$, and C_{1-6} alkyl, wherein the C_{1-6} alkyl, is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, $-NO_2$, and $-NH_2$;

R^1 is selected from:

$-OR^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, $-C(O)N(R^7)_2$, $-N(R^7)C(O)R^7$, $-N(R^7)C(O)N(R^7)_2$, $-OC(O)N(R^7)_2$, $-N(R^7)C(O)OR^7$, $-C(O)OR^7$, $-OC(O)R^7$, $-S(O)R^7$, $-S(O)_2R^7$, $-OS(O)_2R^7$, $-OP(O)(OR^7)_2$, $-OP(S)(OR^7)_2$, $-SP(O)(OR^7)_2$, $-OP(O)(SR^7)(OR^7)$, $-OP(O)(OR^7)N(R^7)_2$, $-OP(S)(OR^7)N(R^7)_2$, $-SP(O)(OR^7)N(R^7)_2$, $-OP(O)(SR^7)N(R^7)_2$, $-OP(O)(N(R^7)_2)_2$, $-OP(S)(N(R^7)_2)_2$, $-SP(O)(N(R^7)_2)_2$, $-OP(OR^7)_2$, $-SP(OR^7)_2$, $-OP(OR^7)(SR^7)$,$-OP(OR^7)N(R^7)_2$, $-OP(SR^7)N(R^7)_2$, $-SP(OR^7)N(R^7)_2$, $-OP(N(R^7)_2)_2$, and $-SP(N(R^7)_2)_2$;

each R^2 is independently selected from:

C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, $-OR^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, $-C(O)N(R^7)_2$, $-N(R^7)C(O)R^7$, $-N(R^7)C(O)N(R^7)_2$, $-OC(O)N(R^7)_2$, $-N(R^7)C(O)OR^7$, $-C(O)OR^7$, $-OC(O)R^7$, and $-S(O)R^7$;

R^3 and R^4 are each independently selected from:

$-OR^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, $-C(O)N(R^7)_2$, $-N(R^7)C(O)R^7$, $-N(R^7)C(O)N(R^7)_2$, $-OC(O)N(R^7)_2$, $-N(R^7)C(O)OR^7$, $-C(O)OR^7$, $-OC(O)R^7$, and $-S(O)R^7$;

each R^5 is independently selected from:

$-OC(O)R^7$, $-OC(O)N(R^7)_2$, $-N(R^7)C(O)R^7$, $-N(R^7)C(O)N(R^7)_2$, $-N(R^7)C(O)OR^7$, $-C(O)R^7$, $-C(O)OR^7$, and $-C(O)N(R^7)_2$;

each R^6 is independently selected from:

hydrogen;

halogen, $-CN$, $-NO_2$, $-OR^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, $-C(O)N(R^7)_2$, $-N(R^7)C(O)R^7$, $-N(R^7)C(O)N(R^7)_2$, $-OC(O)N(R^7)_2$, $-N(R^7)C(O)OR^7$, $-C(O)OR^7$, $-OC(O)R^7$, and $-S(O)R^7$; and

C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, $-CN$, $-NO_2$, $-OR^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, $-C(O)N(R^7)_2$, $-N(R^7)C(O)R^7$, $-N(R^7)C(O)N(R^7)_2$, $-OC(O)N(R^7)_2$, $-N(R^7)C(O)OR^7$, $-C(O)OR^7$, $-OC(O)R^7$, and $-S(O)R^7$;

each R^7 is independently selected from:

hydrogen;

C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, $-CN$, $-OH$, $-SH$, $-NO_2$, $-NH_2$, $=O$, $=S$, $-O-C_{1-6}$ alkyl, $-S-C_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)_2$, $-NH(C_{1-6}$ alkyl), C_{3-10} carbocycle, and 3- to 10-membered heterocycle; and

C_{3-10} carbocycle, and 3- to 10-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, $-CN$, $-OH$, $-SH$, $-NO_2$, $-NH_2$, $=O$, $=S$, $-O-C_{1-6}$ alkyl, $-S-C_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)_2$, $-NH(C_{1-6}$ alkyl), C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, and C_{1-6} haloalkyl.

[0041] In some embodiments, each w is independently selected from any value from 1 to 20. In some embodiments, each w is independently selected from any value from 1 to 15. In some embodiments, each w is independently selected from any value from 1 to 10. In some embodiments, each w is independently selected from any value from 1 to 5. In some embodiments, each w is independently selected from any value from 1 to 4. In some embodiments, each w is independently selected from any value from 1 to 3. In some embodiments, each w is independently selected from any value from 1 to 2. In some embodiments, W is 1. In some embodiments, w is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20.

[0042] In some embodiments, each v is independently selected from any value from 1 to 20. In some embodiments, each v is independently selected from any value from 1 to 15. In some embodiments, each v is independently selected from any value from 1 to 10. In some embodiments, each v is independently selected from any value from 1 to 5. In some embodiments, each v is independently selected from any value from 1 to 4. In some embodiments, each v is independently selected from any value from 1 to 3. In

some embodiments, each v is independently selected from any value from 1 to 2. In some embodiments, each v is independently 1. In some embodiments, v is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20.

[0043] In some embodiments, n is selected from any value from 1 to 20. In some embodiments, n is selected from any value from 1 to 15. In some embodiments, n is selected from any value from 1 to 10. In some embodiments, n is selected from any value from 1 to 9. In some embodiments, n is selected from any value from 1 to 8. In some embodiments, n is selected from any value from 1 to 7. In some embodiments, n is selected from any value from 1 to 6. In some embodiments, n is selected from any value from 1 to 5. In some embodiments, n is selected from any value from 1 to 4. In some embodiments, n is selected from any value from 2 to 4. In some embodiments, n is selected from any value from 1 to 3. In some embodiments, n is 2 or 3. In some embodiments, n is 3. In some embodiments, n is selected from any value from 1 to 2. In some embodiments, n is 2. In some embodiments, n is 1. In some embodiments, n is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20.

[0044] In some embodiments, m is selected from any value from 1 to 20. In some embodiments, m is selected from any value from 1 to 15. In some embodiments, m is selected from any value from 1 to 10. In some embodiments, m is selected from any value from 1 to 9. In some embodiments, m is selected from any value from 1 to 8. In some embodiments, m is selected from any value from 1 to 7. In some embodiments, m is selected from any value from 3 to 7. In some embodiments, m is selected from any value from 1 to 6. In some embodiments, m is selected from any value from 2 to 6. In some embodiments, m is selected from any value from 3 to 6. In some embodiments, m is selected from any value from 4 to 6. In some embodiments, m is 6. In some embodiments, m is selected from any value from 1 to 5. In some embodiments, m is selected from any value from 3 to 5. In some embodiments, m is 5. In some embodiments, m is 4 or 5. In some embodiments, m is selected from any value from 1 to 4. In some embodiments, m is 4. In some embodiments, m is 3 or 4. In some embodiments, m is selected from any value from 2 to 4. In some embodiments, m is selected from any value from 1 to 3. In some embodiments, m is 3. In some embodiments, m is selected from any value from 1 to 2. In some embodiments, m is 2. In some embodiments, m is 1. In some embodiments, m is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20.

[0045] In some embodiments, z is selected from any value from 1 to 3. In some embodiments, z is 3 and Y is C. In some embodiments, z is 2 and Y is CR^6. In some embodiments, z is 1 and Y is $C(R^6)_2$.

[0046] In some embodiments, Q is selected from C_{3-10} carbocycle optionally substituted with one or more substituents independently selected from halogen, -CN, $-NO_2$, $-OR^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, $-C(O)N(R^7)_2$, $-N(R^7)C(O)R^7$, $-N(R^7)C(O)N(R^7)_2$, $-OC(O)N(R^7)_2$, $-N(R^7)C(O)OR^7$, $-C(O)OR^7$, $-OC(O)R^7$, $-S(O)R^7$, and C_{1-6} alkyl, wherein the C_{1-6} alkyl, is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, $-NO_2$, and $-NH_2$. In some embodiments, Q is selected from C_{3-6} carbocycle optionally substituted with one or more substituents independently selected from halogen, -CN, $-NO_2$, $-OR^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, $-C(O)N(R^7)_2$, $-N(R^7)C(O)R^7$, $-N(R^7)C(O)N(R^7)_2$, $-OC(O)N(R^7)_2$, $-N(R^7)C(O)OR^7$, $-C(O)OR^7$, $-OC(O)R^7$, $-S(O)R^7$, and C_{1-6} alkyl, wherein the C_{1-6} alkyl, is

optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, $-NO_2$, and $-NH_2$. In some embodiments, Q is selected from C_{5-6} carbocycle optionally substituted with one or more substituents independently selected from halogen, -CN, $-NO_2$, $-OR^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, $-C(O)N(R^7)_2$, $-N(R^7)C(O)R^7$, $-N(R^7)C(O)N(R^7)_2$, $-OC(O)N(R^7)_2$, $-N(R^7)C(O)OR^7$, $-C(O)OR^7$, $-OC(O)R^7$, and $-S(O)R^7$. In some embodiments, Q is selected from C_6 carbocycle optionally substituted with one or more substituents independently selected from halogen, -CN, $-NO_2$, $-OR^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, $-C(O)N(R^7)_2$, $-N(R^7)C(O)R^7$, $-N(R^7)C(O)N(R^7)_2$, $-OC(O)N(R^7)_2$, $-N(R^7)C(O)OR^7$, $-C(O)OR^7$, $-OC(O)R^7$, and $-S(O)R^7$. In some embodiments, Q is selected from C_5 carbocycle optionally substituted with one or more substituents independently selected from halogen, -CN, $-NO_2$, $-OR^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, $-C(O)N(R^7)_2$, $-N(R^7)C(O)R^7$, $-N(R^7)C(O)N(R^7)_2$, $-OC(O)N(R^7)_2$, $-N(R^7)C(O)OR^7$, $-C(O)OR^7$, $-OC(O)R^7$, and $-S(O)R^7$. In some embodiments, Q is selected from C_{5-6} carbocycle optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, $-NO_2$, and $-NH_2$. In some embodiments, Q is selected from phenyl, cyclohexyl, cyclopentadiene, and cyclopentyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, $-NO_2$, and $-NH_2$. In some embodiments, Q is selected from phenyl and cyclohexyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, $-NO_2$, and $-NH_2$. In some embodiments, Q is selected from phenyl and cyclohexyl. In some embodiments, Q is phenyl. In some embodiments, Q is cyclohexyl.

[0047] In some embodiments, R^1 is selected from-OR^7, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, $-C(O)N(R^7)_2$, $-N(R^7)C(O)R^7$, $-N(R^7)C(O)N(R^7)_2$, $-OC(O)N(R^7)_2$, $-N(R^7)C(O)OR^7$, $-C(O)OR^7$, $-OC(O)R^7$, $-S(O)R^7$, $-S(O)_2R^7$, $-OS(O)_2R^7$, $-OP(O)(OR^7)_2$, $-OP(S)(OR^7)_2$, $-SP(O)(OR^7)_2$, $-OP(O)(SR^7)(OR^7)$, $-OP(O)(OR^7)N(R^7)_2$, $-OP(S)(OR^7)N(R^7)_2$, $-SP(O)(OR^7)N(R^7)_2$, $-OP(O)(SR^7)N(R^7)_2$, $-OP(O)(N(R^7)_2)_2$, $-OP(S)(N(R^7)_2)_2$, $-SP(O)(N(R^7)_2)_2$, $-OP(OR^7)_2$, $-SP(OR^7)_2$, $-OP(OR^7)(SR^7)$,$-OP(OR^7)N(R^7)_2$, $-OP(SR^7)N(R^7)_2$, $-SP(OR^7)N(R^7)_2$, $-OP(N(R^7)_2)_2$, and $-SP(N(R^7)_2)_2$. In some embodiments, R^1 is selected from-OR^7, $-N(R^7)_2$, $-C(O)R^7$, $-C(O)N(R^7)_2$, $-N(R^7)C(O)R^7$, $-N(R^7)C(O)N(R^7)_2$, $-OC(O)N(R^7)_2$, $-N(R^7)C(O)OR^7$, $-C(O)OR^7$, $-OC(O)R^7$, $-OP(O)(OR^7)_2$, $-OP(O)(OR^7)N(R^7)_2$, $-OP(O)(N(R^7)_2)_2$, $-OP(OR^7)_2$, $OP(OR^7)N(R^7)_2$, and $-OP(N(R^7)_2)_2$. In some embodiments, R^1 is selected from $-SR^7$, $-S(O)R^7$, $-S(O)_2R^7$, $-OS(O)_2R^7$, $-OP(S)(OR^7)_2$, $-SP(O)(OR^7)_2$, $-OP(O)(SR^7)(OR^7)$, $-OP(S)(OR^7)N(R^7)_2$, $-SP(O)(OR^7)N(R^7)_2$, $-OP(O)(SR^7)N(R^7)_2$, $-OP(S)(N(R^7)_2)_2$, $-SP(O)(N(R^7)_2)_2$, $-SP(OR^7)_2$, $-OP(OR^7)(SR^7)$, $-OP(SR^7)N(R^7)_2$, $-SP(OR^7)N(R^7)_2$, and $-SP(N(R^7)_2)_2$. In some embodiments, R^1 is selected from-$OP(O)(OR^7)_2$, $-OP(S)(OR^7)_2$, $-SP(O)(OR^7)_2$, $-OP(O)(SR^7)(OR^7)$, $-OP(O)(OR^7)N(R^7)_2$, $-OP(S)(OR^7)N(R^7)_2$, $-SP(O)(OR^7)N(R^7)_2$, $-OP(O)(SR^7)N(R^7)_2$, $-OP(O)(N(R^7)_2)_2$, $-OP(S)(N(R^7)_2)_2$, $-SP(O)(N(R^7)_2)_2$, $-OP(OR^7)_2$, $-SP(OR^7)_2$, $-OP(OR^7)(SR^7)$,$-OP(OR^7)N(R^7)_2$, $-OP(SR^7)N(R^7)_2$, $-SP(OR^7)N(R^7)_2$, $-OP(N(R^7)_2)_2$, and $-SP(N(R^7)_2)_2$. In some embodiments, R^1 is a selected from $-OP(O)(OR^7)_2$, $-OP(O)(OR^7)N(R^7)_2$, $-OP(O)(N(R^7)_2)_2$, $-OP(OR^7)_2$, $-OP(OR^7)N(R^7)_2$, and $-OP((NR^7)_2)_2$. In some embodiments, R^1 is a selected from $-OP(O)(OR^7)_2$ and $-OP(OR^7)N(R^7)_2$. In some embodiments, R^1 is selected from $-OP(O)(OCH_2CH_3)OH$ and $-OP(OCH_2CH_2CN)N(CH(CH_3)_2)_2$. In some embodiments, R^1 is $-OP(OCH_2CH_2CN)N(CH(CH_3)_2)_2$.

[0048] In some embodiments, each R^2 is independently selected from C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, $-OR^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, $-C(O)N(R^7)_2$, $-N(R^7)C(O)R^7$, $-N(R^7)C(O)N(R^7)_2$, $-OC(O)N(R^7)_2$, $-N(R^7)C(O)OR^7$, $-C(O)OR^7$, $-OC(O)R^7$, and $-S(O)R^7$. In some embodiments, each R^2 is independently selected from C_{1-3} alkyl substituted with one or more substituents independently selected from halogen, $-OR^7$, $-OC(O)R^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, and $-S(O)R^7$. In some embodiments, each R^2 is independently selected from C_{1-3} alkyl substituted with one or more substituents independently selected from $-OR^7$, $-OC(O)R^7$, $-SR^7$, and $-N(R^7)_2$. In some embodiments, each R^2 is independently selected from C_1 alkyl substituted with one or more substituents independently selected from $-OR^7$ and $-OC(O)R^7$. In some embodiments, each R^2 is independently selected from $-CH_2OH$ and $-CH_2OC(O)CH_3$.

[0049] In some embodiments, each R^3 is independently selected from $-OR^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, $-C(O)N(R^7)_2$, $-N(R^7)C(O)R^7$, $-N(R^7)C(O)N(R^7)_2$, $-OC(O)N(R^7)_2$, $-N(R^7)C(O)OR^7$, $-C(O)OR^7$, $-OC(O)R^7$, and $-S(O)R^7$. In some embodiments, each R^3 is independently selected from halogen, $-OR^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, $-OC(O)R^7$, and $-S(O)R^7$. In some embodiments, each R^3 is independently selected from $-OR^7$, $-OC(O)R^7$, $-SR^7$, and $-N(R^7)_2$. In some embodiments, each R^3 is independently selected from $-OR^7$ and $-OC(O)R^7$. In some embodiments, R^3 is independently selected from -OH and $-OC(O)CH_3$.

[0050] In some embodiments, each R^4 is independently selected from $-OR^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, $-C(O)N(R^7)_2$, $-N(R^7)C(O)R^7$, $-N(R^7)C(O)N(R^7)_2$, $-OC(O)N(R^7)_2$, $-N(R^7)C(O)OR^7$, $-C(O)OR^7$, $-OC(O)R^7$, and $-S(O)R^7$. In some embodiments, each R^4 is independently selected from halogen, $-OR^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, $-OC(O)R^7$, and $-S(O)R^7$. In some embodiments, each R^4 is independently selected from $-OR^7$, $-OC(O)R^7$, $-SR^7$, and $-N(R^7)_2$. In some embodiments, each R^4 is independently selected from $-OR^7$ and $-OC(O)R^7$. In some embodiments, R^4 is independently selected from -OH and $-OC(O)CH_3$.

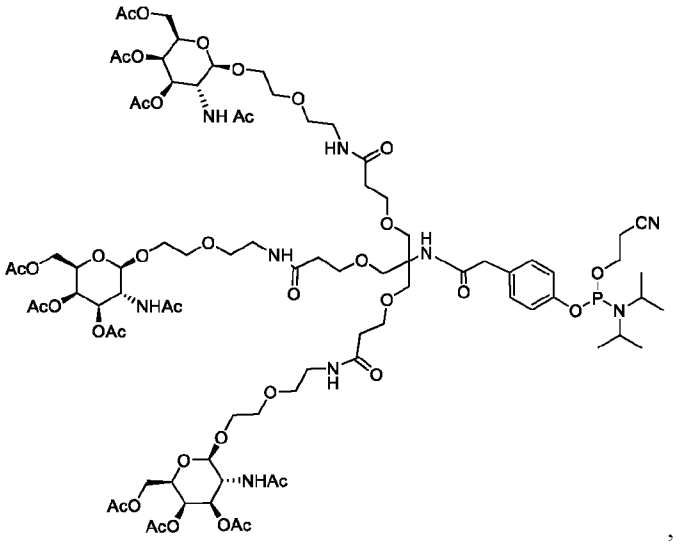
[0051] In some embodiments, each R^5 is independently selected from$-OC(O)R^7$, $-OC(O)N(R^7)_2$, $-N(R^7)C(O)R^7$, $-N(R^7)C(O)N(R^7)_2$, $-N(R^7)C(O)OR^7$, $-C(O)R^7$, $-C(O)OR^7$, and $-C(O)N(R^7)_2$. In some embodiments, each R^5 is selected from $-OC(O)R^7$, $-OC(O)N(R^7)_2$, $-N(R^7)C(O)R^7$, $-N(R^7)C(O)N(R^7)_2$, and $-N(R^7)C(O)OR^7$. In some embodiments, each R^5 is independently selected from $-OC(O)R^7$ and $-N(R^7)C(O)R^7$. In some embodiments, each R^5 is independently selected from $-N(H)C(O)CH_3$.

[0052] In some embodiments, each R^6 is independently selected from hydrogen, halogen, -CN, $-OR^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, $-C(O)N(R^7)_2$, $-N(R^7)C(O)R^7$, $-N(R^7)C(O)N(R^7)_2$, $-OC(O)N(R^7)_2$, $-N(R^7)C(O)OR^7$, $-C(O)OR^7$, $-OC(O)R^7$, and $-S(O)R^7$; and C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, -CN, $-OR^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, $-C(O)N(R^7)_2$, $-N(R^7)C(O)R^7$, $-N(R^7)C(O)N(R^7)_2$, $-OC(O)N(R^7)_2$, $-N(R^7)C(O)OR^7$, $-C(O)OR^7$, $-OC(O)R^7$, and $-S(O)R^7$. In some embodiments, each R^6 is independently selected from hydrogen, halogen, -CN $-OR^7$, $-SR^7$, $-N(R^7)_2$, and C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, $-OR^7$, $-SR^7$, and $-N(R^7)_2$. In some embodiments, each R^6 is independently selected from hydrogen, halogen, -CN, -OH, -SH, and $-NH_2$.

[0053] In some embodiments, each R^7 is independently selected from: hydrogen; C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is optionally substituted with one or more substituents independently

selected from halogen, -CN, -OH, -SH, $-NO_2$, $-NH_2$, =O, =S, $-O-C_{1-6}$ alkyl, $-S-C_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)_2$, $-NH(C_{1-6}$ alkyl), C_{3-10} carbocycle, and 3- to 10-membered heterocycle; and C_{3-10} carbocycle, and 3- to 10-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, $-NO_2$, $-NH_2$, =O, =S, $-O-C_{1-6}$ alkyl, $-S-C_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)_2$, $-NH(C_{1-6}$ alkyl), C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, and C_{1-6} haloalkyl. In some embodiments, each R^7 is independently selected from: hydrogen; and C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, $-NO_2$, $-NH_2$, =O, =S, $-O-C_{1-6}$ alkyl, $-S-C_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)_2$, $-NH(C_{1-6}$ alkyl), C_{3-10} carbocycle, 3- to 10-membered heterocycle. In some embodiments, each R^7 is independently selected from C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, $-NO_2$, $-NH_2$, =O, =S, $-O-C_{1-6}$ alkyl, $-S-C_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)_2$, and $-NH(C_{1-6}$ alkyl). In some embodiments, each R^7 is independently selected from hydrogen. In some embodiments, each R^7 is independently selected from C_{1-3} alkyl optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, $-NO_2$, $-NH_2$, $-O-C_{1-6}$ alkyl, $-S-C_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)_2$, and $-NH(C_{1-6}$ alkyl). In some embodiments, each R^7 is independently selected from C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, and -SH.

[0054] In some embodiments, a compound of Formula (A) is selected from:



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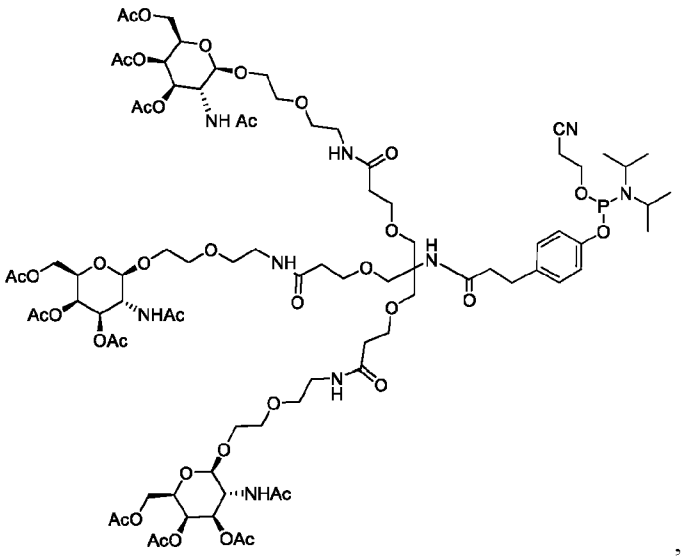

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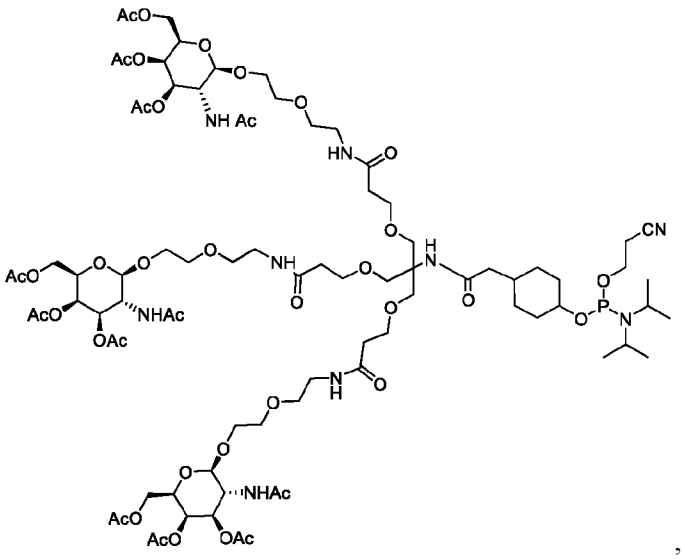

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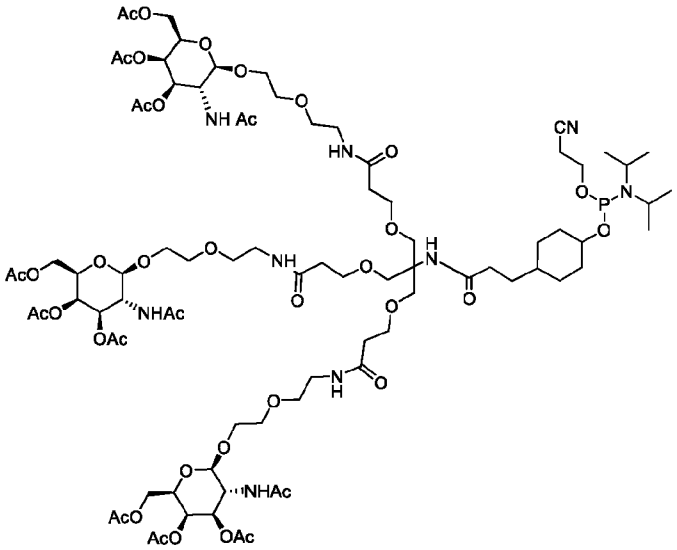

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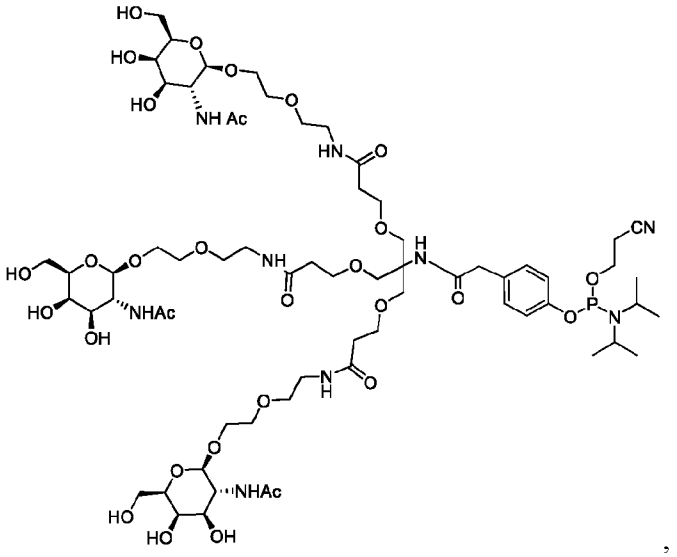

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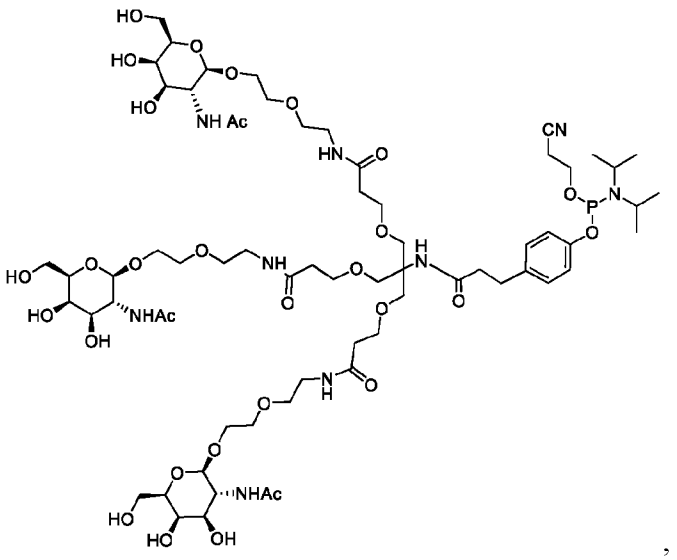

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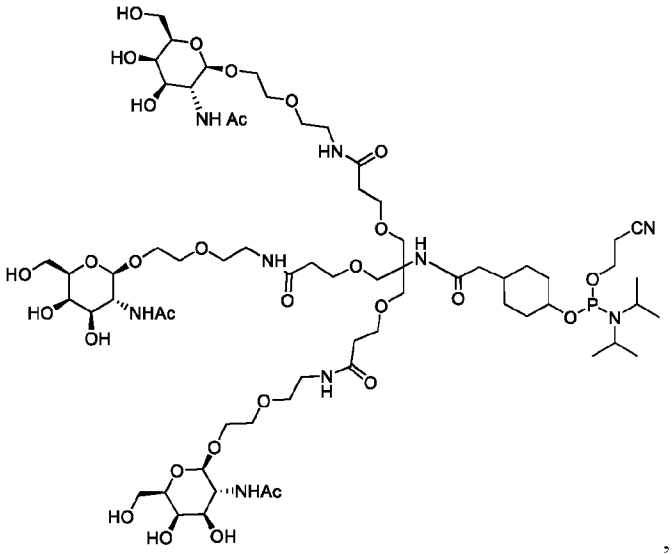

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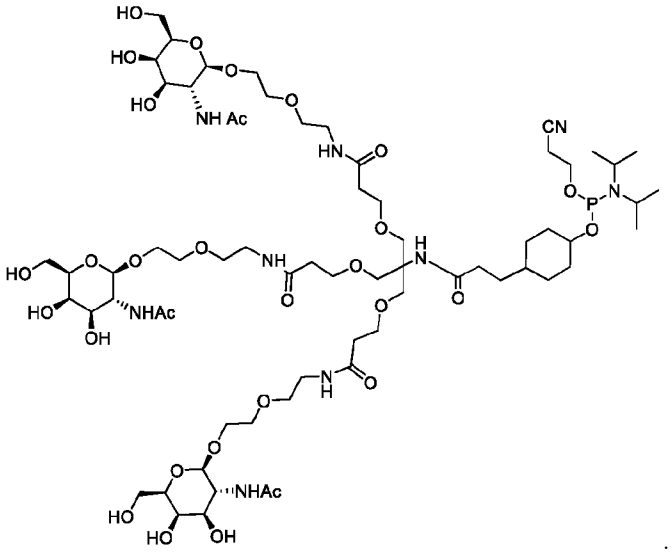

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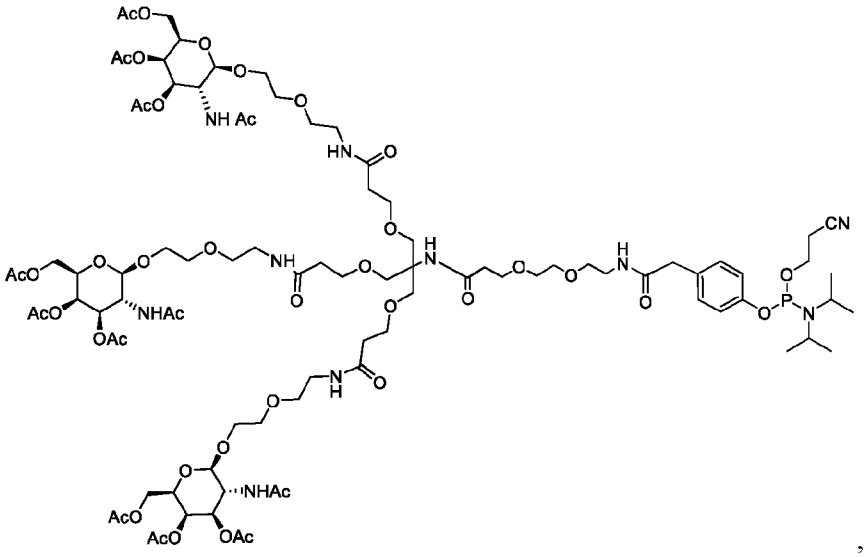
[0055] Provided herein, in some embodiments, is a compound represented by Formula (B):



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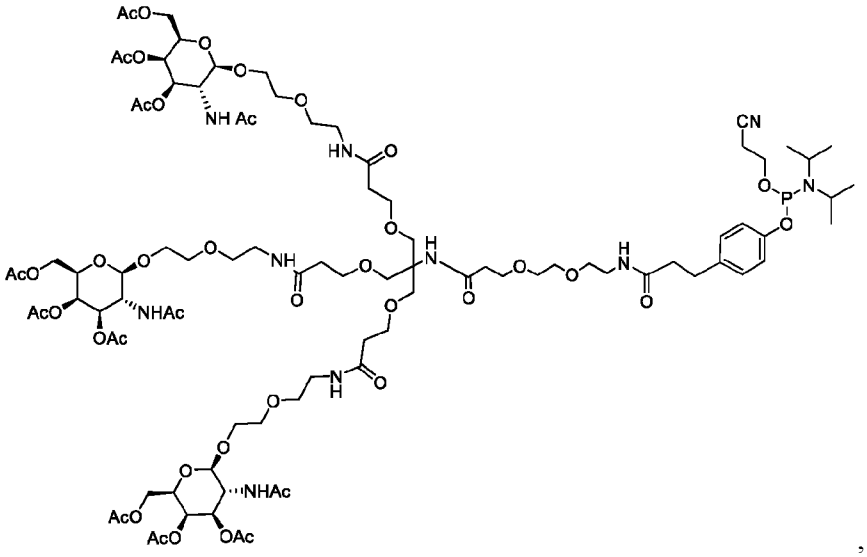

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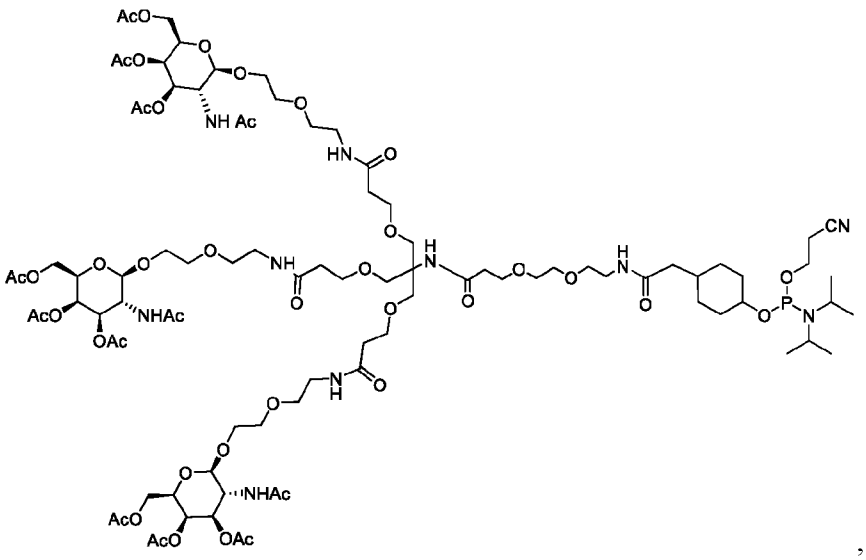

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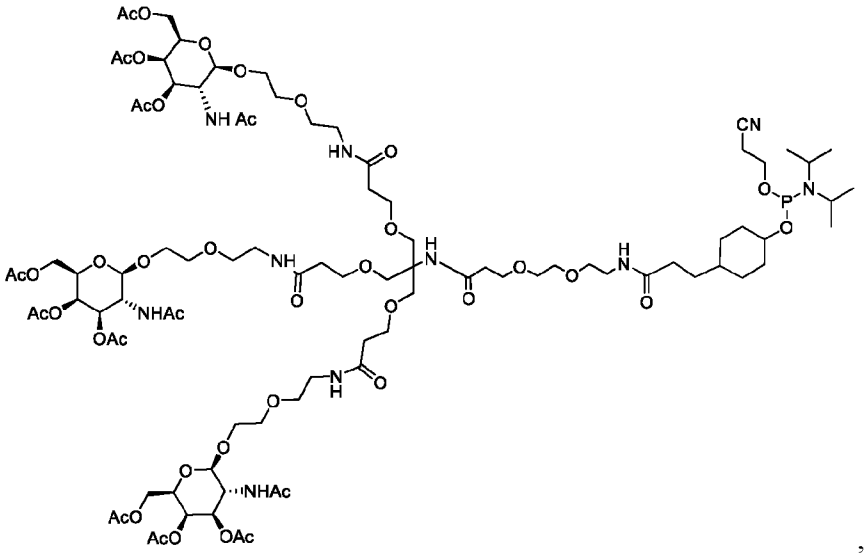

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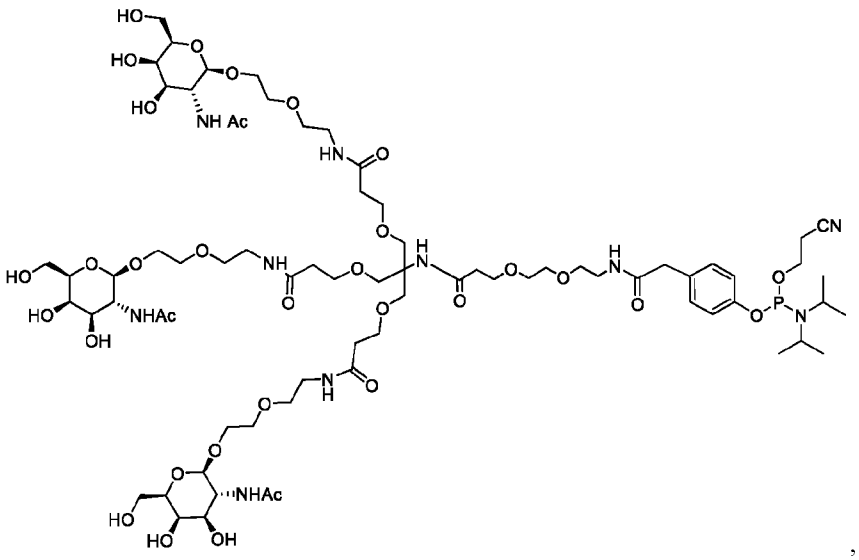

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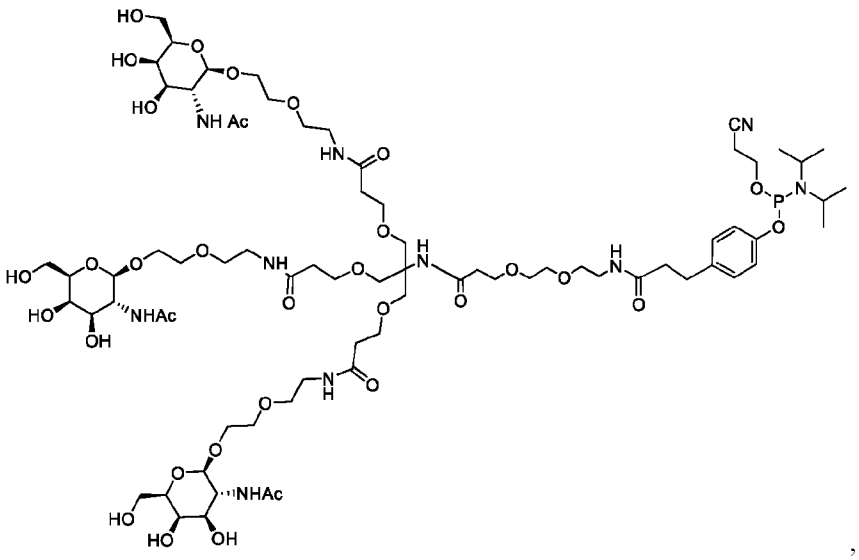

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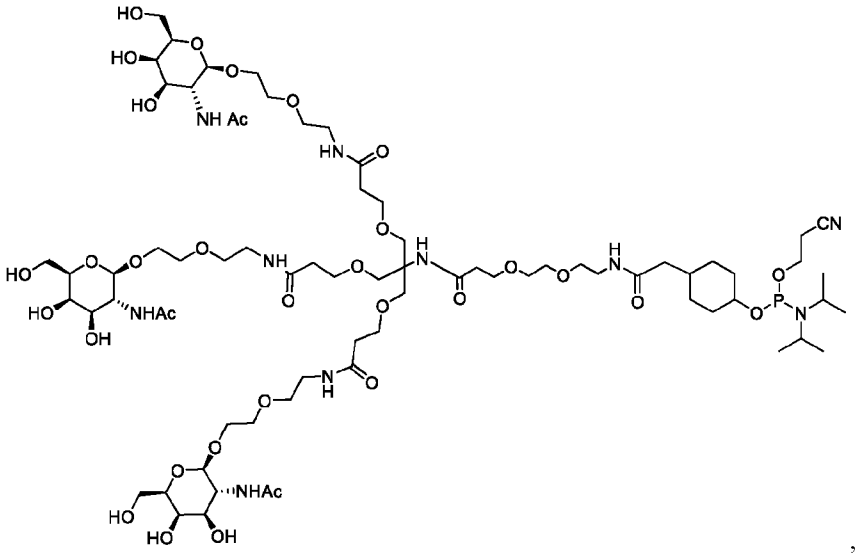

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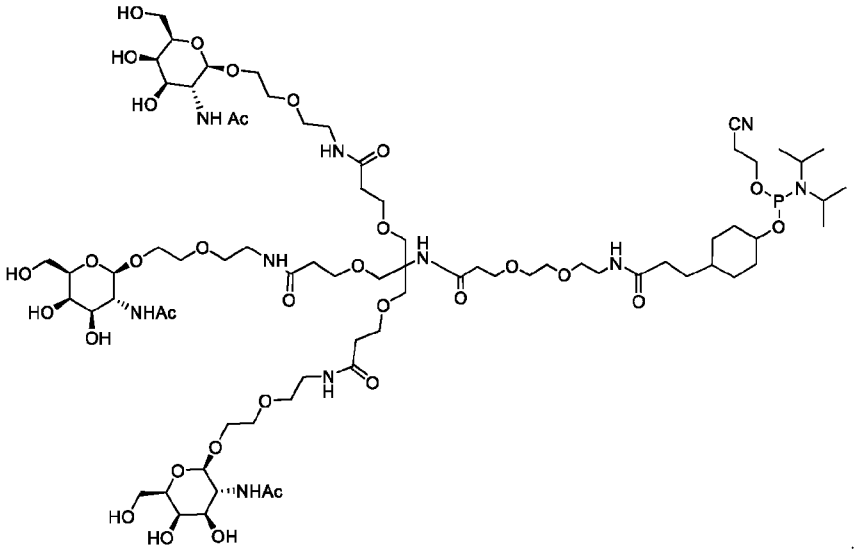
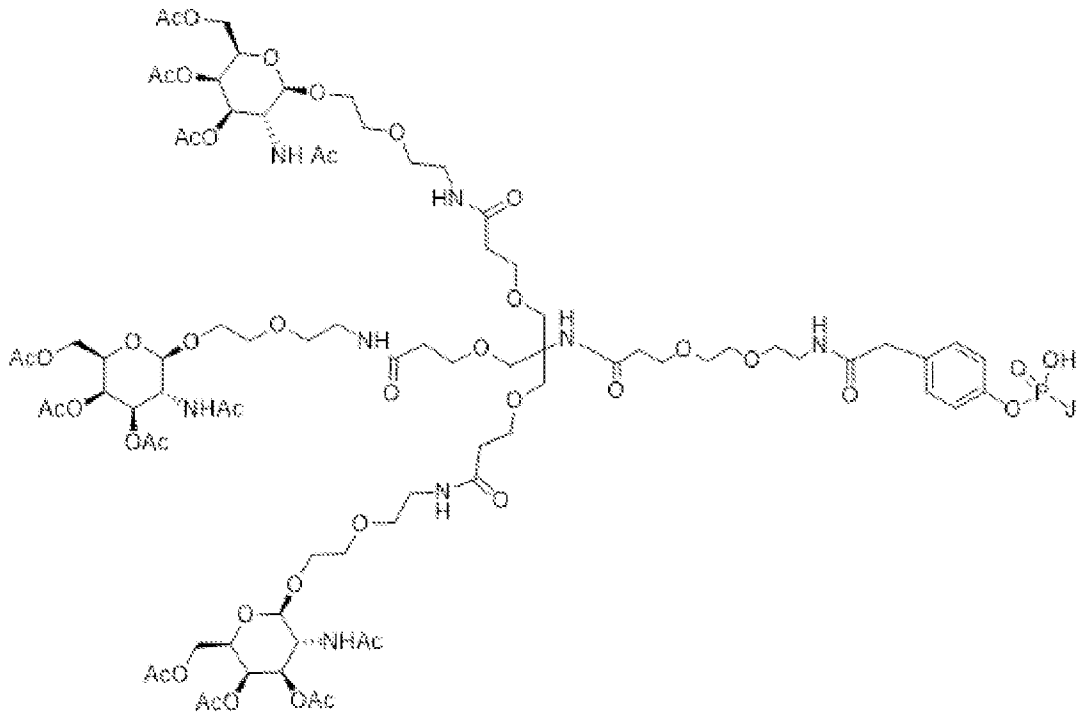


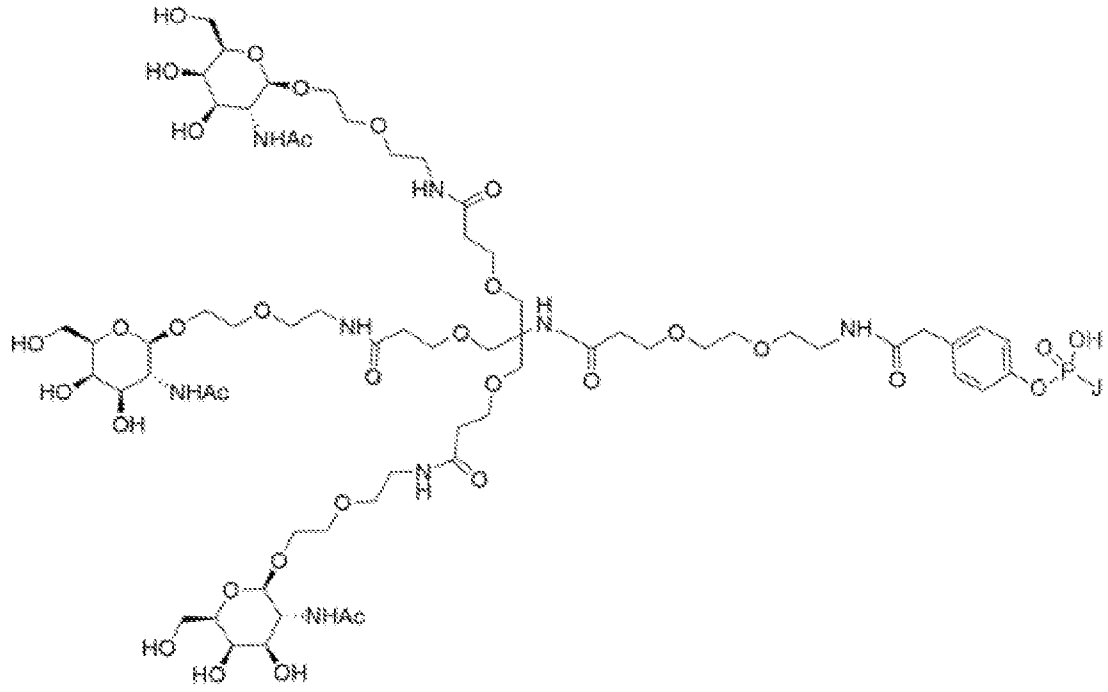
[0056] In some embodiments, the phosphate is deprotonated to form a salt of Formula (I), (II), (A), or (B). In some embodiments, the cation is a metal ion such as a metal cation. Non limiting examples of metal cations include Na^+, K^+, Mg^{2+}, and Ca^{2+}. In some embodiments, the metal cation comprises Na^+. In some embodiments, the metal cation comprises K^+. In some embodiments, the metal cation comprises Mg^{2+}. In some embodiments, the metal cation comprises Ca^{2+}. In some embodiments, the cation is an organic or inorganic small molecule. In some embodiments wherein the compound is a deprotonated form of Formula (I) or (II), the cation is a positively charged nucleic acid present in the oligonucleotide.

[0057] Some embodiments include the following, where J is the oligonucleotide:



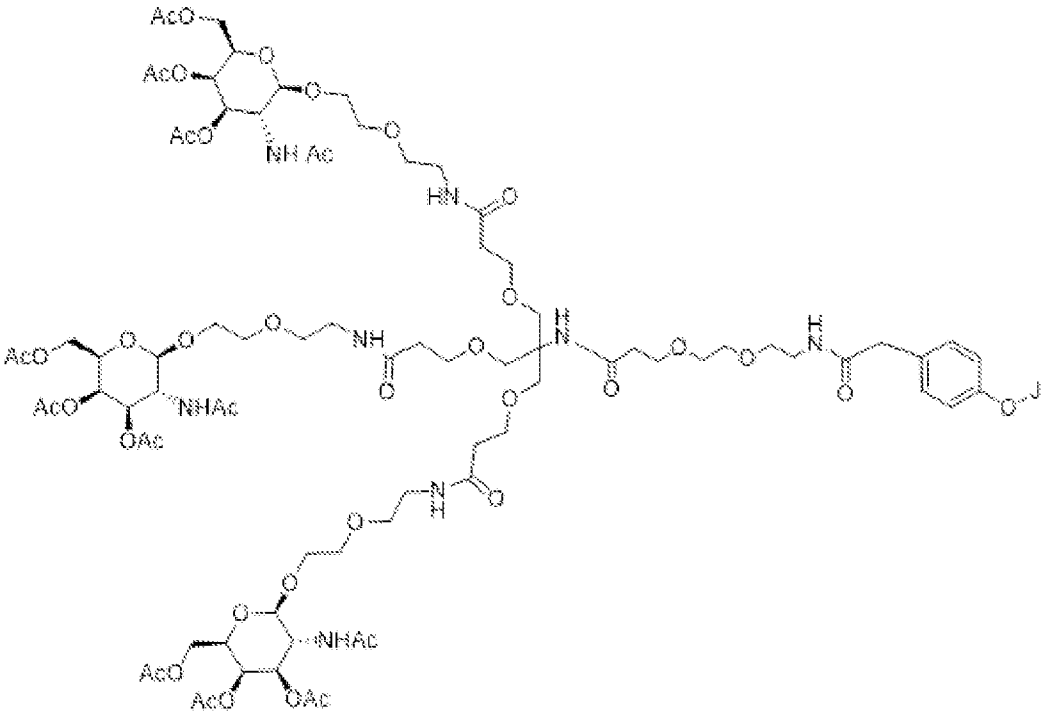
. J may include one or more additional phosphates, or one or more phosphorothioates linking to the oligonucleotide. J may include one or more additional phosphates linking to the oligonucleotide. J may include one or more phosphorothioates linking to the oligonucleotide.

[0058] Some embodiments include the following, where J is the oligonucleotide:



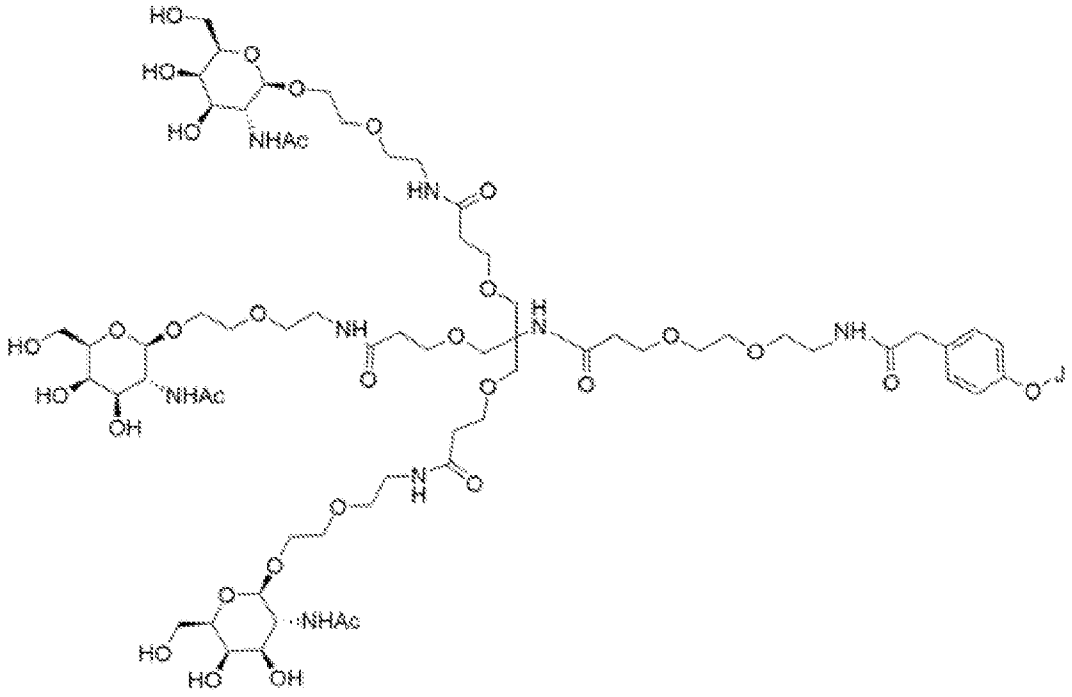
. J may include one or more additional phosphates, or one or more phosphorothioates linking to the oligonucleotide. J may include one or more additional phosphates linking to the oligonucleotide. J may include one or more phosphorothioates linking to the oligonucleotide.

[0059] Some embodiments include the following, where J is the oligonucleotide:



. J may include one or more phosphates or phosphorothioates linking to the oligonucleotide. J may include one or more phosphates linking to the oligonucleotide. J may include a phosphate linking to the oligonucleotide. J may include one or more phosphorothioates linking to the oligonucleotide. J may include a phosphorothioate linking to the oligonucleotide.

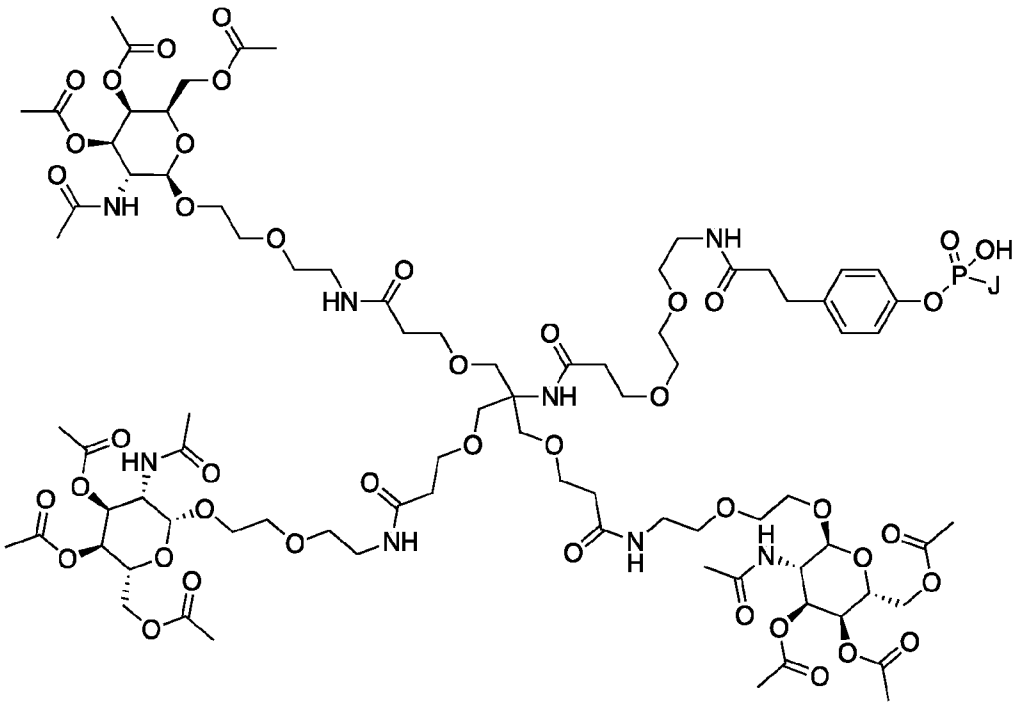
[0060] Some embodiments include the following, where J is the oligonucleotide:



. The structure in this compound attached to the oligonucleotide (J) is an example of a GalNAc moiety. J may include one or more phosphates or phosphorothioates linking to the oligonucleotide. J may include one or more phosphates linking to the oligonucleotide. J may include a phosphate linking to the oligonucleotide.

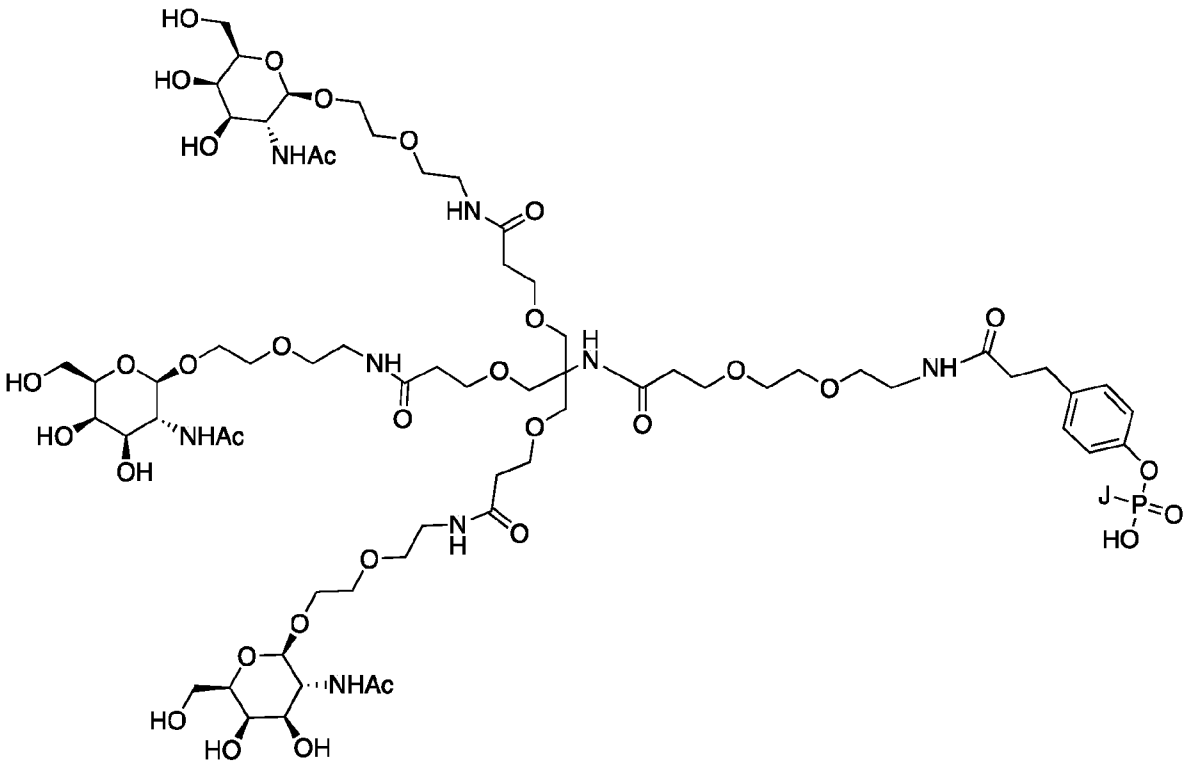
J may include one or more phosphorothioates linking to the oligonucleotide. J may include a phosphorothioate linking to the oligonucleotide.

[0061] Some embodiments include the following, where J is the oligonucleotide:



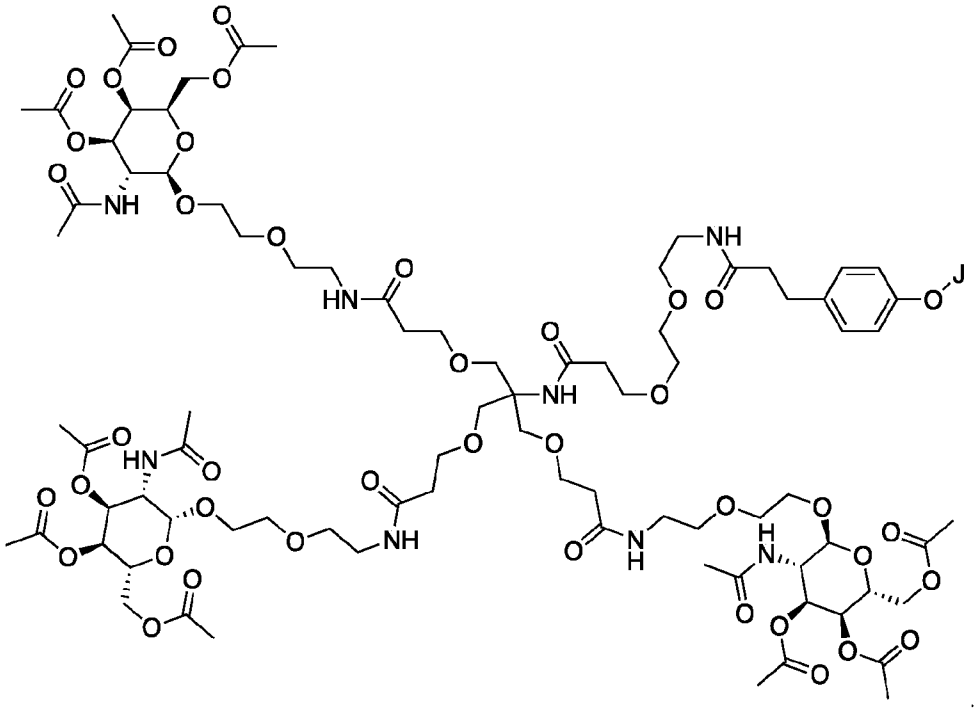
. J may include one or more additional phosphates, or one or more phosphorothioates linking to the oligonucleotide. J may include one or more additional phosphates linking to the oligonucleotide. J may include one or more phosphorothioates linking to the oligonucleotide.

[0062] Some embodiments include the following, where J is the oligonucleotide:



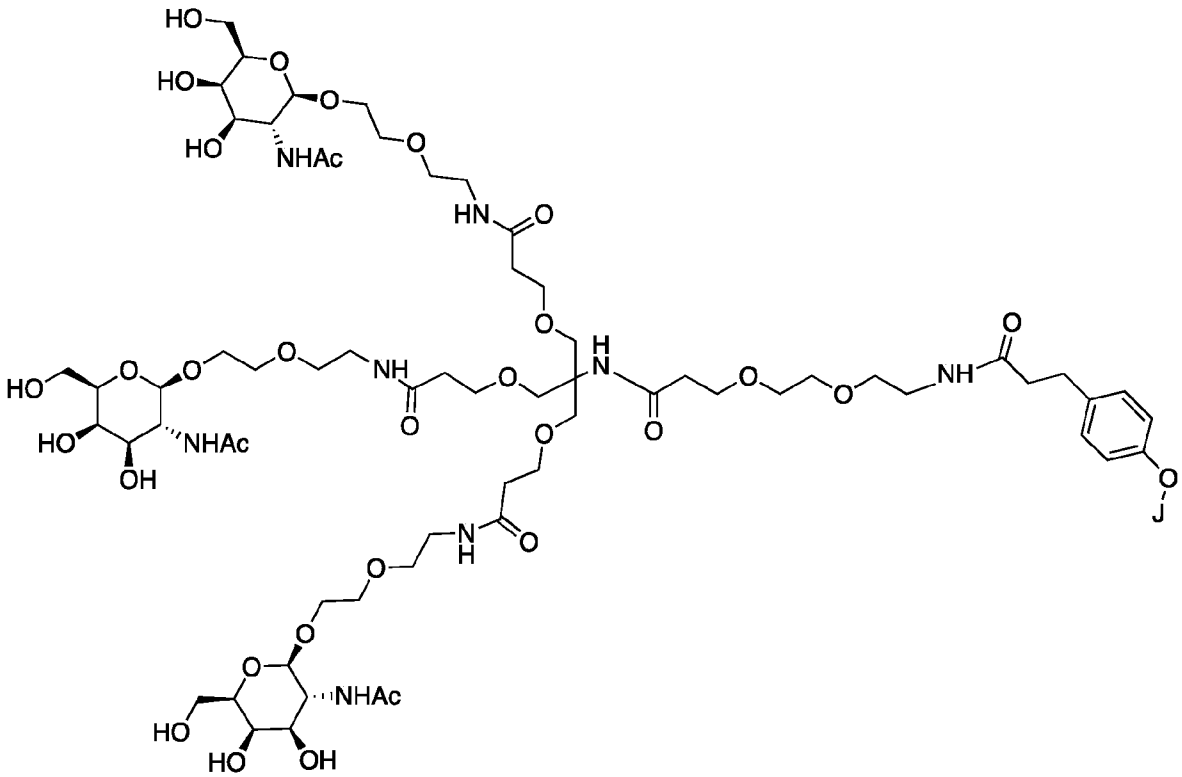
. J may include one or more additional phosphates, or one or more phosphorothioates linking to the oligonucleotide. J may include one or more additional phosphates linking to the oligonucleotide. J may include one or more phosphorothioates linking to the oligonucleotide.

[0063] Some embodiments include the following, where J is the oligonucleotide:



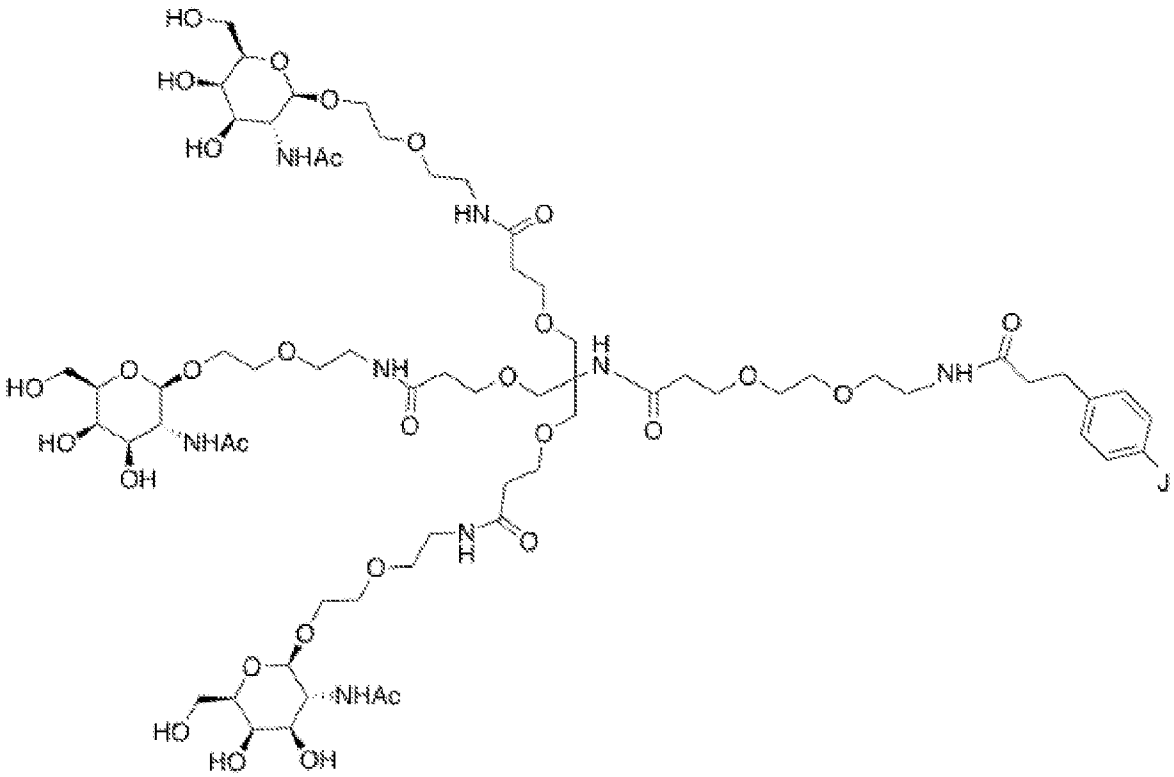
. J may include one or more phosphates or phosphorothioates linking to the oligonucleotide. J may include one or more phosphates linking to the oligonucleotide. J may include a phosphate linking to the oligonucleotide. J may include one or more phosphorothioates linking to the oligonucleotide. J may include a phosphorothioate linking to the oligonucleotide.

[0064] Some embodiments include the following, where J is the oligonucleotide:



The structure in this compound attached to the oligonucleotide (J) may be referred to as "ETL17," and is an example of a GalNAc moiety. J may include one or more phosphates or phosphorothioates linking to the oligonucleotide. J may include one or more phosphates linking to the oligonucleotide. J may include a phosphate linking to the oligonucleotide. J may include one or more phosphorothioates linking to the oligonucleotide. J may include a phosphorothioate linking to the oligonucleotide.

[0065] Some embodiments include the following, where J is the oligonucleotide:

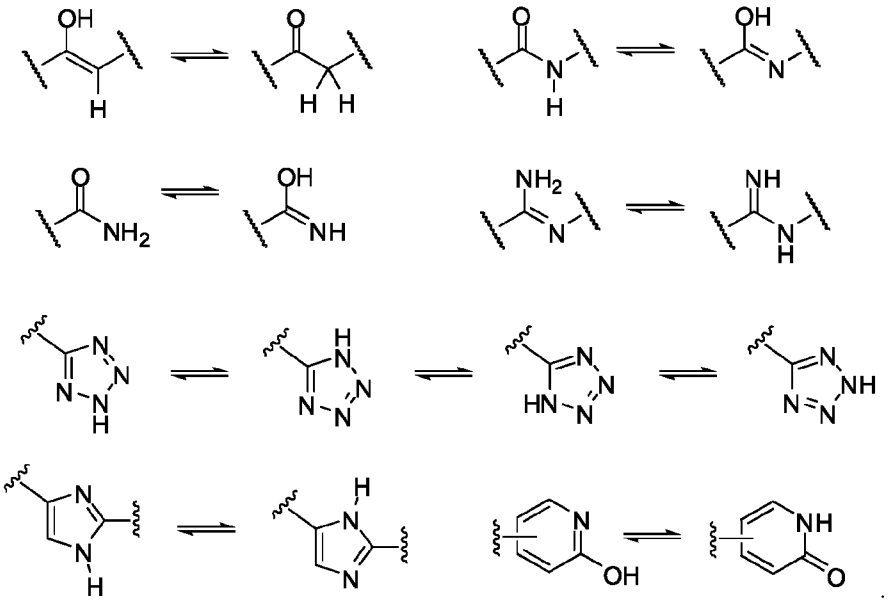


The structure in this compound attached to the oligonucleotide (J) is an example of a GalNAc moiety. J may include one or more phosphates or phosphorothioates linking to the oligonucleotide. J may include one or more phosphates linking to the oligonucleotide. J may include a phosphate linking to the oligonucleotide. J may include one or more phosphorothioates linking to the oligonucleotide. J may include a phosphorothioate linking to the oligonucleotide. In any embodiment, J may include an additional linker.

1. Analogues

[0066] Chemical entities having carbon-carbon double bonds or carbon-nitrogen double bonds may exist in *Z*- or *E*- form (or *cis*- or *trans*- form). Furthermore, some chemical entities may exist in various tautomeric forms. Unless otherwise specified, compounds described herein are intended to include all *Z*-, *E*- and tautomeric forms as well.

[0067] **A "tautomer" refers** to a molecule or moiety wherein a proton shift from one atom of a molecule to another atom of the same molecule is possible. The compounds presented herein, in certain embodiments, exist as tautomers. In circumstances where tautomerization is possible, a chemical equilibrium of the tautomers will exist. The exact ratio of the tautomers depends on several factors, including physical state, temperature, solvent, and pH. Some examples of tautomeric equilibrium include:



[0068] The compounds and moieties disclosed herein, in some embodiments, are used in different enriched isotopic forms, e.g., enriched in the content of ^{2}H, ^{3}H, ^{11}C, ^{13}C and/or ^{14}C. In one particular embodiment, the compound is deuterated in at least one position. Such deuterated forms can be made by the procedure described in U.S. Patent Nos. 5,846,514 and 6,334,997. As described in U.S. Patent Nos. 5,846,514 and 6,334,997, deuteration can improve the metabolic stability and or efficacy, thus increasing the duration of action of drugs.

[0069] Unless otherwise stated, compounds described herein and moieties are intended to include compounds and moieties which differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of a hydrogen by a deuterium or tritium, or the replacement of a carbon by ^{13}C- or ^{14}C-enriched carbon are within the scope of the present disclosure.

[0070] The compounds and moieties of the present disclosure optionally contain unnatural proportions of atomic isotopes at one or more atoms that constitute such compounds. For example, the compounds may be labeled with isotopes, such as for example, deuterium (^{2}H), tritium (^{3}H), iodine-125 (^{125}I) or carbon-14 (^{14}C). Isotopic substitution with ^{2}H, ^{11}C, ^{13}C, ^{14}C, ^{15}C, ^{12}N, ^{13}N, ^{15}N, ^{16}N, ^{16}O, ^{17}O, ^{14}F, ^{15}F, ^{16}F, ^{17}F, ^{18}F, ^{33}S, ^{34}S, ^{35}S, ^{36}S, ^{35}Cl, ^{37}Cl, ^{79}Br, ^{81}Br, and ^{125}I are all contemplated. All isotopic variations of the compounds and moieties of the present invention, whether radioactive or not, are encompassed within the scope of the present invention.

[0071] In certain embodiments, the compounds and moieties disclosed herein have some or all of the ^{1}H atoms replaced with ^{2}H atoms. The methods of synthesis for deuterium-containing compounds are known in the art and include, by way of non-limiting example only, the following synthetic methods.

[0072] Deuterium substituted compounds are synthesized using various methods such as described in: Dean, Dennis C.; Editor. Recent Advances in the Synthesis and Applications of Radiolabeled Compounds for Drug Discovery and Development. [In: Curr., Pharm. Des., 2000; 6(10)] 2000, 110 pp; George W.; Varma, Rajender S. The Synthesis of Radiolabeled Compounds via Organometallic Intermediates,

Tetrahedron, 1989, 45(21), 6601-21; and Evans, E. Anthony. Synthesis of radiolabeled compounds, J. Radioanal. Chem., 1981, 64(1-2), 9-32.

[0073] Deuterated starting materials are readily available and are subjected to the synthetic methods described herein to provide for the synthesis of deuterium-containing compounds. Large numbers of deuterium-containing reagents and building blocks are available commercially from chemical vendors, such as Aldrich Chemical Co.

[0074] Included in the present disclosure are salts, particularly pharmaceutically acceptable salts, of the compounds described herein. The compounds of the present disclosure that possess a sufficiently acidic, a sufficiently basic, or both functional groups, can react with any of a number of inorganic bases, and inorganic and organic acids, to form a salt. Alternatively, compounds that are inherently charged, such as those with a quaternary nitrogen, can form a salt with an appropriate counterion, e.g., a halide such as bromide, chloride, or fluoride, particularly bromide.

[0075] The compounds described herein may in some cases exist as diastereomers, enantiomers, or other stereoisomeric forms. The compounds presented herein include all diastereomeric, enantiomeric, and epimeric forms as well as the appropriate mixtures thereof. Separation of stereoisomers may be performed by chromatography or by forming diastereomers and separating by recrystallization, or chromatography, **or any combination thereof. (Jean Jacques, Andre Collet, Samuel H. Wilen,** "Enantiomers, Racemates and **Resolutions", John Wiley And Sons, Inc., 1981, herein incorporated by reference for this disclosure).** Stereoisomers may also be obtained by stereoselective synthesis.

[0076] The methods and compositions described herein include the use of amorphous forms as well as crystalline forms (also known as polymorphs). The compounds described herein may be in the form of pharmaceutically acceptable salts. As well, in some embodiments, active metabolites of these compounds having the same type of activity are included in the scope of the present disclosure. In addition, the compounds described herein can exist in unsolvated or solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. The solvated forms of the compounds presented herein are also considered to be disclosed herein.

B. Oligonucleotides

[0077] Provided herein, in some embodiments, are compositions or compounds comprising an oligonucleotide. The oligonucleotide may be conjugated to a GalNAc moiety. The oligonucleotide may be directly connected to a linker connected to the GalNAc moiety. The oligonucleotide may be used in a method described herein.

[0078] In some embodiments, the oligonucleotide binds to a target oligonucleotide. Examples of target oligonucleotides include a target RNA or a target DNA. In some embodiments, the oligonucleotide binds to a target DNA. In some embodiments, the oligonucleotide binds to a target DNA, and inhibits RNA (e.g. mRNA) expression from the target DNA. In some embodiments, the oligonucleotide binds to a target RNA. The target RNA may include a target mRNA. In some embodiments, the oligonucleotide binds to a target mRNA. In some embodiments, the oligonucleotide inhibits the target mRNA such as by reducing

an amount of the target mRNA, causing degradation of the target mRNA, or decreasing or preventing translation of the target mRNA. In some embodiments, the oligonucleotide reduces an amount of a target protein produced from the target mRNA, for example by inhibiting the target mRNA. The oligonucleotide may include a small interfering RNA (siRNA). The oligonucleotide may include an antisense oligonucleotide (ASO).

[0079] In some embodiments, the composition comprises an oligonucleotide that binds to a target oligonucleotide and inhibits expression of a target protein encoded by the target oligonucleotide. In some embodiments, the composition comprises an oligonucleotide that binds to a target RNA and inhibits expression of a target protein encoded by the target RNA. In some embodiments, the composition comprises an oligonucleotide that binds to a target mRNA and inhibits expression of a target protein encoded by the target mRNA.

[0080] In some embodiments, the composition comprises an oligonucleotide that binds to a target oligonucleotide and inhibits expression of a second oligonucleotide encoded by the target oligonucleotide. In some embodiments, the composition comprises an oligonucleotide that binds to a target DNA and inhibits expression of a target RNA encoded by the target DNA. In some embodiments, the composition comprises an oligonucleotide that binds to a target DNA and inhibits expression of a target mRNA encoded by the target DNA.

[0081] Target oligonucleotides may be identified by a variety of ways. In some instances, the target oligonucleotide comprises an mRNA that has expression levels that are associated with incidence of a disorder (e.g. a liver disorder). In some instances, the target oligonucleotide comprises an mRNA that is encoded by a gene that has a particular genotype associated with the disorder. Large-scale human genetic data can improve the success rate of pharmaceutical discovery and development. A Genome Wide Association Study (GWAS) may detect associations between genetic variants and traits in a population sample. A GWAS may enable better understanding of the biology of disease, and provide applicable treatments. A GWAS can utilize genotyping and/or sequencing data, and often involves an evaluation of millions of genetic variants that are relatively evenly distributed across the genome. The most common GWAS design is the case-control study, which involves comparing variant frequencies in cases versus controls. If a variant has a significantly different frequency in cases versus controls, that variant is said to be associated with disease. Association statistics that may be used in a GWAS are p-values, as a measure of statistical significance; odds ratios (OR), as a measure of effect size; or beta coefficients (beta), as a measure of effect size. Researchers often assume an additive genetic model and calculate an allelic odds ratio, which is the increased (or decreased) risk of disease conferred by each additional copy of an allele (compared to carrying no copies of that allele). An additional concept in design and interpretation of GWAS is that of linkage disequilibrium, which is the non-random association of alleles. The presence of **linkage disequilibrium can obfuscate which variant is "causal."**

[0082] Functional annotation of variants and/or wet lab experimentation can identify the causal genetic variant identified via GWAS, and in many cases may lead to the identification of disease-causing genes. In particular, understanding the functional effect of a causal genetic variant (for example, loss of protein

function, gain of protein function, increase in gene expression, or decrease in gene expression) may allow that variant to be used as a proxy for therapeutic modulation of the target gene, or to gain insight into potential therapeutic efficacy and safety of a therapeutic that modulates that target.

[0083] Identification of such gene-disease associations has provided insights into disease biology and may be used to identify novel therapeutic targets for the pharmaceutical industry. In order to translate the therapeutic insights derived from human genetics, disease biology in patients may be exogenously 'programmed' into replicating the observation from human genetics. There are several potential options for therapeutic modalities that may be brought to bear in translating therapeutic targets identified via human genetics into novel medicines. These may include well established therapeutic modalities such as small molecules and monoclonal antibodies, maturing modalities such as oligonucleotides, and emerging modalities such as gene therapy and gene editing. The choice of therapeutic modality can depend on several factors including the location of a target (for example, intracellular, extracellular, or secreted), a relevant tissue (for example, liver) and a relevant indication. Such studies may be conducted to identify specific liver disorder-related targets for siRNA or ASO inhibition by a composition or compound described herein.

[0084] Some embodiments include a method of making an oligonucleotide or siRNA using a method disclosed herein. For example, any aspect of an Example herein that includes steps for synthesis may be used. Some embodiments include making a GalNAc moiety, or making an oligonucleotide with a GalNAc moiety.

1. siRNAs

[0085] In some embodiments, the composition comprises an oligonucleotide that binds to a target oligonucleotide (e.g. mRNA), wherein the oligonucleotide comprises a small interfering RNA (siRNA). In some embodiments, the composition comprises an oligonucleotide that binds to a target oligonucleotide (e.g. mRNA), wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand. In some embodiments, the sense strand comprises RNA. In some embodiments, the antisense strand comprises RNA.

[0086] In some embodiments, the sense strand is 12-30 nucleosides in length. In some embodiments, the sense strand is 14-30 nucleosides in length. In some embodiments, the sense strand is at least about 10, 11, 12, 13, 14, 15, 16, 17, 18,19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleosides in length. In some embodiments, the sense strand is at least 12 nucleotides in length. In some embodiments, the sense strand is at least 14 nucleotides in length. In some embodiments, the sense strand is at least 16 nucleotides in length. In some embodiments, the sense strand is at least 18 nucleotides in length. In some embodiments, the sense strand is at least 20 nucleotides in length. In some embodiments, the sense strand is at least 22 nucleotides in length. In some embodiments, the sense strand is at least 24 nucleotides in length. In some embodiments, the sense strand is at least 26 nucleotides in length. In some embodiments, the sense strand is at least 28 nucleotides in length. In some embodiments, the sense strand is at least 30 nucleotides in length. In some embodiments, the sense strand is no more than about 10, 11, 12, 13, 14, 15, 16, 17, 18,19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleosides in length. In some embodiments, the sense strand

is no more than 12 nucleotides in length. In some embodiments, the sense strand is no more than 14 nucleotides in length. In some embodiments, the sense strand is no more than 16 nucleotides in length. In some embodiments, the sense strand is no more than 18 nucleotides in length. In some embodiments, the sense strand is no more than 20 nucleotides in length. In some embodiments, the sense strand is no more than 22 nucleotides in length. In some embodiments, the sense strand is no more than 24 nucleotides in length. In some embodiments, the sense strand is no more than 26 nucleotides in length. In some embodiments, the sense strand is no more than 28 nucleotides in length. In some embodiments, the sense strand is no more than 30 nucleotides in length.

[0087] In some embodiments, the antisense strand is 12-30 nucleosides in length. In some embodiments, the antisense strand is 14-30 nucleosides in length. In some embodiments, the antisense strand is at least about 10, 11, 12, 13, 14, 15, 16, 17, 18,19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleosides in length. In some embodiments, the antisense strand is at least 12 nucleotides in length. In some embodiments, the antisense strand is at least 14 nucleotides in length. In some embodiments, the antisense strand is at least 16 nucleotides in length. In some embodiments, the antisense strand is at least 18 nucleotides in length. In some embodiments, the antisense strand is at least 20 nucleotides in length. In some embodiments, the antisense strand is at least 22 nucleotides in length. In some embodiments, the antisense strand is at least 24 nucleotides in length. In some embodiments, the antisense strand is at least 26 nucleotides in length. In some embodiments, the antisense strand is at least 28 nucleotides in length. In some embodiments, the antisense strand is at least 30 nucleotides in length. In some embodiments, the antisense strand is no more than about 10, 11, 12, 13, 14, 15, 16, 17, 18,19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleosides in length. In some embodiments, the antisense strand is no more than 12 nucleotides in length. In some embodiments, the antisense strand is no more than 14 nucleotides in length. In some embodiments, the antisense strand is no more than 16 nucleotides in length. In some embodiments, the antisense strand is no more than 18 nucleotides in length. In some embodiments, the antisense strand is no more than 20 nucleotides in length. In some embodiments, the antisense strand is no more than 22 nucleotides in length. In some embodiments, the antisense strand is no more than 24 nucleotides in length. In some embodiments, the antisense strand is no more than 26 nucleotides in length. In some embodiments, the antisense strand is no more than 28 nucleotides in length. In some embodiments, the antisense strand is no more than 30 nucleotides in length. In some embodiments, the antisense strand is the same length as the sense strand.

[0088] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of a target oligonucleotide (e.g. mRNA), wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, wherein the sense strand is 12-30 nucleosides in length. In some embodiments, the composition comprises a sense strange that is 10, 11, 12, 13, 14, 15, 16, 17, 18,19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleosides in length, or a range defined by any of the two aforementioned numbers. In some embodiments, the composition comprises an antisense strand is 12-30 nucleosides in length. In some embodiments, the composition comprises an antisense strange that is 10,

11, 12, 13, 14, 15, 16, 17, 18,19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleosides in length, or a range defined by any of the two aforementioned numbers.

[0089] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of a target oligonucleotide (e.g. mRNA), wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, each strand is independently about 14-30 nucleosides in length, and at least one of the sense strand and the antisense strand comprises a nucleoside sequence comprising about 12-30 contiguous nucleosides of a full-length human target mRNA sequence. In some embodiments, at least one of the sense strand and the antisense strand comprise a nucleoside sequence comprising at least about 10, 11, 12, 13, 14, 15, 16, 17, 18,19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, or more contiguous nucleosides of one of the full-length human target mRNA sequence.

[0090] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of a target protein, wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, wherein the sense strand and the antisense strand form a double-stranded RNA duplex. In some embodiments, the first base pair of the double-stranded RNA duplex is an AU base pair.

[0091] In some embodiments, the sense strand further comprises a 3' overhang. In some embodiments, the 3' overhang comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleosides, or a range of nucleotides defined by any two of the aforementioned numbers. In some embodiments, the 3' overhang comprises 1, 2, or more nucleosides. In some embodiments, the 3' overhang comprises 2 nucleosides. In some embodiments, the sense strand further comprises a 5' overhang. In some embodiments, the 5' overhang comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleosides, or a range of nucleotides defined by any two of the aforementioned numbers. In some embodiments, the 5' overhang comprises 1, 2, or more nucleosides. In some embodiments, the 5' overhang comprises 2 nucleosides.

[0092] In some embodiments, the antisense strand further comprises a 3' overhang. In some embodiments, the 3' overhang comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleosides, or a range of nucleotides defined by any two of the aforementioned numbers. In some embodiments, the 3' overhang comprises 1, 2, or more nucleosides. In some embodiments, the 3' overhang comprises 2 nucleosides. In some embodiments, the antisense strand further comprises a 5' overhang. In some embodiments, the 5' overhang comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleosides, or a range of nucleotides defined by any two of the aforementioned numbers. In some embodiments, the 5' overhang comprises 1, 2, or more nucleosides. In some embodiments, the 5' overhang comprises 2 nucleosides.

[0093] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of a target protein, wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, wherein the siRNA binds with a 19mer in a human target mRNA encoding the target protein. In some embodiments, the siRNA binds with a 12mer, a 13mer, a 14mer, a 15mer, a 16mer, a 17mer, a 18mer, a 19mer, a 20mer, a 21mer, a 22mer, a 23mer, a 24mer, or a 25mer in a human target mRNA.

[0094] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of a target protein, wherein the oligonucleotide comprises an siRNA comprising a sense strand and an

antisense strand, wherein the siRNA binds with a 17mer in a non-human primate target mRNA encoding the target protein. In some embodiments, the siRNA binds with a 12mer, a 13mer, a 14mer, a 15mer, a 16mer, a 17mer, a 18mer, a 19mer, a 20mer, a 21mer, a 22mer, a 23mer, a 24mer, or a 25mer in a non-human primate target mRNA.

[0095] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of a target protein, wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, wherein the siRNA binds with a 19mer in a human target mRNA encoding the target protein, or a combination thereof. In some embodiments, the siRNA binds with a 12mer, a 13mer, a 14mer, a 15mer, a 16mer, a 17mer, and 18mer, a 19mer, a 20mer, a 21mer, a 22mer, a 23mer, a 24mer, or a 25mer in a human target mRNA.

2. ASOs

[0096] In some embodiments, the composition comprises an oligonucleotide that inhibits expression of a target oligonucleotide (e.g. mRNA), wherein the oligonucleotide comprises an antisense oligonucleotide (ASO). In some embodiments, the ASO is 12-30 nucleosides in length. In some embodiments, the ASO is 14-30 nucleosides in length. In some embodiments, the ASO is 10, 11, 12, 13, 14, 15, 16, 17, 18,19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleosides in length, or a range defined by any of the two aforementioned numbers. In some embodiments, the ASO is 15-25 nucleosides in length. In some embodiments, the ASO is 20 nucleosides in length. In some embodiments, the ASO comprises DNA.

[0097] In some embodiments, the ASO is 12-30 nucleosides in length. In some embodiments, the ASO is 14-30 nucleosides in length. In some embodiments, the ASO is at least about 10, 11, 12, 13, 14, 15, 16, 17, 18,19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleosides in length. In some embodiments, the ASO is at least 12 nucleotides in length. In some embodiments, the ASO is at least 14 nucleotides in length. In some embodiments, the ASO is at least 16 nucleotides in length. In some embodiments, the ASO is at least 18 nucleotides in length. In some embodiments, the ASO is at least 20 nucleotides in length. In some embodiments, the ASO is at least 22 nucleotides in length. In some embodiments, the ASO is at least 24 nucleotides in length. In some embodiments, the ASO is at least 26 nucleotides in length. In some embodiments, the ASO is at least 28 nucleotides in length. In some embodiments, the ASO is at least 30 nucleotides in length. In some embodiments, the ASO is no more than about 10, 11, 12, 13, 14, 15, 16, 17, 18,19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleosides in length. In some embodiments, the ASO is no more than 12 nucleotides in length. In some embodiments, the ASO is no more than 14 nucleotides in length. In some embodiments, the ASO is no more than 16 nucleotides in length. In some embodiments, the ASO is no more than 18 nucleotides in length. In some embodiments, the ASO is no more than 20 nucleotides in length. In some embodiments, the ASO is no more than 22 nucleotides in length. In some embodiments, the ASO is no more than 24 nucleotides in length. In some embodiments, the ASO is no more than 26 nucleotides in length. In some embodiments, the ASO is no more than 28 nucleotides in length. In some embodiments, the ASO is no more than 30 nucleotides in length.

[0098] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of a target protein, wherein the oligonucleotide comprises an ASO about 12-30 nucleosides in length and comprising a nucleoside sequence complementary to about 12-30 contiguous nucleosides of a full-length human pre-mRNA target sequence encoding the target protein; wherein (i) the oligonucleotide comprises a modification comprising a modified nucleoside and/or a modified internucleoside linkage, and/or (ii) the composition comprises a pharmaceutically acceptable carrier.

[0099] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of a target protein, wherein the oligonucleotide comprises an ASO about 12-30 nucleosides in length and comprising a nucleoside sequence complementary to about 12-30 contiguous nucleosides of a full-length human target mRNA sequence encoding the target protein; wherein (i) the oligonucleotide comprises a modification comprising a modified nucleoside and/or a modified internucleoside linkage, and/or (ii) the composition comprises a pharmaceutically acceptable carrier.

1. Oligonucleotide modification patterns

[00100] In some embodiments, the composition comprises an oligonucleotide that binds to a target oligonucleotide, wherein the oligonucleotide comprises a modification comprising a modified nucleoside and/or a modified internucleoside linkage, and/or (ii) the composition comprises a pharmaceutically acceptable carrier. In some embodiments, the oligonucleotide comprises a modification comprising a modified nucleoside and/or a modified internucleoside linkage. In some embodiments, the oligonucleotide comprises a modified internucleoside linkage. In some embodiments, the modified internucleoside linkage comprises alkylphosphonate, phosphorothioate, methylphosphonate, phosphorodithioate, alkylphosphonothioate, phosphoramidate, carbamate, carbonate, phosphate triester, acetamidate, or carboxymethyl ester, or a combination thereof. In some embodiments, the modified internucleoside linkage comprises one or more phosphorothioate linkages. Benefits of the modified internucleoside linkage may include decreased toxicity or improved pharmacokinetics.

[00101] In some embodiments, the composition comprises an oligonucleotide that binds to a target oligonucleotide, wherein the oligonucleotide comprises a modified internucleoside linkage, wherein the oligonucleotide comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 modified internucleoside linkages, or a range of modified internucleoside linkages defined by any two of the aforementioned numbers. In some embodiments, the oligonucleotide comprises no more than 18 modified internucleoside linkages. In some embodiments, the oligonucleotide comprises no more than 20 modified internucleoside linkages. In some embodiments, the oligonucleotide comprises 2 or more modified internucleoside linkages, 3 or more modified internucleoside linkages, 4 or more modified internucleoside linkages, 5 or more modified internucleoside linkages, 6 or more modified internucleoside linkages, 7 or more modified internucleoside linkages, 8 or more modified internucleoside linkages, 9 or more modified internucleoside linkages, 10 or more modified internucleoside linkages, 11 or more modified internucleoside linkages, 12 or more modified internucleoside linkages, 13 or more modified internucleoside linkages, 14 or more modified internucleoside linkages, 15 or more modified internucleoside linkages, 16 or more modified internucleoside linkages, 17 or more modified

internucleoside linkages, 18 or more modified internucleoside linkages, 19 or more modified internucleoside linkages, or 20 or more modified internucleoside linkages.

[00102] In some embodiments, the composition comprises an oligonucleotide that binds to a target oligonucleotide, wherein the oligonucleotide comprises the modified nucleoside. In some embodiments, the modified nucleoside comprises a locked nucleic acid (LNA), hexitol nucleic acid (HLA), cyclohexene nucleic acid (CeNA), 2'- methoxyethyl, 2'-O-alkyl, 2'-O-allyl, 2'-fluoro, or 2'-deoxy, or a combination thereof. In some embodiments, the modified nucleoside comprises a LNA. In some embodiments, the **modified nucleoside comprises a 2',4' constrained ethyl nucleic acid. In some embodiments, the modified** nucleoside comprises HLA. In some embodiments, the modified nucleoside comprises CeNA. In some embodiments, the modified nucleoside comprises a 2'- methoxyethyl group. In some embodiments, the modified nucleoside comprises a 2'-O-alkyl group. In some embodiments, the modified nucleoside comprises a 2'-O-allyl group. In some embodiments, the modified nucleoside comprises a 2'-fluoro group. In some embodiments, the modified nucleoside comprises a 2'-deoxy group. In some embodiments, the modified nucleoside comprises a 2'-O-methyl nucleoside, 2'-deoxyfluoro nucleoside, 2'-O-N-methylacetamido (2'-O-NMA) nucleoside, a 2'-O- dimethylaminoethoxyethyl (2'-O-DMAEOE) nucleoside, 2'-O-aminopropyl (2'-O-AP) nucleoside, or 2'-ara-F, or a combination thereof. In some embodiments, the modified nucleoside comprises a 2'-O-methyl nucleoside. In some embodiments, the modified nucleoside comprises a 2'-deoxyfluoro nucleoside. In some embodiments, the modified nucleoside comprises a 2'-O-NMA nucleoside. In some embodiments, the modified nucleoside comprises a 2'-O-DMAEOE nucleoside. In some embodiments, the modified nucleoside comprises a 2'-O-aminopropyl (2'-O-AP) nucleoside. In some embodiments, the modified nucleoside comprises 2'-ara-F. In **some embodiments, the modified nucleoside comprises one or more 2'fluoro** modified nucleosides. In some embodiments, the modified nucleoside comprises a 2' O-alkyl modified nucleoside. Benefits of the modified nucleoside may include decreased toxicity or improved pharmacokinetics.

[00103] In some embodiments, the oligonucleotide comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or 21 modified nucleosides, or a range of nucleosides defined by any two of the aforementioned numbers. In some embodiments, the oligonucleotide comprises no more than 19 modified nucleosides. In some embodiments, the oligonucleotide comprises no more than 21 modified nucleosides. In some embodiments, the oligonucleotide comprises 2 or more modified nucleosides, 3 or more modified nucleosides, 4 or more modified nucleosides, 5 or more modified nucleosides, 6 or more modified nucleosides, 7 or more modified nucleosides, 8 or more modified nucleosides, 9 or more modified nucleosides, 10 or more modified nucleosides, 11 or more modified nucleosides, 12 or more modified nucleosides, 13 or more modified nucleosides, 14 or more modified nucleosides, 15 or more modified nucleosides, 16 or more modified nucleosides, 17 or more modified nucleosides, 18 or more modified nucleosides, 19 or more modified nucleosides, 20 or more modified nucleosides, or 21 or more modified nucleosides.

[00104] In some embodiments, the composition comprises an oligonucleotide that binds to a target oligonucleotide**, wherein the oligonucleotide comprises a lipid attached at a 3' or 5' terminus of the**

oligonucleotide. In some embodiments, the lipid comprises cholesterol, myristoyl, palmitoyl, stearoyl, lithocholoyl, docosanoyl, docosahexaenoyl, myristyl, palmityl stearyl, or α-tocopherol, or a combination thereof.

[00105] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of a target mRNA, wherein the oligonucleotide comprises a sugar moiety. The sugar moiety may include an N-acetyl galactose moiety (e.g. an N-acetylgalactosamine (GalNAc) moiety), an N-acetyl glucose moiety (e.g. an N-acetylglucosamine (GlcNAc) moiety), a fucose moiety, or a mannose moiety. The sugar moiety may include 1, 2, 3, or more sugar molecules. The sugar moiety may be attached at a 3' or 5' terminus of the oligonucleotide. The sugar moiety may include an N-acetyl galactose moiety. The sugar moiety may include an N-acetylgalactosamine (GalNAc) moiety. The sugar moiety may include an N-acetyl glucose moiety. The sugar moiety may include N-acetylglucosamine (GlcNAc) moiety. The sugar moiety may include a fucose moiety. The sugar moiety may include a mannose moiety. N-acetyl glucose, GlcNAc, fucose, or mannose may be useful for targeting macrophages since they may target or bind a mannose receptor such as CD206.

[00106] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of a target mRNA, wherein the oligonucleotide comprises an N-acetylgalactosamine (GalNAc) moiety. GalNAc may be useful for hepatocyte targeting. In some embodiments, the composition comprises GalNAc. In some embodiments, the composition comprises a GalNAc derivative. The GalNAc moiety may include 1, 2, 3, or more GalNAc molecules. The GalNAc moiety may include a bivalent or trivalent branched linker. The oligo may be attached to 1, 2 or 3 GalNAcs through a bivalent or trivalent branched linker. The GalNAc moiety may be attached at a 3' or 5' terminus of the oligonucleotide.

[00107] The oligonucleotide may include purines. Examples of purines include adenine (A) or guanine (G), or modified versions thereof. The oligonucleotide may include pyrimidines. Examples of pyrimidines include cytosine (C), thymine (T), or uracil (U), or modified versions thereof.

[00108] In some embodiments, purines of the oligonucleotide comprise 2' fluoro modified purines. In some embodiments, purines of the oligonucleotide comprise 2'-O-methyl modified purines. In some embodiments, purines of the oligonucleotide comprise a mixture of 2' fluoro and 2'-O-methyl modified purines. In some embodiments, all purines of the oligonucleotide comprise 2' fluoro modified purines. In some embodiments, all purines of the oligonucleotide comprise 2'-O-methyl modified purines. In some embodiments, all purines of the oligonucleotide comprise a mixture of 2' fluoro and 2'-O-methyl modified purines. In some embodiments, 2'-O-methyl includes 2' O-methyl.

[00109] In some embodiments, pyrimidines of the oligonucleotide comprise 2' fluoro modified pyrimidines. In some embodiments, pyrimidines of the oligonucleotide comprise 2'-O-methyl modified pyrimidines. In some embodiments, pyrimidines of the oligonucleotide comprise a mixture of 2' fluoro and 2'-O-methyl modified pyrimidines. In some embodiments, all pyrimidines of the oligonucleotide comprise 2' fluoro modified pyrimidines. In some embodiments, all pyrimidines of the oligonucleotide comprise 2'-O-methyl modified pyrimidines. In some embodiments, all pyrimidines of the oligonucleotide comprise a mixture of 2' fluoro and 2'-O-methyl modified pyrimidines.

[00110] In some embodiments, purines of the oligonucleotide comprise 2' fluoro modified purines, and pyrimidines of the oligonucleotide comprise a mixture of 2' fluoro and 2'-O-methyl modified pyrimidines. In some embodiments, purines of the oligonucleotide comprise 2'-O-methyl modified purines, and pyrimidines of the oligonucleotide comprise a mixture of 2' fluoro and 2'-O-methyl modified pyrimidines. In some embodiments, purines of the oligonucleotide comprise 2' fluoro modified purines, and pyrimidines of the oligonucleotide comprise 2'-O-methyl modified pyrimidines. In some embodiments, purines of the oligonucleotide comprise 2'-O-methyl modified purines, and pyrimidines of the oligonucleotide comprise 2' fluoro modified pyrimidines. In some embodiments, pyrimidines of the oligonucleotide comprise 2' fluoro modified pyrimidines, and purines of the oligonucleotide comprise a mixture of 2' fluoro and 2'-O-methyl modified purines. In some embodiments, pyrimidines of the oligonucleotide comprise 2'-O-methyl modified pyrimidines, and purines of the oligonucleotide comprise a mixture of 2' fluoro and 2'-O-methyl modified purines. In some embodiments, pyrimidines of the oligonucleotide comprise 2' fluoro modified pyrimidines, and purines of the oligonucleotide comprise 2'-O-methyl modified purines. In some embodiments, pyrimidines of the oligonucleotide comprise 2'-O-methyl modified pyrimidines, and purines of the oligonucleotide comprise 2' fluoro modified purines.

[00111] In some embodiments, all purines of the oligonucleotide comprise 2' fluoro modified purines, and all pyrimidines of the oligonucleotide comprise a mixture of 2' fluoro and 2'-O-methyl modified pyrimidines. In some embodiments, all purines of the oligonucleotide comprise 2'-O-methyl modified purines, and all pyrimidines of the oligonucleotide comprise a mixture of 2' fluoro and 2'-O-methyl modified pyrimidines. In some embodiments, all purines of the oligonucleotide comprise 2' fluoro modified purines, and all pyrimidines of the oligonucleotide comprise 2'-O-methyl modified pyrimidines. In some embodiments, all pyrimidines of the oligonucleotide comprise 2' fluoro modified pyrimidines. In some embodiments, all pyrimidines of the oligonucleotide comprise 2' fluoro modified pyrimidines, and all purines of the oligonucleotide comprise a mixture of 2' fluoro and 2'-O-methyl modified purines. In some embodiments, all pyrimidines of the oligonucleotide comprise 2'-O-methyl modified pyrimidines, and all purines of the oligonucleotide comprise a mixture of 2' fluoro and 2'-O-methyl modified purines. In some embodiments, all pyrimidines of the oligonucleotide comprise 2' fluoro modified pyrimidines, and all purines of the oligonucleotide comprise 2'-O-methyl modified purines. In some embodiments, all pyrimidines of the oligonucleotide comprise 2'-O-methyl modified pyrimidines, and all purines of the oligonucleotide comprise 2' fluoro modified purines.

2. siRNA modification patterns

[00112] In some embodiments, the sense strand comprises 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, or 29 modified internucleoside linkages, or a range of modified internucleoside linkages defined by any two of the aforementioned integers. In some embodiments, the sense strand comprises 1-11 modified internucleoside linkages. In some embodiments, the sense strand comprises 2-6 modified internucleoside linkages. In some embodiments, the sense strand

comprises 5 modified internucleoside linkages. In some embodiments, the sense strand comprises 4 modified internucleoside linkages.

[00113] In some embodiments, the antisense strand comprises 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, or 29 modified internucleoside linkages, or a range of modified internucleoside linkages defined by any two of the aforementioned integers. In some embodiments, the antisense strand comprises 1-11 modified internucleoside linkages. In some embodiments, the antisense strand comprises 2-6 modified internucleoside linkages. In some embodiments, the antisense strand comprises 5 modified internucleoside linkages. In some embodiments, the antisense strand comprises 4 modified internucleoside linkages.

[00114] In some embodiments, the sense strand comprises 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 modified nucleosides, or a range of modified nucleosides defined by any two of the aforementioned integers. In some embodiments, the sense strand comprises 12-19 modified nucleosides. In some embodiments, the sense strand comprises 12-21 modified nucleosides. In some embodiments, the sense strand comprises 19 modified nucleosides. In some embodiments, the sense strand comprises 21 modified nucleosides.

[00115] In some embodiments, the antisense strand comprises 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 modified nucleosides, or a range of modified nucleosides defined by any two of the aforementioned integers. In some embodiments, the antisense strand comprises 12-19 modified nucleosides. In some embodiments, the antisense strand comprises 12-21 modified nucleosides. In some embodiments, the antisense strand comprises 19 modified nucleosides. In some embodiments, the antisense strand comprises 21 modified nucleosides.

[00116] In some embodiments, the sense strand or the antisense strand further comprises at least 2 **additional nucleosides attached to a 3' terminus of the sense strand or the antisense strand. In some** embodiments, the sense strand **or the antisense strand comprises 2 additional nucleosides attached to a 3'** terminus of the sense strand or the antisense strand. As part of the sense strand, the additional nucleosides may or may not be complementary to a target mRNA. The additional nucleosides of the antisense strand may include a uracil. The 2 additional nucleosides of the antisense strand may both include uracil.

[00117] In some embodiments, the sense strand or the sense strand further comprises at least 2 additional nucleosides attached to a **3' terminus of the sense strand or the sense strand. In some embodiments, the sense strand or the sense strand comprises 2 additional nucleosides attached to a 3' terminus of the sense** strand or the sense strand. The additional nucleosides of the sense strand may include a uracil. The 2 additional nucleosides of the sense strand may both include uracil.

[00118] In some embodiments, the composition comprises an oligonucleotide that binds to a target oligonucleotide, wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, wherein the sense strand comprises a modification pattern. In some embodiments, the **sense strand comprises modification pattern 1S:** 5'-NfsnsNfnNfnNfNfNfnNfnNfnNfnNfnNfsnsn-3', **wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a** phosphorothioate linkage. In some embodiments, the sense strand comprises modification pattern 1S#2:

5'-NfnNfnNfnNfNfNfnNfnNfnNfnNfnNfsnsn-3', wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments, the sense strand comprises modification pattern 2S: 5'-nsnsnnNfnNfNfNfnnnnnnnnnnsnsn-3' , wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments, the sense strand comprises modification pattern 2S#2: 5'-nnnnNfnNfNfNfnnnnnnnnnnsnsn-3', wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments, the sense strand comprises modification pattern 3S: 5'-nsnsnnNfnNfnNfnnnnnnnnnnsnsn-3' , wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments, the sense strand comprises modification pattern 3S#2: 5'-nnnnNfnNfnNfnnnnnnnnnnsnsn-3', wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments, the sense strand comprises modification pattern 4S: 5'-NfsnsNfnNfnNfNfNfnNfnNfnNfnNfnNfsnsnN-3', wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, "s" is a phosphorothioate linkage, and N comprises one or more nucleosides. In some embodiments, the sense strand comprises modification pattern 4S#2: 5'-NfnNfnNfnNfNfNfnNfnNfnNfnNfnNfsnsnN-3', wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, "s" is a phosphorothioate linkage, and N comprises one or more nucleosides. In some embodiments, the sense strand comprises modification pattern 5S: 5'-nsnsnnNfnNfNfNfnnnnnnnnnnsnsnN-3', wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, "s" is a phosphorothioate linkage, and N comprises one or more nucleosides. In some embodiments, the sense strand comprises modification pattern 5S#2: 5'-nnnnNfnNfNfNfnnnnnnnnnnsnsnN-3', wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, "s" is a phosphorothioate linkage, and N comprises one or more nucleosides. In some embodiments, the sense strand comprises modification pattern 6S: 5'-NfsnsNfnNfnNfnNfnNfnNfnNfnNfnNfsnsn-3', wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, "s" is a phosphorothioate linkage, and N comprises one or more nucleosides. In some embodiments, the sense strand comprises modification pattern 6S#2: 5'-NfnNfnNfnNfnNfnNfnNfnNfnNfnNfsnsn-3', wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, "s" is a phosphorothioate linkage, and N comprises one or more nucleosides. In some embodiments, the sense strand comprises any one of modification patterns 1S, 2S, 3S, 4S, 5S, or 6S. In some embodiments, the sense strand comprises any one of modification patterns 1S#2, 2S#2, 3S#2, 4S#2, 5S#2, or 6S#2. In some embodiments, the sense strand comprises any one of modification patterns 1S, 3S, 4S, or 6S. In some embodiments, the sense strand comprises any one of modification patterns 1S#2, 3S#2, 4S#2, or 6S#2. Any one of modification patterns 1S-6S may include a GalNAc ligand attached to the 3' end. Any one of modification patterns 1S-6S may include a GalNAc ligand attached to the 5' end. Any one of modification patterns 1S-6S#2 may include a GalNAc ligand attached to the 3' end. Any one of modification patterns 1S-6S#2 may include a GalNAc ligand attached to the 5' end.

[00119] In some embodiments, the composition comprises an oligonucleotide that binds to a target oligonucleotide, wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, wherein the antisense strand comprises a modification pattern. In some embodiments, the antisense strand comprises **modification pattern 1AS: 5'-nsNfsnNfnNfnNfnNfnnnNfnNfnNfnsnsn-3', wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a** phosphorothioate linkage. In some embodiments, the antisense strand comprises modification pattern **2AS: 5'-nsNfsnnnNfnNfNfnnnnNfnNfnnnsnsn-3', wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments, the** antisense **strand comprises modification pattern 3AS: 5'-nsNfsnnnNfnnnnnnnNfnNfnnnsnsn-3', wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a** phosphorothioate linkage. In some embodiments, the antisense strand comprises modification pattern **4AS: 5'-nsNfsnNfnNfnnnnnnnNfnNfnnnsnsn-3', wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage.** In some embodiments, the antisense strand comprises modi**fication pattern 5AS: 5'-nsNfsnnnNfnNfnnnnnNfnNfnnnsnsn-3', wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a** phosphorothioate linkage. In some embodiments, the antisense strand comprises modification pattern **6AS: 5'-nsNfsnNfnNfnNfnNfnNfnNfnNfnNfnsnsn-3', wherein "Nf" is a 2' fluoro-**modified nucleoside, **"n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments,** the antisense strand comprises modification pattern **7AS: 5'-nsNfsnNfnNfnNfNfnnnnNfnNfnnnsnsn-3', wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a** phosphorothioate linkage. In some embodiments, the antisense strand comprises modification pattern **8AS: 5'-nsNfsnnnnnnnnnnnNfnnnnnsnsn-3', wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments, the antisense strand comprises modification pattern 9AS: 5'-nsNfsnnnNfnnnnnnnNfnNfnNfnsnsn-3', wherein "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate** linkage. Any one of modification patterns 1AS-**9AS may include a GalNAc ligand attached to the 3' end.** Any one of modification patterns 1AS-**9AS may include a GalNAc ligand attached to the 5' end.**

[00120] The modifications in any of the modification patterns may be optional. For example, 1, 2, 3, or more phosphorothioate linkages in any of modification patterns 1S-6S, 1S#2-6S#2, or 1AS-9AS may be replaced with an unmodified linkage, or with a different modified linkage. In some cases, 1, 2, 3, or more modified nucleosides in any of modification patterns 1S-6S or 1AS-9AS may be replaced with an unmodified nucleoside, or with a different modified nucleoside.

[00121] In some embodiments, the composition comprises an oligonucleotide that inhibits the expression of a target mRNA wherein the oligonucleotide comprises an siRNA comprising a sense strand and an antisense strand, wherein the sense strand comprises modification pattern 1S and the antisense strand comprises modification pattern 1AS, 2AS, 3AS, 4AS, 5AS, 6AS, 7AS, 8AS, or 9AS. In some embodiments, the sense strand comprises modification pattern 2S and the antisense strand comprises modification pattern 1AS, 2AS, 3AS, 4AS, 5AS, 6AS, 7AS, 8AS, or 9AS. In some embodiments, the

sense strand comprises modification pattern 3S and the antisense strand comprises modification pattern 1AS, 2AS, 3AS, 4AS, 5AS, 6AS, 7AS, 8AS, or 9AS. In some embodiments, the sense strand comprises modification pattern 4S and the antisense strand comprises modification pattern 1AS, 2AS, 3AS, 4AS, 5AS, 6AS, 7AS, 8AS, or 9AS. In some embodiments, the sense strand comprises modification pattern 5S and the antisense strand comprises modification pattern 1AS, 2AS, 3AS, 4AS, 5AS, 6AS, 7AS, 8AS, or 9AS. In some embodiments, the sense strand comprises modification pattern 6S and the antisense strand comprises modification pattern 1AS, 2AS, 3AS, 4AS, 5AS, 6AS, 7AS, 8AS, or 9AS. In some embodiments, the sense strand comprises modification pattern 1AS, 2AS, 3AS, 4AS, 5AS, 6AS, 7AS, 8AS, or 9AS. In some embodiments, the sense strand comprises modification pattern 1S#2 and the antisense strand comprises modification pattern 1AS, 2AS, 3AS, 4AS, 5AS, 6AS, 7AS, 8AS, or 9AS. In some embodiments, the sense strand comprises modification pattern 2S#2 and the antisense strand comprises modification pattern 1AS, 2AS, 3AS, 4AS, 5AS, 6AS, 7AS, 8AS, or 9AS. In some embodiments, the sense strand comprises modification pattern 3S#2 and the antisense strand comprises modification pattern 1AS, 2AS, 3AS, 4AS, 5AS, 6AS, 7AS, 8AS, or 9AS. In some embodiments, the sense strand comprises modification pattern 4S#2 and the antisense strand comprises modification pattern 1AS, 2AS, 3AS, 4AS, 5AS, 6AS, 7AS, 8AS, or 9AS. In some embodiments, the sense strand comprises modification pattern 5S#2 and the antisense strand comprises modification pattern 1AS, 2AS, 3AS, 4AS, 5AS, 6AS, 7AS, 8AS, or 9AS. In some embodiments, the sense strand comprises modification pattern 6S#2 and the antisense strand comprises modification pattern 1AS, 2AS, 3AS, 4AS, 5AS, 6AS, 7AS, 8AS, or 9AS. In some embodiments, the antisense strand comprises modification pattern 1AS, 2AS, 3AS, 4AS, 5AS, 6AS, 7AS, 8AS, or 9AS. In some embodiments, the sense strand or the antisense strand comprises modification pattern ASO1.

[00122] Any combination of sense and antisense modification patterns may be used. In some embodiments, the sense strand comprises modification pattern 1S, and the antisense strand comprises modification pattern 1AS. In some embodiments, the sense strand comprises modification pattern 2S, and the antisense strand comprises modification pattern 2AS. In some embodiments, the sense strand comprises modification pattern 2S, and the antisense strand comprises modification pattern 3AS. In some embodiments, the sense strand comprises modification pattern 3S, and the antisense strand comprises modification pattern 1AS. In some embodiments, the sense strand comprises modification pattern 3S, and the antisense strand comprises modification pattern 4AS. In some embodiments, the sense strand comprises modification pattern 3S, and the antisense strand comprises modification pattern 5AS. In some embodiments, the sense strand comprises modification pattern 3S, and the antisense strand comprises modification pattern 6AS. In some embodiments, the sense strand comprises modification pattern 3S, and the antisense strand comprises modification pattern 7AS. In some embodiments, the sense strand comprises modification pattern 3S, and the antisense strand comprises modification pattern 8AS. In some embodiments, the sense strand comprises modification pattern 6S, and the antisense strand comprises modification pattern 1AS. In some embodiments, the sense strand comprises modification pattern 6S, and the antisense strand comprises modification pattern 4AS. In some embodiments, the sense strand

comprises modification pattern 6S, and the antisense strand comprises modification pattern 5AS. In some embodiments, the sense strand comprises modification pattern 6S, and the antisense strand comprises modification pattern 6AS. In some embodiments, the sense strand comprises modification pattern 6S, and the antisense strand comprises modification pattern 7AS. In some embodiments, the sense strand comprises modification pattern 6S, and the antisense strand comprises modification pattern 8AS. In some embodiments, the sense strand comprises modification pattern 1S#2, and the antisense strand comprises modification pattern 1AS. In some embodiments, the sense strand comprises modification pattern 2S#2, and the antisense strand comprises modification pattern 2AS. In some embodiments, the sense strand comprises modification pattern 2S#2, and the antisense strand comprises modification pattern 3AS. In some embodiments, the sense strand comprises modification pattern 3S#2, and the antisense strand comprises modification pattern 1AS. In some embodiments, the sense strand comprises modification pattern 3S#2, and the antisense strand comprises modification pattern 4AS. In some embodiments, the sense strand comprises modification pattern 3S#2, and the antisense strand comprises modification pattern 5AS. In some embodiments, the sense strand comprises modification pattern 3S#2, and the antisense strand comprises modification pattern 6AS. In some embodiments, the sense strand comprises modification pattern 3S#2, and the antisense strand comprises modification pattern 7AS. In some embodiments, the sense strand comprises modification pattern 3S#2, and the antisense strand comprises modification pattern 8AS. In some embodiments, the sense strand comprises modification pattern 6S#2, and the antisense strand comprises modification pattern 1AS. In some embodiments, the sense strand comprises modification pattern 6S#2, and the antisense strand comprises modification pattern 4AS. In some embodiments, the sense strand comprises modification pattern 6S#2, and the antisense strand comprises modification pattern 5AS. In some embodiments, the sense strand comprises modification pattern 6S#2, and the antisense strand comprises modification pattern 6AS. In some embodiments, the sense strand comprises modification pattern 6S#2, and the antisense strand comprises modification pattern 7AS. In some embodiments, the sense strand comprises modification pattern 6S#2, and the antisense strand comprises modification pattern 8AS.

[00123] In some embodiments, purines of the sense strand comprise 2' fluoro modified purines. In some embodiments, purines of the sense strand comprise 2'-O-methyl modified purines. In some embodiments, purines of the sense strand comprise **a mixture of 2' fluoro and** 2'-O-methyl modified purines. In some **embodiments, all purines of the sense strand comprise 2' fluoro modified purines. In some embodiments,** all **purines of the sense strand comprise** 2'-O-methyl modified purines. In some embodiments, all purines **of the sense strand comprise a mixture of 2' fluoro and** 2'-O-methyl modified purines.

[00124] In some embodiments, pyrimidines of the sense strand comprise 2' fluoro modified pyrimidines. In some embodiments, pyrimidines of the sense strand **comprise** 2'-O-methyl modified pyrimidines. In **some embodiments, pyrimidines of the sense strand comprise a mixture of 2' fluoro and** 2'-O-methyl **modified pyrimidines. In some embodiments, all pyrimidines of the sense strand comprise** 2' fluoro modified pyrimidines. **In some embodiments, all pyrimidines of the sense strand comprise** 2'-O-methyl

modified pyrimidines. In some embodiments, all pyrimidines of the sense strand comprise a mixture of 2' fluoro and 2'-O-methyl modified pyrimidines.

[00125] In some embodiments, purines of the sense strand comprise 2' fluoro modified purines, and pyrimidines of the sense strand comprise a mixture of 2' fluoro and 2'-O-methyl modified pyrimidines. In some embodiments, purines of the sense strand comprise 2'-O-methyl modified purines, and pyrimidines of the sense strand comprise a mixture of 2' fluoro and 2'-O-methyl modified pyrimidines. In some embodiments, purines of the sense strand comprise 2' fluoro modified purines, and pyrimidines of the sense strand comprise 2'-O-methyl modified pyrimidines. In some embodiments, purines of the sense strand comprise 2'-O-methyl modified purines, and pyrimidines of the sense strand comprise 2' fluoro modified pyrimidines. In some embodiments, pyrimidines of the sense strand comprise 2' fluoro modified pyrimidines, and purines of the sense strand comprise a mixture of 2' fluoro and 2'-O-methyl modified purines. In some embodiments, pyrimidines of the sense strand comprise 2'-O-methyl modified pyrimidines, and purines of the sense strand comprise a mixture of 2' fluoro and 2'-O-methyl modified purines. In some embodiments, pyrimidines of the sense strand comprise 2' fluoro modified pyrimidines, and purines of the sense strand comprise 2'-O-methyl modified purines. In some embodiments, pyrimidines of the sense strand comprise 2'-O-methyl modified pyrimidines, and purines of the sense strand comprise 2' fluoro modified purines.

[00126] In some embodiments, all purines of the sense strand comprise 2' fluoro modified purines, and all pyrimidines of the sense strand comprise a mixture of 2' fluoro and 2'-O-methyl modified pyrimidines. In some embodiments, all purines of the sense strand comprise 2'-O-methyl modified purines, and all pyrimidines of the sense strand comprise a mixture of 2' fluoro and 2'-O-methyl modified pyrimidines. In some embodiments, all purines of the sense strand comprise 2' fluoro modified purines, and all pyrimidines of the sense strand comprise 2'-O-methyl modified pyrimidines. In some embodiments, all purines of the sense strand comprise 2'-O-methyl modified purines, and all pyrimidines of the sense strand comprise 2' fluoro modified pyrimidines. In some embodiments, all pyrimidines of the sense strand comprise 2' fluoro modified pyrimidines, and all purines of the sense strand comprise a mixture of 2' fluoro and 2'-O-methyl modified purines. In some embodiments, all pyrimidines of the sense strand comprise 2'-O-methyl modified pyrimidines, and all purines of the sense strand comprise a mixture of 2' fluoro and 2'-O-methyl modified purines. In some embodiments, all pyrimidines of the sense strand comprise 2' fluoro modified pyrimidines, and all purines of the sense strand comprise 2'-O-methyl modified purines. In some embodiments, all pyrimidines of the sense strand comprise 2'-O-methyl modified pyrimidines, and all purines of the sense strand comprise 2' fluoro modified purines.

[00127] In some embodiments, purines of the antisense strand comprise 2' fluoro modified purines. In some embodiments, purines of the antisense strand comprise 2'-O-methyl modified purines. In some embodiments, purines of the antisense strand comprise a mixture of 2' fluoro and 2'-O-methyl modified purines. In some embodiments, all purines of the antisense strand comprise 2' fluoro modified purines. In some embodiments, all purines of the antisense strand comprise 2'-O-methyl modified purines. In some

embodiments, all purines of the antisense strand comprise a mixture of 2' fluoro and 2'-O-methyl modified purines.

[00128] In some embodiments, pyrimidines of the antisense strand comprise 2' fluoro modified pyrimidines. In some embodiments, pyrimidines of the antisense strand comprise 2'-O-methyl modified pyrimidines. In some embodiments, pyrimidines of the antisense strand comprise a mixture of 2' fluoro and 2'-O-methyl modified pyrimidines. In some embodiments, all pyrimidines of the antisense strand comprise 2' fluoro modified pyrimidines. In some embodiments, all pyrimidines of the antisense strand comprise 2'-O-methyl modified pyrimidines. In some embodiments, all pyrimidines of the antisense strand comprise a mixture of 2' fluoro and 2'-O-methyl modified pyrimidines.

[00129] In some embodiments, purines of the antisense strand comprise 2' fluoro modified purines, and pyrimidines of the antisense strand comprise a mixture of 2' fluoro and 2'-O-methyl modified pyrimidines. In some embodiments, purines of the antisense strand comprise 2'-O-methyl modified purines, and pyrimidines of the antisense strand comprise a mixture of 2' fluoro and 2'-O-methyl modified pyrimidines. In some embodiments, purines of the antisense strand comprise 2' fluoro modified purines, and pyrimidines of the antisense strand comprise 2'-O-methyl modified pyrimidines. In some embodiments, purines of the antisense strand comprise 2'-O-methyl modified purines, and pyrimidines of the antisense strand comprise 2' fluoro modified pyrimidines. In some embodiments, pyrimidines of the antisense strand comprise 2' fluoro modified pyrimidines, and purines of the antisense strand comprise a mixture of 2' fluoro and 2'-O-methyl modified purines. In some embodiments, pyrimidines of the antisense strand comprise 2'-O-methyl modified pyrimidines, and purines of the antisense strand comprise a mixture of 2' fluoro and 2'-O-methyl modified purines. In some embodiments, pyrimidines of the antisense strand comprise 2' fluoro modified pyrimidines, and purines of the antisense strand comprise 2'-O-methyl modified purines. In some embodiments, pyrimidines of the antisense strand comprise 2'-O-methyl modified pyrimidines, and purines of the antisense strand comprise 2' fluoro modified purines.

[00130] In some embodiments, all purines of the antisense strand comprise 2' fluoro modified purines, and all pyrimidines of the antisense strand comprise a mixture of 2' fluoro and 2'-O-methyl modified pyrimidines. In some embodiments, all purines of the antisense strand comprise 2'-O-methyl modified purines, and all pyrimidines of the antisense strand comprise a mixture of 2' fluoro and 2'-O-methyl modified pyrimidines. In some embodiments, all purines of the antisense strand comprise 2' fluoro modified purines, and all pyrimidines of the antisense strand comprise 2'-O-methyl modified pyrimidines. In some embodiments, all purines of the antisense strand comprise 2'-O-methyl modified purines, and all pyrimidines of the antisense strand comprise 2' fluoro modified pyrimidines. In some embodiments, all pyrimidines of the antisense strand comprise 2' fluoro modified pyrimidines, and all purines of the antisense strand comprise a mixture of 2' fluoro and 2'-O-methyl modified purines. In some embodiments, all pyrimidines of the antisense strand comprise 2'-O-methyl modified pyrimidines, and all purines of the antisense strand comprise a mixture of 2' fluoro and 2'-O-methyl modified purines. In some embodiments, all pyrimidines of the antisense strand comprise 2' fluoro modified pyrimidines, and all purines of the antisense strand comprise 2'-O-methyl modified purines. In some embodiments, all

pyrimidines of the antisense strand comprise 2'-O-methyl modified pyrimidines, and all purines of the antisense strand comprise 2' fluoro modified purines.

[00131] In some cases, the oligonucleotide comprises a particular modification pattern. In some embodiments, position 9 counting from the 5' end of the of a strand of the oligonucleotide may have a 2'F modification. In some embodiments, when position 9 of a strand of the oligonucleotide is a pyrimidine, then all purines in a strand of the oligonucleotide have a 2'OMe modification. In some embodiments, when position 9 is the only pyrimidine between positions 5 and 11 of the sense stand, then position 9 is the only position with a 2'F modification in a strand of the oligonucleotide. In some embodiments, when position 9 and only one other base between positions 5 and 11 of a strand of the oligonucleotide are pyrimidines, then both of these pyrimidines are the only two positions with a 2'F modification in a strand of the oligonucleotide. In some embodiments, when position 9 and only two other bases between positions 5 and 11 of a strand of the oligonucleotide are pyrimidines, and those two other pyrimidines are in adjacent positions so that there would be not three 2'F modifications in a row, then any combination of 2'F modifications can be made that give three 2'F modifications in total. In some embodiments, when there are more than 2 pyrimidines between positions 5 and 11 of a strand of the oligonucleotide, then all combinations of pyrimidines having the 2'F modification are allowed that have three to five 2'F modifications in total, provided that a strand of the oligonucleotide does not have three 2'F modifications in a row. In some cases, a strand of the oligonucleotide of any of the siRNAs comprises a modification pattern which conforms to any or all of these a strand of the oligonucleotide rules.

[00132] In some embodiments, when position 9 of a strand of the oligonucleotide is a purine, then all purines in a strand of the oligonucleotide have a 2'OMe modification. In some embodiments, when position 9 is the only purine between positions 5 and 11 of the sense stand, then position 9 is the only position with a 2'F modification in a strand of the oligonucleotide. In some embodiments, when position 9 and only one other base between positions 5 and 11 of a strand of the oligonucleotide are purines, then both of these purines are the only two positions with a 2'F modification in a strand of the oligonucleotide. In some embodiments, when position 9 and only two other bases between positions 5 and 11 of a strand of the oligonucleotide are purines, and those two other purines are in adjacent positions so that there would be not three 2'F modifications in a row, then any combination of 2'F modifications can be made that give three 2'F modifications in total. In some embodiments, when there are more than 2 purines between positions 5 and 11 of a strand of the oligonucleotide, then all combinations of purines having the 2'F modification are allowed that have three to five 2'F modifications in total, provided that a strand of the oligonucleotide does not have three 2'F modifications in a row. In some cases, a strand of the oligonucleotide of any of the siRNAs comprises a modification pattern which conforms to any or all of these a strand of the oligonucleotide rules.

[00133] In some cases, position 9 of a strand of the oligonucleotide can be a 2'deoxy. In these cases, 2'F and 2'OMe modifications may occur at the other positions of a strand of the oligonucleotide. In some cases, a strand of the oligonucleotide of any of the siRNAs comprises a modification pattern which conforms to these a strand of the oligonucleotide rules.

[00134] In some embodiments, position nine of the sense strand comprises a 2' fluoro-modified pyrimidine. In some embodiments, all purines of the sense strand comprise 2'-O-methyl modified purines. In some embodiments, 1, 2, 3, 4, or 5 pyrimidines between positions 5 and 11 comprise a 2'flouro-modified pyrimidine, provided there are not three 2' fluoro-modified pyrimidines in a row. In some embodiments, the odd-numbered positions of the antisense strand comprise 2'-O-methyl modified nucleotides. In some embodiments, the even-numbered positions of the antisense strand comprise 2'flouro-modified nucleotides and unmodified deoxyribonucleotide. In some embodiments, the even-numbered positions of the antisense strand comprise 2'flouro-modified nucleotides, 2'-O-methyl modified nucleotides and unmodified deoxyribonucleotide. In some embodiments, position nine of the sense strand comprises a 2' fluoro-modified pyrimidine; all purines of the sense strand comprises 2'-O-methyl modified purines; 1, 2, 3, 4, or 5 pyrimidines between positions 5 and 11 comprise a 2'flouro-modified pyrimidine, provided there are not three 2' fluoro-modified pyrimidines in a row; the odd-numbered positions of the antisense strand comprise 2'-O-methyl modified nucleotides; and the even-numbered positions of the antisense strand comprise 2'flouro-modified nucleotides and unmodified deoxyribonucleotides.

[00135] In some embodiments, position nine of the sense strand comprises a 2' fluoro-modified purine. In some embodiments, all pyrimidines of the sense strand comprise 2'-O-methyl modified purines. In some embodiments, 1, 2, 3, 4, or 5 purines between positions 5 and 11 comprise a 2'flouro-modified purine, provided there are not three 2' fluoro-modified purine in a row. In some embodiments, the odd-numbered positions of the antisense strand comprise 2'-O-methyl modified nucleotides. In some embodiments, the even-numbered positions of the antisense strand comprise 2'flouro-modified nucleotides and unmodified deoxyribonucleotide. In some embodiments, the even-numbered positions of the antisense strand comprise 2'flouro-modified nucleotides, 2'-O-methyl modified nucleotides and unmodified deoxyribonucleotide. In some embodiments, position nine of the sense strand comprises a 2' fluoro-modified purine; all pyrimidine of the sense strand comprises 2'-O-methyl modified pyrimidines; 1, 2, 3, 4, or 5 purines between positions 5 and 11 comprise a 2'flouro-modified purines, provided there are not three 2' fluoro-modified purines in a row; the odd-numbered positions of the antisense strand comprise 2'-O-methyl modified nucleotides; and the even-numbered positions of the antisense strand comprise 2'flouro-modified nucleotides and unmodified deoxyribonucleotides. In some embodiments, there are not three 2' fluoro-modified purines in a row. In some embodiments, there are not three 2' fluoro-modified pyrimidines in a row.

[00136] In some embodiments, position nine of the sense strand comprises an unmodified deoxyribonucleotide. In some embodiments, positions 5, 7, and 8 of the sense strand comprise 2'fluoro-modifed nucleotides. In some embodiments, all pyrimidines in positions 10 to 21 of the sense strand comprise 2'-O-methyl modified pyrimidines and all purines in positions 10 to 21 of the comprise 2'-O-methyl modified purines or 2'fluoro-modified purines. In some embodiments, the odd-numbered positions of the antisense strand comprise 2'-O-methyl modified nucleotides. In some embodiments, the even-numbered positions of the antisense strand comprise 2'flouro-modified nucleotides and unmodified

deoxyribonucleotides. In some embodiments, the even-numbered positions of the antisense strand comprise 2'flouro-modified nucleotides, 2'-O-methyl modified nucleotides and unmodified deoxyribonucleotides. In some embodiments, position nine of the sense strand comprises an unmodified deoxyribonucleotide; positions 5, 7, and 8 of the sense strand comprise 2'fluoro-modifed nucleotides; all pyrimidines in positions 10 to 21 of the sense strand comprise 2'-O-methyl modified pyrimidines and all purines in positions 10 to 21 of the comprise 2'-O-methyl modified purines or 2'fluoro-modified purines; the odd-numbered positions of the antisense strand comprise 2'-O-methyl modified nucleotides; and the even-numbered positions of the antisense strand comprise 2'flouro-modified nucleotides and unmodified deoxyribonucleotides.

[00137] In some embodiments, position nine of the sense strand comprises an unmodified deoxyribonucleotide. In some embodiments, positions 5, 7, and 8 of the sense strand comprise 2'fluoro-modifed nucleotides. In some embodiments, all purines in positions 10 to 21 of the sense strand comprise 2'-O-methyl modified purines and all pyrimidines in positions 10 to 21 of the comprise 2'-O-methyl modified pyrimidines or 2'fluoro-modified pyrimidines. In some embodiments, the odd-numbered positions of the antisense strand comprise 2'-O-methyl modified nucleotides. In some embodiments, the even-numbered positions of the antisense strand comprise 2'flouro-modified nucleotides and unmodified deoxyribonucleotides. In some embodiments, the even-numbered positions of the antisense strand comprise 2'flouro-modified nucleotides, 2'-O-methyl modified nucleotides and unmodified deoxyribonucleotides. In some embodiments, position nine of the sense strand comprises an unmodified deoxyribonucleotide; positions 5, 7, and 8 of the sense strand comprise 2'fluoro-modifed nucleotides; all purines in positions 10 to 21 of the sense strand comprise 2'-O-methyl modified purines and all pyrimidines in positions 10 to 21 of the comprise 2'-O-methyl modified pyrimidines or 2'fluoro-modified pyrimidines; the odd-numbered positions of the antisense strand comprise 2'-O-methyl modified nucleotides; and the even-numbered positions of the antisense strand comprise 2'flouro-modified nucleotides and unmodified deoxyribonucleotide.

3. ASO modification patterns

[00138] In some embodiments, the composition comprises an oligonucleotide that binds to a target oligonucleotide, wherein the oligonucleotide comprises an antisense oligonucleotide (ASO). In some embodiments, the ASO comprises modification pattern ASO1:
5'-nsnsnsnsnsdNsdNsdNsdNsdNsdNsdNsdNsdNsnsnsnsnsn-3', wherein "dN" is any deoxynucleotide, "n" is a 2'O-methyl or 2'O-methoxyethyl-modified nucleoside, and "s" is a phosphorothioate linkage. In some embodiments, the ASO comprises modification pattern 1S, 2S, 3S, 4S, 5S, 6S, 1AS, 2AS, 3AS, 4AS, 5AS, 6AS, 7AS, 8AS, or 9AS.

[00139] In some embodiments, the ASO is conjugated to a GalNAc moiety. The GalNAc moiety may be conjugated to the ASO at a 5' terminus or the 3' terminus. In some embodiments, the GalNAc moiety is conjugated to the 5' terminus of the ASO. In some embodiments, the GalNAc moiety is conjugated to the 3' terminus of the ASO.

C. Formulations

[00140] In some embodiments, the composition is a pharmaceutical composition. In some embodiments, the composition is sterile. In some embodiments, the composition further comprises a pharmaceutically acceptable carrier. The formulation may include a compound such as a GalNAc moiety, and an oligonucleotide conjugated to a GalNAc moiety described herein.

[00141] In some embodiments, the pharmaceutically acceptable carrier comprises water. In some embodiments, the pharmaceutically acceptable carrier comprises a buffer. In some embodiments, the pharmaceutically acceptable carrier comprises a saline solution. In some embodiments, the pharmaceutically acceptable carrier comprises water, a buffer, or a saline solution. In some embodiments, the composition comprises a liposome. In some embodiments, the pharmaceutically acceptable carrier comprises liposomes, lipids, nanoparticles, proteins, protein-antibody complexes, peptides, cellulose, nanogel, or a combination thereof.

II. METHODS AND USES

[00142] Disclosed herein, in some embodiments, are methods of administering a composition described herein to a subject. Some embodiments relate to use a composition described herein, such as administering the composition to a subject.

[00143] Some embodiments relate to a method of treating a disorder in a subject in need thereof. Some embodiments relate to use of a composition described herein in the method of treatment. Some embodiments include administering a composition described herein to a subject with the disorder. In some embodiments, the administration treats the disorder in the subject. In some embodiments, the composition treats the disorder in the subject.

[00144] In some embodiments, the treatment comprises prevention, inhibition, or reversion of the disorder in the subject. Some embodiments relate to use of a composition described herein in the method of preventing, inhibiting, or reversing the disorder. Some embodiments relate to a method of preventing, inhibiting, or reversing a disorder a disorder in a subject in need thereof. Some embodiments include administering a composition described herein to a subject with the disorder. In some embodiments, the administration prevents, inhibits, or reverses the disorder in the subject. In some embodiments, the composition prevents, inhibits, or reverses the disorder in the subject.

[00145] Some embodiments relate to a method of preventing a disorder a disorder in a subject in need thereof. Some embodiments relate to use of a composition described herein in the method of preventing the disorder. Some embodiments include administering a composition described herein to a subject with the disorder. In some embodiments, the administration prevents the disorder in the subject. In some embodiments, the composition prevents the disorder in the subject.

[00146] Some embodiments relate to a method of inhibiting a disorder a disorder in a subject in need thereof. Some embodiments relate to use of a composition described herein in the method of inhibiting the disorder. Some embodiments include administering a composition described herein to a subject with the

disorder. In some embodiments, the administration inhibits the disorder in the subject. In some embodiments, the composition inhibits the disorder in the subject.

[00147] Some embodiments relate to a method of reversing a disorder a disorder in a subject in need thereof. Some embodiments relate to use of a composition described herein in the method of reversing the disorder. Some embodiments include administering a composition described herein to a subject with the disorder. In some embodiments, the administration reverses the disorder in the subject. In some embodiments, the composition reverses the disorder in the subject.

A. Disorders

[00148] Some embodiments of the methods described herein include treating a disorder in a subject in need thereof. In some embodiments, the disorder is a liver disorder. Non-limiting examples of liver disorders include liver inflammation, liver cancer, liver fibrosis, cholestasis, a gall bladder disease, a biliary tree disease, alcoholic liver disease, non-alcoholic steatohepatitis, a liver infection, or an inherited liver disorder. In some embodiments, the liver disorder comprises liver inflammation. In some embodiments, the liver disorder comprises liver cancer. In some embodiments, the liver disorder comprises liver fibrosis. In some embodiments, the liver disorder comprises cholestasis. In some embodiments, the liver disorder comprises a gall bladder disease. In some embodiments, the liver disorder comprises a biliary tree disease. In some embodiments, the liver disorder comprises alcoholic liver disease. In some embodiments, the liver disorder comprises non-alcoholic steatohepatitis.

[00149] In some embodiments, the liver disorder comprises a liver infection. In some embodiments, the liver infection comprises hepatitis A. In some embodiments, the liver infection comprises hepatitis B. In some embodiments, the liver infection comprises hepatitis C.

[00150] In some embodiments, the liver disorder comprises an inherited liver disorder. In some embodiments, the inherited liver disorder comprises hemochromatosis. In some embodiments, the inherited liver disorder comprises Wilson disease.

B. Subjects

[00151] Some embodiments of the methods described herein include treatment of a subject. Non-limiting examples of subjects include vertebrates, animals, mammals, dogs, cats, cattle, rodents, mice, rats, primates, monkeys, and humans. In some embodiments, the subject is a vertebrate. In some embodiments, the subject is an animal. In some embodiments, the subject is a mammal. In some embodiments, the subject is a dog. In some embodiments, the subject is a cat. In some embodiments, the subject is a cattle. In some embodiments, the subject is a mouse. In some embodiments, the subject is a rat. In some embodiments, the subject is a primate. In some embodiments, the subject is a monkey. In some embodiments, the subject is an animal, a mammal, a dog, a cat, cattle, a rodent, a mouse, a rat, a primate, or a monkey. In some embodiments, the subject is a human.

[00152] In some embodiments, the subject is male. In some embodiments, the subject is female.

[00153] In some embodiments, the subject has a body mass index (BMI) of 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, or more, or a range defined by any two of the aforementioned integers. In some embodiments, the subject is overweight. In some embodiments, the subject has a BMI of 25 or more. In some embodiments, the subject has a BMI of 25-29. In some embodiments, the subject is obese. In some embodiments, the subject has a BMI of 30 or more. In some embodiments, the subject has a BMI of 30-39. In some embodiments, the subject has a BMI of 40-50. In some embodiments, the subject has a BMI of 25-50.

[00154] In some embodiments, the subject is ≥ 90 years of age. In some embodiments, the subject is ≥ 85 years of age. In some embodiments, the subject is ≥ 80 years of age. In some embodiments, the subject is ≥ 70 years of age. In some embodiments, the subject is ≥ 60 years of age. In some embodiments, the subject is ≥ 50 years of age. In some embodiments, the subject is ≥ 40 years of age. In some embodiments, the subject is ≥ 30 years of age. In some embodiments, the subject is ≥ 20 years of age. In some embodiments, the subject is ≥ 10 years of age. In some embodiments, the subject is ≥ 1 years of age. In some embodiments, the subject is ≥ 0 years of age.

[00155] In some embodiments, the subject is ≤ 100 years of age. In some embodiments, the subject is ≤ 90 years of age. In some embodiments, the subject is ≤ 85 years of age. In some embodiments, the subject is ≤ 80 years of age. In some embodiments, the subject is ≤ 70 years of age. In some embodiments, the subject is ≤ 60 years of age. In some embodiments, the subject is ≤ 50 years of age. In some embodiments, the subject is ≤ 40 years of age. In some embodiments, the subject is ≤ 30 years of age. In some embodiments, the subject is ≤ 20 years of age. In some embodiments, the subject is ≤ 10 years of age. In some embodiments, the subject is ≤ 1 years of age.

[00156] In some embodiments, the subject is between 0 and 100 years of age. In some embodiments, the subject is between 20 and 90 years of age. In some embodiments, the subject is between 30 and 80 years of age. In some embodiments, the subject is between 40 and 75 years of age. In some embodiments, the subject is between 50 and 70 years of age. In some embodiments, the subject is between 40 and 85 years of age.

C. Baseline measurements

[00157] Some embodiments of the methods described herein include obtaining a baseline measurement from a subject. For example, in some embodiments, a baseline measurement is obtained from the subject prior to treating the subject. Non-limiting examples of baseline measurements include a baseline symptom (e.g. a liver disorder symptom) measurement, a baseline protective phenotype measurement, a baseline target oligonucleotide (e.g. mRNA) measurement or a baseline target protein measurement.

[00158] In some embodiments, the baseline measurement is obtained directly from the subject. In some embodiments, the baseline measurement is obtained by observation, for example by observation of the subject or of the subject's tissue. In some embodiments, the baseline measurement is obtained noninvasively using an imaging device. In some embodiments, the baseline measurement is obtained in a sample from the subject. In some embodiments, the baseline measurement is obtained in one or more

histological tissue sections. In some embodiments, the baseline measurement is obtained by performing an assay such as an immunoassay, a colorimetric assay, or a fluorescence assay, on the sample obtained from the subject. In some embodiments, the baseline measurement is obtained by an immunoassay, a colorimetric assay, or a fluorescence assay. In some embodiments, the baseline measurement is obtained by PCR.

[00159] In some embodiments, the baseline measurement is a baseline symptom measurement. The symptom may be a symptom of a disorder associated with a target oligonucleotide. The disorder may be a liver disorder.

[00160] In some embodiments, the baseline measurement is a baseline protective phenotype measurement. The protective phenotype may protect a subject from having a disorder associated with a target oligonucleotide. The protective phenotype may be inversely correlated with an incidence of the disorder.

[00161] In some embodiments, the baseline measurement is a baseline target protein measurement. In some embodiments, the baseline target protein measurement comprises a baseline target protein level. In some embodiments, the baseline target protein level is indicated as a mass or percentage of target protein per sample weight. In some embodiments, the baseline target protein level is indicated as a mass or percentage of target protein per sample volume. In some embodiments, the baseline target protein level is indicated as a mass or percentage of target protein per total protein within the sample. In some embodiments, the baseline target protein measurement is a baseline liver or hepatocyte target protein measurement. In some embodiments, the baseline target protein measurement is a baseline circulating target protein measurement. In some embodiments, the baseline target protein measurement is obtained by an assay such as an immunoassay, a colorimetric assay, or a fluorescence assay.

[00162] In some embodiments, the baseline measurement is a baseline target mRNA measurement. In some embodiments, the baseline target mRNA measurement comprises a baseline target mRNA level. In some embodiments, the baseline target mRNA level is indicated as a mass or percentage of target mRNA per sample weight. In some embodiments, the baseline target mRNA level is indicated as a mass or percentage of target mRNA per sample volume. In some embodiments, the baseline target mRNA level is indicated as a mass or percentage of target mRNA per total mRNA within the sample. In some embodiments, the baseline target mRNA level is indicated as a mass or percentage of target mRNA per total nucleic acids within the sample. In some embodiments, the baseline target mRNA level is indicated relative to another mRNA level, such as an mRNA level of a housekeeping gene, within the sample. In some embodiments, the baseline target mRNA measurement is a baseline liver or hepatocyte target mRNA measurement. In some embodiments, the baseline target mRNA measurement is obtained by an assay such as a polymerase chain reaction (PCR) assay. In some embodiments, the PCR comprises quantitative PCR (qPCR). In some embodiments, the PCR comprises reverse transcription of the target mRNA.

[00163] Some embodiments of the methods described herein include obtaining a sample from a subject. In some embodiments, the baseline measurement is obtained in a sample obtained from the subject. In some embodiments, the sample is obtained from the subject prior to administration or treatment of the subject

with a composition described herein. In some embodiments, a baseline measurement is obtained in a sample obtained from the subject prior to administering the composition to the subject. In some embodiments, the sample is obtained from the subject in a fasted state. In some embodiments, the sample is obtained from the subject after an overnight fasting period. In some embodiments, the sample is obtained from the subject in a fed state.

[00164] In some embodiments, the sample comprises a fluid. In some embodiments, the sample is a fluid sample. In some embodiments, the sample is a blood, plasma, or serum sample. In some embodiments, the sample comprises blood. In some embodiments, the sample is a blood sample. In some embodiments, the sample is a whole-blood sample. In some embodiments, the blood is fractionated or centrifuged. In some embodiments, the sample comprises plasma. In some embodiments, the sample is a plasma sample. In some embodiments, the sample comprises serum. In some embodiments, the sample is a serum sample.

[00165] In some embodiments, the sample comprises a tissue. In some embodiments, the sample is a tissue sample. In some embodiments, the sample comprises liver tissue. In some embodiments, the sample is a liver sample. In some embodiments, the sample comprises hepatocytes. In some embodiments, the sample consists of hepatocytes. For example, the baseline target mRNA measurement, or the baseline target protein measurement, may be obtained in a liver or hepatocyte sample from the patient. In some embodiments, the sample comprises adipose tissue. In some embodiments, the sample is an adipose sample. The adipose sample may comprise or consist of white adipose tissue. The adipose sample may comprise or consist of brown adipose tissue. In some embodiments, the sample comprises kidney tissue. In some embodiments, the sample is an kidney sample. In some embodiments, the sample comprises cardiac tissue such as ventricular or atrial tissue. In some embodiments, the sample is a cardiac sample. In some embodiments, the sample comprises intestinal tissue such as small intestinal tissue. In some embodiments, the sample is a small intestine sample. In some embodiments, the sample comprises lymph node tissue such as mesenteric lymph node tissue. In some embodiments, the sample is a mesenteric lymph node sample. In some embodiments, the sample comprises muscle tissue. In some embodiments, the sample is an muscle sample. In some embodiments, the tissue sample comprises liver, adipose, kidney, or cardiac tissue. In some embodiments, the tissue sample comprises brown adipose tissue, white adipose tissue, kidney tissue, intestinal tissue, mesenteric lymph node, or muscle tissue.

D. Effects

[00166] In some embodiments, the composition or administration of the composition affects a measurement such as symptom (e.g. a liver disorder symptom) measurement, a protective phenotype measurement, a target oligonucleotide (e.g. mRNA) measurement or a target protein measurement (e.g. liver tissue target protein levels), relative to the baseline measurement.

[00167] Some embodiments of the methods described herein include obtaining the measurement from a subject. For example, the measurement may be obtained from the subject after treating the subject. In some embodiments, the measurement is obtained in a second sample (such as a fluid or tissue sample

described herein) obtained from the subject after the composition is administered to the subject. In some embodiments, the measurement is an indication that the disorder has been treated.

[00168] In some embodiments, the measurement is obtained directly from the subject. In some embodiments, the measurement is obtained noninvasively using an imaging device. In some embodiments, the measurement is obtained in a second sample from the subject. In some embodiments, the measurement is obtained in one or more histological tissue sections. In some embodiments, the measurement is obtained by performing an assay on the second sample obtained from the subject. In some embodiments, the measurement is obtained by an assay, such as an assay described herein. In some embodiments, the assay is an immunoassay, a colorimetric assay, a fluorescence assay, or a PCR assay. In some embodiments, the measurement is obtained by an assay such as an immunoassay, a colorimetric assay, or a fluorescence assay. In some embodiments, the measurement is obtained by PCR. In some embodiments, the measurement is obtained by histology. In some embodiments, the measurement is obtained by observation. In some embodiments, additional measurements are made, such as in a 3rd sample, a 4th sample, or a fifth sample.

[00169] In some embodiments, the measurement is obtained within 1 hour, within 2 hours, within 3 hours, within 4 hours, within 5 hours, within 6 hours, within 12 hours, within 18 hours, or within 24 hours after the administration of the composition. In some embodiments, the measurement is obtained within 1 day, within 2 days, within 3 days, within 4 days, within 5 days, within 6 days, or within 7 days after the administration of the composition. In some embodiments, the measurement is obtained within 1 week, within 2 weeks, within 3 weeks, within 1 month, within 2 months, within 3 months, within 6 months, within 1 year, within 2 years, within 3 years, within 4 years, or within 5 years after the administration of the composition. In some embodiments, the measurement is obtained after 1 hour, after 2 hours, after 3 hours, after 4 hours, after 5 hours, after 6 hours, after 12 hours, after 18 hours, or after 24 hours after the administration of the composition. In some embodiments, the measurement is obtained after 1 day, after 2 days, after 3 days, after 4 days, after 5 days, after 6 days, or after 7 days after the administration of the composition. In some embodiments, the measurement is obtained after 1 week, after 2 weeks, after 3 weeks, after 1 month, after 2 months, after 3 months, after 6 months, after 1 year, after 2 years, after 3 years, after 4 years, or after 5 years, following the administration of the composition.

[00170] In some embodiments, the measurement of the symptom or the parameter related to the disorder in the subject is decreased or affected for an extended period of time, relative to the baseline measurement. In some embodiments, the measurement is decreased or affected for at least about 1 day, about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, about 7 days, about 8 days, about 9 days, about 10 days, about 11 days, about 12 days, about 13 days, about 14 days, about 15 days, about 16 days, about 17 days, about 18 days, about 19 days, about 20 days, about 21 days, about 22 days, about 23 days, about 24 days, about 25 days, about 26 days, about 27 days, about 28 days, about 29 days, about 30 days, about 35 days, about 40 days, about 45 days, about 50 days, about 55 days, about 60 days, about 65 days, about 70 days, about 75 days, about 80 days, about 85 days, about 90 days, about 95 days, about 100 days, about 105 days, about 110 days, about 115 days, or about 120 days, following administration, or a

range of time following administration comprising a range defined by any two of the aforementioned numbers of days. In some embodiments, the measurement is decreased or affected for at least 1 day, at least 2 days, at least 3 days, at least 4 days, at least 5 days, at least 6 days, at least 7 days, at least 8 days, at least 9 days, at least 10 days, at least 11 days, at least 12 days, at least 13 days, at least 14 days, at least 15 days, at least 16 days, at least 17 days, at least 18 days, at least 19 days, at least 20 days, at least 21 days, at least 22 days, at least 23 days, at least 24 days, at least 25 days, at least 26 days, at least 27 days, at least 28 days, at least 29 days, at least 30 days, at least 35 days, at least 40 days, at least 45 days, at least 50 days, at least 55 days, at least 60 days, at least 65 days, at least 70 days, at least 75 days, at least 80 days, at least 85 days, at least 90 days, at least 95 days, at least 100 days, at least 105 days, at least 110 days, at least 115 days, or at least 120 days, following administration. In some embodiments, the measurement is decreased or affected for no more than 1 day, no more than 2 days, no more than 3 days, no more than 4 days, no more than 5 days, no more than 6 days, no more than 7 days, no more than 8 days, no more than 9 days, no more than 10 days, no more than 11 days, no more than 12 days, no more than 13 days, no more than 14 days, no more than 15 days, no more than 16 days, no more than 17 days, no more than 18 days, no more than 19 days, no more than 20 days, no more than 21 days, no more than 22 days, no more than 23 days, no more than 24 days, no more than 25 days, no more than 26 days, no more than 27 days, no more than 28 days, no more than 29 days, no more than 30 days, no more than 35 days, no more than 40 days, no more than 45 days, no more than 50 days, no more than 55 days, no more than 60 days, no more than 65 days, no more than 70 days, no more than 75 days, no more than 80 days, no more than 85 days, no more than 90 days, no more than 95 days, no more than 100 days, no more than 105 days, no more than 110 days, no more than 115 days, or no more than 120 days, following administration. In some embodiments, the measurement is decreased or affected for at least about 5 days. In some embodiments, the measurement is decreased or affected for at least about 10 days. In some embodiments, the measurement is decreased or affected for at least about 15 days. In some embodiments, the measurement is decreased or affected for at least about 20 days. In some embodiments, the measurement is decreased or affected for at least about 25 days. In some embodiments, the measurement is decreased or affected for at least about 30 days. In some embodiments, the measurement is decreased or affected for at least about 40 days. In some embodiments, the measurement is decreased or affected for at least about 50 days. In some embodiments, the measurement is decreased or affected for at least about 60 days. In some embodiments, the measurement is decreased or affected for at least about 70 days. In some embodiments, the measurement is decreased or affected for at least about 80 days. In some embodiments, the measurement is decreased or affected for at least about 90 days. In some embodiments, the measurement is decreased or affected for at least about 100 days. In some embodiments, the measurement is decreased or affected for at least about 110 days. In some embodiments, the measurement is decreased or affected for at least about 120 days. An example of a measurement of a symptom or parameter related to a disorder may include a target mRNA measurement, a target protein measurement, a biomarker measurement, or a physiological measurement. The measurement may be in a tissue (e.g. liver) or in a biofluid (e.g. blood, serum, or plasma).

[00171] In some embodiments, the composition reduces the symptom measurement relative to the baseline symptom measurement. In some embodiments, the reduction is measured in a second tissue sample obtained from the subject after administering the composition to the subject. In some embodiments, the reduction is measured directly in the subject after administering the composition to the subject. In some embodiments, the symptom measurement is decreased by about 2.5% or more, about 5% or more, or about 7.5% or more, relative to the baseline symptom measurement. In some embodiments, the symptom measurement is decreased by about 10% or more, relative to the baseline symptom measurement. In some embodiments, the symptom measurement is decreased by about 20% or more, about 30% or more, about 40% or more, about 50% or more, about 60% or more, about 70% or more, about 80% or more, about 90% or more, relative to the baseline symptom measurement. In some embodiments, the symptom measurement is decreased by no more than about 2.5%, no more than about 5%, or no more than about 7.5%, relative to the baseline symptom measurement. In some embodiments, the symptom measurement is decreased by no more than about 10%, relative to the baseline symptom measurement. In some embodiments, the symptom measurement is decreased by no more than about 20%, no more than about 30%, no more than about 40%, no more than about 50%, no more than about 60%, no more than about 70%, no more than about 80%, no more than about 90%, or no more than about 100% relative to the baseline symptom measurement. In some embodiments, the symptom measurement is decreased by 2.5%, 5%, 7.5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100%, or by a range defined by any of the two aforementioned percentages.

[00172] In some embodiments, the composition increases the protective phenotype measurement relative to the baseline protective phenotype measurement. In some embodiments, the increase is measured in a second tissue sample obtained from the subject after administering the composition to the subject. In some embodiments, the increase is measured directly in the subject after administering the composition to the subject. In some embodiments, the protective phenotype measurement is increased by about 2.5% or more, about 5% or more, or about 7.5% or more, relative to the baseline protective phenotype measurement. In some embodiments, the protective phenotype measurement is increased by about 10% or more, relative to the baseline protective phenotype measurement. In some embodiments, the protective phenotype measurement is increased by about 20% or more, about 30% or more, about 40% or more, about 50% or more, about 60% or more, about 70% or more, about 80% or more, about 90% or more, relative to the baseline protective phenotype measurement. In some embodiments, the protective phenotype measurement is increased by about 100% or more, increased by about 250% or more, increased by about 500% or more, increased by about 750% or more, or increased by about 1000% or more, relative to the baseline protective phenotype measurement. In some embodiments, the protective phenotype measurement is increased by no more than about 2.5%, no more than about 5%, or no more than about 7.5%, relative to the baseline protective phenotype measurement. In some embodiments, the protective phenotype measurement is increased by no more than about 10%, relative to the baseline protective phenotype measurement. In some embodiments, the protective phenotype measurement is increased by no more than about 20%, no more than about 30%, no more than about 40%, no more than about 50%, no

more than about 60%, no more than about 70%, no more than about 80%, no more than about 90%, or no more than about 100% relative to the baseline protective phenotype measurement. In some embodiments, the protective phenotype measurement is increased by no more than about 100%, increased by no more than about 250%, increased by no more than about 500%, increased by no more than about 750%, or increased by no more than about 1000%, relative to the baseline protective phenotype measurement. In some embodiments, the protective phenotype measurement is increased by 2.5%, 5%, 7.5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 250%, 500%, 750%, or 1000%, or by a range defined by any of the two aforementioned percentages.

[00173] In some embodiments, the measurement is a target protein measurement. In some embodiments, the target protein measurement comprises a target protein level. In some embodiments, the target protein level is indicated as a mass or percentage of target protein per sample weight. In some embodiments, the target protein level is indicated as a mass or percentage of target protein per sample volume. In some embodiments, the target protein level is indicated as a mass or percentage of target protein per total protein within the sample. In some embodiments, the target protein measurement is a cell (e.g. hepatocyte) target protein measurement. In some embodiments, the target protein measurement is a tissue (e.g. liver tissue) target protein measurement. In some embodiments, the target protein measurement is a circulating target protein measurement. In some embodiments, the baseline target protein measurement is obtained by an assay such as an immunoassay, a colorimetric assay, or a fluorescence assay.

[00174] In some embodiments, the composition reduces the target protein measurement relative to the baseline target protein measurement. In some embodiments, the composition reduces tissue target protein levels (such as, but not limited to, liver tissue target protein levels) relative to the baseline target protein measurement. In some embodiments, the composition reduces cell target protein levels (such as, but not limited to, hepatocyte target protein levels) relative to the baseline target protein measurement. In some embodiments, the composition reduces circulating target protein levels relative to the baseline target protein measurement. In some embodiments, the reduced target protein levels are measured in a second sample obtained from the subject after administering the composition to the subject.

[00175] In some embodiments, the target protein measurement is decreased by about 2.5% or more, about 5% or more, or about 7.5% or more, relative to the baseline target protein measurement. In some embodiments, the target protein measurement is decreased by about 10% or more, relative to the baseline target protein measurement. In some embodiments, the target protein measurement is decreased by about 20% or more, about 30% or more, about 40% or more, about 50% or more, about 60% or more, about 70% or more, about 80% or more, about 90% or more, or about 100% relative to the baseline target protein measurement. In some embodiments, the target protein measurement is decreased by no more than about 2.5%, no more than about 5%, or no more than about 7.5%, relative to the baseline target protein measurement. In some embodiments, the target protein measurement is decreased by no more than about 10%, relative to the baseline target protein measurement. In some embodiments, the target protein measurement is decreased by no more than about 20%, no more than about 30%, no more than about 40%, no more than about 50%, no more than about 60%, no more than about 70%, no more than about

80%, no more than about 90%, or about 100% relative to the baseline target protein measurement. In some embodiments, the target protein measurement is decreased by 2.5%, 5%, 7.5%, 19%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100%, or by a range defined by any of the two aforementioned percentages. The target protein measurement may be decreased for an extended period of time. In some embodiments, the target protein measurement is decreased for 7 days, 14 days, 28 days, 42 days, 56 days, 70 days, 77 days, 84 days, 91 days, 98 days, 105 days, or a range therebetween. In some embodiments, the target protein measurement is decreased for about 7 days, about 14 days, about 28 days, about 42 days, about 56 days, about 70 days, about 77 days, about 84 days, about 91 days, about 98 days, about 105 days, or a range therebetween.

[00176] In some embodiments, the measurement is a target mRNA measurement. In some embodiments, the target mRNA measurement comprises a target mRNA level. In some embodiments, the target mRNA level is indicated as a mass or percentage of target mRNA per sample weight. In some embodiments, the target mRNA level is indicated as a mass or percentage of target mRNA per sample volume. In some embodiments, the target mRNA level is indicated as a mass or percentage of target mRNA per total mRNA within the sample. In some embodiments, the target mRNA level is indicated as a mass or percentage of target mRNA per total nucleic acids within the sample. In some embodiments, the target mRNA level is indicated relative to another mRNA level, such as an mRNA level of a housekeeping gene, within the sample. In some embodiments, the target mRNA measurement is obtained by an assay such as a PCR assay. In some embodiments, the PCR comprises qPCR. In some embodiments, the PCR comprises reverse transcription of the target mRNA.

[00177] In some embodiments, the composition reduces the target mRNA measurement relative to the baseline target mRNA measurement. In some embodiments, the target mRNA measurement is obtained in a second sample obtained from the subject after administering the composition to the subject. In some embodiments, the composition reduces target mRNA levels relative to the baseline target mRNA levels. In some embodiments, the reduced target mRNA levels are measured in a second sample obtained from the subject after administering the composition to the subject. In some embodiments, the second sample is a second liver sample. In some embodiments, the second sample is second hepatocyte sample.

[00178] In some embodiments, the target mRNA measurement is reduced by about 2.5% or more, about 5% or more, or about 7.5% or more, relative to the baseline target mRNA measurement. In some embodiments, the target mRNA measurement is decreased by about 10% or more, relative to the baseline target mRNA measurement. In some embodiments, the target mRNA measurement is decreased by about 20% or more, about 30% or more, about 40% or more, about 50% or more, about 60% or more, about 70% or more, about 80% or more, about 90% or more, or about 100% relative to the baseline target mRNA measurement. In some embodiments, the target mRNA measurement is decreased by no more than about 2.5%, no more than about 5%, or no more than about 7.5%, relative to the baseline target mRNA measurement. In some embodiments, the target mRNA measurement is decreased by no more than about 10%, relative to the baseline target mRNA measurement. In some embodiments, the target mRNA measurement is decreased by no more than about 20%, no more than about 30%, no more than about

40%, no more than about 50%, no more than about 60%, no more than about 70%, no more than about 80%, no more than about 90%, or about 100% relative to the baseline target mRNA measurement. In some embodiments, the target mRNA measurement is decreased by 2.5%, 5%, 7.5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, or by a range defined by any of the two aforementioned percentages. The target mRNA measurement may be decreased for an extended period of time. In some embodiments, the target mRNA measurement is decreased for 7 days, 14 days, 28 days, 42 days, 56 days, 70 days, 77 days, 84 days, 91 days, 98 days, 105 days, or a range therebetween. In some embodiments, the target protein measurement is decreased for about 7 days, about 14 days, about 28 days, about 42 days, about 56 days, about 70 days, about 77 days, about 84 days, about 91 days, about 98 days, about 105 days, or a range therebetween. Some embodiments include decreasing an RNA measurement other than an mRNA measurement.

III. DEFINITIONS

[00179] Unless defined otherwise, all terms of art, notations and other technical and scientific terms or terminology used herein are intended to have the same meaning as is commonly understood by one of ordinary skill in the art to which the claimed subject matter pertains. In some cases, terms with commonly understood meanings are defined herein for clarity and/or for ready reference, and the inclusion of such definitions herein should not necessarily be construed to represent a substantial difference over what is generally understood in the art.

[00180] Throughout this application, various embodiments may be presented in a range format. It should be understood that the description in range format is merely for convenience and brevity and should not be construed as an inflexible limitation on the scope of the disclosure. Accordingly, the description of a range should be considered to have specifically disclosed all the possible subranges as well as individual numerical values within that range. For example, description of a range such as from 1 to 6 should be considered to have specifically disclosed subranges such as from 1 to 3, from 1 to 4, from 1 to 5, from 2 to 4, from 2 to 6, from 3 to 6 etc., as well as individual numbers within that range, for example, 1, 2, 3, 4, 5, and 6. This applies regardless of the breadth of the range.

[00181] As used in the specification and claims, the singular forms "a", "an" and "the" include plural references unless the context clearly dictates otherwise. For example, the term "a sample" includes a plurality of samples, including mixtures thereof.

[00182] Some examples relate to a sequence. To any extent that the sequence listing contradicts the disclosure in the specification, the specification takes precedent.

[00183] The terms "determining," "measuring," "evaluating," "assessing," "assaying," and "analyzing" are often used interchangeably herein to refer to forms of measurement. The terms include determining if an element is present or not (for example, detection). These terms can include quantitative, qualitative or quantitative and qualitative determinations. Assessing can be relative or absolute. "Detecting the presence of" can include determining the amount of something present in addition to determining whether it is present or absent depending on the context.

[00184] The terms "subject," and "patient" may be used interchangeably herein. A "subject" can be a biological entity containing expressed genetic materials. The biological entity can be a plant, animal, or microorganism, including, for example, bacteria, viruses, fungi, and protozoa. The subject can be a mammal. The mammal can be a human. The subject may be diagnosed or suspected of being at high risk for a disease. In some cases, the subject is not necessarily diagnosed or suspected of being at high risk for the disease.

[00185] As used herein, the term "about" a number refers to that number plus or minus 10% of that number. The term "about" a range refers to that range minus 10% of its lowest value and plus 10% of its greatest value.

[00186] As used herein, the terms "treatment" or "treating" are used in reference to a pharmaceutical or other intervention regimen for obtaining beneficial or desired results in the recipient. Beneficial or desired results include but are not limited to a therapeutic benefit and/or a prophylactic benefit. A therapeutic benefit may refer to eradication or amelioration of symptoms or of an underlying disorder being treated. Also, a therapeutic benefit can be achieved with the eradication or amelioration of one or more of the physiological symptoms associated with the underlying disorder such that an improvement is observed in the subject, notwithstanding that the subject may still be afflicted with the underlying disorder. A prophylactic effect includes delaying, preventing, or eliminating the appearance of a disease or condition, delaying or eliminating the onset of symptoms of a disease or condition, slowing, halting, or reversing the progression of a disease or condition, or any combination thereof. For prophylactic benefit, a subject at risk of developing a particular disease, or to a subject reporting one or more of the physiological symptoms of a disease may undergo treatment, even though a diagnosis of this disease may not have been made.

[00187] "Treatment" or "treating" may include an approach for obtaining beneficial or desired results with respect to a disease, disorder, or medical condition including but not limited to a therapeutic benefit and/or a prophylactic benefit. A therapeutic benefit can include, for example, the eradication or amelioration of the underlying disorder being treated. Also, a therapeutic benefit can include, for example, the eradication or amelioration of one or more of the physiological symptoms associated with the underlying disorder such that an improvement is observed in the subject, notwithstanding that the subject may still be afflicted with the underlying disorder. In certain embodiments, for prophylactic benefit, the compositions are administered to a subject at risk of developing a particular disease, or to a subject reporting one or more of the physiological symptoms of a disease, even though a diagnosis of this disease may not have been made. Treatment via administration of a compound described herein does not necessarily require the involvement of a medical professional.

[00188] The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

[00189] The term "C_{x-y}" or "C_x-C_y" when used in conjunction with a chemical moiety, such as alkyl, alkenyl, or alkynyl is meant to include groups that contain from x to y carbons in the chain. For example, **the term "C_{1-6} alkyl" refers to** substituted or unsubstituted saturated hydrocarbon groups, including

straight-chain alkyl and branched-chain alkyl groups that contain from 1 to 6 carbons. The term "C_{x-y}" or "C_x-C_y" is not meant to limit the number of carbon atoms which may be attached to the chemical moiety when the chemical moiety is substituted with a second chemical moiety. For example, the term "C_{1-6} alkyl" or "C_1 to C_6 alkyl" refers to saturated, substituted or unsubstituted, hydrocarbon groups, including straight-chain alkyl groups (e.g., linear alkyl groups) and branched alkyl groups that contain 1, 2, 3, 4, 5, or 6 carbon atoms, plus however many carbon atoms may be present in any substituents of the C_{1-6} alkyl. For example, if a C_{1-6} alkyl is optionally substituted with a second chemical moiety comprising two carbon atoms, then it will be understood that the C_{1-6} alkyl can include between 1 and 8 carbon atoms.

[00190] The terms "C_{x-y}alkenyl" and "C_{x-y}alkynyl" refer to substituted or unsubstituted unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double or triple bond, respectively.

[00191] "Amino" refers to the $-NH_2$ moiety.

[00192] "Cyano" refers to the -CN moiety.

[00193] "Nitro" refers to the $-NO_2$ moiety.

[00194] "Oxa" refers to the -O- moiety.

[00195] "Oxo" refers to the =O moiety.

[00196] "Thioxo" refers to the =S moiety.

[00197] "Imino" refers to the =N-H moiety.

[00198] "Oximo" refers to the =N-OH moiety.

[00199] "Hydrazino" refers to the $=N-NH_2$ moiety.

[00200] "Alkyl" refers to a straight or branched hydrocarbon moiety consisting solely of carbon and hydrogen atoms, fully saturated. In certain embodiments, "alkyl" comprises one to fifteen carbon atoms (*e.g.*, C_1-C_{15} alkyl). In certain embodiments, an alkyl comprises one to thirteen carbon atoms (*e.g.*, C_1-C_{13} alkyl). In certain embodiments, an alkyl comprises one to eight carbon atoms (*e.g.*, C_1-C_8 alkyl). In certain embodiments, an alkyl comprises one to six carbon atoms (*e.g.*, C_1-C_6 alkyl). In other embodiments, an alkyl comprises one to five carbon atoms (*e.g.*, C_1-C_5 alkyl). In other embodiments, an alkyl comprises one to four carbon atoms (*e.g.*, C_1-C_4 alkyl). In other embodiments, an alkyl comprises one to three carbon atoms (*e.g.*, C_1-C_3 alkyl). In other embodiments, an alkyl comprises one to two carbon atoms (*e.g.*, C_1-C_2 alkyl). In other embodiments, an alkyl comprises one carbon atom (*e.g.*, C_1 alkyl, e.g., methyl). In other embodiments, an alkyl comprises five to fifteen carbon atoms (*e.g.*, C_5-C_{15} alkyl). In other embodiments, an alkyl comprises five to eight carbon atoms (*e.g.*, C_5-C_8 alkyl). In other embodiments, an alkyl comprises two to five carbon atoms (*e.g.*, C_2-C_5 alkyl). In other embodiments, an alkyl comprises three to five carbon atoms (*e.g.*, C_3-C_5 alkyl). In other embodiments, the alkyl group is selected from methyl, ethyl, 1-propyl (*n*-propyl), 1-methylethyl (2-propyl, *iso*-propyl), 1-butyl (*n*-butyl), 1-methylpropyl (*sec*-butyl), 2-methylpropyl (*iso*-butyl), 1,1-dimethylethyl (*tert*-butyl), and 1-pentyl (*n*-pentyl). The alkyl is attached to the rest of the molecule by a single bond.

[00201] **"Aminoalkyl" refers to a moiety boded through a nitrogen** atom of the form –N(H)(alkyl) or N(alkyl)(alkyl), wherein when the moiety is N(alkyl)(alkyl), the two alkyl groups bonded to nitrogen can be the same alkyl groups or different alkyl groups.

[00202] "Alkoxy" refers to a moiety bonded through an oxygen atom of the formula –O-alkyl, where alkyl is an alkyl chain as defined above.

[00203] "Alkenyl" refers to a straight or branched hydrocarbon moiety consisting solely of carbon and hydrogen atoms, containing at least one carbon-carbon double bond. In certain embodiments, an alkenyl comprisestwo to twelve carbon atoms. In certain embodiments, an alkenyl comprises two to eight carbon atoms. In other embodiments, an alkenyl comprises two to four carbon atoms. The alkenyl is attached to the rest of the molecule by a single bond, for example, ethenyl (*i.e.*, vinyl), prop-1-enyl (*i.e.*, allyl), but-1-enyl, pent-1-enyl, penta-1,4-dienyl, and the like.

[00204] "Alkynyl" refers to a straight or branched hydrocarbon moiety consisting solely of carbon and hydrogen atoms, containing at least one carbon-carbon triple bond, having from two to twelve carbon atoms, and optionally further comprising at least one carbon-carbon double bond. In certain embodiments, an alkynyl comprises two to eight carbon atoms. In other embodiments, an alkynyl comprises two to six carbon atoms. In other embodiments, an alkynyl comprises two to four carbon atoms. The alkynyl is attached to the rest of the molecule by a single bond, for example, ethynyl, propynyl, butynyl, pentynyl, hexynyl, and the like.

[00205] "Alkylene" or "alkylene chain" refers to a linear (e.g., straight), or branched, divalent, **hydrocarbon moiety. An "alkylene" or "alkylene chain" can link a portion of the molecule to a second moiety. An "alkylene" or "alkylene chain"** consists solely of carbon and hydrogen atoms (substitution of an alkylene with one or more substituents comprising atoms other than hydrogen, such as N, O, and S, **may be specified). An "alkylene" or "alkylene chain" can contain no unsaturation (notwithstanding the** points of attachment of an **alkylene to the rest of the molecule). In certain embodiments, the "alkylene" or "alkylene chain" and comprises one to twelve carbon atoms,** for example, methylene, ethylene, propylene, *n*-butylene, and the like. The alkylene chain can be attached to the portion of the molecule through a single bond and to the second moiety through a single bond. The points of attachment of an alkylene chain to the rest of the molecule and to the second moiety can be through one carbon in the alkylene chain or through any two carbons within the alkylene. In certain embodiments, an alkylene comprises one to eight carbon atoms (*e.g.*, C_1-C_8 alkylene). In other embodiments, an alkylene comprises one to five carbon atoms (*e.g.*, C_1-C_5 alkylene). In other embodiments, an alkylene comprises one to four carbon atoms (*e.g.*, C_1-C_4 alkylene). In other embodiments, an alkylene comprises one to three carbon atoms (*e.g.*, C_1-C_3 alkylene). In other embodiments, an alkylene comprises one to two carbon atoms (*e.g.*, C_1-C_2 alkylene). In other embodiments, an alkylene comprises one carbon atom (*e.g.*, C_1 alkylene). In other embodiments, an alkylene comprises five to eight carbon atoms (*e.g.*, C_5-C_8 alkylene). In other embodiments, an alkylene comprises two to five carbon atoms (*e.g.*, C_2-C_5 alkylene). In other embodiments, an alkylene comprises three to five carbon atoms (*e.g.*, C_3-C_5 alkylene).

[00206] "Alkenylene" or "alkenylene chain" refers to a linear (e.g., straight), or branched, divalent, hydrocarbon moiety. An "alkenylene" or "alkenylene chain" can link a portion of the molecule to a second moiety. An "alkenylene" or "alkenylene chain" consists solely of carbon and hydrogen atoms (substitution of an alkenylene with one or more substituents comprising atoms other than hydrogen, such as N, O, and S, may be specified). An "alkenylene" or "alkenylene chain" comprises at least one carbon-carbon double bond. In certain embodiments, an "alkenylene" or "alkenylene chain" comprises from two to twelve carbon atoms. The alkenylene chain can be attached to the portion of the molecule through a single bond and to the second moiety through a single bond. The points of attachment of an alkenylene chain to the rest of the molecule and to the second moiety can be through one carbon in the alkenylene chain or through any two carbons within the alkenylene chain. In certain embodiments, an alkenylene comprises two to eight carbon atoms (*e.g.*, C_2-C_8 alkenylene). In other embodiments, an alkenylene comprises two to five carbon atoms (*e.g.*, C_2-C_5 alkenylene). In other embodiments, an alkenylene comprises two to four carbon atoms (*e.g.*, C_2-C_4 alkenylene). In other embodiments, an alkenylene comprises two to three carbon atoms (*e.g.*, C_2-C_3 alkenylene). In other embodiments, an alkenylene comprises five to eight carbon atoms (*e.g.*, C_5-C_8 alkenylene). In other embodiments, an alkenylene comprises two to five carbon atoms (*e.g.*, C_2-C_5 alkenylene). In other embodiments, an alkenylene comprises three to five carbon atoms (*e.g.*, C_3-C_5 alkenylene).

[00207] "Alkynylene" or "alkynylene chain" refers to a linear (e.g., straight), or branched, divalent, hydrocarbon moiety. An "alkynylene" or "alkynylene chain" can link a portion of the molecule to a second moiety. An "alkynylene" or "alkynylene chain" consists solely of carbon and hydrogen (substitution of an alkynylene with one or more substituents comprising atoms other than hydrogen, such as N, O, and S, may be specified). An "alkynylene" or "alkynylene chain" comprises at least one carbon-carbon triple bond. In certain embodiments, an "alkynylene" or "alkynylene chain" comprises from two to twelve carbon atoms. An alkynylene chain can be attached to the portion of the molecule through a single bond and to the second moiety through a single bond. The points of attachment of an alkynylene chain to the rest of the molecule and to the second moiety can be through one carbon in the alkynylene chain or through any two carbons within the alkynylene chain. In certain embodiments, an alkynylene comprises two to eight carbon atoms (*e.g.*, C_2-C_8 alkynylene). In other embodiments, an alkynylene comprises two to five carbon atoms (*e.g.*, C_2-C_5 alkynylene). In other embodiments, an alkynylene comprises two to four carbon atoms (*e.g.*, C_2-C_4 alkynylene). In other embodiments, an alkynylene comprises two to three carbon atoms (*e.g.*, C_2-C_3 alkynylene). In other embodiments, an alkynylene comprises two carbon atom (*e.g.*, C_2 alkylene). In other embodiments, an alkynylene comprises five to eight carbon atoms (*e.g.*, C_5-C_8 alkynylene). In other embodiments, an alkynylene comprises three to five carbon atoms (*e.g.*, C_3-C_5 alkynylene).

[00208] The term "carbocycle" as used herein refers to a saturated, unsaturated or aromatic ring in which each atom of the ring is carbon. Carbocycle includes 3- to 10-membered monocyclic rings, 5- to 12-membered bicyclic rings, 5- to 12-membered spiro bicycles, and 5- to 12-membered bridged rings. Each ring of a bicyclic carbocycle may be selected from saturated, unsaturated, and aromatic rings. In an

exemplary embodiment, an aromatic ring, e.g., phenyl, may be fused to a saturated or unsaturated ring, e.g., cyclohexane, cyclopentane, or cyclohexene. A bicyclic carbocycle includes any combination of saturated, unsaturated and aromatic bicyclic rings, as valence permits. A bicyclic carbocycle further includes spiro bicyclic rings such as spiropentane. A bicyclic carbocycle includes any combination of ring sizes such as 3-3 spiro ring systems, 4-4 spiro ring systems, 4-5 fused ring systems, 5-5 fused ring systems, 5-6 fused ring systems, 6-6 fused ring systems, 5-7 fused ring systems, 6-7 fused ring systems, 5-8 fused ring systems, and 6-8 fused ring systems. Exemplary carbocycles include cyclopentyl, cyclohexyl, cyclohexenyl, adamantyl, phenyl, indanyl, naphthyl, and bicyclo[1.1.1]pentanyl. **"Carbocycle"** may include **"aryl" and "cycloalkyl."**

[00209] The term "aryl" refers to an aromatic monocyclic or aromatic multicyclic hydrocarbon ring system. The aromatic monocyclic or aromatic multicyclic hydrocarbon ring system contains only hydrogen and carbon and from five to eighteen carbon atoms, where at least one of the rings in the ring **system is aromatic, i.e., it contains a cyclic, delocalized (4n+2)** π-electron system in accordance with the Hückel theory. The ring system from which aryl groups are derived include, but are not limited to, groups such as benzene, fluorene, indane, indene, tetralin and naphthalene. In some embodiments, the aryl substituent is positively or negatively charged. In some embodiments, the aryl substituent is neutral. In some embodiments, the aryl substituent is zwitterionic; alternatively, or in addition, in some embodiments, the aryl substituent is not charged. In some embodiments, the aryl substituent bears no charges. In some embodiments, the aryl substituent bears no net charge. In some embodiments, the aryl substituent bears no net charge and is not zwitterionic.

[00210] The term "cycloalkyl" refers to a saturated ring in which each atom of the ring is carbon. Cycloalkyl may include monocyclic and polycyclic rings such as 3- to 10-membered monocyclic rings, 5- to 12-membered bicyclic rings, 5- to 12-membered spiro bicycles, and 5- to 12-membered bridged rings. In certain embodiments, a cycloalkyl comprises three to ten carbon atoms. In other embodiments, a cycloalkyl comprises five to seven carbon atoms. The cycloalkyl may be attached to the rest of the molecule by a single bond. Examples of monocyclic cycloalkyls include, e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Polycyclic cycloalkyl radicals include, for example, adamantyl, spiropentane, norbornyl (i.e., bicyclo[2.2.1]heptanyl), decalinyl, 7,7 dimethyl bicyclo[2.2.1]heptanyl, bicyclo[1.1.1]pentanyl, and the like.

[00211] The term "cycloalkenyl" refers to a saturated ring in which each atom of the ring is carbon and there is at least one double bond between two ring carbons. Cycloalkenyl may include monocyclic and polycyclic rings such as 3- to 10-membered monocyclic rings, 6- to 12-membered bicyclic rings, and 5- to 12-membered bridged rings. In other embodiments, a cycloalkenyl comprises five to seven carbon atoms. The cycloalkenyl may be attached to the rest of the molecule by a single bond. Examples of monocyclic cycloalkenyls include, *e.g.*, cyclopentenyl, cyclohexenyl, cycloheptenyl, and cyclooctenyl.

[00212] The term "halo" or, alternatively, "halogen" or "halide," means fluoro, chloro, bromo or iodo. In some embodiments, halo is fluoro, chloro, or bromo.

[00213] The term "haloalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more halo radicals, for example, trifluoromethyl, dichloromethyl, bromomethyl, 2,2,2-trifluoroethyl, 1-chloromethyl-2-fluoroethyl, and the like. In some embodiments, the alkyl part of the haloalkyl radical is optionally further substituted as described herein.

[00214] The term "heterocycle" as used herein refers to a saturated, unsaturated or aromatic ring comprising one or more heteroatoms. Exemplary heteroatoms include N, O, Si, P, B, and S atoms. Heterocycles include 3- to 10-membered monocyclic rings, 6- to 12-membered bicyclic rings, 5- to 12-membered spiro bicycles, and 5- to 12-membered bridged rings. A bicyclic heterocycle includes any combination of saturated, unsaturated and aromatic bicyclic rings, as valence permits. In an exemplary embodiment, an aromatic ring, e.g., pyridyl, may be fused to a saturated or unsaturated ring, e.g., cyclohexane, cyclopentane, morpholine, piperidine or cyclohexene. A bicyclic heterocycle includes any combination of ring sizes such as 4-5 fused ring systems, 5-5 fused ring systems, 5-6 fused ring systems, 6-6 fused ring systems, 5-7 fused ring systems, 6-7 fused ring systems, 5-8 fused ring systems, and 6-8 fused ring systems. A bicyclic heterocycle further includes spiro bicyclic rings, e.g., 5 to 12-membered spiro bicycles, such as 2-oxa-6-azaspiro[3.3]heptane. **"Heterocycle" may include "heteroaryl" and "heterocycloalkyl".**

[00215] The term "heteroaryl" refers to a radical derived from a 5 to 18 membered aromatic ring radical that comprises two to seventeen carbon atoms and from one to six heteroatoms selected from nitrogen, oxygen and sulfur. As used herein, the heteroaryl radical is a monocyclic, bicyclic, tricyclic or tetracyclic ring system, wherein at least one of the rings in the ring system is aromatic, i.e., it contains a cyclic, **delocalized (4n+2)** π-electron system in accordance with the Hückel theory. Heteroaryl includes fused or bridged ring systems. The heteroatom(s) in the heteroaryl radical is optionally oxidized. One or more nitrogen atoms, if present, are optionally quaternized. The heteroaryl is attached to the rest of the molecule through any atom of the ring(s). Examples of heteroaryls include, but are not limited to, azepinyl, acridinyl, benzimidazolyl, benzindolyl, 1,3-benzodioxolyl, benzofuranyl, benzoxazolyl, benzo[d]thiazolyl, benzothiadiazolyl, benzo[*b*][1,4]dioxepinyl, benzo[b][1,4]oxazinyl, 1,4-benzodioxanyl, benzonaphthofuranyl, benzoxazolyl, benzodioxolyl, benzodioxinyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzofuranonyl, benzothienyl (benzothiophenyl), benzothieno[3,2-d]pyrimidinyl, benzotriazolyl, benzo[4,6]imidazo[1,2-a]pyridinyl, carbazolyl, cinnolinyl, cyclopenta[d]pyrimidinyl, 6,7-dihydro-5H-cyclopenta[4,5]thieno[2,3-d]pyrimidinyl, 5,6-dihydrobenzo[h]quinazolinyl, 5,6-dihydrobenzo[h]cinnolinyl, 6,7-dihydro-5H-benzo[6,7]cyclohepta[1,2-c]pyridazinyl, dibenzofuranyl, dibenzothiophenyl, furanyl, furanonyl, furo[3,2-c]pyridinyl, 5,6,7,8,9,10-hexahydrocycloocta[d]pyrimidinyl, 5,6,7,8,9,10-hexahydrocycloocta[d]pyridazinyl, 5,6,7,8,9,10-hexahydrocycloocta[d]pyridinyl, isothiazolyl, imidazolyl, indazolyl, indolyl, indazolyl, isoindolyl, indolinyl, isoindolinyl, isoquinolyl, indolizinyl, isoxazolyl, 5,8-methano-5,6,7,8-tetrahydroquinazolinyl, naphthyridinyl, 1,6-naphthyridinonyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, oxiranyl, 5,6,6a,7,8,9,10,10a-octahydrobenzo[h]quinazolinyl, 1-phenyl-1*H*-pyrrolyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl,

pyrrolyl, pyrazolyl, pyrazolo[3,4-d]pyrimidinyl, pyridinyl, pyrido[3,2-d]pyrimidinyl, pyrido[3,4-d]pyrimidinyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrrolyl, quinazolinyl, quinoxalinyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, 5,6,7,8-tetrahydroquinazolinyl, 5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidinyl, 6,7,8,9-tetrahydro-5H-cyclohepta[4,5]thieno[2,3-d]pyrimidinyl, 5,6,7,8-tetrahydropyrido[4,5-c]pyridazinyl, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl, triazinyl, thieno[2,3-d]pyrimidinyl, thieno[3,2-d]pyrimidinyl, thieno[2,3-c]pyridinyl, and thiophenyl (*i.e.* thienyl).

[00216] One or more nitrogen atoms, if present, may be optionally quaternized. In some embodiments, the heterocycle substituent is positively or negatively charged. In some embodiments, the heterocycle substituent is neutral. In some embodiments, the heterocycle substituent is zwitterionic; alternatively, or in addition, in some embodiments, the heterocycle substituent is not charged. In some embodiments, the heterocycle substituent bears no charges. In some embodiments, the heterocycle substituent bears no net charge. In some embodiments, the heterocycle substituent bears no net charge and is not zwitterionic.

[00217] The term "heterocycloalkyl" refers to a saturated ring with carbon atoms and at least one heteroatom. Exemplary heteroatoms include N, O, Si, P, B, and S atoms. Heterocycloalkyl may include monocyclic and polycyclic rings such as 3- to 10-membered monocyclic rings, 6- to 12-membered bicyclic rings, 5- to 12-membered spiro bicycles, and 5- to 12-membered bridged rings. The heteroatoms in the heterocycloalkyl radical are optionally oxidized. One or more nitrogen atoms, if present, are optionally quaternized. The heterocycloalkyl is attached to the rest of the molecule through any atom of the heterocycloalkyl, valence permitting, such as any carbon or nitrogen atoms of the heterocycloalkyl. Examples of heterocycloalkyl radicals include, but are not limited to, dioxolanyl, thienyl[1,3]dithianyl, decahydroisoquinolyl, imidazolinyl, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidinyl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidinyl, quinuclidinyl, thiazolidinyl, tetrahydrofuryl, trithianyl, tetrahydropyranyl, thiomorpholinyl, thiamorpholinyl, 1-oxo-thiomorpholinyl, 2-oxa-6-azaspiro[3.3]heptane, and 1,1-dioxo-thiomorpholinyl. In some embodiments, a heterocycloalkyl comprises one heteroatom. In some embodiments, a heterocycloalkyl comprises one heteroatom selected from N, O, and S. In some embodiments, a heterocycloalkyl comprises multiple heteroatoms. In some embodiments, a heterocycloalkyl comprises multiple heteroatoms selected from N, O, and S.

[00218] The term "heterocycloalkenyl" refers to an unsaturated ring with carbon atoms and at least one heteroatom and there is at least one double bond between two ring carbons. Heterocycloalkenyl does not include heteroaryl rings. Exemplary heteroatoms include N, O, Si, P, B, and S atoms. Heterocycloalkenyl may include monocyclic and polycyclic rings such as 3- to 10-membered monocyclic rings, 6- to 12-membered bicyclic rings, and 5- to 12-membered bridged rings. In other embodiments, a heterocycloalkenyl comprises five to seven ring atoms. The heterocycloalkenyl may be attached to the rest

of the molecule by a single bond. Examples of monocyclic cycloalkenyls include, *e.g.*, pyrroline (dihydropyrrole), pyrazoline (dihydropyrazole), imidazoline (dihydroimidazole), triazoline (dihydrotriazole), dihydrofuran, dihydrothiophene, oxazoline (dihydrooxazole), isoxazoline (dihydroisoxazole), thiazoline (dihydrothiazole), isothiazoline (dihydroisothiazole), oxadiazoline (dihydrooxadiazole), thiadiazoline (dihydrothiadiazole), dihydropyridine, tetrahydropyridine, dihydropyridazine, tetrahydropyridazine, dihydropyrimidine, tetrahydropyrimidine, dihydropyrazine, tetrahydropyrazine, pyran, dihydropyran, thiopyran, dihydrothiopyran, dioxine, dihydrodioxine, oxazine, dihydrooxazine, thiazine, and dihydrothiazine.

[00219] The term "substituted" refers to moieties having substituents replacing a hydrogen on one or more carbons or substitutable heteroatoms, e.g., an NH or NH_2 of a compound. It will be understood that **"substitution" or "substituted with" includes the** implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, *i.e.*, a compound which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc. In certain embodiments, substituted refers to moieties having substituents replacing two hydrogen atoms on the same carbon atom, such as substituting the two hydrogen atoms on a single carbon with an oxo, imino or thioxo group. As used herein, the term **"substituted" is contemplated to include all permissible substituents of organic compounds. In a broad** aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and non-aromatic substituents of organic compounds. The permissible substituents can be one or more and the same or different for appropriate organic compounds.

[00220] In some embodiments, substituents may include any substituents described herein, for example: halogen, hydroxy, oxo (=O), thioxo (=S), cyano (-CN), nitro ($-NO_2$), imino (=N-H), oximo (=N-OH), hydrazino (=N-NH_2), $-R^b-OR^a$, $-R^b-OC(O)-R^a$, $-R^b-OC(O)-OR^a$, $-R^b-OC(O)-N(R^a)_2$, $-R^b-N(R^a)_2$, $-R^b-C(O)R^a$, $-R^b-C(O)OR^a$, $-R^b-C(O)N(R^a)_2$, $-R^b-O-R^c-C(O)N(R^a)_2$, $-R^b-N(R^a)C(O)OR^a$, $-R^b-N(R^a)C(O)R^a$, $-R^b-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tOR^a$ (where t is 1 or 2), and $-R^b-S(O)_tN(R^a)_2$ (where t is 1 or 2); and alkyl, alkenyl, alkynyl, aryl, aralkyl, aralkenyl, aralkynyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, and heteroarylalkyl, any of which may be optionally substituted by alkyl, alkenyl, alkynyl, halogen, haloalkyl, haloalkenyl, haloalkynyl, oxo (=O), thioxo (=S), cyano (-CN), nitro ($-NO_2$), imino (=N-H), oximo (=N-OH), hydrazine (=N-NH_2), $-R^b-OR^a$, $-R^b-OC(O)-R^a$, $-R^b-OC(O)-OR^a$, $-R^b-OC(O)-N(R^a)_2$, $-R^b-N(R^a)_2$, $-R^b-C(O)R^a$, $-R^b-C(O)OR^a$, $-R^b-C(O)N(R^a)_2$, $-R^b-O-R^c-C(O)N(R^a)_2$, $-R^b-N(R^a)C(O)OR^a$, $-R^b-N(R^a)C(O)R^a$, $-R^b-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tOR^a$ (where t is 1 or 2) and $-R^b-S(O)_tN(R^a)_2$ (where t is 1 or 2); wherein each R^a is independently selected from hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, or heteroarylalkyl, wherein each R^a, valence permitting, may be optionally substituted with alkyl, alkenyl, alkynyl, halogen, haloalkyl, haloalkenyl, haloalkynyl, oxo (=O), thioxo (=S), cyano (-CN), nitro ($-NO_2$), imino (=N-H), oximo (=N-OH), hydrazine (=N-NH_2), $-R^b-OR^a$, $-R^b-OC(O)-R^a$, $-R^b-OC(O)-OR^a$, $-R^b-OC(O)-N(R^a)_2$, $-R^b-N(R^a)_2$, $-R^b-C(O)R^a$, $-R^b-C(O)OR^a$, $-R^b-C(O)N(R^a)_2$, $-R^b-O-R^c-C(O)N(R^a)_2$, -

R^b-$N(R^a)C(O)OR^a$, -R^b-$N(R^a)C(O)R^a$, -R^b-$N(R^a)S(O)_tR^a$ (where t is 1 or 2), -R^b-$S(O)_tR^a$ (where t is 1 or 2), -R^b-$S(O)_tOR^a$ (where t is 1 or 2) and -R^b-$S(O)_tN(R^a)_2$ (where t is 1 or 2); and wherein each R^b is independently selected from a direct bond or a straight or branched alkylene, alkenylene, or alkynylene chain, and each R^c is a straight or branched alkylene, alkenylene or alkynylene chain.

[00221] Double bonds to oxygen atoms, such as oxo groups, are represented herein as both "=O" and "(O)". Double bonds to nitrogen atoms are represented as both "=NR" and "(NR)". Double bonds to sulfur atoms are represented as both "=S" and "(S)".

[00222] 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, intra-arterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal and intrasternal injection and infusion.

[00223] 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.

[00224] The phrase "pharmaceutically acceptable excipient" or "pharmaceutically acceptable carrier" as used herein means a pharmaceutically acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient. Some examples of materials which can serve as pharmaceutically acceptable carriers include: (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) phosphate buffer solutions; and (21) other non-toxic compatible substances employed in pharmaceutical formulations.

[00225] The term "salt" or "pharmaceutically acceptable salt" refers to salts derived from a variety of organic and inorganic counter ions well known in the art. Pharmaceutically acceptable acid addition salts can be formed with inorganic acids and organic acids. Inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like. Organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, *p*-

toluenesulfonic acid, salicylic acid, and the like. Pharmaceutically acceptable base addition salts can be formed with inorganic and organic bases. Inorganic bases from which salts can be derived include, for example, sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum, and the like. Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, basic ion exchange resins, and the like, specifically such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, and ethanolamine. In some embodiments, the pharmaceutically acceptable base addition salt is chosen from ammonium, potassium, sodium, calcium, and magnesium salts.

VI. EXAMPLES

Example 1: Identification of variants in a target oligonucleotide associated with increased or decreased risk of a disorder

[00226] Approximately 30,000,000 imputed variants are to be analyzed in ~375,000 individuals from a Biobank cohort for associations with liver disorders such as non-alcoholic steatohepatitis.

[00227] Protective or maladaptive associations are observed between specific allelic variants of various target genes and liver diseases. The associations will suggest that in some cases therapeutic inhibition or modulation of a target protein encoded by any of the target genes may be an effective genetically-informed method of treatment for any of the liver disorders.

Example 2: Bioinformatic selection of sequences in order to identify therapeutic siRNAs to downmodulate expression of a target mRNA

[00228] Screening sets are to be defined based on bioinformatic analysis. Therapeutic siRNAs are designed to bind human target mRNAs, and the target mRNA sequence of at least one toxicology-relevant species such as a non-human primate (NHP) species (e.g. a rhesus or cynomolgus monkey). Drivers for the design of the screening set are predicted specificity of the siRNAs against the transcriptome of the relevant species as well as cross-reactivity between species. Predicted specificity in human, rhesus monkey, cynomolgus monkey, mouse and rat are determined for sense (S) and antisense (AS) strands. These are assigned a "specificity score" which considers the likelihood of unintended downregulation of any other transcript by full or partial complementarity of an siRNA strand (up to 4 mismatches within positions 2-18) as well as the number and positions of mismatches. Thus, off-target(s) for antisense and sense strands of each siRNA are identified. In addition, the number of potential off-targets are used as an additional specificity factor in the specificity score. As identified, siRNAs with high specificity and a low number of predicted off-targets provide a benefit of increased targeting specificity.

[00229] In addition to selecting siRNA sequences with high sequence specificity to the target mRNA, siRNA sequences within a seed region are analyzed for similarity to seed regions of known miRNAs. siRNAs can function in a miRNA like manner via base-pairing with complementary sequences within the 3'-UTR of mRNA molecules. The complementarity typically encompasses the 5'-bases at positions 2-7 of

the miRNA (seed region). To circumvent siRNAs to act via functional miRNA binding sites, siRNA strands containing natural miRNA seed regions are avoided. Seed regions identified in miRNAs from **human, mouse, rat, rhesus monkey, dog, rabbit and pig are referred to as "conserved". Combining the "specificity score" with miRNA seed analysis yields a "specificity category". This is divided into** categories 1-4, with 1 having the highest specificity and 4 having the lowest specificity. Each strand of the siRNA is assigned to a specificity category.

[00230] Species cross-reactivity are assessed for human, cynomolgus monkey, rhesus monkey, mouse and rat. The analysis is based on a canonical siRNA design using 19 bases and 17 bases (without considering positions 1 and 19) for cross-reactivity. Full match as well as single mismatch analyses are included.

[00231] Analysis of the human Single Nucleotide Polymorphism (SNP) database (NCBI-DB-SNP) to identify siRNAs targeting regions with known SNPs are also carried out to identify siRNAs that may be non-functional in individuals containing the SNP. Information regarding the positions of SNPs within the target sequence as well as minor allele frequency (MAF) in case data are obtained in this analysis.

[00232] The above methods can be used to identify therapeutic siRNAs to downmodulate expression of a target mRNA. Bioinformatic methods may also be used to identify ASOs that bind and downmodulate expression of a target mRNA.

Example 3: Chemically modified siRNAs

[00233] siRNAs that bind a target mRNA can be synthesized with chemical modifications with the sense strand having a modification such as modification pattern 1S, and the antisense strand having a modification such as modification pattern 1AS. In addition, adenosine can be placed at position 19 in the sense strand and uridine at position 1 in the antisense strand.

[00234] The siRNAs that bind a target mRNA can also be synthesized with chemical modifications with the sense strand having modification pattern 2S and the antisense strand having modification pattern 3AS. In addition, adenosine can be placed at position 19 in the sense strand and uridine at position 1 in the antisense strand.

[00235] The siRNAs that bind a target mRNA can also be synthesized with chemical modifications with the sense strand having modification pattern 2S and the antisense strand having modification pattern 9AS. In addition, adenosine can be placed at position 19 in the sense strand and uridine at position 1 in the antisense strand.

[00236] The siRNAs targeting that bind a target mRNA can also be synthesized with chemical modifications with the sense strand having modification pattern 3S and the antisense strand having modification pattern 3AS. In addition, adenosine can be placed at position 19 in the sense strand and uridine at position 1 in the antisense strand.

[00237] The siRNAs targeting that bind a target mRNA can also be synthesized with chemical modifications with the sense strand having any of the **following: all purines comprising 2' fluoro modified purines, and all pyrimidines comprising a mixture of 2' fluoro and** 2'-O-methyl modified pyrimidines; all **purines comprising** 2'-O-**methyl modified purines, and all pyrimidines comprising a mixture of** 2' fluoro

and 2'-O-methyl modified pyrimidines; all purines comprising 2' fluoro modified purines, and all pyrimidines comprising 2'-O-methyl modified pyrimidines; all pyrimidines comprising 2' fluoro modified pyrimidines, and all purines comprising a mixture of 2' fluoro and 2'-O-methyl modified purines; all pyrimidines comprising 2'-O-methyl modified pyrimidines, and all purines comprising a mixture of 2' fluoro and 2'-O-methyl modified purines; or all pyrimidines comprising 2' fluoro modified pyrimidines, and all purines comprising 2'-O-methyl modified purines; and further with the antisense strand having any of the following: all purines comprising 2' fluoro modified purines, and all pyrimidines comprising a mixture of 2' fluoro and 2'-O-methyl modified pyrimidines; all purines comprising 2'-O-methyl modified purines, and all pyrimidines comprising a mixture of 2' fluoro and 2'-O-methyl modified pyrimidines; all purines comprising 2'-O-methyl modified purines, and all pyrimidines comprising 2' fluoro modified pyrimidines; all pyrimidines comprising 2' fluoro modified pyrimidines, and all purines comprising a mixture of 2' fluoro and 2'-O-methyl modified purines; all pyrimidines comprising 2'-O-methyl modified pyrimidines, and all purines comprising a mixture of 2' fluoro and 2'-O-methyl modified purines; or all pyrimidines comprising 2'-O-methyl modified pyrimidines, and all purines comprising 2' fluoro modified purines.

Example 4: Screening siRNAs for activity in cells in culture

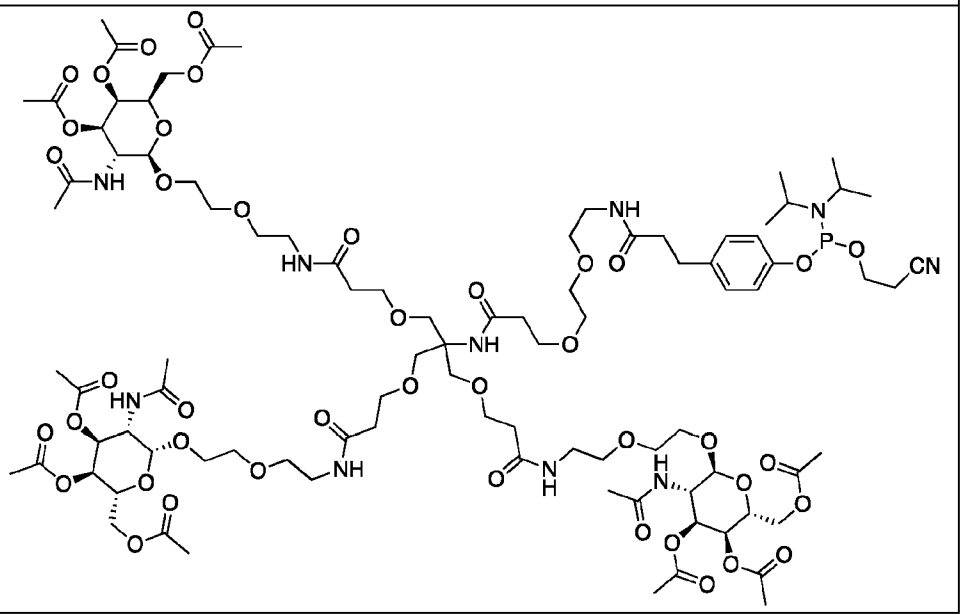
[00238] The chemically modified siRNAs derived from sequences in the previous Examples will be assayed for target mRNA knockdown activity in cells in culture. A cell line that expresses the target mRNA is to be seeded in 96-well tissue culture plates at a cell density of 10,000 cells per well in DMEM supplemented with 10% fetal bovine serum and incubated overnight in a water-jacketed, humidified incubator at 37°C in an atmosphere composed of air plus 5% carbon dioxide. The siRNAs are individually transfected into cells in duplicate wells at 10 nM final concentration using 0.3 µL Lipofectamine RNAiMax (Fisher) per well. Silencer Select Negative Control #1 (ThermoFisher, Catalog# 4390843) and a positive control siRNA are transfected at 10 nM final concentration as controls. After incubation for 48 hours at 37°C, total RNA is harvested from each well and cDNA prepared using TaqMan® Fast Advanced Cells-to-CT™ Kit (ThermoFisher, Catalog# A35374) according to the manufacturer's instructions. The level of target mRNA in each well will be measured in triplicate by real-time qPCR on an Applied Biosystems 7500 Fast Real-Time PCR machine using TaqMan Gene Expression Assay for the human target mRNA. The level of PPIA mRNA will be measured using TaqMan Gene Expression Assay (ThermoFisher) and used to determine relative target mRNA levels in each well using the delta-delta Ct method. Data will be normalized to relative target mRNA levels in untreated cells.

[00239] The siRNAs showing the greatest degree of knockdown of target mRNA at 10 nM will be tested in a second screen for activity at 1 nM concentration using the transfection procedures as described above. Similar experiments may be performed using ASOs. Thus, siRNAs and ASOs may be identified that most effectively downmodulate expression of the target mRNA.

Example 5: GalNAc ligands for hepatocyte targeting of oligonucleotides

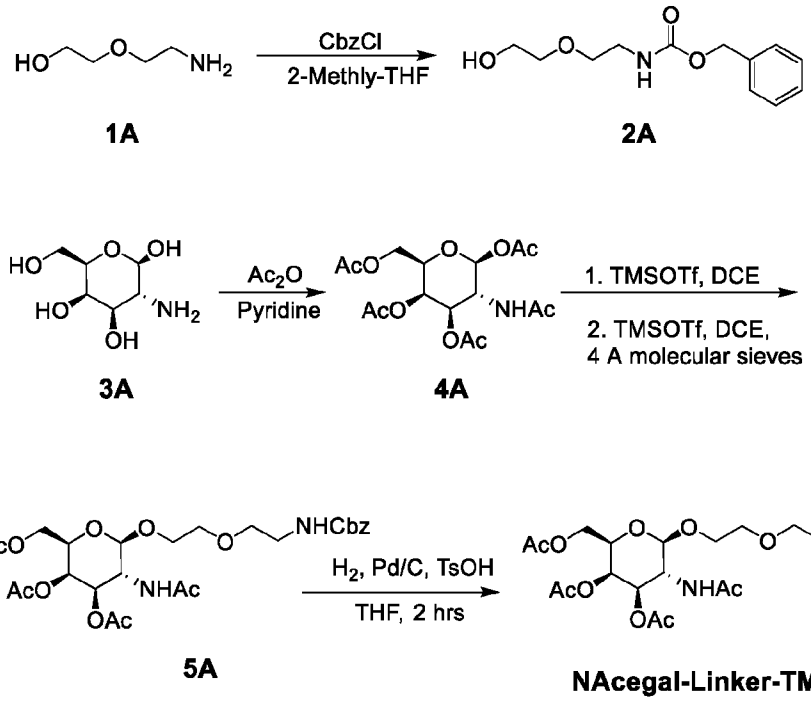
[00240] Without limiting the disclosure to these individual methods, there are at least two general methods for attachment of multivalent N-acetylgalactosamine (GalNAc) ligands to oligonucleotides: solid or solution-phase conjugations. GalNAc ligands may be attached to solid phase resin for 3' conjugation or at the 5' terminus using GalNAc phosphoramidite reagents. GalNAc phosphoramidites may be coupled on solid phase as for other nucleosides in the oligonucleotide sequence at any position in the sequence. A non-limiting example of a phosphoramidite reagent for GalNAc conjugation to a 5' end oligonucleotide is shown in **Table 1.**

Table 1. GalNAc Conjugation Reagent

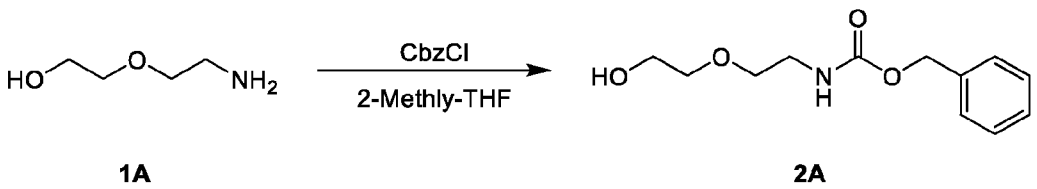
Type of conjugation	Structure
Solid phase 5' attachment phosphoramidite	

Example 6: Synthesis of GalNAc ligands

Scheme for the preparation of NAcegal-Linker-TMSOTf

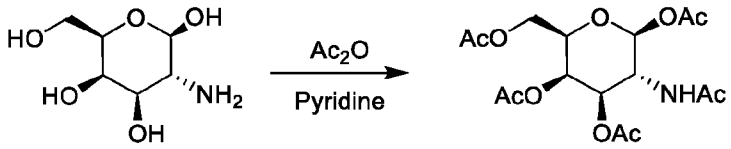


General procedure for preparation of Compound 2A



[00241] To a solution of Compound 1A (500 g, 4.76 mol, 476 mL) in 2-Methly-THF (2.00 L) was added CbzCl (406 g, 2.38 mol, 338 mL) in 2-Methyl-THF (750 mL) dropwise at 0 °C. The mixture was stirred at 25 °C for 2 hrs under N_2 atmosphere. TLC (DCM: MeOH = 20:1, PMA) indicated CbzCl was consumed completely and one new spot (R_f = 0.43) formed. The reaction mixture was added HCl/EtOAc (1 N, 180 mL) and stirred for 30 mins, white solid was removed by filtration through celite, the filtrate was concentrated under vacuum to give Compound 2A (540 g, 2.26 mol, 47.5% yield) as a pale yellow oil and used into the next step without further purification. ^{1}H NMR: δ 7.28 - 7.41 (m, 5 H), 5.55 (br s, 1 H), 5.01 - 5.22 (m, 2 H), 3.63 - 3.80 (m, 2 H), 3.46 - 3.59 (m, 4 H), 3.29 - 3.44 (m, 2 H), 2.83 - 3.02 (m, 1 H).

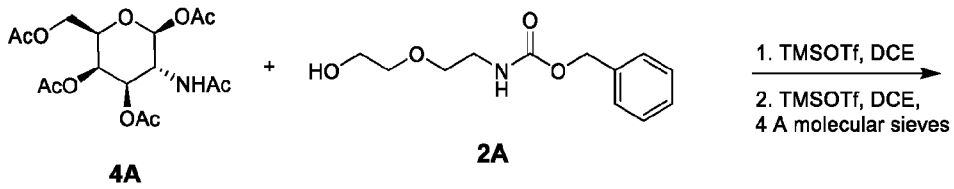
General procedure for preparation of Compound 4A



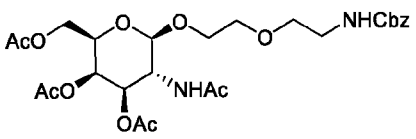
3A **4A**

[00242] To a solution of Compound 3A (1.00 kg, 4.64 mol, HCl) in pyridine (5.00 L) was added acetyl acetate (4.73 kg, 46.4 mol, 4.34 L) dropwise at 0 °C under N_2 atmosphere. The mixture was stirred at 25 °C for 16 hrs under N_2 atmosphere. TLC (DCM: MeOH = 20:1, PMA) indicated Compound 3A was consumed completely and two new spots (R_f = 0.35) formed. The reaction mixture was added to cold water (30.0 L) and stirred at 0 °C for 0.5 hr, white solid formed, filtered and dried to give Compound 4A (1.55 kg, 3.98 mol, 85.8% yield) as a white solid and used in the next step without further purification. ^{1}H NMR: **δ 7.90 (d,** *J* = 9.29 Hz, 1 H), 5.64 (d, *J* = 8.78 Hz, 1 H), 5.26 (d, *J* = 3.01 Hz, 1 H), 5.06 (dd, *J* = 11.29, 3.26 Hz, 1 H), 4.22 (t, *J* = 6.15 Hz, 1 H), 3.95 - 4.16 (m, 3 H), 2.12 (s, 3 H), 2.03 (s, 3 H), 1.99 (s, 3 H), 1.90 (s, 3 H), 1.78 (s, 3 H).

General procedure for preparation of Compound 5A



4A **2A**

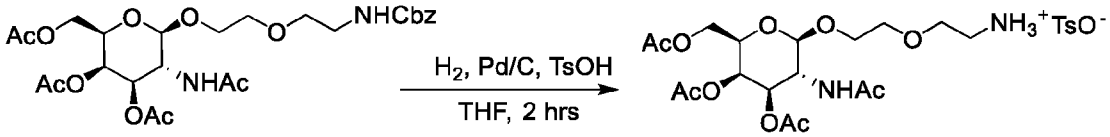


5A

[00243] To a solution of Compound 4A (300 g, 771 mmol) in DCE (1.50 L) was added TMSOTf (257 g, 1.16 mol, 209 mL) and stirred for 2 hrs at 60 °C, and then stirred for 1 hr at 25 °C. Compound 2A (203 g, 848 mmol) was dissolved in DCE (1.50 L) and added 4 Å powder molecular sieves (150 g) stirring for 30 mins under N_2 atmosphere. Then the solution of Compound 4A in DCE was added dropwise to the mixture at 0 °C. The mixture was stirred at 25 °C for 16 hrs under N_2 atmosphere. TLC (DCM: MeOH = 25:1, PMA) indicated Compound 4A was consumed completely and new spot (R_f = 0.24) formed. The reaction mixture was filtered and washed with sat. $NaHCO_3$ (2.00 L), water (2.00 L) and sat. brine (2.00 L). The organic layer was dried over anhydrous Na_2SO4, filtered and concentrated under reduced pressure to give a residue. The residue was triturated with 2-Me-THE/heptane (5/3, v/v, 1.80 L) for 2 hrs,

filtered and dried to give Compound 5A (225 g, 389 mmol, 50.3% yield, 98.4% purity) as a white solid. ^{1}H NMR: **δ 7.81 (d,** *J* = 9.29 Hz, 1 H), 7.20 - 7.42 (m, 6 H), 5.21 (d, *J* = 3.26 Hz, 1 H), 4.92 - 5.05 (m, 3 H), 4.55 (d, *J* = 8.28 Hz, 1 H), 3.98 - 4.07 (m, 3 H), 3.82 - 3.93 (m, 1 H),3.71 - 3.81 (m, 1 H), 3.55 - 3.62 (m, 1 H), 3.43 - 3.53 (m, 2 H), 3.37 - 3.43 (m, 2 H), 3.14 (q, *J* = 5.77 Hz, 2 H), 2.10 (s, 3 H), 1.99 (s, 3 H), 1.89 (s, 3 H), 1.77 (s, 3 H).

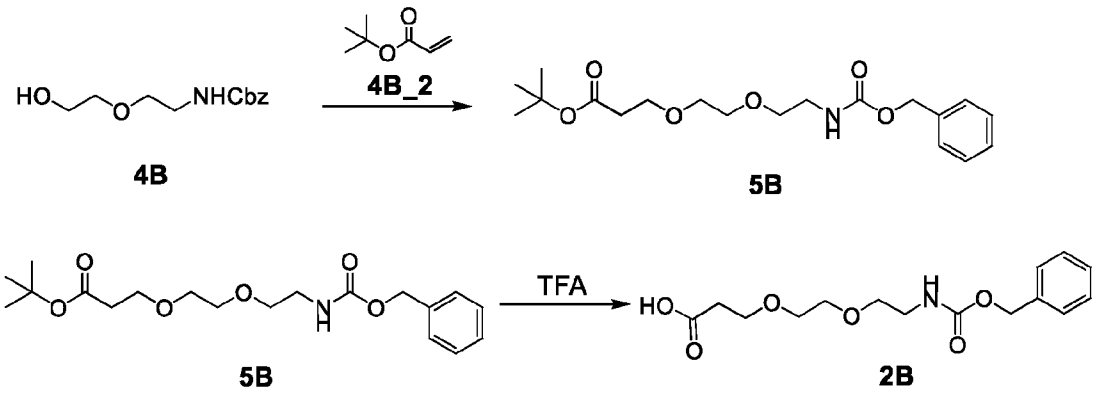
General procedure for preparation of NAcegal-Linker-Tosylate salt



5A **NAcegal-Linker-TMSOTf**

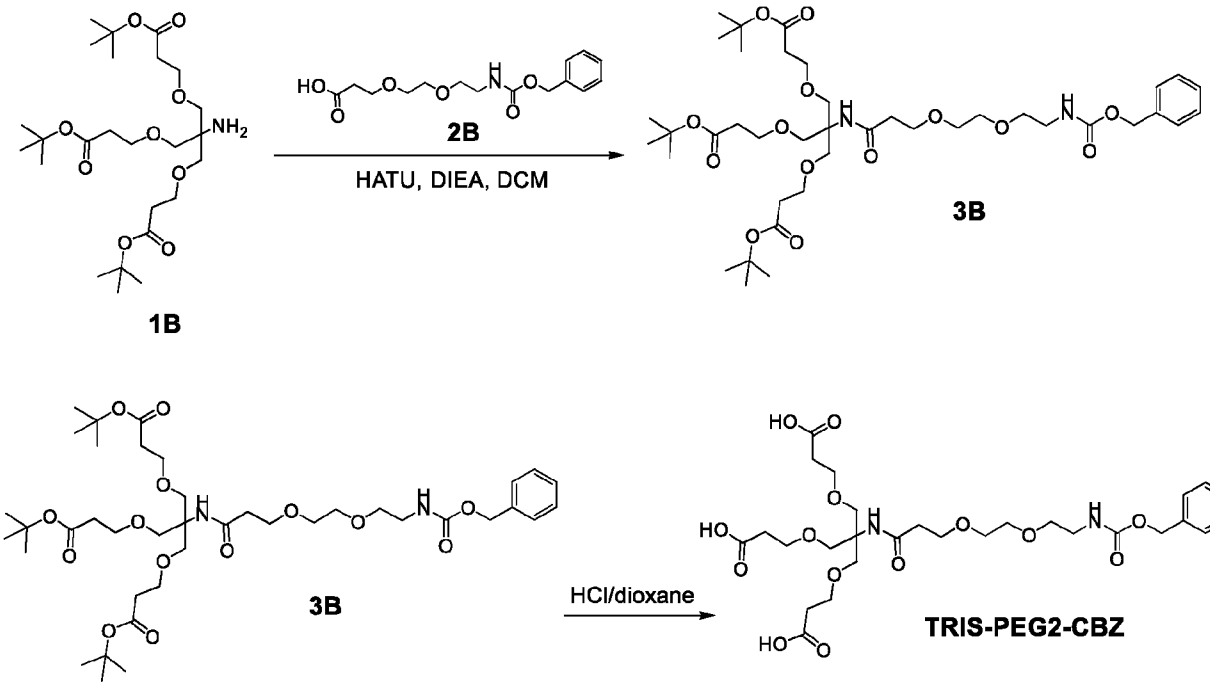
[00244] To a solution of Compound 5A (200 g, 352 mmol) in THF (1.0 L) was added dry Pd/C (15.0 g, 10% purity) and TsOH (60.6 g, 352 mmol) under N_2 atmosphere. The suspension was degassed under vacuum and purged with H_2 several times. The mixture was stirred at 25 °C for 3 hrs under H_2 (45 psi) atmosphere. TLC (DCM: MeOH = 10:1, PMA) indicated Compound 5A was consumed completely and one new spot (R_f = **0.04) was formed. The reaction mixture was filtered and concentrated (≤ 40 °C) under** reduced pressure to give a residue. Diluted with anhydrous DCM (500 mL, dried overnight with 4 Å molecular sieves (dried at 300 °C for 12 hrs)) and concentrate to give a residue and run Karl Fisher (KF) to check for water content. This was repeated 3 times with anhydrous DCM (500 mL) dilutions and concentration to give NAcegal-Linker-TMSOTf (205 g, 95.8% yield, TsOH salt) as a foamy white solid. ^{1}H NMR: **δ 7.91 (d,** *J* = 9.03 Hz, 1 H), 7.53 - 7.86 (m, 2 H), 7.49 (d, *J* = 8.03 Hz, 2 H), 7.13 (d, *J* = 8.03 Hz, 2 H), 5.22 (d, *J* = 3.26 Hz, 1 H), 4.98 (dd, *J* = 11.29, 3.26 Hz, 1 H), 4.57 (d, *J* = 8.53 Hz, 1 H), 3.99 - 4.05 (m, 3 H), 3.87 - 3.94 (m, 1 H), 3.79 - 3.85 (m, 1 H), 3.51 - 3.62 (m, 5 H), 2.96 (br t, *J* = 5.14 Hz, 2 H), 2.29 (s, 3 H), 2.10 (s, 3 H), 2.00 (s, 3 H), 1.89 (s, 3 H), 1.78 (s, 3 H).

Scheme for the preparation of TRIS-PEG2-CBZ

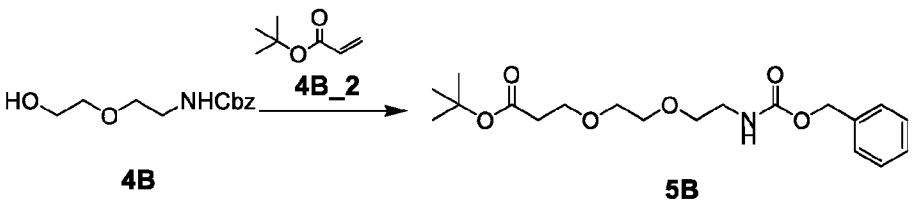


4B **5B**

5B **2B**

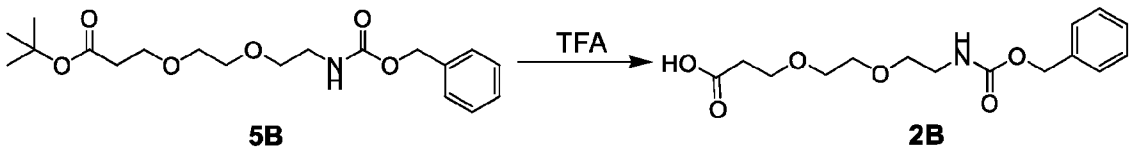


General procedure for preparation of Compound 5B



[00245] To a solution of Compound 4B (400 g, 1.67 mol, 1.00 *eq*) and NaOH (10 M, 16.7 mL, 0.10 *eq*) in THF (2.00 L) was added Compound 4B_2 (1.07 kg, 8.36 mol, 1.20 L, 5.00 *eq*), the mixture was stirred at 30 °C for 2 hrs. LCMS showed the desired MS was given. Five batches of solution were combined to one batch, then the mixture was diluted with water (6.00 L), extracted with ethyl acetate (3.00 L*3), the combined organic layer was washed with brine (3.00 L), dried over Na_2SO_4, filtered and concentrated under vacuum. The crude was purified by column chromatography (SiO_2, petroleum ether : ethyl acetate=100:1-10:1, R_f=0.5) to give Compound 5B (2.36 kg, 6.43 mol, 76.9% yield) as light yellow oil. **HNMR: δ 7.31**-7.36 (m, 5 H), 5.38 (s, 1 H), 5.11-5.16 (m, 2 H), 3.75 (t, J=6.4 Hz), 3.54-3.62 (m, 6 H), 3.39 (d, *J*=5.2 Hz), 2.61 (t, *J*=6.0 Hz).

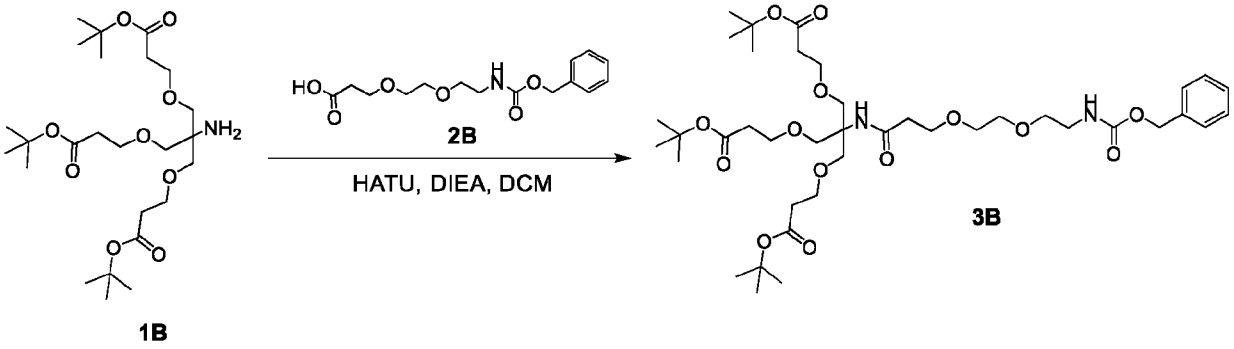
General procedure for preparation of 3-oxo-1-phenyl-2,7,10-trioxa-4-azatridecan-13-oic acid (Compound 2B below)



[00246] To a solution of Compound 5B (741 g, 2.02 mol, 1.00 *eq*) in DCM (2.80 L) was added TFA (1.43 kg, 12.5 mol, 928 mL, 6.22 *eq*), the mixture was stirred at 25 °C for 3 hrs. LCMS showed the desired MS

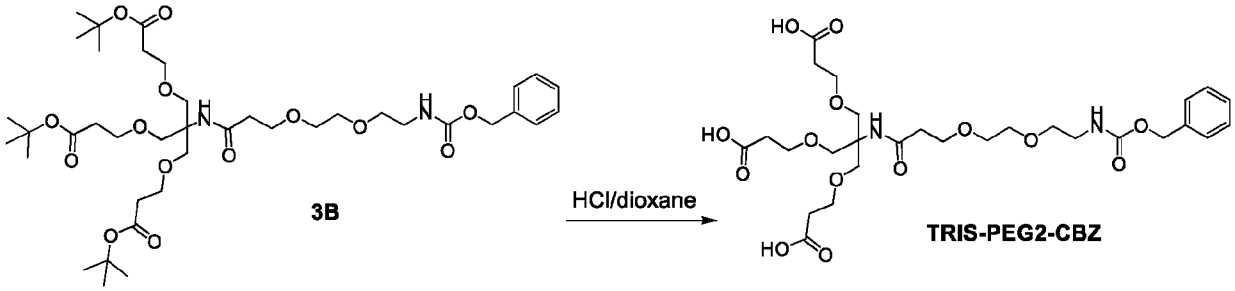
was given. The mixture was diluted with DCM (5.00 L), washed with water (3.00 L*3), brine (2.00 L), the combined organic layer was dried over Na_2SO_4, filtered and concentrated under vacuum to give **Compound 2B (1800 g, crude) as light yellow oil. HNMR: δ 9.46 (s, 5 H),** 7.27-7.34 (m, 5 H), 6.50-6.65 (m, 1 H), 5.71 (s, 1 H), 5.10-5.15 (m, 2 H), 3.68-3.70 (m, 14 H), 3.58-3.61 (m, 6 H), 3.39 (s, 2 H), 2.55 (s, 6 H), 2.44 (s, 2 H).

General procedure for preparation of Compound 3B



[00247] To a solution of Compound 2B (375 g, 999 mmol, 83.0% purity, 1.00 *eq*) in DCM (1.80 L) was added HATU (570 g, 1.50 mol, 1.50 *eq*) and DIEA (258 g, 2.00 mol, 348 mL, 2.00 *eq*) at 0 °C, the mixture was stirred at 0 °C for 30 min, then Compound 1B (606 g, 1.20 mol, 1.20 *eq*) was added, the mixture was stirred at 25 °C for 1 hr. LCMS showed desired MS was given. The mixture was combined to one batch, then the mixture was diluted with DCM (5.00 L), washed with 1 N HCl aqueous solution (2.00 L*2), then the organic layer was washed with saturated Na_2CO_3 aqueous solution (2.00 L *2) and brine (2.00 L), the organic layer was dried over Na_2SO_4, filtered and concentrated under vacuum to give Compound 3B (3.88 kg, crude) as yellow oil.

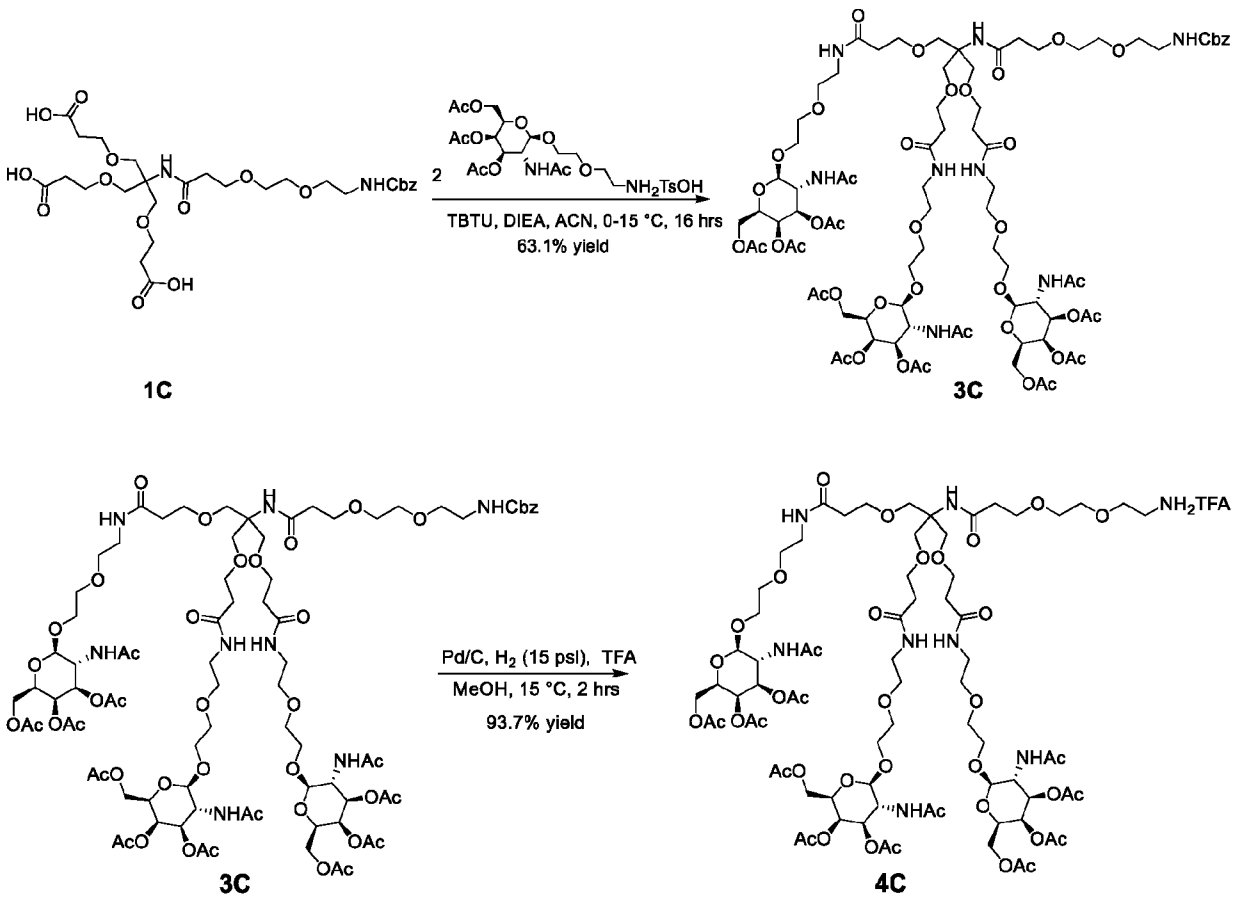
General procedure for preparation of TRIS-PEG2-CBZ.

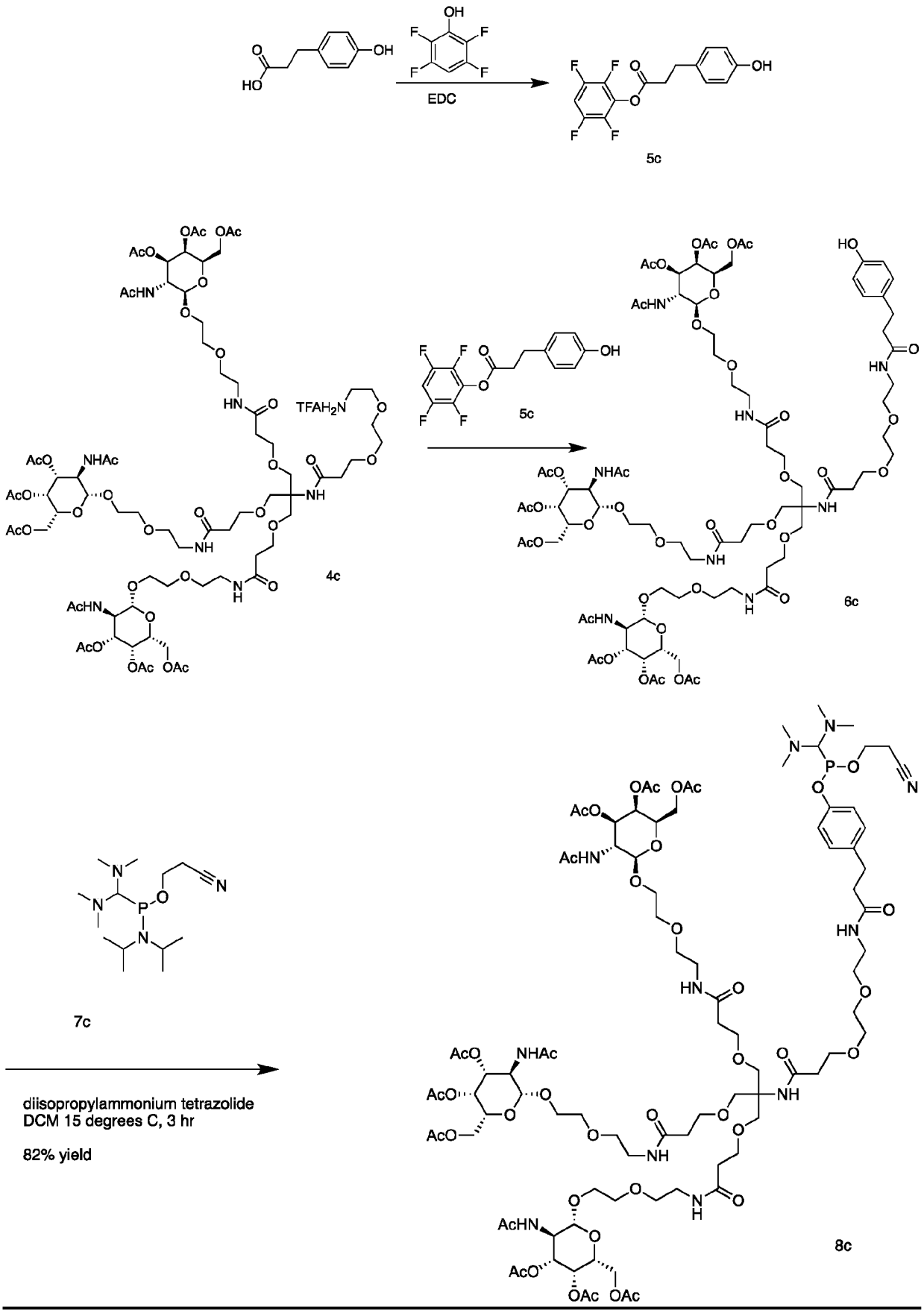


[00248] A solution of Compound 3B (775 g, 487 mmol, 50.3% purity, 1.00 *eq*) in HCl/dioxane (4 M, 2.91 L, 23.8 *eq*) was stirred at 25 °C for 2 hrs. LCMS showed the desired MS was given. The mixture was concentrated under vacuum to give a residue. Then the combined residue was diluted with DCM (5.00 L), adjusted to pH=8 with 2.5 M NaOH aqueous solution, and separated. The aqueous phase was extracted with DCM (3.00 L) again, then the aqueous solution was adjusted to pH=3 with 1 N HCl aqueous solution, then extracted with DCM (5.00 L*2), the combined organic layer was washed with brine (3.00 L), dried over Na_2SO_4, filtered and concentrated under vacuum. The crude was purified by column

chromatography (SiO_2, DCM:MeOH=0:1-12:1, 0.1% HOAc, R_f=0.4). The residue was diluted with DCM (5.00 L), adjusted to pH=8 with 2.5 M NaOH aqueous solution, separated, the aqueous solution was extracted with DCM (3.00 L) again, then the aqueous solution was adjusted to pH=3 with 6 N HCl aqueous solution, extracted with DCM:MeOH=10:1 (5.00 L*2), the combined organic layer was washed with brine (2.00 L), dried over Na_2SO_4, filtered and concentrated under vacuum to give a residue. Then the residue was diluted with MeCN (5.00 L), concentrated under vacuum, repeat this procedure twice to remove water to give TRIS-PEG2-CBZ (1.25 kg, 1.91 mol, 78.1% yield, 95.8% purity) as light yellow oil. ^{1}HNMR: 400 MHz, MeOD, δ 7.30-7.35 (5 H), 5.07 (s, 2 H), 3.65-3.70 (m, 16 H), 3.59 (s, 4 H), 3.45 (t, *J*=5.6 Hz), 2.51 (t, *J*=6.0 Hz), 2.43 (t, 6.4 Hz).

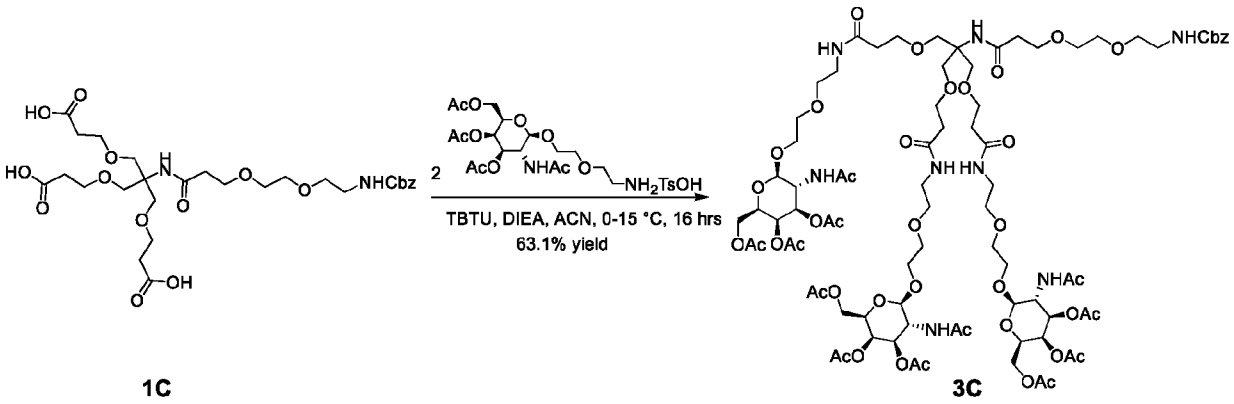
Scheme for the preparation of TriNGal-TRIS-Peg2-Phosph 8c





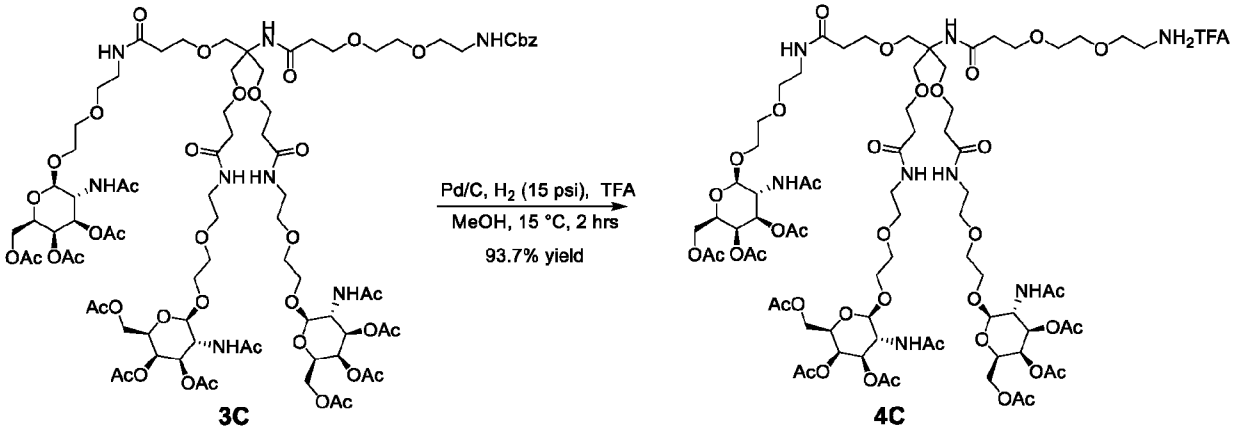
TriGNal-TRIS-Peg2-Phosph 8c

General procedure for preparation of Compound 3C



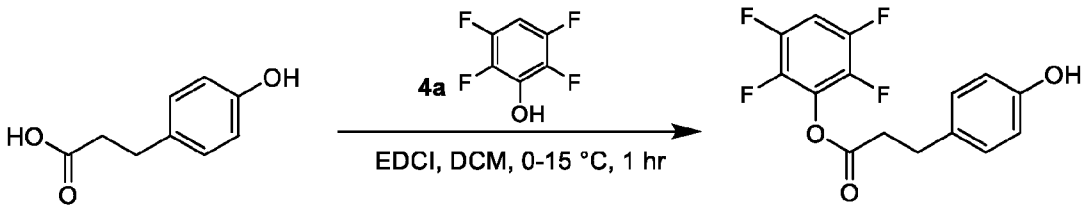
[00249] To a solution of Compound 1C (155 g, 245 mmol, 1.00 *eq*) in ACN (1500 mL) was added TBTU (260 g, 811 mmol, 3.30 *eq*), DIEA (209 g, 1.62 mol, 282 mL, 6.60 *eq*) and Compound 2C (492 g, 811 mmol, 3.30 *eq*, TsOH) at 0 °C, the mixture was stirred at 15 °C for 16 hrs. LCMS showed the desired MS was given. The mixture was concentrated under vacuum to give a residue, then the mixture was diluted with DCM (2000 mL), washed with 1 N HCl aqueous solution (700 mL * 2), then saturated $NaHCO_3$ aqueous solution (700 mL *2) and concentrated under vacuum. The crude was purified by column chromatography to give Compound 3C (304 g, 155 mmol, 63.1% yield, 96.0% purity) as a yellow solid.

General procedure for preparation of Compound 4C



[00250] Two batches solution of Compound 3C (55.0 g, 29.2 mmol, 1.00 *eq*) in MeOH (1600 mL) was added Pd/C (6.60 g, 19.1 mmol, 10.0 % purity) and TFA (3.34 g, 29.2 mmol, 2.17 mL, 1.00 *eq*), the mixture was degassed under vacuum and purged with H_2. The mixture was stirred under H_2 (15 psi) at 15 °C for 2 hours. LCMS showed the desired MS was given. The mixture was filtered and the filtrate was concentrated under vacuum to give Compound 4C (106 g, 54.8 mmol, 93.7% yield, 96.2% purity, TFA) as a white solid.

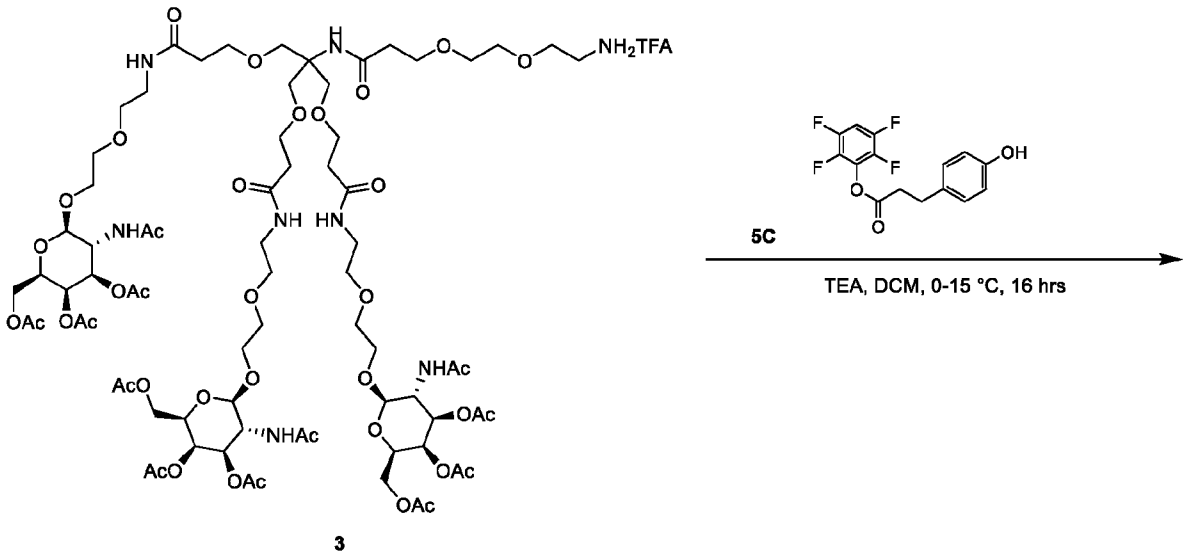
General procedure for preparation of compound 5C



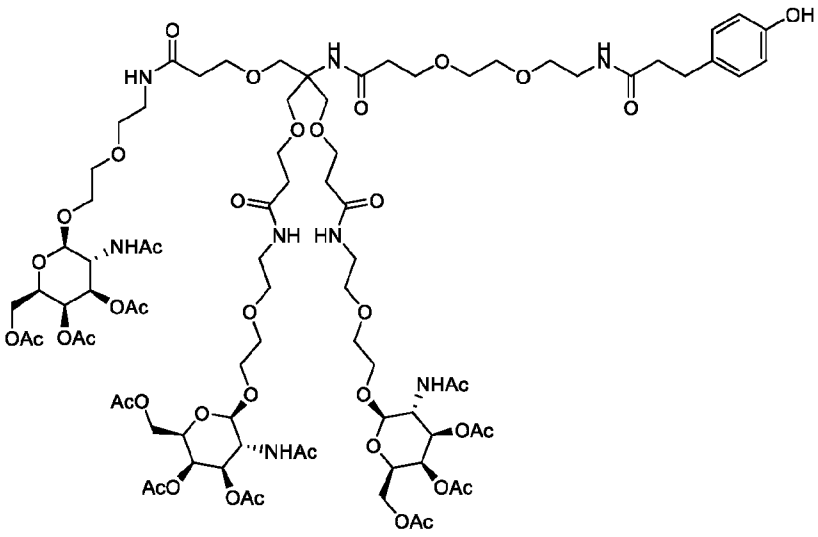
4 **5C**

Two batches in parallel. To a solution of EDCI (28.8 g, 150 mmol, 1.00 eq) in DCM (125 mL) was added compound **4a** (25.0 g, 150 mmol, 1.00 eq) dropwise at 0 °C, then the mixture was added to compound **4** (25.0 g, 150 mmol, 1.00 eq) in DCM (125 mL) at 0 °C, then the mixture was stirred at 25 °C for 1 hr. TLC (Petroleum ether : Ethyl acetate = 3 : 1, R_f = 0.45) showed the reactant was consumed and one new spot was formed. The reaction mixture was diluted with DCM (100 mL) then washed with aq.$NaHCO_3$ (250 mL * 1) and brine (250 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether : Ethyl acetate = 100 : 1 to 3 : 1), TLC (SiO_2, Petroleum ether : Ethyl acetate = 3:1), R_f = 0.45 , then concentrated under reduced pressure to give a residue. Compound **5C** (57.0 g, 176 mmol, 58.4% yield, 96.9% purity) was obtained as colorless oil and confirmed **^{1}HNMR:** EW33072-2-P1A, 400 MHz, DMSO
δ 9.21 (s, 1 H), 7.07-7.09 (m, 2 H), 6.67-6.70 (m, 2 H), 3.02-3.04 (m, 2 H), 2.86-2.90 (m, 2 H)

General procedure for preparation of compound 6



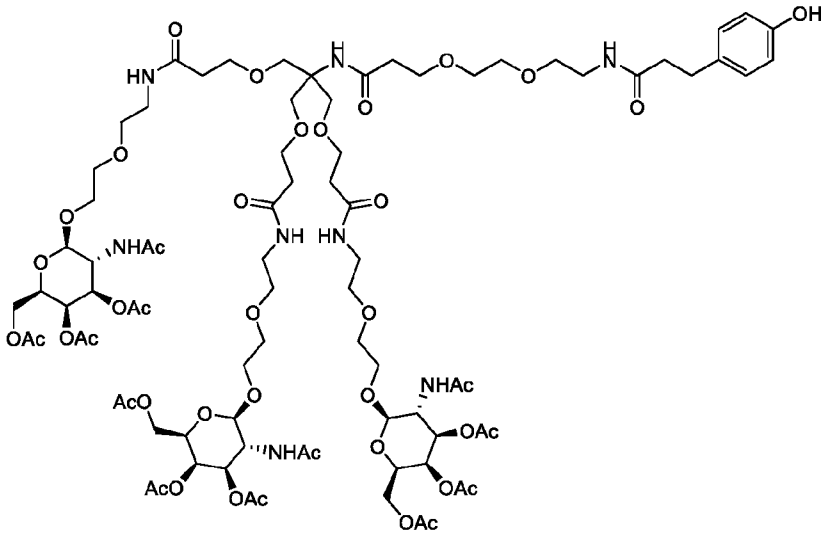
3



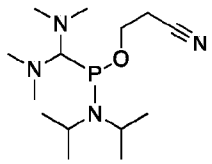
6C

To a mixture of compound **3** (79.0 g, 41.0 mmol, 96.4% purity, 1.00 eq, TFA) and compound **6C** (14.2 g, 43.8 mmol, 96.9% purity, 1.07 eq) in DCM (800 mL) was added TEA (16.6 g, 164 mmol, 22.8 mL, 4.00 eq) dropwise at 0 °C, the mixture was stirred at 15 °C for 16 hrs. LCMS (EW33072-12-P1B, Rt = 0.844 min) showed the desired mass was detected. The reaction mixture was diluted with DCM (400 mL) and washed with aq.$NaHCO_3$ (400 mL * 1) and brine(400 mL * 1), then the mixture was diluted with DCM (2.00 L) and washed with 0.7 M Na_2CO_3 (1000 mL * 3) and brine(800 mL * 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was used to next step directly without purification. Compound **6** (80.0 g, crude) was obtained as white solid and confirmed via **^{1}HNMR:** EW33072-12-P1A, 400 MHz, MeOD δ 7.02 - 7.04 (m, 2 H), 6.68 - 6.70 (m, 2 H), 5.34 - 5.35 (s, 3 H), 5.07 - 5.08 (d, J = 4.00 Hz, 3 H), 4.62 - 4.64 (d, J = 8.00 Hz, 3 H), 3.71 - 4.16 (m, 16 H), 3.31 - 3.70 (m, 44 H), 2.80 - 2.83 (m, 2 H), 2.68 (m, 2 H), 2.46 - 2.47 (m, 10 H), 2.14 (s, 9 H), 2.03 (s, 9 H), 1.94 - 1.95 (d, J = 4.00 Hz, 18 H).

General procedure for preparation of TriGNal-TRIS-Peg2-Phosph 8c



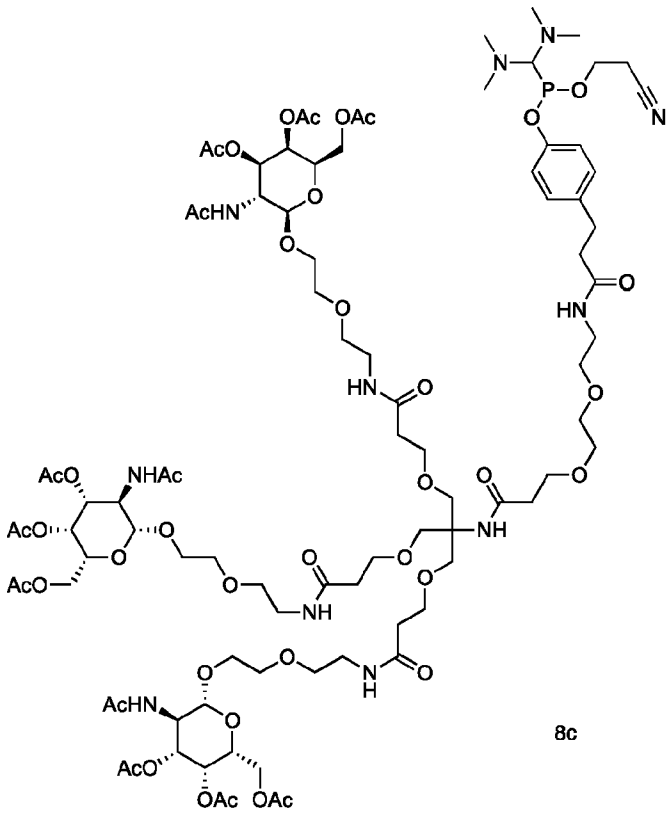
6C



7c

diisopropylammonium tetrazolide
DCM 15 degrees C, 3 hr

82% yield



8c

Two batches were synthesized in parallel. To a solution of compound **6C** (40.0 g, 21.1 mmol, 1.00 eq in DCM (600 mL) was added diisopropylammonium tetrazolide (3.62 g, 21.1 mmol, 1.00 eq) and compound **7c** (6.37 g, 21.1 mmol, 6.71 mL, 1.00 eq) in DCM (8.00 mL) drop-wise, the mixture was stirred at 30 °C for 1 hr, then added compound **7c** (3.18 g, 10.6 mmol, 3.35 mL, 0.50 eq) in DCM (8.00 mL) drop-wise, the mixture was stirred at 30 °C for 30 mins, then added compound **7c** (3.18 g, 10.6 mmol, 3.35 mL, 0.50 eq) in DCM (8.00 mL) drop-wise, the mixture was stirred at 30 °C for 1.5 hrs. LCMS (EW33072-17-P1C1, Rt = 0.921 min) showed the desired MS+1 was detected. LCMS (EW33072-17-P1C2, Rt = 0.919 min) showed the desired MS+1 was detected. Two batches were combined for

work-up. The mixture was diluted with DCM (1.20 L), washed with saturated $NaHCO_3$ aqueous solution (1.60 L * 2), 3% DMF in H_2O (1.60 L * 2), H_2O (1.60 L * 3), brine (1.60 L), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, DCM : MeOH : TEA = 100 : 3 : 2) TLC (SiO_2, DCM: MeOH = 10:1, R_f = 0.45), then concentrated under reduced pressure to give a residue. **Compound 8C** (76.0 g, 34.8 mmol, 82.5% yield, 96.0% purity) was obtained as white solid and confirmed via **^{1}HNMR:** EW33072-19-P1C, 400 MHz, MeOD

δ 7.13-7.15 (d, J = 8.50 Hz, 2 H), 6.95-6.97 (dd, J =8.38, 1.13 Hz, 2 H), 5.34 (d, J =2.88 Hz, 3 H), .09 (dd, J =11.26, 3.38 Hz, 3 H), 4.64 (d, J =8.50 Hz, 3 H), 3.99 - 4.20 (m, 12 H), 3.88 - 3.98 (m, 5 H), 3.66 - 3.83 (m, 20 H), 3.51 - 3.65 (m, 17 H), 3.33 - 3.50 (m, 9 H), 2.87 (t, J =7.63 Hz, 2 H), 2.76 (t, J =5.94 Hz, 2 H), 2.42 - 2.50 (m, 10 H), 2.14 (s, 9 H), 2.03 (s, 9 H), 1.94 - 1.95 (d, J =6.13 Hz, 18 H), 1.24-1.26 (d, J =6.75 Hz, 6 H), 1.18-1.20 (d, J =6.75 Hz, 6 H)

Example 7: *In vitro* hepatocyte targeting using GalNAc-conjugated siRNAs and ASOs

[00251] In this experiment, a hepatocyte cell line expressing asialoglycoprotein receptors and GFP will be treated with anti-GFP siRNAs or ASOs conjugated to a GalNAc moiety compared to a control experiment where the hepatocyte cell line is treated with anti-GFP siRNAs or ASOs that are not conjugated to the GalNAc moiety. GFP mRNA and protein expression are measured, and the amount of GFP mRNA or protein expression in cells treated with the GalNAc-conjugated siRNAs or ASOs is normalized and compared to the amount of GFP mRNA or protein expression in cells treated with the siRNAs or ASOs that are not GalNAc-conjugated. This may allow for a determination of the hepatocyte targeting ability of the GalNAc moiety. Multiple GalNAc moieties may be conjugated to the siRNAs or ASOs and compared to see which GalNAc moiety results in optimal hepatocyte targeting. The GalNAc moieties to be tested in these experiments may a GalNAc moiety described herein.

[00252] Similar experiments may be performed in primary hepatocytes treated with the siRNAs or ASOs conjugated or not to a GalNAc moiety, and a target mRNA or target protein other than GFP may be assessed in the primary hepatocytes.

Example 8: *In Vivo* hepatocyte targeting using GalNAc-conjugated siRNAs and ASOs

[00253] In this experiment, siRNAs or ASOs targeting a target mRNA will be conjugated to a GalNAc moiety and administered to mice (n = 5 / group), and compared to a control experiment where the mice are administered siRNAs or ASOs without GalNAc conjugation. Mice are sacrificed 2 days later, and livers are frozen, later homogenized, and tested for target mRNA and protein expression. The amount of target mRNA or protein expression in the livers of mice treated with the GalNAc-conjugated siRNAs or ASOs is normalized and compared to the amount of GFP mRNA or protein expression in the livers of mice treated with the siRNAs or ASOs that are not GalNAc-conjugated. This may allow for a determination of the liver targeting ability of the GalNAc moiety. Multiple GalNAc moieties may be conjugated to the siRNAs or ASOs and compared to see which GalNAc moiety results in optimal liver

targeting. The GalNAc moieties included in this experiment may be those that exhibit the greatest degree of hepatocyte targeting. The GalNAc moieties to be tested in these experiments may a GalNAc moiety described herein.

Example 9: Inhibition of a target mRNA in a mouse model of a liver disease using GalNAc-conjugated siRNAs and ASOs

[00254] In this experiment, a murine model of a liver disease (in this case, fatty liver disease) will be used to evaluate the effect of siRNA or ASO inhibition of a target mRNA. The target mRNA may encode any target protein where overexpression or overactivation plays a pathological role in the liver disease. In the murine model, fatty liver disease is induced by feeding mice a Western Diet (WD) containing 21.1% fat, 41% Sucrose, and 1.25% Cholesterol by weight (Teklad diets, TD. 120528) and a high sugar solution (23.1g/L d-fructose (Sigma-Aldrich, G8270) and 18.9 g/L d-glucose (Sigma-Aldrich, F0127)) for 12 weeks. At 4-week-old C57BL/6J mice are fed a Western Diet instead of regular chow for 12 weeks. The GalNAc moieties to be used in this experiments may a GalNAc moiety described herein.

[00255] Briefly, mice are divided into five groups: Group 1: a fatty liver disease group treated with non-targeting control siRNA, Group 2: a fatty liver disease group treated with non-targeting control ASO, Group 3: a fatty liver disease group treated with an siRNA targeting a target mRNA, Group 4: a fatty liver disease group treated with an ASO targeting a target mRNA, Group 5: control mice on a normal chow diet. Each group contains eight mice (4 males, 4 females). The siRNAs and ASOs of Groups 1-4 each include a GalNAc moiety attached to the siRNA or ASO.

[00256] At weeks 12 weeks of Western Diet, blood samples are to be collected from each group prior first treatment.

[00257] Administration of siRNA or ASO is achieved with a 200 μL subcutaneous injection of naked siRNA or ASO resuspended in PBS at concentration of 10 μM. On Study Day 0, Group 1 mice will be injected subcutaneously with non-targeting control siRNA, Group 2 mice will be injected subcutaneously with non-targeting control ASO, Group 3 mice will be injected subcutaneously with siRNA1 targeting the target mRNA in a mouse, Group 4 mice will be injected subcutaneously with ASO1 targeting the target mRNA in a mouse, and Group 5 mice will be injected subcutaneously with vehicle. Every other week thereafter starting on Day 14 the animals from each group will be dosed as on Day 0 for a total of 5 injections.

[00258] Weekly blood draws will be taken and serum and plasma isolated. Serum ALT, AST, total cholesterol and triglyceride levels are measured using VITROS 5,1 FS (Ortho Clinical Diagnostics). Non-fasting plasma insulin is measured with the Ultrasensitive Mouse Insulin ELISA kit (Crystal Chem, 90080) according to the manufacturer's instructions. Non-fasting blood glucose is assayed with the One Touch Ultra (Life Scan). HOMA IR and QUICKI will be calculated.

[00259] At the end of 12 weeks of Western Diet and siRNA/ASO treatment, mice are to be sacrificed by cervical dislocation following an intraperitoneal injection of 0.3 ml Nembutal (5 mg/ml). Terminal serum draw is collected via cardiac puncture and final serum ALT, AST, total cholesterol and triglyceride levels

are measure along with non-fasting plasma insulin and glucose. Livers are removed and divided into three sections; one section placed in RNAlater for mRNA isolation, one section flash-frozen for protein isolation, one section fixed in formalin and then paraffin-embedded.

[00260] mRNA is isolated from tissue placed in RNAlater solution using the PureLink kit according to the manufacturer's protocol (ThermoFisher Cat. No. 12183020). The reverse transcriptase reaction is performed according to the manufacturer's protocol. Samples are stored at -80 °C until real-time qPCR is performed in triplicate using TaqMan Gene Expression Assays (Applied Biosystems FAM-probes using a BioRad iCycler). A decrease in target mRNA expression in the liver tissue from mice is dosed with the siRNAs and ASOs compared to target mRNA levels in the liver tissue from mice is dosed with the non-specific control siRNA and ASO. There is an expected decrease in the amount of SDF-1 in the liver tissue from mice that receive the siRNAs and ASOs compared to the amount of SDF-1 in the liver tissue from mice that receive the non-specific control siRNA or ASO. These results show that the siRNAs and ASOs elicit knockdown of the target mRNA and target protein in liver tissue, and that the decrease in target mRNA and target protein expression is correlated with a decrease in SDF-1 production.

[00261] Formalin-fixed, paraffin-embedded liver sections are stained with hematoxylin and eosin (H&E) for assessment of liver histology, with Sirius Red (Sigma, 365548-5G)/Fast Green (Sigma, F258) for assessment of fibrosis, and with periodic acid-Schiff (PAS) for assessment of glycogen accumulation. NAFLD Activity Score (NAS) and fibrosis stage are evaluated by an expert pathologist according to the NASH CRN scoring system13. The histological scoring is performed blinded, with no knowledge by the pathologist of the treatment(s) received. These results show that the siRNAs and ASOs elicit knockdown of the target mRNA and target protein in liver tissue, and that the decrease in expression of the target mRNA and target protein is correlated with a decrease in NAS and NASH CRN.

Example 10: Inhibition of a mouse model of a liver disease

[00262] In this experiment, a murine model of a liver disease (in this case, hypertriglyceridemia) will be used to evaluate the effect of siRNA or ASO inhibition of a target protein expressed in the liver compared to an anti-mouse target protein antibody. The mouse strain C57Bl/6 Apoetm1Unc mice will be maintained on a high fat Western diet (Research Diets, D12492; 60% fat by calories). The target protein may be any target protein where overexpression or overactivation plays a pathological role in the liver disease. The GalNAc moieties to be used in this experiments may a GalNAc moiety described herein.

[00263] Four groups of mice (n=16/group) will be utilized in this study. Animals will be maintained on a high fat diet during the study. On Day -4 before the first injection, chow will be removed for an overnight fast. On Day -3 before the first injection, all animals will be anesthetized and 300 µL of blood collected in serum separator tubes via the submandibular vein to assess baseline triglyceride, serum glucose, insulin sensitivity, total cholesterol levels, HDL Cholesterol levels, liver function and serum levels of target protein. On Study Day 0, Group 1 mice will be injected intraperitoneally with 600 µL normal saline, Group 2 mice will be injected intraperitoneally with 600 µg of anti-mouse target protein antibody in 600 µL, Group 3 mice will be injected subcutaneously with 150 µg of GalNAc-siRNA targeting an mRNA

encoding the target protein in a mouse in 200 μL of normal saline, and Group 4 mice will be injected subcutaneously with 150 μg of GalNAc-ASO targeting the mRNA encoding the target protein in 200 μL of normal saline. On the afternoon of Day 3, the chow will be removed from all Groups for an overnight fast. On Day 4, the animals from all Groups will be anesthetized and 150 μL of blood collected in serum separator tubes via the submandibular vein to assess serum triglycerides, glucose, total cholesterol, HDL cholesterol and levels of the target protein. Animals from all groups will then undergo an oral glucose tolerance test and insulin tolerance test to evaluate insulin sensitivity. Chow will be supplied again as normal after blood has been collected and insulin sensitivity tests conducted. Weekly thereafter starting on Day 7 the animals from Group 2 will be dosed as on Day 0 for a total of 15 injections. Every other week thereafter starting on Day 14 the animals from Group 3 and Group 4 will be dosed as on Day 0 for a total of 8 injections. Every other week starting on Day 10, the mice from all Groups will be fasted (overnight) and bled (150 μL into serum separator tubes) to assess serum triglyceride, glucose, total cholesterol, HDL cholesterol and levels of target protein, and undergo insulin sensitivity tests. On the third day after the final injection, the chow will be removed from all Groups for an overnight fast. On the fourth day after the final injection, the animals from all Groups will be anesthetized, euthanized and bled via cardiac puncture to collect 500 μL of blood into serum separator tubes to assess triglyceride, serum glucose, insulin sensitivity, total cholesterol levels, HDL cholesterol levels, liver function and serum levels of target protein. Tissue from the liver, small intestine and mesenteric lymph nodes will be collected from all animals and immersed in 10% neutral buffered formalin for histopathological analysis. A liver sample will also be collected from all animals and placed in RNAlater. The levels of target mRNA will be assessed by RT-qPCR using TaqMan assays for the mouse target protein and the mouse housekeeping gene PPIA.

[00264] Animals treated with the antibody (Group 2), mice treated with the GalNAc-siRNA (Group 3), and mice treated with the GalNAc-ASO (Group 4) are expected to have decreased triglycerides, total serum cholesterol, serum glucose as well as decreased serum target protein levels, and increased HDL cholesterol and insulin sensitivity, compared with mice from Group 1 (saline). Animals in Group 2 and Group 3 are also expected to have decreased target mRNA in liver samples.

Example 11: Inhibition of a target mRNA in non-human primates using GalNAc-siRNA and GalNAc-ASO

[00265] In this experiment, a NHP model of hypertriglyceridemia is used to evaluate the effect of siRNA or ASO inhibition of the target mRNA expressed in the liver. The target protein may be any target protein where overexpression or overactivation plays a pathological role in the liver disease. Three groups of cynomolgus monkeys will be used (n=5/group) that are placed on a high-fat diet (Western Primate Diet, 5S2T) before the initiation of the study. Alternatively, three groups of rhesus monkeys will be used (n=5/group) that are placed on a high fructose diet before the initiation of the study. Animals are to be given 7 biweekly subcutaneous injections of saline (Group 1), GalNAc-siRNA (Group 2), or GalNAc-ASO (Group 3). The modified GalNAc-siRNA sequences may include any modification pattern described

herein. The GalNAc moieties to be used in this experiments may a GalNAc moiety described herein. Blood samples for lipid and glycemic measurements will be collected at baseline and at 4, 8, and 14 weeks of the study and analyzed for lipid content, serum glucose, insulin sensitivity and target protein. All animals from each group are necropsied 2 weeks after the last blood collection. Tissue from the liver, small intestine and mesenteric lymph nodes will be collected from all animals and immersed in 10% neutral buffered formalin for histopathological analysis. A liver sample will also be collected from all animals and placed in RNAlater. The levels of target mRNA will be assessed by RT-qPCR using TaqMan assays for cynomolgus or rhesus target protein and the cynomolgus or rhesus housekeeping gene PPIA.

[00266] It is expected that animals treated with the GalNAc-siRNA (Group 2) and animals treated with the GalNAc-ASO (Group 3) will show decreased triglycerides, total serum cholesterol and serum glucose as well as decreased serum target protein levels, and increased HDL cholesterol and insulin sensitivity, compared with animals from Group 1 (saline). It is also expected that animals in Group 1 and Group 3 will show decreased target mRNA in liver samples.

Example 12: Inhibition of a target mRNA in a clinical trial using GalNAc-siRNA and GalNAc-ASO

[00267] In this study, human subjects with hypertriglyceridemia are used to evaluate the effect of siRNA or ASO inhibition of a target mRNA expressed in the liver. The target protein may be any target protein where overexpression or overactivation plays a pathological role in the liver disease. Selection criteria for inclusion in the study are ages 40-**90, BMI ≥ 30, and serum triglycerides ≥ 250 mg/dL. Three groups of** subjects will be included (n=15/group) in the study. Subjects are to be given 5 weekly subcutaneous injections of saline (Group 1), GalNAc-siRNA (Group 2), or GalNAc-ASO (Group 3). The GalNAc moieties to be used in these experiments may include a GalNAc moiety described herein.

[00268] . The siRNA or ASO sequences are to be from a selection set that shows high activity in cells in culture or in experiments describe in the other examples. Blood samples for lipid and glycemic measurements will be collected at baseline and at 3, 6, and 12 weeks of the study and analyzed for lipid content, serum glucose, insulin sensitivity, target protein, and liver and kidney function.

[00269] It is expected that subjects treated with the GalNAc-siRNA (Group 2) and subjects treated with GalNAc-ASO (Group 3) will show decreased triglycerides, total serum cholesterol and serum glucose as well as decreased serum target protein levels, and increased HDL cholesterol and insulin sensitivity, compared with subjects from Group 1 (saline).

Example 13: Oligonucleotide Synthesis

[00270] RNAi agents (e.g. siRNAs) were synthesized according to phosphoramidite technology on a solid phase used in oligonucleotide synthesis. A K&A oligonucleotide synthesizer was used. Syntheses were performed on a solid support made of controlled pore **glass (CPG, 500 Å or 600 Å, obtained from AM Chemicals, Oceanside, CA, USA). All 2′-OMe and 2**'-F phosphoramidites were purchased from Hongene Biotech (Union City, CA, USA). All phosphoramidites were dissolved in anhydrous acetonitrile (100 mM) and molecular **sieves (3 Å) were added.** 5-Benzylthio-1H-tetrazole (BTT, 250 mM in acetonitrile) or

5-Ethylthio-1H-tetrazole (ETT, 250 mM in acetonitrile) was used as activator solution. Coupling times were 9-18 min (EmpGalNAc), 6 min (2'OMe and 2'F). In order to introduce phosphorothioate linkages, a 100 mM solution of 3-phenyl 1,2,4-dithiazoline-5-one (POS, obtained from PolyOrg, Inc., Leominster, Mass., USA) in anhydrous acetonitrile was employed.

[00271] After solid phase synthesis, the dried solid support was treated with a 1:1 volume solution of 40 wt. % methylamine in water and 28% ammonium hydroxide solution (Aldrich) for two hours at 30° C. The solution was evaporated and the solid residue was reconstituted in water and purified by anionic exchange HPLC using a TKSgel SuperQ-5PW 13u column. Buffer A was 20 mM Tris, 5 mM EDTA, pH 9.0 and contained 20% Acetonitrile and buffer B was the same as buffer A with the addition of 1 M sodium chloride. UV traces at 260 nm were recorded. Appropriate fractions were pooled then desalted using Sephadex G-25 medium.

[00272] Equimolar amounts of sense and antisense strand were combined to prepare a duplex. The duplex solution was prepared in 0.1×PBS (Phosphate-Buffered Saline, 1×, Gibco). The duplex solution was annealed at 95° C. for 5 min, and cooled to room temperature slowly. Duplex concentration was determined by measuring the solution absorbance on a UV-Vis spectrometer at 260 nm in 0.1×PBS. For some experiments, a conversion factor was calculated from an experimentally determined extinction coefficient.

Example 14: *In Vivo* hepatocyte targeting using GalNAc-conjugated siRNAs and ASOs

[00273] In this experiment, siRNAs or ASOs targeting a target mRNA will be conjugated to a GalNAc moiety and administered to mice (n = 5 / group), and compared to a control experiment where the mice are administered siRNAs or ASOs without GalNAc conjugation. Mice are sacrificed 2 days later, and livers are frozen, later homogenized, and tested for target mRNA and protein expression. The amount of target mRNA or protein expression in the livers of mice treated with the GalNAc-conjugated siRNAs or ASOs is normalized and compared to the amount of GFP mRNA or protein expression in the livers of mice treated with the siRNAs or ASOs that are not GalNAc-conjugated. This may allow for a determination of the liver targeting ability of the GalNAc moiety. Multiple GalNAc moieties may be conjugated to the siRNAs or ASOs and compared to see which GalNAc moiety results in optimal liver targeting. The GalNAc moieties may be those that exhibit the greatest degree of hepatocyte targeting in Example 6. The GalNAc moieties to be tested in these experiments may a GalNAc moiety described herein such as Compound 1or Compound 2.

Example 15: Knockdown of PLIN1 in mice by GalNAc-conjugated siRNAs

[00274] An example GalNAc Moiety, ETL17, was conjugated to siRNAs targeting an example target mRNA. Sequences are shown in **Table 2**. In the table, Nf (e.g. Af, Cf, Gf, Tf, or Uf) is a 2' fluoro-modified nucleoside, n (e.g. a, c, g, t, or u) is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage. The siRNAs were tested for activity in mice.

[00275] Six to eight week old female mice (C57Bl/6) were injected with 10 uL of a recombinant adeno-associated virus 8 (AAV8) vector (1.7 x $10E^{13}$ genome copies/mL) by the retroorbital route on Day -14. The recombinant AAV8 contained the sequence of human PLIN1 (NM_002666.5) under the control of the human thyroxine binding globulin promoter in an AAV2 backbone packaged in AAV8 capsid (AAV8-TBG-h-PLIN1). On Day 0, infected mice (n=4) were given a subcutaneous injection of a single 100 ug dose of a GalNAc-conjugated siRNA or PBS as vehicle control.

[00276] Mice were euthanized on Day 10 after subcutaneous injection and a liver sample from each was collected and placed in RNAlater (ThermoFisher Catalog# AM7020) until processing. Total liver RNA was prepared by homogenizing the liver tissue in homogenization buffer (Maxwell RSC simplyRNA Tissue Kit) using a Percellys 24 tissue homogenizer (Bertin Instruments) set at 5000 rpm for two 10 second cycles. Total RNA from the lysate was purified on a Maxwell RSC 48 platform (Promega Corporation) according to the manufacturer's recommendations. Preparation of cDNA was performed using Quanta qScript cDNA SuperMix (VWR, Catalog# 95048-500) according to the manufacturer's instructions. The relative levels of liver PLIN1 mRNA were assessed by RT-qPCR in triplicate on a QuantStudio™ 6 Pro Real-Time PCR System using TaqMan assays for human PLIN1 (ThermoFisher, assay# Hs01106925_m1) and the mouse housekeeping gene PPIA (ThermoFisher, assay# Mm02342430_g1) and PerfeCTa® qPCR FastMix®, Low ROX™ (VWR, Catalog# 101419-222). Data were normalized to the mean PLIN1 mRNA level in animals receiving PBS. Results are shown in **Table 3.** All of the siRNAs tested caused a reduction in mean liver PLIN1 mRNA on Day 10 relative to mice receiving PBS. These data indicate that siRNAs conjugated to a GalNAc moiety such as ETL17 are useful for knocking down a target mRNA in the liver.

Table 2. Example siRNA Sequences

siRNA Name	SEQ ID NO	Sense Strand Sequence (5′-3′) with GalNAc moiety	SEQ ID NO	Antisense Strand Sequence (5′-3′)
ETD01899	1	[ETL17]scaguuuuuAfaGfggacaccasusu	8	usGfsgUfgUfcCfcUfuAfaAfaAfcUfgsusu
ETD01900	2	[ETL17]suuuuuAfAfGfGfgAfcaccagaasusu	9	usUfscUfgGfuGfuCfcCfuUfaAfaAfasusu
ETD01901	3	[ETL17]suuuugaCfaCfaUfucuuagcasusu	10	usGfscUfaAfgAfaUfgUfgUfcAfaAfasusu
ETD01902	4	[ETL17]suugaCfaCfaUfuCfuuagcacasusu	11	usGfsuGfcUfaAfgAfaUfgUfgUfcAfasusu
ETD01903	5	[ETL17]sacauucuuAfGfcacugaacasusu	12	usGfsuUfcAfgUfgCfuAfaGfaAfuGfususu
ETD01904	6	[ETL17]sugcaUfagUfCfaCfucuuuugasusu	13	usCfsaAfaAfgAfgUfgAfcUfaUfgCfasusu
ETD01905	7	[ETL17]saacuaCfUfgCfaUfaauauggasusu	14	usCfscAfuAfuUfaUfgCfaGfuAfgUfususu

Table 3. Relative human PLIN1 mRNA Levels in Livers of Mice

Group	n	Treatment	Dose (ug)	Mean PLIN1 mRNA (Normalized to Group 1, Day 10)
1	4	PBS	0	1.00
2	4	ETD01899	100	0.79
3	4	ETD01900	100	0.30
4	4	ETD01901	100	0.37
5	4	ETD01902	100	0.24
6	4	ETD01903	100	0.83
7	4	ETD01904	100	0.58

Example 16: Knockdown of MST1 in mice by GalNAc-conjugated siRNAs

[00277] ETL17 was conjugated to siRNAs targeting another example target mRNA. The siRNAs were attached to the GalNAc ligand ETL17 followed by a phosphorothioate linkage at the 5' end of the sense strand. The siRNAs are described in **Table 6**. In the table, Nf (e.g. Af, Cf, Gf, Tf, or Uf) is a 2' fluoro-modified nucleoside, dN (e.g. dA, dC, dG, dT, or dU) is a 2' deoxy-modified nucleoside, n (e.g. a, c, g, t, or u) is a 2' O-methyl modified nucleoside, and "s" is a phosphorothioate linkage.

[00278] Six to eight week old female mice (C57Bl/6) were injected with 5 uL of a recombinant adeno-associated virus 8 (AAV8) vector (2.7 x 10E13 genome copies/mL) by the retroorbital route. The recombinant AAV8 contained the open reading frame and the majority of the 3'UTR of the human MST1 sequence (NM_020998.4) under the control of the human thyroxine binding globulin promoter in an AAV2 backbone packaged in AAV8 capsid (AAV8-TBG-h-MST1). On Day 13 after infection, serum was collected and the level of human MSP in each mouse was measured using the Human MSP/MST1 DuoSet ELISA from R&D (Catalog# DY352). The manufacturer's instructions regarding all reagent preparations for buffers and solutions was followed. A serum sample dilution of 1:50 was utilized for all test samples. Recombinant MSP included in the kit was used to create a standard curve of 10,000 pg/mL to 0 pg/mL. The optical density of the plate was read at 450 nm using a PerkinElmer Envision multimode plate reader. The concentration of MSP in each mouse serum sample was calculated from the standard curve by interpolation using least squares fit (Prism version 9, Software MacKiev).

[00279] Mice were allocated into groups (n=3) such that the groups had similar serum levels of MSP and then given a subcutaneous injection of a single 60 ug dose of a GalNAc-conjugated siRNA or PBS as vehicle control. On Days 0, 4 and 12 after injection, serum was collected to assess serum MSP concentrations by ELISA using the methods described above. The MSP serum concentration at each timepoint was made relative to the level of MSP in the Day 0 sample for each individual mouse. The results are shown in **Table 4**. These data indicate that siRNAs conjugated to a GalNAc moiety such as ETL17 are useful for knocking down proteins secreted by an additional target mRNA in the liver.

[00280] Mice were sacrificed on Day 12 and a liver sample from each was collected and placed in RNAlater (ThermoFisher Cat#AM7020) until processing. Total liver RNA was prepared by homogenizing the liver tissue in homogenization buffer (Maxwell RSC simplyRNA Tissue Kit) using a Percellys 24 tissue homogenizer (Bertin Instruments) set at 5000 rpm for two 10 second cycles. Total RNA from the lysate was purified on a Maxwell RSC 48 platform (Promega Corporation) according to the manufacturer's recommendations. Preparation of cDNA was performed using Quanta qScript cDNA SuperMix (VWR, Catalog# 95048-500) according to the manufacturer's instructions. The relative levels of liver MST1 mRNA were assessed by RT-qPCR in triplicate on a QuantStudio™ 6 Pro Real-Time PCR System using TaqMan assays for human MST1 (ThermoFisher, assay# Hs00360684_m1) and the mouse housekeeping gene PPIA (ThermoFisher, assay# Mm02342430_g1) and PerfeCTa® qPCR FastMix®, Low ROX™ (VWR, Catalog# 101419-222). Data were normalized to the level in animals receiving PBS. Results are shown in **Table 5.** These data indicated that siRNAs conjugated to a GalNAc moiety such as ETL17 are useful for knocking down the additional target mRNA in the liver

Table 4. Relative Mean Serum Human MSP Levels in AAV8-TBG-h-MST1 Mice

Group	n	Treatment	Dose (ug)	Mean serum human MSP (Relative to Day 0)		
				Day 0	Day 4	Day 12
1	3	PBS		1.00	1.12	1.54
2	3	ETD01867	60	1.00	0.35	0.24
3	3	ETD01963	60	1.00	0.46	0.42
4	3	ETD01964	60	1.00	0.35	0.15
5	3	ETD01965	60	1.00	0.32	0.26
6	3	ETD01966	60	1.00	0.30	0.16
7	3	ETD01868	60	1.00	0.67	ND
8	3	ETD01967	60	1.00	0.41	0.27
9	3	ETD01968	60	1.00	0.53	0.30
10	3	ETD01969	60	1.00	0.68	0.45
11	3	ETD01970	60	1.00	0.51	0.59
12	3	ETD01971	60	1.00	0.60	0.42
13	3	ETD01972	60	1.00	0.24	0.17

ND, not determined

Table 5. Relative Human MST1 mRNA Levels in Livers of AAV8-TBG-h-MST1 Mice

Group	n	Treatment	Dose (ug)	Mean human MST1 mRNA (Relative to Group 1, Day 12)
1	3	PBS		1.00
2	3	ETD01867	60	0.40
3	3	ETD01963	60	0.76
4	3	ETD01964	60	0.60
5	3	ETD01965	60	0.25
6	3	ETD01966	60	0.33
7	3	ETD01868	60	0.28
8	3	ETD01967	60	0.07
9	3	ETD01968	60	0.32
10	3	ETD01969	60	0.15
11	3	ETD01970	60	0.24
12	3	ETD01971	60	0.31
13	3	ETD01972	60	0.08

Table 6. siRNAs Screened for Activity in AAV8-TBG-h-MST1 Mice

siRNA Name	SEQ ID NO	Sense Strand Sequence (5′-3′) with GalNAc Moiety	SEQ ID NO.	Antisense Strand Sequence (5′-3′)
ETD01867	43	[ETL17]sucuuGfucAfGfacau aaagcasusu	54	usGfscUfuUfaUfgUfcUfgAfcAfa Gfasusu
ETD01963	44	[ETL17]sucuuGfucAfGfacau aaagcasusu	55	usGfscuuUfaUfgUfcUfgAfcAfaG fasusu
ETD01964	45	[ETL17]sucuuGfucAfGfacau aaagcasusu	56	usGfscuuUfaugUfcUfgAfcAfaGf asusu
ETD01965	46	[ETL17]sucuuGfucAfGfacau aaagcasusu	57	usGfscUfuUfaUfgucUfgAfcAfaG fasusu
ETD01966	47	[ETL17]sucuuGfucAfGfacau aaagcasusu	58	usGfscUfuuAfugUfcUfgAfcAfa Gfasusu

ETD01967	48	[ETL17]suuguCfadGaCfaUfa aagccaasusu	59	usUfsgGfcUfuUfaUfgUfcUfgAfc Afasusu
ETD01968	49	[ETL17]suugucagaCfdAUfaa agccaasusu	60	usUfsgGfcUfuUfaUfgUfcUfgAfc Afasusu
ETD01969	50	[ETL17]suuguCfagaCfaUfaa agccaasusu	61	usUfsggcUfuUfaUfgUfcUfgAfc Afasusu
ETD01970	51	[ETL17]suuguCfagaCfaUfaa agccaasusu	62	usUfsgGfcUfuUfaugUfcUfgAfc Afasusu
ETD01971	52	[ETL17]suuguCfagaCfaUfaa agccaasusu	63	usUfsggcUfuUfaugUfcUfgAfcAf asusu
ETD01972	53	[ETL17]suuguCfagaCfaUfaa agccaasusu	64	usUfsggCfuuuaUfgUfcUfgAfcAf asusu

Example 17: Knockdown of an additional target mRNA in mice by GalNAc-conjugated siRNAs

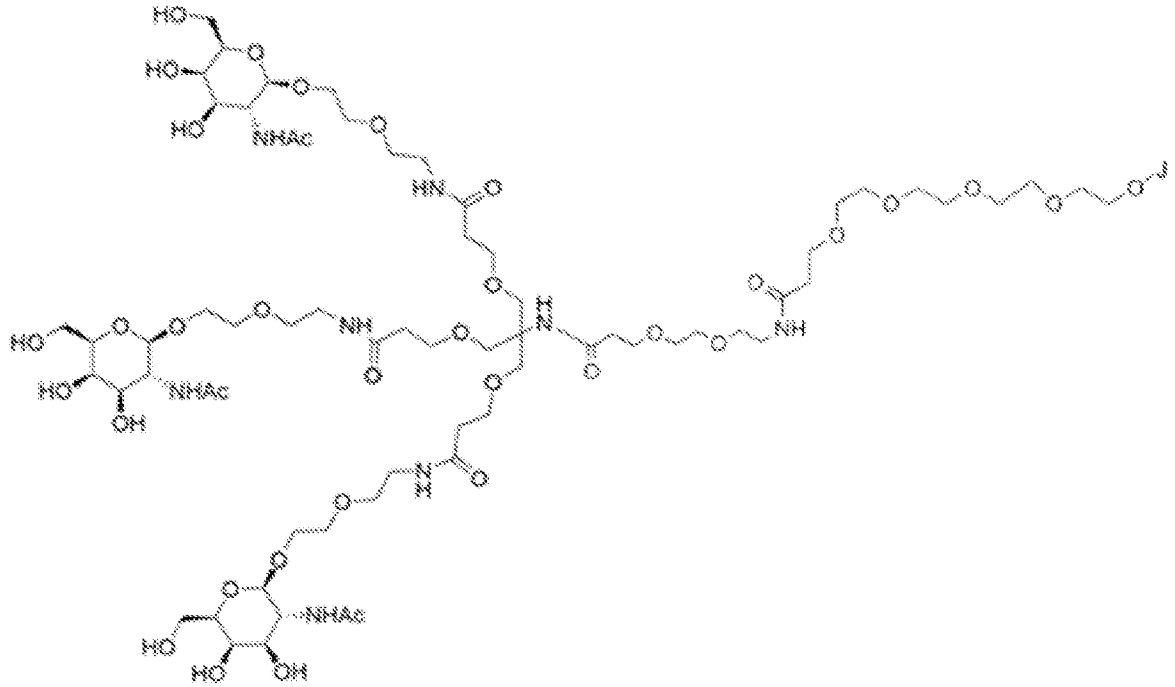
[00281] Three groups (n=4/group) of 8-week-old male ICR mice (Invigo) were utilized in a study. On Study Day 0, Group 1 mice were injected subcutaneously with 100 uL of sterile PBS, Group 2 mice were subcutaneously injected with 60 ug of siRNA 1811 in 100 uL of sterile PBS, and Group 3 mice were subcutaneously injected with 200 ug siRNA 1818 in 100 uL of sterile PBS. On Study Day 14, the animals from all Groups were anesthetized and then euthanized. A liver sample was collected from all animals and placed in RNAlater™ Stabilization Solution (Thermo Fisher, Catalog# AM7020). The liver samples were processed in homogenization buffer (Maxwell RSC simplyRNA Tissue Kit) using Soft Tissue Homogenizing Kit CK14 (Bertin Instruments, catalog# P000933-LYSK0-A) in a Percellys 24 tissue homogenizer (Bertin Instruments) set at 5000 rpm for two 10 second cycles. Total RNA from the liver lysate was purified on a Maxwell RSC 48 platform (Promega Corporation) according to the manufacturer's recommendations. The relative level of Gene A mRNA in each liver sample was assessed by RT-qPCR on a QuantStudio 6 Pro instrument (Applied Biosystems) using TaqMan assays for mouse Gene A and the mouse housekeeping gene PPIA, and then normalized to the mean value of the control mice (Group 1) using the delta-delta Ct method.

[00282] In this example, an additional GalNAc moiety (ETL1) was compared to ETL17. The results of the liver mRNA analyses are shown in **Table 7**. Animals treated with ETL1-targeted siRNA (ETD01811, Group 2) had 78% relative knockdown while ETL17-targeted siRNA (siRNA 1818, Group 3) had 83% knockdown of liver Gene A mRNA levels, compared with mice injected with PBS (Group 1). Thus, a compound having a GalNAc moiety described herein may be superior or at least as effective relative to another GalNAc moiety in knocking down a target such as a target mRNA.

Table 7: Day 14 Gene A mRNA liver levels in mice treated with siRNAs targeting Gene A

Group #	Treatment	Mean
1	PBS	1.00
2	siRNA 1811 (with control GalNAc ETL1)	0.22
3	siRNA 1818 (with ETL17)	0.17

[00283] ETL1 is shown below, in which J indicates an attachment to an oligonucleotide:



Example 18. Testing the activity of *MST1* siRNAs ETD01821, ETD01822, ETD01823 and ETD01826 in non-human primates

[00284] Four groups (n=3/group) of 3-6 kg male cynomolgus monkeys (Zhaoqing Chuangyao Biotechnology Co., Ltd and Guangzhou Xiannggguan Biotechnology Co., Ltd) were utilized for this study.

[00285] On Study Day 0, Group 1 cynomolgus monkeys were injected subcutaneously with a single 5 mg/kg dose (0.2 mL dose volume/kg body weight) of ETD01821 at an siRNA concentration of 25 mg/mL formulated in PBS, Group 2 cynomolgus monkeys were injected with a single 5 mg/kg dose (0.2 mL dose volume/kg body weight) of ETD01822 at an siRNA concentration of 25 mg/mL formulated in PBS, Group 3 cynomolgus monkeys were injected with a single 5 mg/kg dose (0.2 mL dose volume/kg body weight) of ETD01823 at an siRNA concentration of 25 mg/mL formulated in PBS, Group 4 cynomolgus monkeys were injected with a single 5 mg/kg dose (0.2 mL dose volume/kg body weight) of ETD01826 at an siRNA concentration of 25 mg/mL formulated in PBS, The siRNA sequences are shown in **Table 8**, **where "Nf" is a 2' fluoro-modified nucleoside, "n" is a 2' O-methyl modified nucleoside, and "s" is a** phosphorothioate linkage. The injection was generally well-tolerated as measured by clinical symptoms.

[00286] All cynomolgus monkeys had no abnormal clinical symptoms during the duration of the study except animal No.101 which was found dead on Day 65 post-dose. Necropsy revealed severe gastric perforation that may have been the cause of death. This can spontaneously occur in cynomolgus monkeys.

[00287] On Study Days -8, -1, 7, 14, 21 and Day 28 body weights were recorded. Results are shown in **Table 9**. Data indicates that the animals in group 1 to 4 did not have a meaningful change in their body weight.

[00288] On Study Days -8, -2, 7, 14, and Day 28 blood was collected into tubes with no anti-coagulant and serum collected. Clinical chemistry parameters containing ALT, AST, ALP, TBIL, DBIL, GLU, GGT, TP, TG, CHOL, HDL, LDL, BUN and CREA were analyzed. Animals treated with ETD01821,

ETD01822, ETD01823, or ETD01926 showed no meaningful change in ALT, AST, ALP, TBIL, DBIL, GLU, GGT, TP, TG, CHOL, HDL, LDL, BUN and CREA starting on Study Day 7 though Study Day 28 when compared to Study Day -8 and Study Day -2, prior to treatment. The results from the clinical chemistry indicated that all the siRNAs were generally well tolerated. Results are shown in **Tables 10-14**.

[00289] On Study Days -8, -2, 7, 14, and Day 28 about 1 mL of whole blood was collected into tubes with EDTA-K2 as the anti-coagulant. Hematology parameters including WBC, NEUT, LYMP, MONO, EOS, BASO, RBC, HGB, HCT, MCV, MCH, MCHC, RDW, PLT, MPV, PCT and PDW were analyzed. Animals treated with ETD01821, ETD01822, ETD01823, or ETD01926 showed no meaningful change in these hematological parameters starting on Study Day 7 though Study Day 28 when compared to Study Day -8 and Study Day -2, prior to treatment. The results from the hematological analyses indicated that all the siRNAs were generally well tolerated. Results are shown in **Tables 15-19**.

[00290] On Study Days -8, -2, 7, 14, 28, 42, 56, 70, 77, 84, 91, 98 and Day 105, blood was collected into tubes with no anti-coagulant and serum collected for determination of serum macrophage stimulating protein (MSP) levels. Additional serum samples were taken at later timepoints, namely on Days 42, 56, 70, 77, 84, 91, 98 and Day 105. A custom AlphaLISA assay (PerkinElmer) was used to evaluate individual macrophage stimulating protein (MSP) concentrations in the monkey serum samples. Briefly, 5 uL of serum sample diluted 1:50 in 1x AlphaLISA HiBlock was placed into a well of a 96 well plate followed by addition of 5 uL of 4x anti-MSP acceptor bead solution. After incubation at room temperature for 30 minutes, 5 uL of 4x biotinylated anti-MSP antibody solution was added and the plate incubated at room temperature for 60 minutes. Next, 5uL of 4x streptavidin donor bead solution was added and the plate incubated for a further 30 minutes at room temperature. The plate was analyzed on an Envision 2105 Multimode Plate Reader (PerkinElmer). A standard curve was generated using recombinant human MSP (R&D Systems). The MSP serum concentration for each individual at each timepoint was made relative to the mean of the MSP serum concentration for that individual on Days -2 and Day -8. Results for Group means are shown in **Table 20** and individual values are shown in **Table 21**. Serum levels of MSP were decreased in all animals after treatment with test articles starting at Day 7 and remained decreased at least through Day 28. Monkeys treated with ETD01821 had the greatest decrease in serum MSP levels relative to pre-dose levels, showing decreased mean serum MSP level compared to pre-dose levels through Day 105.

[00291] On Study Day -8 and Day 28, the animals were anesthetized with Zoletil (1.5 - 5.0 mg/kg, i.m.) and xylazine (0.5 - 2.0 mg/kg, i.m.) and 3-4mg liver biopsy was collected. The biopsy was then placed in **10 v/v RNAlater in 20 seconds and stored for 24 hrs at 4°C, the RNAlater™ Stabilization Solution** (Thermo Fisher, Catalog# AM7020) was then removed and the liver tissue was stored in freezer until they were shipped to Empirico. There were no abnormal clinical observations for all animals after liver biopsy collection on Day -2 or Day 28. The liver samples were processed in homogenization buffer (Maxwell RSC simplyRNA Tissue Kit) using Soft Tissue Homogenizing Kit CK14 (Bertin Instruments, catalog# P000933-LYSK0-A) in a Percellys 24 tissue homogenizer (Bertin Instruments) set at 5000 rpm for two 10 second cycles. Total RNA from the liver lysate was purified on a Maxwell RSC 48 platform (Promega

Corporation) according to the manufacturer's recommendations. Preparation of cDNA was performed using Quanta qScript cDNA SuperMix (VWR, Catalog# 95048-500) according to the manufacturer's instructions. The relative levels of liver MST1 mRNA were assessed in biplexed reactions by RT-qPCR in triplicate using TaqMan assays for Macaca fascicularis MST1 (ThermoFisher, assay# Mf01117426_g1) and the Macaca fascicularis housekeeping gene GAPDH (ThermoFisher, assay# Mf04392546_g1) in PerfeCTa qPCR FastMix Reaction Mix (VWR). The samples were assessed on a QuantStudio™ 6 Pro Real-Time PCR System. The delta-delta Ct method was used to calculate relative amounts of MST1 mRNA. Group mean relative MST1 mRNA levels relative to Day -8 are shown in **Table 22**. Consistent with the decrease in serum MSP levels as measured by AlphaLISA, treatment with 5 mg/kg of the test articles ETD01821, ETD01822, ETD01823 or ETD01826 resulted in a decrease in the liver levels of MST1 mRNA on Day 28 compared to the pre-dose Day -8 levels.

Table 8. Example siRNA Sequences

siRNA Name	Sense Strand SEQ ID NO:	Sense Strand Sequence (5′-3′) with GalNAc moiety	Antisense Strand SEQ ID NO:	Antisense Strand Sequence (5′-3′)
ETD01821	15	[ETL17]sgguccuGfGfAfAfGfg aauuauasusu	19	usAfsuAfaUfuCfcUfuCfcAfg GfaCfcsusu
ETD01822	16	[ETL17]sAfaCfuUfcUfudGuCf agaCfaUfaasusu	20	usUfsaUfgUfcUfgAfcAfaGfa AfgUfususu
ETD01823	17	[ETL17]scuucUfUfgUfCfagaca uaaaasusu	21	usUfsuUfaUfgUfcUfgAfcAfa GfaAfgsusu
ETD01826	18	[ETL17]scaaccAfGfGfAfGfug uaacauasusu	22	usAfsuGfuUfaCfaCfuCfcUfg GfuUfgsusu

Table 9. Body Weight (kg)

Treatment group	Animal No.	Gender	Days prior to dose and post-dose						
			-8	-1	0	7	14	21	28
G1: ETD01821	101	Male	5.6	5.5	5.6	5.7	5.7	5.8	5.6
	102	Male	6.0	6.0	6.0	5.9	6.1	6.2	6.1
	103	Male	4.5	4.6	4.5	4.6	4.6	4.7	4.5
G2: ETD01822	201	Male	6.5	6.5	6.5	6.6	6.5	6.5	6.5
	202	Male	4.3	4.3	4.4	4.4	4.5	4.6	4.4
	203	Male	5.5	5.5	5.6	5.6	5.6	5.4	5.6
G3: ETD01823	301	Male	4.7	4.5	4.6	4.7	4.8	4.7	4.9
	302	Male	4.6	4.6	4.6	4.6	4.6	4.7	4.5
	303	Male	3.8	3.8	3.7	3.8	3.7	3.6	3.7
G4: ETD01826	401	Male	3.7	3.6	3.7	3.8	3.7	3.8	3.7
	402	Male	5.9	5.9	6.0	5.9	6.0	6.1	6.0
	403	Male	4.5	4.6	4.6	4.6	4.5	4.5	4.6

Table 10. Individual and Mean Clinical Chemistry Parameters Results on Pre-dose (Day-8)

Treatment group		G1: ETD01821					G2: ETD01822				
Animal No.		101	102	103	Mean	SD	201	202	203	Mean	SD
Gender		Male	Male	Male			Male	Male	Male		
Animal ID		SC1702037	SC1509029	175151C			SC1508015	SC1704115	SC1703011		
Parameters (unit)	ALT (U/L)	27.5	15.2	27.0	23.2	6.96	15.0	29.0	31.4	25.1	8.86
	AST (U/L)	29.9	22.8	29.6	27.4	4.02	20.6	42.3	29.2	30.7	10.9
	ALP (U/L)	530	228↓	667	475	224	209↓	473	675	453	234
	TBIL (μmol/L)	1.54	1.37	1.28	1.40	0.13	1.04	1.68	2.06	1.59	0.52
	DBIL (μmol/L)	0.11	0.53	0.46	0.37	0.23	0.17	0.38	0.36	0.30	0.12
	GLU (mmol/L)	3.92	3.38	3.03	3.44	0.45	2.88	2.92	3.54	3.11	0.37
	GGT (U/L)	102	76.2	91.4	89.8	12.8	71.0	69.4	64.2	68.2	3.57
	TP (g/L)	73.4	68.2	70.2	70.6	2.60	64.4	69.1	67.8	67.1	2.40
	TG (mmol/L)	0.96	0.37	0.78	0.70	0.30	0.31	0.22	0.55	0.36	0.17
	BUN (mmol/L)	14.3	10.9	13.6	13.0	1.78	17.4	10.7	15.3	14.5	3.44
	CREA (μmol/L)	75.2	64.9	71.5	70.5	5.22	76.9	67.2	76.7	73.6	5.54
Treatment group		G3: ETD01823					G4: ETD01826				
Animal No.		301	302	303	Mean	SD	401	402	403	Mean	SD
Gender		Male	Male	Male			Male	Male	Male		
Animal ID		177695C	SC1704077	176313C			SC1708089	SC1604087	SC1703023		
Parameters (unit)	ALT (U/L)	41.2	35.4	26.5	34.4	7.40	19.6	32.4	12.0	21.3	10.31
	AST (U/L)	33.4	32.5	29.2	31.7	2.21	28.2	28.0	28.7	28.3	0.36
	ALP (U/L)	735	837	585	719	127	775	346	492	538	218
	TBIL (μmol/L)	2.03	2.71	1.47	2.07	0.62	1.80	3.67	1.49	2.32	1.18

	DBIL (μmol/L)	0.49	1.00	0.29	0.59	0.37	0.89	2.40	0.70	1.33	0.93
	GLU (mmol/L)	4.13	3.17	3.82	3.71	0.49	2.93	4.14	3.49	3.52	0.61
	GGT (U/L)	119	100	91.1	104	14.2	84.1	69.5	47.2	66.9	18.6
	TP (g/L)	64.5	60.5	67.3	64.1	3.41	62.5	61.2	50.3	58.0	6.68
	TG (mmol/L)	0.31	0.19	0.70	0.40	0.27	0.45	0.22	0.53	0.40	0.16
	BUN (mmol/L)	13.4	11.5	17.2	14.0	2.93	11.5	11.9	17.9	13.7	3.59
	CREA (μmol/L)	61.0	59.3	79.4	66.6	11.1	64.3	90.2	85.5	80.0	13.8

Note: The ↓ next to the value means the result was slightly lower than that of other animals.

Table 11. Individual and Mean Clinical Chemistry Parameters Results on Pre-dose (Day-2)

Treatment group		G1: ETD01821					G2: ETD01822				
Animal No.		101	102	103	Mean	SD	201	202	203	Mean	SD
Gender		Male	Male	Male			Male	Male	Male		
Animal ID		SC1702037	SC1509029	175151C			SC1508015	SC1704115	SC1703011		
Parameters (unit)	ALT (U/L)	34.4	23.3	45.4	34.4	11.1	21.0	31.5	33.4	28.6	6.68
	AST (U/L)	20.9	20.3	44.7	28.6	13.9	20.1	30.0	34.0	28.0	7.16
	ALP (U/L)	477	251↓	634	454	192	279↓	489	630	466	177
	TBIL (μmol/L)	1.83	1.48	1.07	1.46	0.38	1.52	2.07	2.69	2.09	0.59
	DBIL (μmol/L)	0.26	0.05	0.02	0.11	0.13	0.01	0.38	0.58	0.32	0.29
	GLU (mmol/L)	3.31	3.56	3.41	3.43	0.13	4.40	3.15	3.45	3.67	0.65
	GGT (U/L)	104	79.4	97.2	93.6	12.7	98.2	70.2	68.7	79.0	16.6
	TP (g/L)	79.9	74.9	77.0	77.3	2.53	79.3	76.6	77.2	77.7	1.43
	TG (mmol/L)	0.73	0.47	1.48	0.89	0.52	0.47	0.24	0.47	0.39	0.13
	BUN (mmol/L)	13.8	11.9	13.9	13.2	1.12	14.1	11.1	15.4	13.5	2.22
	CREA (μmol/L)	85.4	70.8	66.1	74.1	10.1	86.5	63.3	81.4	77.1	12.2
Treatment group		G3: ETD01823					G4: ETD01826				

Animal No.		301	302	303	Mean	SD	401	402	403	Mean	SD
Gender		Male	Male	Male			Male	Male	Male		
Animal ID		177695C	SC1704077	176313C			SC1708089	SC1604087	SC1703023		
Parameters (unit)	ALT (U/L)	32.6	42.6	38.3	37.8	5.02	24.5	42.5	11.9	26.3	15.4
	AST (U/L)	28.7	30.9	33.0	30.9	2.15	25.7	31.7	24.1	27.2	4.01
	ALP (U/L)	679	821	580	693	121	762	478	427	556	180
	TBIL (μmol/L)	2.89	2.74	2.33	2.65	0.29	2.15	1.89	0.74	1.59	0.75
	DBIL (μmol/L)	0.72	0.39	0.69	0.60	0.18	0.51	0.21	----	0.36	0.21
	GLU (mmol/L)	3.50	3.76	3.85	3.70	0.18	3.98	6.44	4.04	4.82	1.40
	GGT (U/L)	116	100	96.9	104	10.0	86.4	86.3	50.6	74.4	20.6
	TP (g/L)	70.8	65.4	71.5	69.2	3.31	67.9	75.8	52.7	65.5	11.7
	TG (mmol/L)	0.32	0.24	0.39	0.32	0.08	0.48	0.32	1.08	0.63	0.40
	BUN (mmol/L)	12.7	10.3	17.5	13.5	3.66	12.6	11.9	16.0	13.5	2.16
	CREA (μmol/L)	60.1	57.7	74.6	64.1	9.14	63.0	106	69.8	79.5	22.9

Note: The ↓ next to the value means the result was slightly lower than that of other animals. '----' means that DBIL of some samples cannot be detected due to the low concentration.

Table 12. Individual and Mean Clinical Chemistry Parameters Results on Day 7 post-dose

Treatment group		G1: ETD01821					G2: ETD01822				
Animal No.		101	102	103	Mean	SD	201	202	203	Mean	SD
Gender		Male	Male	Male			Male	Male	Male		
Animal ID		SC1702037	SC1509029	175151C			SC1508015	SC1704115	SC1703011		
Parameters (unit)	ALT (U/L)	32.5	22.7	38.2	31.1	7.84	19.9	36.2	28.7	28.3	8.16
	AST (U/L)	22.3	20.0	32.1	24.8	6.43	16.4	34.2	25.4	25.3	8.90
	ALP (U/L)	453	276↓	749	493	239	272↓	535	628	479	185
	TBIL (μmol/L)	1.56	1.50	1.92	1.66	0.23	1.66	2.22	2.11	2.00	0.30
	DBIL (μmol/L)	0.09	----	0.30	0.20	0.15	0.58	----	0.97	0.78	0.28

	GLU (mmol/L)	3.69	3.91	3.83	3.81	0.11	4.49	4.53	4.32	4.45	0.11
	GGT (U/L)	104	78.4	103	95.1	14.4	90.8	71.2	64.5	75.5	13.7
	TP (g/L)	82.8	78.8	82.8	81.4	2.30	76.1	80.8	76.5	77.8	2.58
	TG (mmol/L)	0.64	0.59	0.81	0.68	0.12	0.30	0.34	0.65	0.43	0.19
	BUN (mmol/L)	14.1	10.5	13.9	12.8	2.02	11.8	11.2	14.2	12.4	1.58
	CREA (μmol/L)	82.1	68.0	62.8	71.0	9.99	85.0	67.7	76.9	76.5	8.66
Treatment group		G3: ETD01823					G4: ETD01826				
Animal No.		301	302	303	Mean	SD	401	402	403	Mean	SD
Gender		Male	Male	Male			Male	Male	Male		
Animal ID		177695C	SC1704077	176313C			SC1708089	SC1604087	SC1703023		
Parameters (unit)	ALT (U/L)	29.9	41.6	30.7	34.1	6.54	23.0	49.4	15.1	29.2	18.0
	AST (U/L)	28.0	29.6	26.2	27.9	1.70	24.5	28.2	21.4	24.7	3.40
	ALP (U/L)	806	776	570	718	129	659	510	433	534	115
	TBIL (μmol/L)	2.70	1.91	1.79	2.13	0.49	2.15	2.29	1.61	2.02	0.36
	DBIL (μmol/L)	0.39	0.81	0.61	0.60	0.21	0.30	0.31	0.60	0.40	0.17
	GLU (mmol/L)	3.93	4.27	3.86	4.02	0.22	3.64	4.60	4.41	4.22	0.51
	GGT (U/L)	129	96.2	87.0	103.9	21.8	82.0	94.0	55.9	77.3	19.5
	TP (g/L)	75.2	66.4	73.4	71.7	4.67	71.4	83.0	58.6	71.0	12.2
	TG (mmol/L)	0.36	0.37	0.47	0.40	0.06	0.47	0.27	0.46	0.40	0.11
	BUN (mmol/L)	11.7	10.2	18.7	13.6	4.52	13.7	13.6	14.0	13.8	0.19
	CREA (μmol/L)	65.8	55.4	70.7	64.0	7.81	60.9	101	75.6	79.0	20.0

Note: The ↓ next to the value means the result was slightly lower than that of other animals. '----' means that DBIL of some samples cannot be detected due to the low concentration.

Table 13. Individual and Mean Clinical Chemistry Parameters Results on Day 14 post-dose

Treatment group	G1: ETD01821					G2: ETD01822				
Animal No.	101	102	103	Mean	SD	201	202	203	Mean	SD

Gender		Male	Male	Male			Male	Male	Male		
Animal ID		SC1702037	SC1509029	175151C			SC1508015	SC1704115	SC1703011		
Parameters (unit)	ALT (U/L)	37.0	25.4	66.9	43.1	21.4	20.0	30.4	29.1	26.5	5.67
	AST (U/L)	26.0	20.5	178	74.9	89.6	18.2	26.1	25.5	23.3	4.40
	ALP (U/L)	557	275↓	781	538	254	298↓	509	630	479	168
	TBIL (μmol/L)	1.60	1.74	1.82	1.72	0.11	1.73	1.88	2.18	1.93	0.23
	DBIL (μmol/L)	----	0.28	----	0.28	0.00	----	0.40	0.73	0.57	0.23
	GLU (mmol/L)	3.32	3.50	5.43	4.08	1.17	4.57	3.52	4.01	4.03	0.53
	GGT (U/L)	118	76.7	101	98.6	20.8	102	66.3	63.3	77.1	21.4
	TP (g/L)	88.7	76.8	83.9	83.1	5.97	80.2	79.4	75.2	78.3	2.69
	TG (mmol/L)	1.09	0.53	0.60	0.74	0.31	0.32	0.24	0.65	0.40	0.22
	BUN (mmol/L)	14.0	10.1	16.5	13.5	3.25	15.9	11.7	13.3	13.6	2.13
	CREA (μmol/L)	98.9	67.8	69.1	78.6	17.6	95.2	69.8	78.7	81.2	12.9
Treatment group		G3: ETD01823					G4: ETD01826				
Animal No.		301	302	303	Mean	SD	401	402	403	Mean	SD
Gender		Male	Male	Male			Male	Male	Male		
Animal ID		177695C	SC1704077	176313C			SC1708089	SC1604087	SC1703023		
Parameters (unit)	ALT (U/L)	34.6	47.0	23.1	34.9	12.0	22.1	16.0	46.3	28.1	16.0
	AST (U/L)	26.3	30.7	25.0	27.3	2.99	29.1	29.6	27.9	28.9	0.87
	ALP (U/L)	782	864	569	738	153	679	467	469	538	122
	TBIL (μmol/L)	1.92	2.66	1.63	2.07	0.53	1.43	0.88	1.78	1.36	0.45
	DBIL (μmol/L)	0.37	0.65	0.46	0.49	0.14	0.27	----	0.22	0.25	0.04
	GLU (mmol/L)	3.59	3.70	4.04	3.78	0.23	3.29	4.64	4.18	4.04	0.69
	GGT (U/L)	128	101	96.4	108	17.1	75.1	54.3	83.7	71.0	15.1
	TP (g/L)	71.2	67.8	71.7	70.2	2.13	65.1	53.6	73.5	64.1	9.99
	TG (mmol/L)	0.38	0.30	0.59	0.42	0.15	0.56	0.78	0.26↓	0.53	0.26

	BUN (mmol/L)	12.3	10.3	15.9	12.8	2.82	13.1	18.1	13.7	15.0	2.78
	CREA (μmol/L)	66.1	61.7	74.8	67.5	6.67	65.1	92.2	100	85.8	18.3

Note: The ↓ next to the value means the result was slightly lower than that of other animals. '----' means that DBIL of some samples cannot be detected due to the low concentration.

Table 14. Individual and Mean Clinical Chemistry Parameters Results on Day 28 post-dose

Treatment group		G1: ETD01821					G2: ETD01822				
Animal No.		101	102	103	Mean	SD	201	202	203	Mean	SD
Gender		Male	Male	Male			Male	Male	Male		
Animal ID		SC1702037	SC1509029	175151C			SC1508015	SC1704115	SC1703011		
Parameters (unit)	ALT (U/L)	34.8	22.1	45.3	34.1	11.6	33.5	45.4	48.8	42.6	8.03
	AST (U/L)	30.1	30.4	35.0	31.8	2.75	25.8	42.4	51.9	40.0	13.2
	ALP (U/L)	364	216↓	503	361	144	226↓	467	634	442	205
	TBIL (μmol/L)	1.17	1.33	1.15	1.22	0.10	1.72	1.08	1.09	1.30	0.37
	DBIL (μmol/L)	0.10	0.33	0.28	0.24	0.12	0.29	----	----	0.29	0.00
	GLU (mmol/L)	3.06	2.97	3.04	3.02	0.05	4.56	3.79	4.61	4.32	0.46
	GGT (U/L)	87.8	66.5	79.8	78.0	10.7	86.6	63.9	62.3	70.9	13.6
	TP (g/L)	72.3	72.4	71.7	72.1	0.36	82.4	74.7	72.4	76.5	5.23
	TG (mmol/L)	0.79	0.43	0.62	0.61	0.18	0.41	0.13	0.40	0.31	0.16
	BUN (mmol/L)	18.2	14.1	15.9	16.1	2.05	16.1	11.4	15.5	14.3	2.54
	CREA (μmol/L)	75.0	63.0	65.9	68.0	6.26	89.3	60.3	76.9	75.5	14.6
Treatment group		G3: ETD01823					G4: ETD01826				
Animal No.		301	302	303	Mean	SD	401	402	403	Mean	SD
Gender		Male	Male	Male			Male	Male	Male		
Animal ID		177695C	SC1704077	176313C			SC1708089	SC1604087	SC1703023		
Parameters (unit)	ALT (U/L)	23.9	34.3	28.4	28.9	5.22	22.8	40.5	24.4	29.2	9.79
	AST (U/L)	24.5	43.1	27.1	31.6	10.1	31.5	30.3	34.6	32.1	2.22

	ALP (U/L)	193	447	563	401	189	570	344	382	432	121
	TBIL (μmol/L)	1.53	1.69	1.30	1.51	0.20	1.37	0.96	0.58	0.97	0.40
	DBIL (μmol/L)	0.45	0.37	0.56	0.46	0.10	----	0.05	----	0.05	0.00
	GLU (mmol/L)	3.83	3.21	3.30	3.45	0.34	2.97	5.57	4.58	4.37	1.31
	GGT (U/L)	77.2	65.3	59.2	67.2	9.13	73.5	75.9	53.8	67.7	12.1
	TP (g/L)	73.5	73.7	68.1	71.7	3.17	65.0	62.4	58.1	61.8	3.48
	TG (mmol/L)	0.28	0.17	0.42	0.29	0.13	0.54	0.15	0.36	0.35	0.20
	BUN (mmol/L)	16.0	11.2	14.9	14.0	2.53	14.8	16.9	16.2	16.0	1.05
	CREA (μmol/L)	86.3	55.1	74.3	71.9	15.7	62.4	96.8	62.2	73.8	19.9

Note: The ↓ next to the value means the result was slightly lower than that of other animals. '---' means that DBIL of some samples cannot be detected due to the low concentration.

Table 15. Individual and Mean Hematology Results on Pre-dose (Day-8)

Treatment group		G1: ETD01821					G2: ETD01822				
Animal No.		101	102	103	Mean	SD	201	202	203	Mean	SD
Gender		Male	Male	Male			Male	Male	Male		
Animal ID		SC1702037	SC1509029	175151C			SC1508015	SC1704115	SC1703011		
Parameters (unit)	WBC (x10^9 /L)	10.4	7.99	8.57	8.99	1.26	6.69	10.4	17.4	11.5	5.43
	abs_neuts (x10^9 /L)	3.14	2.59	1.33	2.35	0.93	2.52	2.97	3.13	2.87	0.32
	abs_lymphs (x10^9 /L)	6.55	4.82	6.61	5.99	1.02	3.76	6.77	13.48	8.00	4.98
	abs_monos (x10^9/L)	0.65	0.48	0.46	0.53	0.10	0.31	0.59	0.66	0.52	0.19
	abs_eos (x10^9/L)	0.07	0.10	0.17	0.11	0.05	0.10	0.04	0.10	0.08	0.03
	abs_basos (x10^9/L)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	%NEUT (%)	30.1	32.4	15.6	26.0	9.11	37.6	28.6	18.0	28.1	9.81
	%LYM (%)	63.0	60.4	77.0	66.8	8.93	56.2	65.3	77.6	66.4	10.7
	%MONO (%)	6.20	6.00	5.40	5.87	0.42	4.70	5.70	3.80	4.73	0.95
	%EOS (%)	0.70	1.20	2.00	1.30	0.66	1.50	0.40	0.60	0.83	0.59

	%BASO (%)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	RBC (x10^{12}/L)	5.43	5.48	5.35	5.42	0.07	5.01	5.33	5.29	5.21	0.17
	HGB (g/L)	135	134	124	131	6.08	126	128	131	128	2.52
	HCT (%)	45.2	43.5	40.4	43.0	2.43	41.0	42.1	42.5	41.9	0.78
	MCV (fL)	83.3	79.5	75.6	79.5	3.85	82.0	79.1	80.4	80.5	1.45
	MCH (pg)	24.8	24.4	23.2	24.1	0.83	25.2	24.1	24.9	24.7	0.57
	MCHC (g/L)	298	307	307	304	5.20	308	304	309	307	2.65
	RDW-SD (fL)	37.1	43.6	38.8	39.8	3.37	41.2	36.7	36.9	38.3	2.54
	RDW-CV (%)	12.2	15.1	14.1	13.8	1.47	13.7	12.7	12.6	13.0	0.61
	PLT (x10^{9}/L)	380	371	247↓	333	74.3	361	301	285	316	40.1
	MPV (fL)	13.1	12.5	9.60	11.7	1.87	11.6	14.2	12.4	12.7	1.33
	PCT (%)	0.50	0.46	0.24↓	0.40	0.14	0.42	0.43	0.36	0.40	0.04
	PDW (fL)	15.5	15.0	15.4	15.3	0.26	14.9	15.6	15.3	15.3	0.35
Treatment group		G3: ETD01823					G4: ETD01826				
Animal No.		301	302	303	Mean	SD	401	402	403	Mean	SD
Gender		Male	Male	Male			Male	Male	Male		
Animal ID		177695C	SC1704077	176313C			SC1708089	SC1604087	SC1703023		
Parameters (unit)	WBC (x10^{9}/L)	13.9	9.37	8.40	10.6	2.93	9.50	5.65↓	15.8	10.3	5.13
	abs_neuts (x10^{9}/L)	1.19	2.31	1.82	1.77	0.56	3.72	1.04↓	6.22	3.66	2.59
	abs_lymphs (x10^{9}/L)	11.3	6.45	6.09	7.96	2.93	5.09	4.13	8.76	5.99	2.44
	abs_monos (x10^{9}/L)	1.28	0.53	0.29	0.70	0.52	0.55	0.38	0.57	0.50	0.10
	abs_eos (x10^{9}/L)	0.09	0.08	0.20	0.12	0.07	0.14	0.10	0.26	0.17	0.08
	abs_basos (x10^{9}/L)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.00	0.01
	%NEUT (%)	8.6	24.7	21.6	18.3	8.54	39.2	18.5	39.3	32.3	12.0
	%LYM (%)	81.5	68.9	72.6	74.3	6.48	53.5	72.9	55.4	60.6	10.7
	%MONO (%)	9.20	5.60	3.40	6.07	2.93	5.80	6.80	3.60	5.40	1.64

	%EOS (%)	0.70	0.80	2.40	1.30	0.95	1.50	1.80	1.70	1.67	0.15
	%BASO (%)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	RBC (x10^{12}/L)	5.36	5.61	5.07	5.35	0.27	5.29	5.09	5.39	5.26	0.15
	HGB (g/L)	130	137	114	127	11.8	129	122	133	128	5.57
	HCT (%)	43.6	43.3	37.3	41.4	3.55	42.2	40.3	43.3	41.9	1.52
	MCV (fL)	81.3	77.3	73.6	77.4	3.85	79.6	79.2	80.3	79.7	0.56
	MCH (pg)	24.2	24.5	22.6	23.8	1.02	24.3	24.1	24.6	24.3	0.25
	MCHC (g/L)	298	316	307	307	9.00	305	304	306	305	1.00
	RDW-SD (fL)	41.1	38.9	36.5	38.8	2.30	36.9	40.2	40.3	39.1	1.93
	RDW-CV (%)	13.8	13.8	13.6	13.7	0.12	12.7	14.0	13.8	13.5	0.70
	PLT (x10^9/L)	372	307	229↓	303	71.6	339	201↓	398	313	101
	MPV (fL)	11.1	11.9	14.4	12.5	1.72	13.1	14.2	10.3	12.5	2.01
	PCT (%)	0.41	0.37	0.33	0.37	0.04	0.44	0.29↓	0.41	0.38	0.08
	PDW (fL)	15.5	15.3	15.8	15.5	0.25	15.5	15.6	15.3	15.5	0.15

Note: The ↓ next to the value means the result was slightly lower than that of other animals.

Table 16. Individual and Mean Hematology Results on Pre-dose (Day-2)

Treatment group		G1: ETD01821					G2: ETD01822				
Animal No.		101	102	103	Mean	SD	201	202	203	Mean	SD
Gender		Male	Male	Male			Male	Male	Male		
Animal ID		SC1702037	SC1509029	175151C			SC1508015	SC1704115	SC1703011		
Parameters (unit)	WBC (x10^9/L)	8.98	14.8	15.4	13.1	3.55	7.48	13.5	19.3	13.4	5.90
	abs_neuts (x10^9/L)	3.44	6.07	5.05	4.85	1.33	3.20	4.94	4.64	4.26	0.93
	abs_lymphs (x10^9/L)	4.69	7.74	9.41	7.28	2.39	3.80	7.46	13.62	8.29	4.96
	abs_monos (x10^9/L)	0.76	0.76	0.75	0.76	0.01	0.41	0.99	0.96	0.79	0.33
	abs_eos (x10^9/L)	0.09	0.20	0.22	0.17	0.07	0.07	0.08	0.05	0.07	0.02

	abs_basos (x10^9/L)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	%NEUT (%)	38.3	41.1	32.7	37.4	4.28	42.8	36.7	24.1	34.5	9.54
	%LYM (%)	52.3	52.4	61.1	55.3	5.05	50.9	55.3	70.6	58.9	10.3
	%MONO (%)	8.40	5.20	4.80	6.13	1.97	5.40	7.40	5.00	5.93	1.29
	%EOS (%)	1.00	1.30	1.40	1.23	0.21	0.90	0.60	0.30	0.60	0.30
	%BASO (%)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	RBC (x10^{12}/L)	5.63	5.70	5.95	5.76	0.17	5.68	5.75	5.54	5.66	0.11
	HGB (g/L)	142	144	140	142	2.00	145	143	141	143	2.00
	HCT (%)	47.1	46.1	45.4	46.2	0.85	47.2	45.9	44.9	46.0	1.15
	MCV (fL)	83.7	80.8	76.3	80.3	3.73	83.1	79.8	81.1	81.3	1.66
	MCH (pg)	25.2	25.2	23.5	24.6	0.98	25.5	24.8	25.4	25.2	0.38
	MCHC (g/L)	301	312	308	307	5.57	307	311	313	310	3.06
	RDW-SD (fL)	36.7	43.3	38.8	39.6	3.37	41.1	37.1	36.9	38.4	2.37
	RDW-CV (%)	12.1	14.7	13.9	13.6	1.33	13.6	12.7	12.6	13.0	0.55
	PLT (x10^9/L)	468	258	292	339	113	346	354	343	348	5.7
	MPV (fL)	11.0	13.5	11.0	11.8	1.44	12.0	13.1	11.5	12.2	0.82
	PCT (%)	0.51	0.35	0.32	0.39	0.10	0.42	0.47	0.40	0.43	0.04
	PDW (fL)	15.1	15.6	15.4	15.4	0.25	15.6	15.7	15.4	15.6	0.15
Treatment group		G3: ETD01823					G4: ETD01826				
Animal No.		301	302	303	Mean	SD	401	402	403	Mean	SD
Gender		Male	Male	Male			Male	Male	Male		
Animal ID		177695C	SC1704077	176313C			SC1708089	SC1604087	SC1703023		
Parameters (unit)	WBC (x10^9/L)	10.9	12.0	12.1	11.7	0.70	11.4	9.31	19.0	13.2	5.13
	abs_neuts (x10^9/L)	1.34	2.94	3.64	2.64	1.18	3.68	1.59	7.33	4.20	2.91
	abs_lymphs (x10^9/L)	8.59	8.05	7.86	8.17	0.38	6.76	6.87	10.76	8.13	2.28
	abs_monos (x10^9/L)	0.86	0.87	0.38	0.70	0.28	0.66	0.70	0.51	0.62	0.10

	abs_eos (x10^9/L)	0.06	0.12	0.25	0.14	0.10	0.27	0.14	0.44	0.28	0.15
	abs_basos (x10^9/L)	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.00	0.00	0.01
	%NEUT (%)	12.3	24.6	30.0	22.3	9.07	32.4	17.1	38.5	29.3	11.0
	%LYM (%)	79.2	67.2	64.8	70.4	7.71	59.4	73.8	56.5	63.2	9.27
	%MONO (%)	7.90	7.20	3.20	6.10	2.54	5.80	7.50	2.70	5.33	2.43
	%EOS (%)	0.60	1.00	2.00	1.20	0.72	2.40	1.50	2.30	2.07	0.49
	%BASO (%)	0.00	0.00	0.00	0.00	0.00	0.00	0.10	0.00	0.03	0.06
	RBC (x10^{12}/L)	5.41	5.86	5.34	5.54	0.28	5.69	5.76	5.19	5.55	0.31
	HGB (g/L)	132	144	122	133	11.0	140	141	126	136	8.39
	HCT (%)	44.1	45.4	39.6	43.0	3.04	45.5	46.0	41.6	44.4	2.41
	MCV (fL)	81.5	77.5	74.2	77.7	3.66	80.0	79.9	80.1	80.0	0.10
	MCH (pg)	24.5	24.5	22.9	24.0	0.92	24.6	24.5	24.2	24.4	0.21
	MCHC (g/L)	300	317	309	309	8.50	308	306	302	305	3.06
	RDW-SD (fL)	41.5	39.1	37.7	39.4	1.92	36.7	40.2	38.9	38.6	1.77
	RDW-CV (%)	14.0	13.9	13.9	13.9	0.06	12.6	13.9	13.4	13.3	0.66
	PLT (x10^9/L)	379	349	237↓	322	74.8	445	302	393	380	72.4
	MPV (fL)	11.4	11.6	15.4	12.8	2.25	11.9	15.5	11.0	12.8	2.38
	PCT (%)	0.43	0.41	0.37	0.40	0.03	0.53	0.47	0.43	0.48	0.05
	PDW (fL)	16.0	15.1	15.9	15.7	0.49	15.7	15.5	15.9	15.7	0.20

Note: The ↓ next to the value means the result was slightly lower than that of other animals.

Table 17. Individual and Mean Hematology Results on Day 7 post-dose

Treatment group	G1: ETD01821					G2: ETD01822				
Animal No.	101	102	103	Mean	SD	201	202	203	Mean	SD
Gender	Male	Male	Male			Male	Male	Male		
Animal ID	SC1702037	SC1509029	175151C			SC1508015	SC1704115	SC1703011		

Parameters (unit)	WBC (x10^9 /L)	8.52	13.8	11.5	11.3	2.67	8.62	12.3	17.4	12.8	4.43
	abs_neuts (x10^9 /L)	2.00	4.12	2.54	2.89	1.10	4.27	3.44	3.85	3.85	0.42
	abs_lymphs (x10^9 /L)	5.75	8.63	8.17	7.52	1.55	3.88	8.07	12.64	8.20	4.38
	abs_monos (x10^9/L)	0.64	0.70	0.61	0.65	0.05	0.43	0.68	0.87	0.66	0.22
	abs_eos (x10^9/L)	0.13	0.39	0.21	0.24	0.13	0.04	0.06	0.08	0.06	0.02
	abs_basos (x10^9/L)	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.00	0.00	0.01
	%NEUT (%)	23.4	29.7	22.1	25.1	4.06	49.5	28.1	22.1	33.2	14.4
	%LYM (%)	67.6	62.4	70.8	66.9	4.24	45.1	65.8	72.4	61.1	14.2
	%MONO (%)	7.50	5.10	5.30	5.97	1.33	5.00	5.50	5.00	5.17	0.29
	%EOS (%)	1.50	2.80	1.80	2.03	0.68	0.40	0.50	0.50	0.47	0.06
	%BASO (%)	0.00	0.00	0.00	0.00	0.00	0.00	0.10	0.00	0.03	0.06
	RBC (x10^{12} /L)	5.49	5.70	6.24	5.81	0.39	5.75	6.04	5.54	5.78	0.25
	HGB (g/L)	141	146	146	144	2.89	146	149	140	145	4.58
	HCT (%)	46.2	46.5	47.7	46.8	0.79	47.2	49.0	45.0	47.1	2.00
	MCV (fL)	84.0	81.5	76.4	80.6	3.87	82.2	81.1	81.3	81.5	0.59
	MCH (pg)	25.6	25.7	23.5	24.9	1.24	25.4	24.6	25.3	25.1	0.44
	MCHC (g/L)	305	315	307	309	5.29	309	303	311	308	4.16
	RDW-SD (fL)	37.8	44.4	39.3	40.5	3.46	40.4	38.4	38.3	39.0	1.18
	RDW-CV (%)	12.3	15.0	14.1	13.8	1.37	13.5	13.1	13.0	13.2	0.26
	PLT (x10^9 /L)	527	390	253↓	390	137	371	283	341	332	44.7
	MPV (fL)	12.6	13.7	11.8	12.7	0.95	12.1	15.3	11.7	13.0	1.97
	PCT (%)	0.67	0.54	0.30	0.50	0.19	0.45	0.43	0.40	0.43	0.02
	PDW (fL)	15.4	15.3	15.8	15.5	0.26	15.3	15.4	15.4	15.4	0.06
Treatment group		G3: ETD01823					G4: ETD01826				
Animal No.		301	302	303	Mean	SD	401	402	403	Mean	SD
Gender		Male	Male	Male			Male	Male	Male		

Animal ID		177695C	SC1704077	176313C			SC1708089	SC1604087	SC1703023		
Parameters (unit)	WBC ($x10^9$ /L)	9.86	14.2	9.42	11.2	2.63	10.8	8.50	16.7	12.0	4.22
	abs_neuts ($x10^9$/L)	1.06	3.85	2.05	2.32	1.41	4.77	1.67	5.55	4.00	2.05
	abs_lymphs ($x10^9$ /L)	7.99	9.18	6.90	8.02	1.14	5.25	6.17	10.3	7.23	2.68
	abs_monos ($x10^9$/L)	0.73	1.04	0.29	0.69	0.38	0.61	0.52	0.51	0.55	0.06
	abs_eos ($x10^9$/L)	0.08	0.11	0.18	0.12	0.05	0.21	0.14	0.35	0.23	0.11
	abs_basos ($x10^9$/L)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	%NEUT (%)	10.8	27.1	21.7	19.9	8.30	44.0	19.6	33.3	32.3	12.2
	%LYM (%)	81.0	64.8	73.3	73.0	8.10	48.4	72.7	61.6	60.9	12.2
	%MONO (%)	7.40	7.30	3.10	5.93	2.45	5.60	6.10	3.00	4.90	1.66
	%EOS (%)	0.80	0.80	1.90	1.17	0.64	2.00	1.60	2.10	1.90	0.26
	%BASO (%)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	RBC ($x10^{12}$/L)	5.74	5.42	5.58	5.58	0.16	5.59	6.15	5.62	5.79	0.32
	HGB (g/L)	143	133	130	135	6.81	141	151	136	143	7.64
	HCT (%)	46.9	42.1	41.0	43.3	3.14	45.0	49.2	45.0	46.4	2.42
	MCV (fL)	81.8	77.7	73.5	77.7	4.15	80.6	80.1	80.0	80.2	0.32
	MCH (pg)	24.9	24.5	23.3	24.2	0.83	25.3	24.6	24.2	24.7	0.56
	MCHC (g/L)	304	315	317	312	7.00	314	307	303	308	5.57
	RDW-SD (fL)	42.9	39.3	36.4	39.5	3.26	37.9	41.3	39.3	39.5	1.71
	RDW-CV (%)	14.4	13.9	13.6	14.0	0.40	12.9	14.2	13.5	13.5	0.65
	PLT ($x10^9$/L)	441	317	256↓	338	94.3	478	258↓	369	368	110
	MPV (fL)	10.7	12.5	15.0	12.7	2.16	12.2	15.6	11.5	13.1	2.19
	PCT (%)	0.47	0.40	0.39	0.42	0.05	0.59	0.40	0.42	0.47	0.10
	PDW (fL)	15.6	15.3	15.9	15.6	0.30	15.3	15.3	15.8	15.5	0.29

Note: The ↓ next to the value means the result was slightly lower than that of other animals.

Table 18. Individual and Mean Hematology Results on Day 14 post-dose

Treatment group		G1: ETD01821					G2: ETD01822				
Animal No.		101	102	103	Mean	SD	201	202	203	Mean	SD
Gender		Male	Male	Male			Male	Male	Male		
Animal ID		SC1702037	SC1509029	175151C			SC1508015	SC1704115	SC1703011		
Parameters (unit)	WBC ($x10^9$ /L)	9.93	10.4	20.7	13.7	6.08	12.0	12.1	17.9	14.0	3.39
	abs_neuts ($x10^9$ /L)	1.82	3.09	13.5↑	6.13	6.40	7.15	2.75	3.78	4.56	2.30
	abs_lymphs ($x10^9$ /L)	7.15	6.21	5.59	6.32	0.79	4.26	8.44	12.97	8.56	4.36
	abs_monos ($x10^9$/L)	0.81	0.73	1.53	1.02	0.44	0.55	0.86	1.06	0.82	0.26
	abs_eos ($x10^9$/L)	0.14	0.35	0.07	0.19	0.15	0.04	0.05	0.11	0.07	0.04
	abs_basos ($x10^9$/L)	0.01	0.00	0.00	0.00	0.01	0.01	0.00	0.00	0.00	0.01
	%NEUT (%)	18.3	29.8	65.2↑	37.8	24.4	59.6	22.7	21.1	34.5	21.8
	%LYM (%)	72.1	59.7	27.1	53.0	23.2	35.5	69.8	72.4	59.2	20.6
	%MONO (%)	8.10	7.10	7.40	7.53	0.51	4.60	7.10	5.90	5.87	1.25
	%EOS (%)	1.40	3.40	0.30	1.70	1.57	0.30	0.40	0.60	0.43	0.15
	%BASO (%)	0.10	0.00	0.00	0.03	0.06	0.00	0.00	0.00	0.00	0.00
	RBC ($x10^{12}$ /L)	5.99	5.33	6.52	5.95	0.60	5.84	6.02	5.39	5.75	0.32
	HGB (g/L)	152	140	157	150	8.74	151	151	138	147	7.51
	HCT (%)	50.1	44.1	49.3	47.8	3.26	49.3	48.5	44.3	47.4	2.69
	MCV (fL)	83.7	82.7	75.7	80.7	4.36	84.5	80.6	82.2	82.4	1.96
	MCH (pg)	25.4	26.3	24.1	25.3	1.11	25.9	25.0	25.7	25.5	0.47
	MCHC (g/L)	304	318	318	313	8.08	307	311	312	310	2.65
	RDW-SD (fL)	37.0	44.1	38.1	39.7	3.82	41.5	37.8	39.1	39.5	1.88
	RDW-CV (%)	12.2	14.6	13.9	13.6	1.23	13.5	12.9	13.2	13.2	0.30
	PLT ($x10^9$ /L)	570	311	192↓	358	193	279	240	322	280	41.0
	MPV (fL)	12.3	13.8	11.80	12.6	1.04	12.8	15.0	11.80	13.2	1.64

	PCT (%)	0.70	0.43	0.23↓	0.45	0.24	0.36	0.36	0.38	0.37	0.01
	PDW (fL)	14.9	15.5	15.9	15.4	0.50	15.8	15.7	15.6	15.7	0.10
Treatment group		G3: ETD01823					G4: ETD01826				
Animal No.		301	302	303	Mean	SD	401	402	403	Mean	SD
Gender		Male	Male	Male			Male	Male	Male		
Animal ID		177695C	SC1704077	176313C			SC1708089	SC1604087	SC1703023		
Parameters (unit)	WBC (x10^9 /L)	9.24	12.1	10.0	10.4	1.45	10.3	7.73	16.9	11.7	4.74
	abs_neuts (x10^9 /L)	0.54↓	2.62	3.13	2.10	1.37	4.47	1.34	5.81	3.87	2.29
	abs_lymphs (x10^9 /L)	7.95	8.52	6.34	7.60	1.13	5.08	5.65	10.25	6.99	2.83
	abs_monos (x10^9/L)	0.67	0.85	0.30	0.61	0.28	0.59	0.57	0.46	0.54	0.07
	abs_eos (x10^9/L)	0.08	0.07	0.26	0.14	0.11	0.19	0.17	0.39	0.25	0.12
	abs_basos (x10^9/L)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.00	0.01
	%NEUT (%)	5.90↓	21.7	31.3	19.6	12.8	43.3	17.4	34.4	31.7	13.2
	%LYM (%)	86.0	70.6	63.1	73.2	11.7	49.2	73.0	60.6	60.9	11.9
	%MONO (%)	7.30	7.10	3.00	5.80	2.43	5.70	7.40	2.70	5.27	2.38
	%EOS (%)	0.80	0.60	2.60	1.33	1.10	1.80	2.20	2.30	2.10	0.26
	%BASO (%)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	RBC (x10^{12} /L)	5.59	5.58	5.52	5.56	0.04	5.25	5.59	5.68	5.51	0.23
	HGB (g/L)	141	138	128	136	6.81	131	139	141	137	5.29
	HCT (%)	45.7	43.9	40.7	43.4	2.53	42.4	45.1	45.5	44.3	1.69
	MCV (fL)	81.7	78.8	73.8	78.1	4.00	80.8	80.7	80.1	80.5	0.38
	MCH (pg)	25.2	24.8	23.1	24.4	1.12	24.9	25.0	24.8	24.9	0.10
	MCHC (g/L)	308	314	313	312	3.21	309	309	310	309	0.58
	RDW-SD (fL)	42.6	40.6	36.6	39.9	3.06	37.1	41.6	38.4	39.0	2.32
	RDW-CV (%)	14.2	14.3	13.6	14.0	0.38	12.6	14.2	13.2	13.3	0.81
	PLT (x10^9 /L)	376	278	218↓	291	79.8	380	250↓	460	363	106

	MPV (fL)	10.2	12.6	16.1	13.0	2.97	11.9	15.1	10.2	12.4	2.49
	PCT (%)	0.38	0.35	0.35	0.36	0.02	0.45	0.38	0.47	0.43	0.05
	PDW (fL)	15.5	15.5	15.7	15.6	0.12	15.7	15.5	15.5	15.6	0.12

Note: The ↓ next to the value means the result was slightly lower than that of other animals.

Table 19. Individual and Mean Hematology Results on Day 28 post-dose

Treatment group		G1: ETD01821					G2: ETD01822				
Animal No.		101	102	103	Mean	SD	201	202	203	Mean	SD
Gender		Male	Male	Male			Male	Male	Male		
Animal ID		SC1702037	SC1509029	175151C			SC1508015	SC1704115	SC1703011		
Parameters (unit)	WBC (x10^9 /L)	5.30↓	8.44	9.93	7.89	2.36	12.4	12.6	11.7	12.2	0.47
	abs_neuts (x10^9 /L)	1.75	3.52	4.22	3.16	1.27	8.91	7.55	4.53	7.00	2.24
	abs_lymphs (x10^9 /L)	3.20	4.41	5.27	4.29	1.04	2.78	4.40	6.49	4.56	1.86
	abs_monos (x10^9/L)	0.32	0.39	0.28	0.33	0.06	0.67	0.62	0.66	0.65	0.03
	abs_eos (x10^9/L)	0.03	0.12	0.16	0.10	0.07	0.02	0.02	0.01	0.02	0.01
	abs_basos (x10^9/L)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	%NEUT (%)	33.1	41.7	42.5	39.1	5.21	72.0	59.9	38.8	56.9	16.8
	%LYM (%)	60.3	52.3	53.1	55.2	4.41	22.5	34.9	55.4	37.6	16.6
	%MONO (%)	6.00	4.60	2.80	4.47	1.60	5.40	5.00	5.70	5.37	0.35
	%EOS (%)	0.60	1.40	1.60	1.20	0.53	0.10	0.20	0.10	0.13	0.06
	%BASO (%)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	RBC (x10^{12} /L)	5.15	5.19	5.09	5.14	0.05	5.90	5.61	5.46	5.66	0.22
	HGB (g/L)	131	136	121	129	7.64	154	140	142	145	7.57
	HCT (%)	42.6	43.6	38.5	41.6	2.70	49.6	44.8	44.7	46.4	2.80
	MCV (fL)	82.8	84.0	75.7	80.8	4.49	84.1	79.8	82.0	82.0	2.15
	MCH (pg)	25.4	26.2	23.7	25.1	1.28	26.1	25.0	26.1	25.7	0.64

	MCHC (g/L)	307	312	313	311	3.21	311	313	318	314	3.61
	RDW-SD (fL)	36.4	41.3	37.2	38.3	2.63	41.0	37.4	39.7	39.4	1.82
	RDW-CV (%)	12.1	13.5	13.5	13.0	0.81	13.4	12.9	13.3	13.2	0.26
	PLT (x10^9/L)	480	368	329	392	78.4	399	355	346	367	28.4
	MPV (fL)	11.2	14.2	10.4	11.9	2.00	11.6	14.0	11.5	12.4	1.42
	PCT (%)	0.54	0.53	0.34	0.47	0.11	0.46	0.50	0.40	0.45	0.05
	PDW (fL)	14.9	15.3	15.2	15.1	0.21	15.5	15.6	15.4	15.5	0.10
Treatment group		G3: ETD01823					G4: ETD01826				
Animal No.		301	302	303	Mean	SD	401	402	403	Mean	SD
Gender		Male	Male	Male			Male	Male	Male		
Animal ID		177695C	SC1704077	176313C			SC1708089	SC1604087	SC1703023		
Parameters (unit)	WBC (x10^9/L)	6.49↓	12.5	14.2	11.1	4.05	6.51↓	7.22	12.7	8.79	3.36
	abs_neuts (x10^9/L)	3.84	4.42	4.13	4.13	0.29	3.62	4.15	6.51	4.76	1.54
	abs_lymphs (x10^9/L)	2.27↓	7.35	9.37	6.33	3.66	2.53↓	2.62↓	5.64	3.60	1.77
	abs_monos (x10^9/L)	0.36	0.65	0.69	0.57	0.18	0.30	0.37	0.34	0.34	0.04
	abs_eos (x10^9/L)	0.02	0.05	0.03	0.03	0.02	0.06	0.08	0.15	0.10	0.05
	abs_basos (x10^9/L)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.00	0.01
	%NEUT (%)	59.2	35.5	29.0	41.2	15.9	55.6	57.5	51.5	54.9	3.07
	%LYM (%)	35.0	58.9	65.9	53.3	16.2	38.9	36.2	44.5	39.9	4.23
	%MONO (%)	5.50	5.20	4.90	5.20	0.30	4.60	5.10	2.70	4.13	1.27
	%EOS (%)	0.30	0.40	0.20	0.30	0.10	0.90	1.20	1.20	1.10	0.17
	%BASO (%)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.10	0.03	0.06
	RBC (x10^{12}/L)	5.02	5.78	4.91	5.24	0.47	5.12	5.05	5.07	5.08	0.04
	HGB (g/L)	132	143	126	134	8.62	128	126	124	126	2.00
	HCT (%)	42.1	45.2	40.4	42.6	2.43	41.1	40.5	40.6	40.7	0.32
	MCV (fL)	83.8	78.2	82.4	81.5	2.91	80.3	80.2	80.0	80.2	0.15

	MCH (pg)	26.3	24.8	25.6	25.6	0.75	25.1	25.0	24.5	24.9	0.32
	MCHC (g/L)	314	316	311	314	2.52	312	312	306	310	3.46
	RDW-SD (fL)	40.5	39.1	39.9	39.8	0.70	36.0	41.3	39.5	38.9	2.70
	RDW-CV (%)	13.3	13.8	13.4	13.5	0.26	12.2	14.1	13.6	13.3	0.98
	PLT ($x10^9$/L)	355	384	307	349	38.9	402	162↓	399	321	137.7
	MPV (fL)	12.4	11.8	11.9	12.0	0.32	11.8	15.3	9.40	12.2	2.97
	PCT (%)	0.44	0.45	0.37	0.42	0.05	0.48	0.25	0.38	0.37	0.11
	PDW (fL)	15.4	15.1	15.2	15.2	0.15	15.5	15.8	15.5	15.6	0.17

Note: The ↓ next to the value means the result was slightly lower than that of other animals.

Table 20. Relative Mean Serum MSP Level in Cynomolgus Monkeys

Group	n	Treatment	Dose (mg/kg)	Day												
				-8	-2	7	14	28	42	56	70	77	84	91	98	105
				Mean Serum MSP Level (Relative to mean of pre-dose level (Day -2 and Day -8))												
1	3	ETD01821	5	1.09	0.91	0.22	0.06	0.04	0.07	0.15	0.18	0.18	0.31	0.42	0.45	0.46
2	3	ETD01822	5	0.99	1.01	0.71	0.32	0.42	0.37	0.76	1.24	1.16	1.48	1.34	1.34	1.57
3	3	ETD01823	5	1.01	0.99	0.44	0.08	0.34	0.10	0.20	0.45	0.39	0.52	0.59	0.91	1.03
4	3	ETD01826	5	0.78	1.22	0.37	0.20	0.30	0.58	0.88	1.01	1.63	1.32	1.86	1.98	1.95

Table 21. Relative Individual Serum MSP Level in Cynomolgus Monkeys

Group	n	Treatment	Dose (mg/kg)	Animal #	Day												
					-8	-2	7	14	28	42	56	70	77	84	91	98	105
					Mean Serum MSP Level (Relative to mean of pre-dose level (Day -2 and Day -8))												
1	3	ETD01821	5	101M	0.99	1.01	0.28	0.08	0.07	0.11	0.23						
				102M	1.12	0.88	0.18	0.07	0.04	0.01	0.16	0.26	0.21	0.31	0.47	0.51	0.39

			103M	1.16	0.84	0.19	0.02	0.01	0.08	0.07	0.09	0.15	0.31	0.37	0.38	0.52
2	3	ETD01822	201M	0.99	1.01	0.64	0.43	0.75	0.59	0.90	1.26	0.95	1.56	1.69	1.75	1.49
			202M	0.99	1.01	0.75	0.30	0.23	0.29	0.86	1.39	1.58	0.96	1.23	1.14	1.82
			203M	1.00	1.00	0.74	0.24	0.28	0.23	0.53	1.07	0.96	1.92	1.10	1.13	1.39
3	3	ETD01823	301M	0.76	1.24	0.24	0.05	0.50	0.06	0.15	0.19	0.18	0.36	0.30	0.41	0.56
			302M	1.18	0.82	0.46	0.09	0.31	0.15	0.26	0.71	0.57	0.84	0.83	1.44	1.40
			303M	1.09	0.91	0.61	0.11	0.22	0.10	0.20	0.45	0.42	0.37	0.65	0.89	1.14
4	3	ETD01826	401M	0.95	1.05	0.26	0.16	0.25	0.43	0.91	0.91	1.32	1.51	1.51	2.25	2.16
			402M	0.91	1.09	0.35	0.07	0.15	0.15	0.41	0.77	1.55	0.89	1.23	1.81	1.54
			403M	0.49	1.51	0.51	0.36	0.49	1.16	1.31	1.35	2.02	1.56	2.84	1.87	2.15

Table 22. Relative MST1 mRNA Level in Liver of Cynomolgus Monkeys

Group	n	Treatment	Dose (mg/kg)	Mean *MST1* mRNA (Relative to Day -8)	
				Day -8	Day 28
1	3	ETD01821	5	1.00	0.33
2	3	ETD01822	5	1.00	0.33
3	3	ETD01823	5	1.00	0.27
4	3	ETD01826	5	1.00	0.57

Example 19: Screening siRNAs targeting human and mouse *MTRES1* in mice

[00292] The following example demonstrates the usefulness of GalNAc moieties described herein *in vivo* when combined oligonucleotides targeting an additional target (MTRES1). Several siRNAs designed to be cross-reactive with human, mouse and cynomolgus monkey *MTRES1* mRNA were tested for activity in mice. The siRNAs were attached to the GalNAc ligand ETL1 or ETL17. The siRNA sequences are shown in **Table 23, where Nf is a 2' fluoro-modified nucleoside, n is a 2' O-methyl modified nucleoside, "d" is a deoxynucleoside, and "s" is a phosphorothioate linkage.**

[00293] Six to eight week old female mice (strain ICR, n=3) were given a subcutaneous injection on Day 0 of a single 200 ug dose of a GalNAc-conjugated siRNA or PBS as vehicle control.

[00294] Mice were euthanized on Day 10 after injection and a liver sample from each was collected and placed in RNAlater (ThermoFisher Catalog# AM7020) until processing. Total liver RNA was prepared by homogenizing the liver tissue in homogenization buffer (Maxwell RSC simplyRNA Tissue Kit) using a Percellys 24 tissue homogenizer (Bertin Instruments) set at 5000 rpm for two 10 second cycles. Total RNA from the lysate was purified on a Maxwell RSC 48 platform (Promega Corporation) according to the **manufacturer's recommendations. Preparation** of cDNA was performed using Quanta qScript cDNA SuperMix (VWR, Catalog# 95048-**500) according to the manufacturer's instructions. The relative levels** of liver *MTRES1* mRNA were assessed by RT-**qPCR in triplicate on a QuantStudio™ 6 Pro Real**-Time PCR System using TaqMan assays for mouse *MTRES1* (ThermoFisher, assay# Mm01229834_m1) and the mouse housekeeping gene PPIA (ThermoFisher, assay# Mm02342430_g1) and PerfeCTa® qPCR **FastMix®, Low ROX™ (VWR, Catalog#** 101419-222). Data were normalized to the mean *MTRES1* mRNA level in animals receiving PBS. Results are shown in **Table 24**. Mice injected with ETD01597, ETD01955, ETD01958, and had substantially lower levels in mean liver *MTRES1* mRNA on Day 10 relative to mice receiving PBS.

Table 23. Example siRNA Sequences

siRNA Name	SEQ ID NO:	Sense Strand Sequence (5′-3′) with GalNAc moiety	SEQ ID NO:	Antisense Strand Sequence (5′-3′)
ETD01597	23	[ETL1]sguaucuccAfgAfauguuauasusu	33	usAfsuAfaCfaUfuCfuGfgAfgAfuAfcsusu
ETD01954	24	[ETL17]sacuuccuGfGfAfAfucgauacasusu	34	usGfsuAfsuCfgAfuUfcCfaGfgAfaGfususu
ETD01955	25	[ETL17]scuuccuGfGfAfAfucgauacuasusu	35	usAfsgUfaUfcGfaUfuCfcAfgGfaAfgsusu

ETD01956	26	[ETL17]scuggAfAfucGfAfuacuuguaasusu	36	usUfsaCfaAfgUfaUfcGfaUfuCfcAfgsusu
ETD01957	27	[ETL17]sggaaUfCfgaUfaCfuuguauuasusu	37	usAfsaUfaCfaAfgUfaUfcGfaUfuCfcsusu
ETD01958	28	[ETL17]sgaugCfUfuUfCfuacaaagguasusu	38	usAfscCfuUfuGfuAfgAfaAfgCfaUfcsusu
ETD01959	29	[ETL17]sagaaAfAfgcAfGfaacggugaasusu	39	usUfscAfcCfgUfuCfuGfcUfuUfuCfususu
ETD01960	30	[ETL17]saagcagAfAfdCGfgugaaaguasusu	40	usAfscUfuUfcAfcCfgUfuCfuGfcUfususu
ETD01961	31	[ETL17]sagugGfGfaGfAfuAfcauuggaasusu	41	usUfscCfaAfuGfuAfuCfuCfcCfaCfususu
ETD01962	32	[ETL17]sugggAfGfauAfcAfuuggaucasusu	42	usGfsaUfcCfaAfuGfuAfuCfuCfcCfasusu

Table 24. Relative MTRES1 mRNA Levels in Livers of Mice

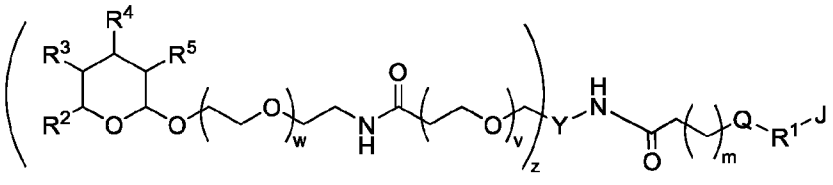
Group	n	Treatment	Dose (ug)	Mean *MTRES1* mRNA (Normalized to Group 1, Day 10)
1	3	PBS		1.00
2	3	ETD01597	200	0.13
3	3	ETD01954	200	1.03
4	3	ETD01955	200	0.16
5	3	ETD01956	200	0.62
6	3	ETD01957	200	0.31
7	3	ETD01958	200	0.18
8	3	ETD01959	200	0.53
9	3	ETD01960	200	0.69
10	3	ETD01961	200	0.33
11	3	ETD01962	200	0.79

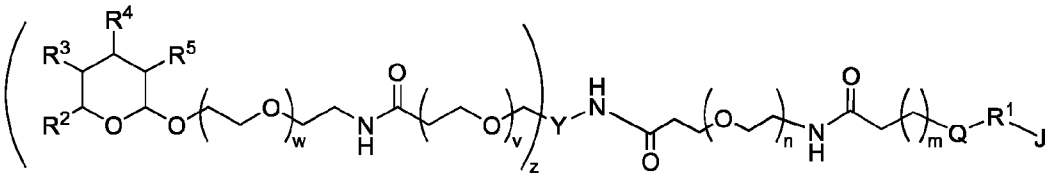
[00295] While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

CLAIMS

WHAT IS CLAIMED IS:

1. A compound represented by Formula (I) or (II):


(I), or


(II);

or a salt thereof, wherein

J is an oligonucleotide;

each w is independently selected from any value from 1 to 20;

each v is independently selected from any value from 1 to 20;

n is selected from any value from 1 to 20;

m is selected from any value from 1 to 20;

z is selected from any value from 1 to 3, wherein

if z is 3, Y is C

if z is 2, Y is CR^6, or

if z is 1, Y is $C(R^6)_2$;

Q is selected from:

C_{3-10} carbocycle optionally substituted with one or more substituents independently selected from halogen, -CN, $-NO_2$, $-OR^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, $-C(O)N(R^7)_2$, $-N(R^7)C(O)R^7$, $-N(R^7)C(O)N(R^7)_2$, $-OC(O)N(R^7)_2$, $-N(R^7)C(O)OR^7$, $-C(O)OR^7$, $-OC(O)R^7$, $-S(O)R^7$, and C_{1-6} alkyl, wherein the C_{1-6} alkyl, is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, $-NO_2$, and $-NH_2$;

R^1 is a linker selected from:

-O-, -S-, $-N(R^7)-$, -C(O)-, $-C(O)N(R^7)-$, $-N(R^7)C(O)-$, $-N(R^7)C(O)N(R^7)-$, $-OC(O)N(R^7)-$, $-N(R^7)C(O)O-$, -C(O)O-, -OC(O)-, -S(O)-, $-S(O)_2-$, $-OS(O)_2-$, $-OP(O)(OR^7)O-$, $-SP(O)(OR^7)O-$, $-OP(S)(OR^7)O-$, $-OP(O)(SR^7)O-$, $-OP(O)(OR^7)S-$, $-OP(O)(O^-)O-$, $-SP(O)(O^-)O-$, $-OP(S)(O^-)O-$, $-OP(O)(S^-)O-$, $-OP(O)(O^-)S-$, $-OP(O)(OR^7)NR^7-$, $-OP(O)(N(R^7)_2)NR^7-$, $-OP(OR^7)O-$, $-OP(N(R^7)_2)O-$, $-OP(OR^7)N(R^7)-$, and $-OPN(R^7)_2NR^7-$;

each R^2 is independently selected from:

C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, $-OR^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, $-C(O)N(R^7)_2$, $-N(R^7)C(O)R^7$, $-N(R^7)C(O)N(R^7)_2$, $-OC(O)N(R^7)_2$, $-N(R^7)C(O)OR^7$, $-C(O)OR^7$, $-OC(O)R^7$, and $-S(O)R^7$;

R^3 and R^4 are each independently selected from:

$-OR^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, $-C(O)N(R^7)_2$, $-N(R^7)C(O)R^7$, $-N(R^7)C(O)N(R^7)_2$, $-OC(O)N(R^7)_2$, $-N(R^7)C(O)OR^7$, $-C(O)OR^7$, $-OC(O)R^7$, and $-S(O)R^7$;

each R^5 is independently selected from:

$-OC(O)R^7$, $-OC(O)N(R^7)_2$, $-N(R^7)C(O)R^7$, $-N(R^7)C(O)N(R^7)_2$, $-N(R^7)C(O)OR^7$, $-C(O)R^7$, $-C(O)OR^7$, and $-C(O)N(R^7)_2$;

each R^6 is independently selected from:

hydrogen;

halogen, $-CN$, $-NO_2$, $-OR^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, $-C(O)N(R^7)_2$, $-N(R^7)C(O)R^7$, $-N(R^7)C(O)N(R^7)_2$, $-OC(O)N(R^7)_2$, $-N(R^7)C(O)OR^7$, $-C(O)OR^7$, $-OC(O)R^7$, and $-S(O)R^7$; and

C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, $-CN$, $-NO_2$, $-OR^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, $-C(O)N(R^7)_2$, $-N(R^7)C(O)R^7$, $-N(R^7)C(O)N(R^7)_2$, $-OC(O)N(R^7)_2$, $-N(R^7)C(O)OR^7$, $-C(O)OR^7$, $-OC(O)R^7$, and $-S(O)R^7$;

each R^7 is independently selected from:

hydrogen;

C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, $-CN$, $-OH$, $-SH$, $-NO_2$, $-NH_2$, $=O$, $=S$, $-O-C_{1-6}$ alkyl, $-S-C_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)_2$, $-NH(C_{1-6}$ alkyl), C_{3-10} carbocycle, and 3- to 10-membered heterocycle; and

C_{3-10} carbocycle, and 3- to 10-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, $-CN$, $-OH$, $-SH$, $-NO_2$, $-NH_2$, $=O$, $=S$, $-O-C_{1-6}$ alkyl, $-S-C_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)_2$, $-NH(C_{1-6}$ alkyl), C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, and C_{1-6} haloalkyl.

2. The compound or salt of claim 1, wherein each w is independently selected from any value from 1 to 10.

3. The compound or salt of claim 1, wherein each w is independently selected from any value from 1 to 5.

4. The compound or salt of claim 1, wherein each w is 1.

5. The compound or salt of claim 1, wherein each v is independently selected from any value from 1 to 10.

6. The compound or salt of claim 1, wherein each v is independently selected from any value from 1 to 5.

7. The compound or salt of claim 1, wherein each v is 1.

8. The compound or salt of claim 1, wherein n is selected from any value from 1 to 10.

9. The compound or salt of claim 1, wherein n is selected from any value from 1 to 5.

10. The compound or salt of claim 1, wherein n is 2.

11. The compound or salt of claim 1, wherein m is selected from any value from 1 to 10.

12. The compound or salt of claim 1, wherein m is selected from any value from 1 to 5.

13. The compound or salt of claim 1, wherein m is selected from 1 and 2.

14. The compound or salt of claim 1, wherein z is 3 and Y is C.

15. The compound or salt of claim 1, wherein Q is selected from C_{5-6} carbocycle optionally substituted with one or more substituents independently selected from halogen, -CN, $-NO_2$, $-OR^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, $-C(O)N(R^7)_2$, $-N(R^7)C(O)R^7$, $-N(R^7)C(O)N(R^7)_2$, $-OC(O)N(R^7)_2$, $-N(R^7)C(O)OR^7$, $-C(O)OR^7$, $-OC(O)R^7$, and $-S(O)R^7$.

16. The compound or salt of claim 1, wherein Q is selected from C_{5-6} carbocycle optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, $-NO_2$, and $-NH_2$.

17. The compound or salt of claim 1, wherein Q is selected from phenyl and cyclohexyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, $-NO_2$, and $-NH_2$.

18. The compound or salt of claim 1, wherein Q is selected from phenyl.

19. The compound or salt of claim 1, wherein Q is selected from cyclohexyl.

20. The compound or salt of claim 1, wherein R^1 is selected from $-OP(O)(OR^7)O-$, $-SP(O)(OR^7)O-$, $-OP(S)(OR^7)O-$, $-OP(O)(SR^7)O-$, $-OP(O)(OR^7)S-$, $-OP(O)(O^-)O-$, $-SP(O)(O^-)O-$, $-OP(S)(O^-)O-$, $-OP(O)(S^-)O-$, $-OP(O)(O^-)S-$, $-OP(O)(OR^7)NR^7-$, $-OP(O)(N(R^7)_2)NR^7-$, $-OP(OR^7)O-$, $-OP(N(R^7)_2)O-$, $-OP(OR^7)N(R^7)-$, and $-OPN(R^7)_2NR^7$.

21. The compound or salt of claim 1, wherein R^1 is selected from $-OP(O)(OR^7)O-$, $-SP(O)(OR^7)O-$, $-OP(S)(OR^7)O-$, $-OP(O)(SR^7)O-$, $-OP(O)(OR^7)S-$, $-OP(O)(O^-)O-$, $-SP(O)(O^-)O-$, $-OP(S)(O^-)O-$, $-OP(O)(S^-)O-$, $-OP(O)(O^-)S-$, and $-OP(OR^7)O-$.

22. The compound or salt of claim 1, wherein R^1 is selected from $-OP(O)(OR^7)O-$, $-OP(S)(OR^7)O-$, $-OP(O)(O^-)O-$, $-OP(S)(O^-)O-$, $-OP(O)(S^-)O-$, and $-OP(OR^7)O-$.

23. The compound or salt of claim 1, wherein R^1 is selected from $-OP(O)(OR^7)O-$ and $-OP(OR^7)O-$.

24. The compound or salt of claim 1, wherein R^2 is selected from C_{1-3} alkyl substituted with one or more substituents independently selected from halogen, $-OR^7$, $-OC(O)R^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, and $-S(O)R^7$.

25. The compound or salt of claim 1, wherein R^2 is selected from C_{1-3} alkyl substituted with one or more substituents independently selected from $-OR^7$, $-OC(O)R^7$, $-SR^7$, and $-N(R^7)_2$.

26. The compound or salt of claim 1, wherein R^2 is selected from C_{1-3} alkyl substituted with one or more substituents independently selected from $-OR^7$ and $-OC(O)R^7$.

27. The compound or salt of claim 1, wherein R^3 is selected from halogen, $-OR^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, $-OC(O)R^7$, and $-S(O)R^7$.

28. The compound or salt of claim 1, wherein R^3 is selected from $-OR^7$ $-SR^7$, $-OC(O)R^7$, and $-N(R^7)_2$.

29. The compound or salt of claim 1, wherein R^3 is selected from $-OR^7$ - and $-OC(O)R^7$.

30. The compound or salt of claim 1, wherein R^4 is selected from halogen, $-OR^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, $-OC(O)R^7$, and $-S(O)R^7$.

31. The compound or salt of claim 1, wherein R^4 is selected from $-OR^7$ $-SR^7$, $-OC(O)R^7$, and $-N(R^7)_2$.

32. The compound or salt of claim 1, wherein R^4 is selected from $-OR^7$ - and $-OC(O)R^7$.

33. The compound or salt of claim 1, wherein R^5 is selected from $-OC(O)R^7$, $-OC(O)N(R^7)_2$, $-N(R^7)C(O)R^7$, $-N(R^7)C(O)N(R^7)_2$, and $-N(R^7)C(O)OR^7$.

34. The compound or salt of claim 1, wherein R^5 is selected from $-OC(O)R^7$ and $-N(R^7)C(O)R^7$.

35. The compound or salt of claim 1, wherein each R^7 is independently selected from:

hydrogen; and

C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, $-NO_2$, $-NH_2$, =O, =S, $-O-C_{1-6}$ alkyl, $-S-C_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)_2$, $-NH(C_{1-6}$ alkyl), C_{3-10} carbocycle, or 3- to 10-membered heterocycle.

36. The compound or salt of any one of claims 1 to 30, wherein each R^7 is independently selected from C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, $-NO_2$, $-NH_2$, =O, =S, $-O-C_{1-6}$ alkyl, $-S-C_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)_2$, and $-NH(C_{1-6}$ alkyl).

37. The compound or salt of any one of claims 1 to 34, wherein each R^7 is independently selected from C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, and -SH.

38. The compound or salt of claim 1, wherein

w is 1;

v is 1;

n is 2;

m is 1 or 2;

z is 3 and Y is C;

Q is phenyl or cyclohexyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, $-NO_2$, $-NH_2$, and C_{1-3} alkyl;

R^1 is selected from $-OP(O)(OR^7)O-$, $-OP(S)(OR^7)O-$, $-OP(O)(O^-)O-$, $-OP(S)(O^-)O-$, $-OP(O)(S^-)O-$, and $-OP(OR^7)O-$;

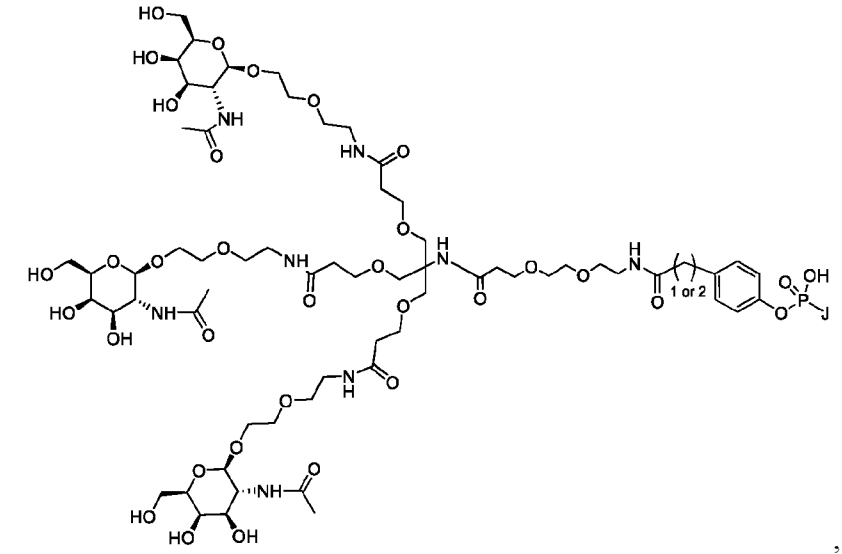
R^2 is C_1 alkyl substituted with -OH or $-OC(O)CH_3$;

R^3 is -OH or $-OC(O)CH_3$;

R^4 is -OH or $-OC(O)CH_3$; and

R^5 is $-NH(O)CH_3$.

39. The compound of claim 1, wherein the compound comprises:



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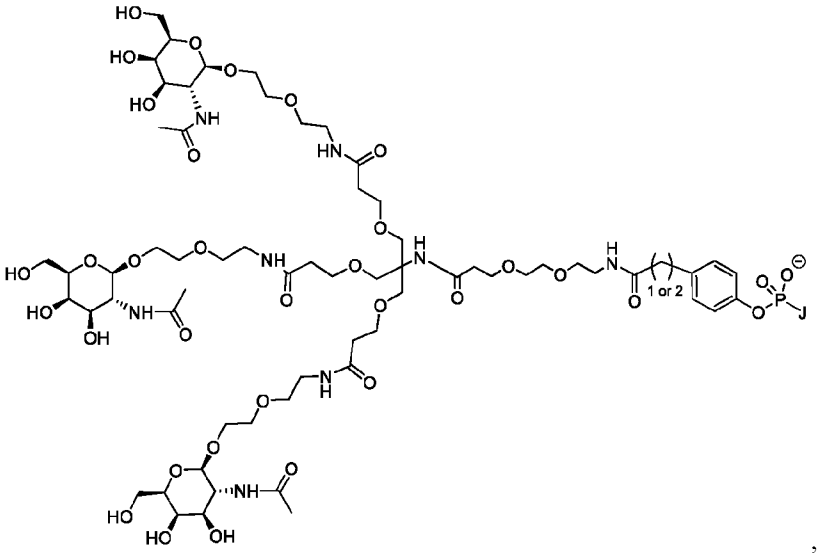

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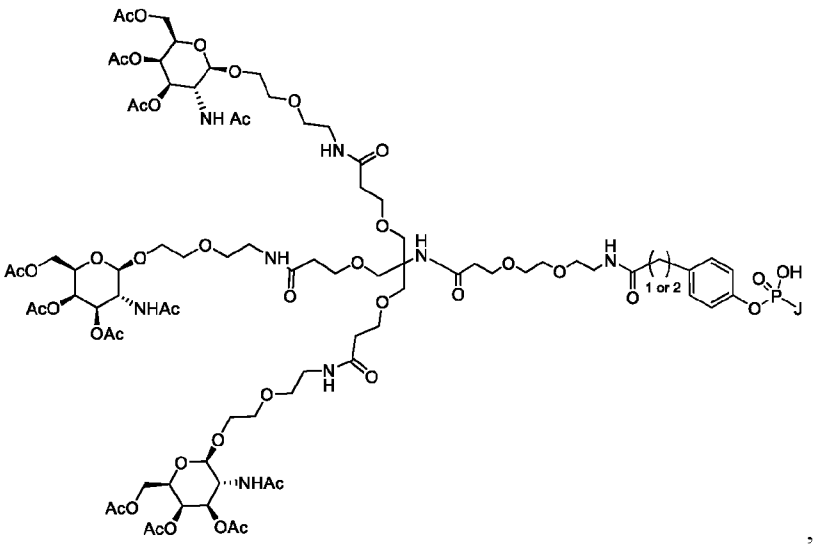

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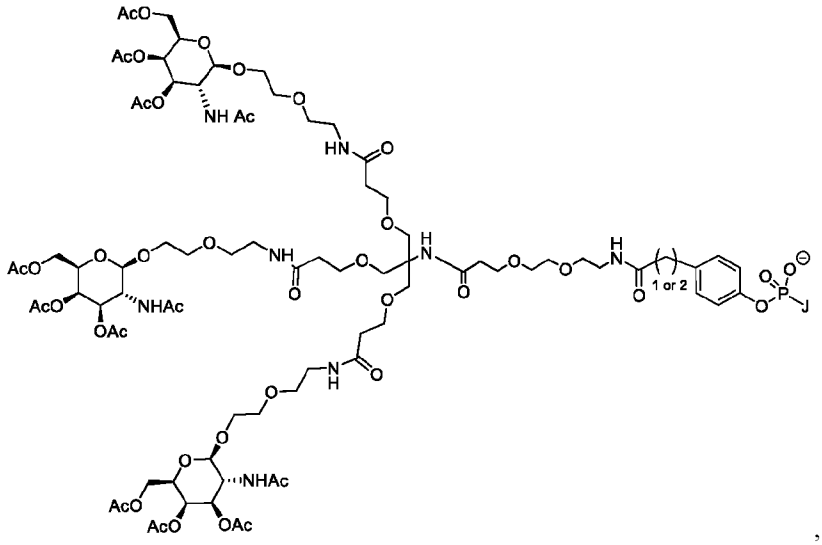

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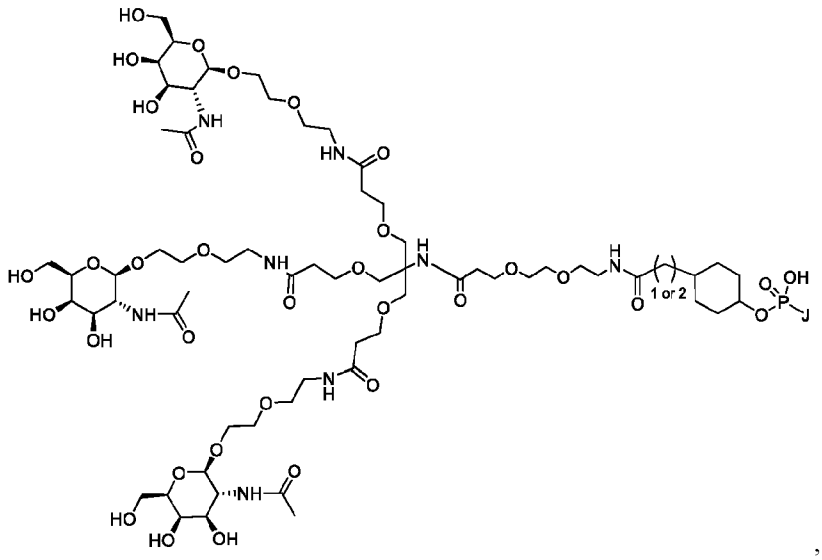

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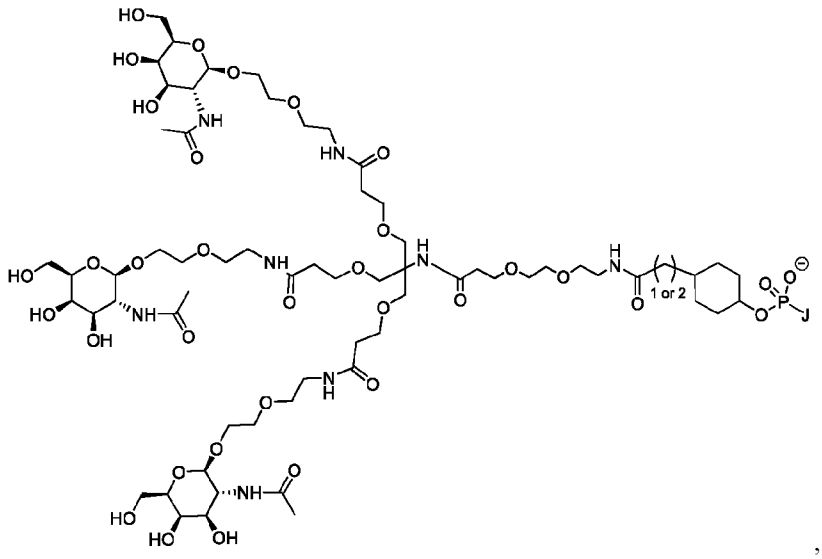

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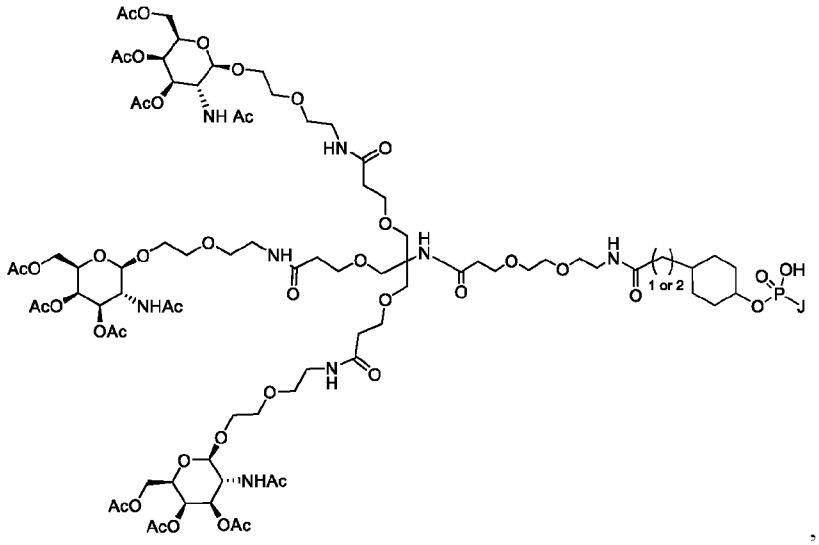

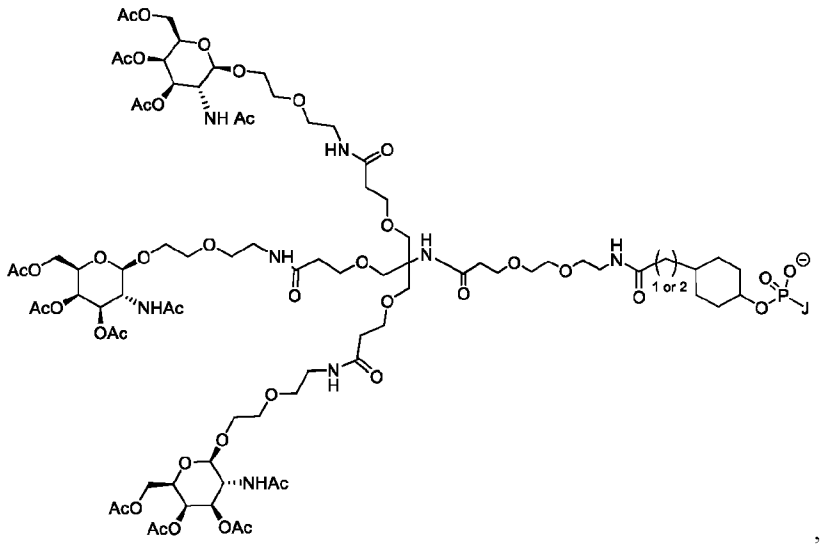

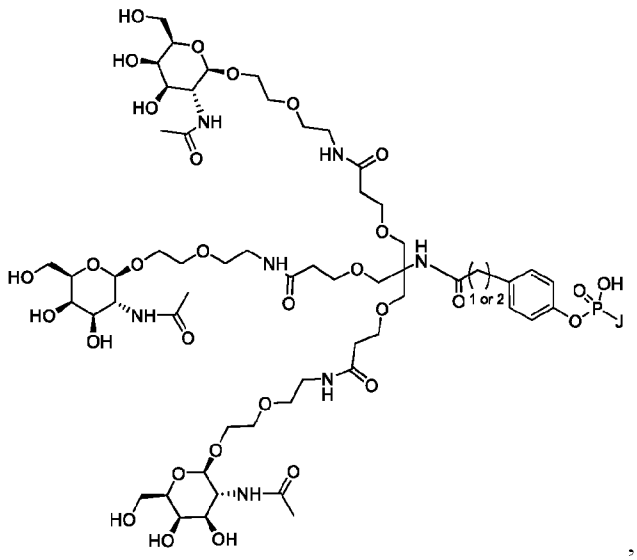

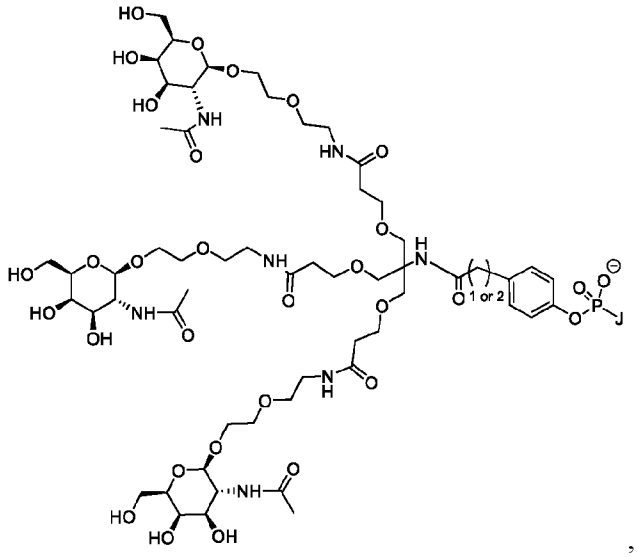

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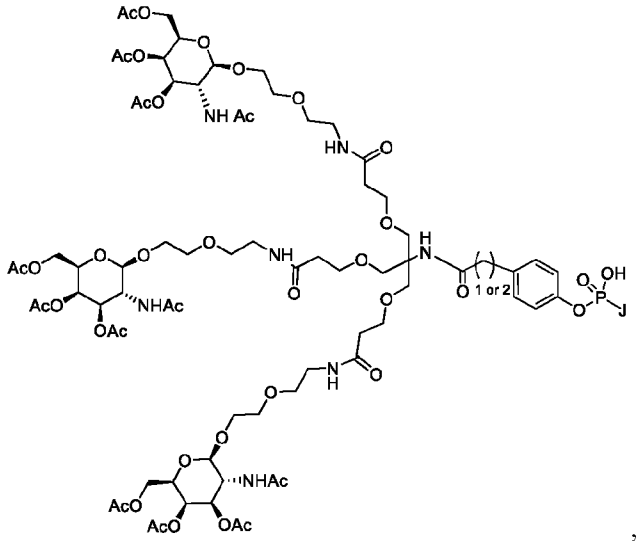

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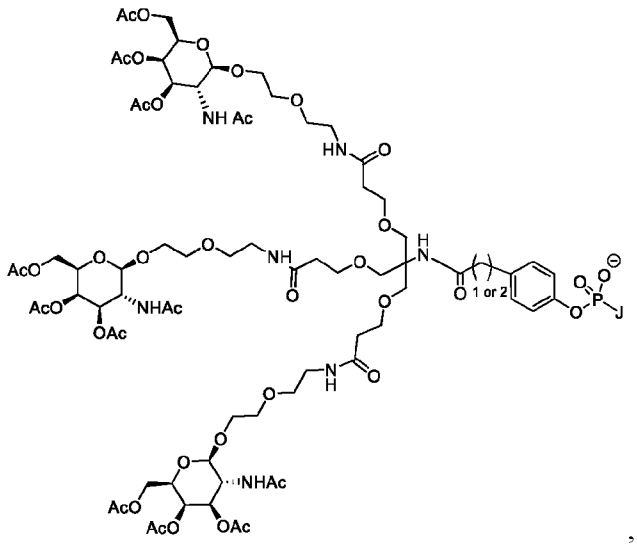

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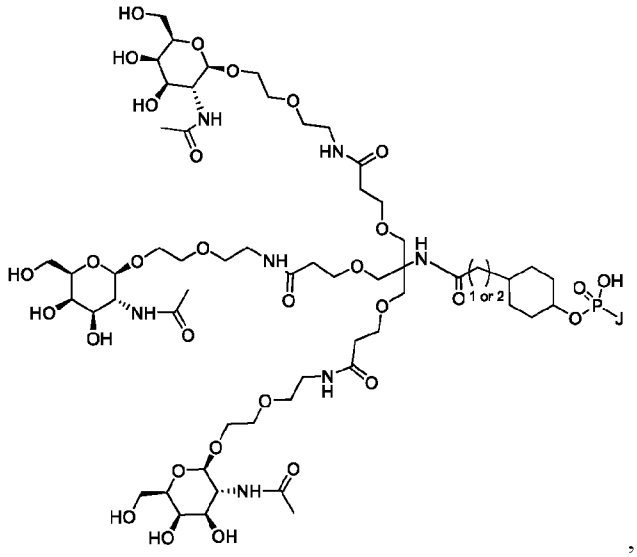

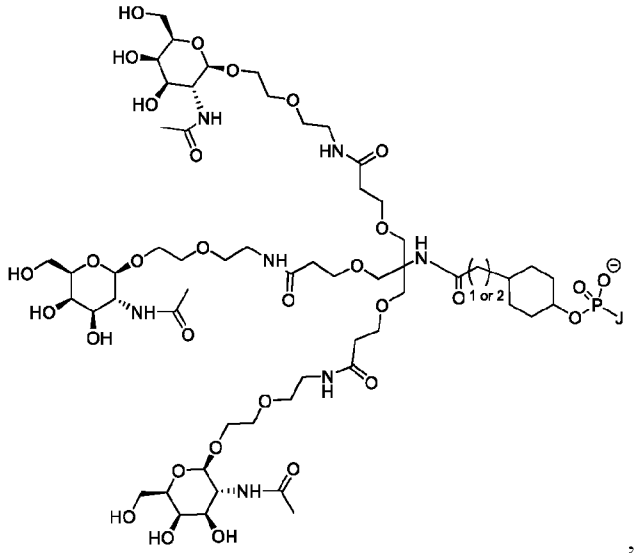

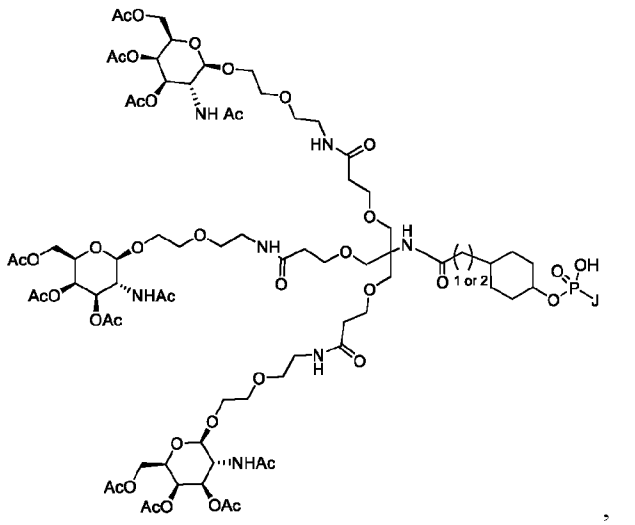

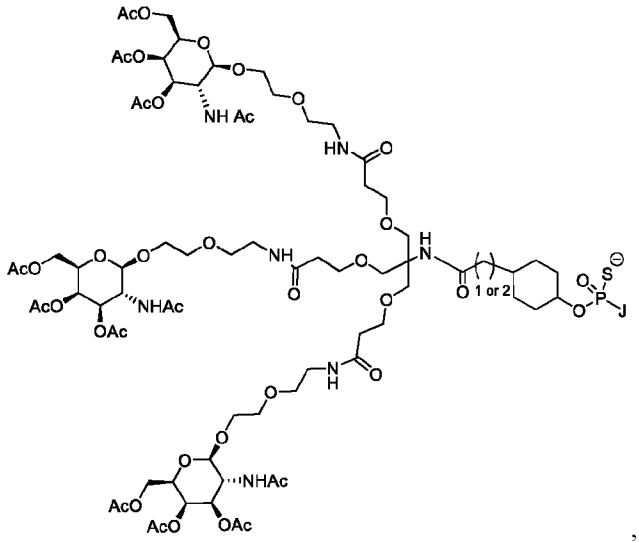

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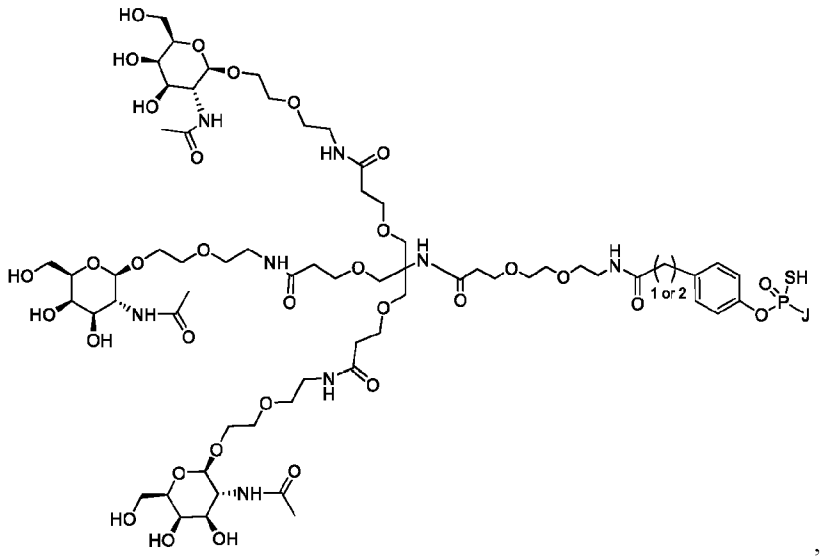

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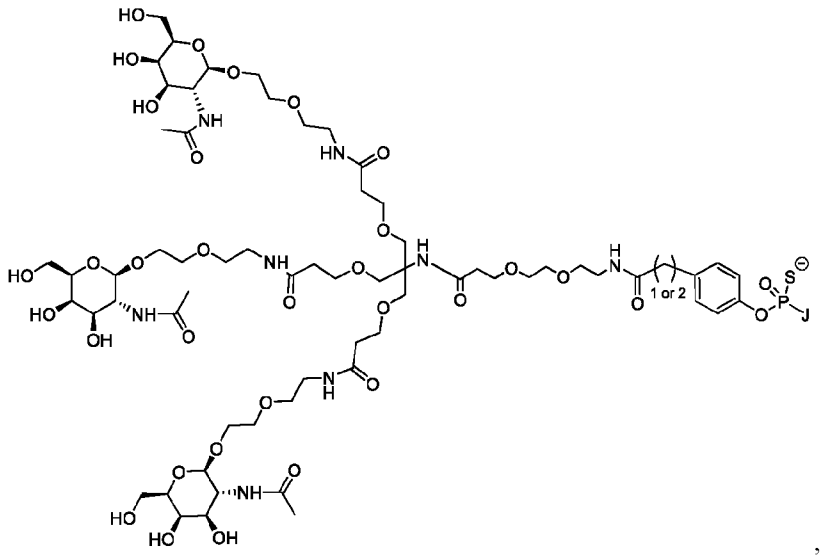

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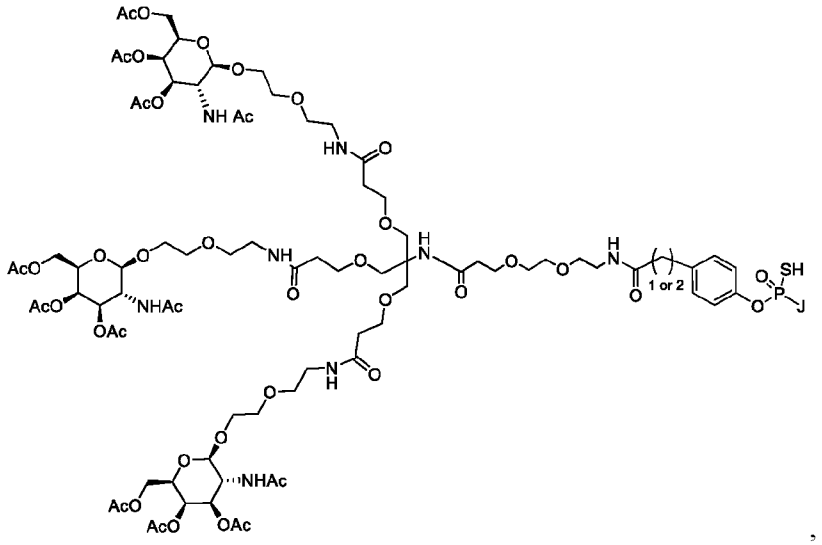

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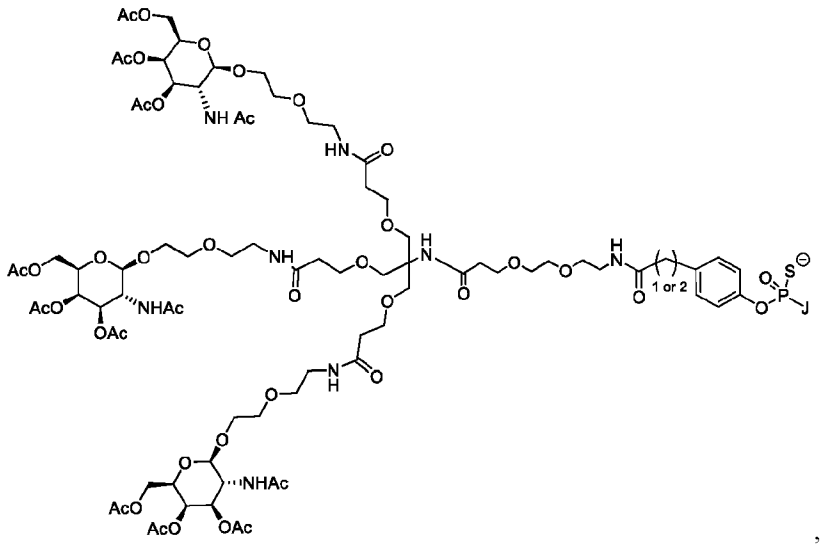

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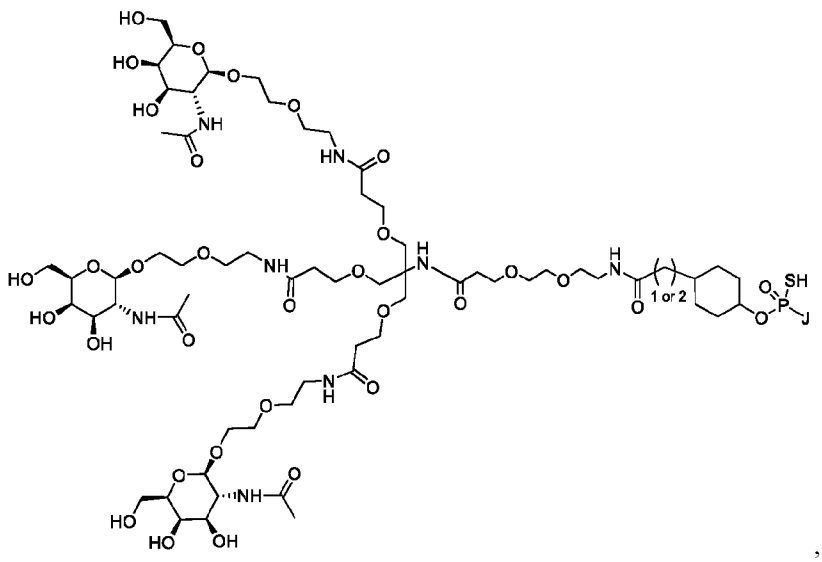

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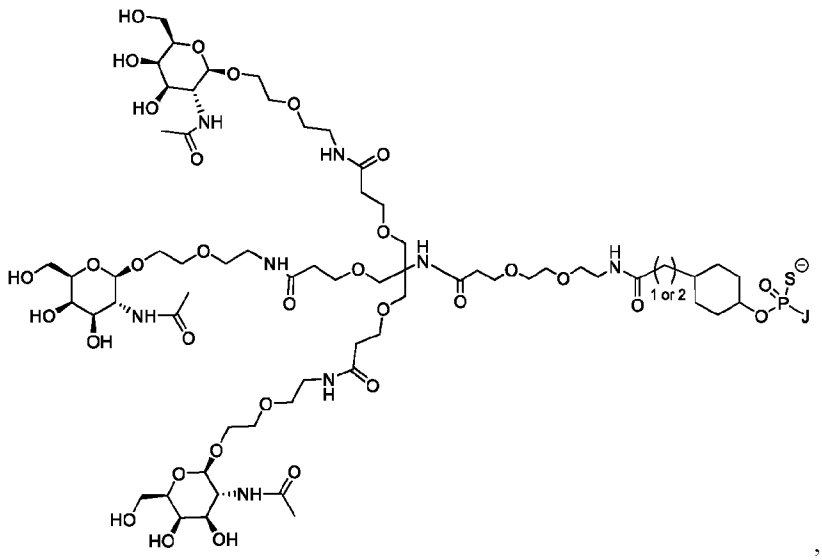

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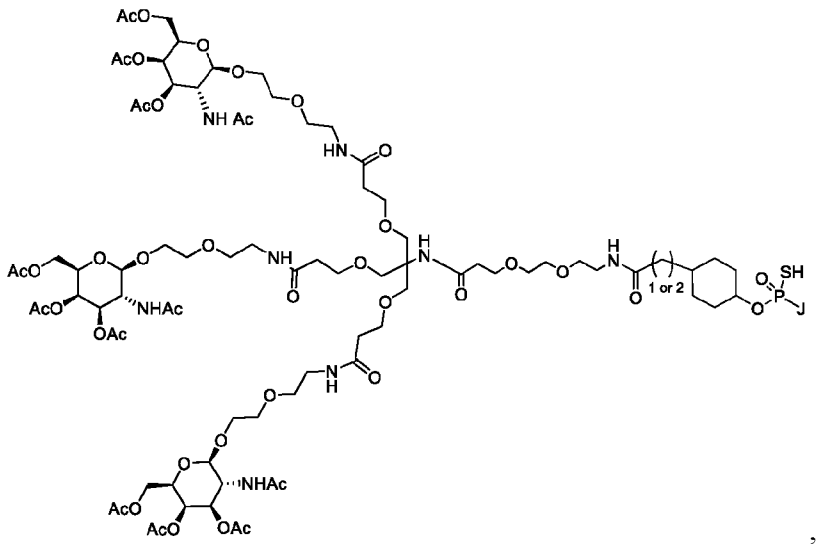

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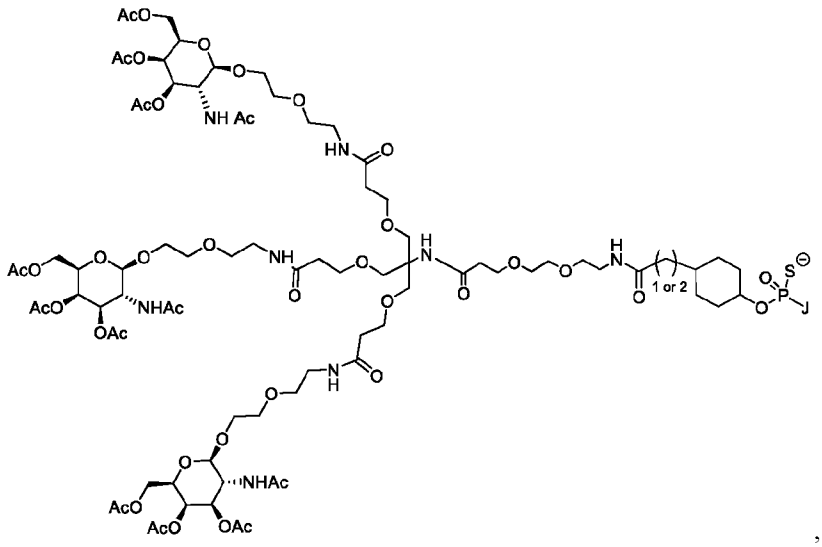

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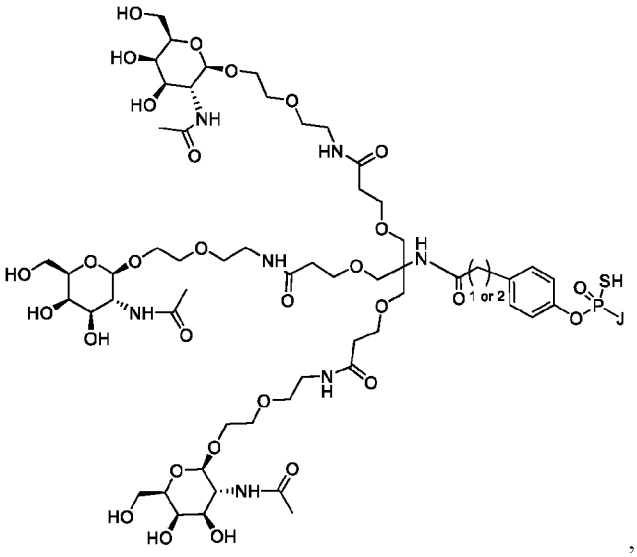

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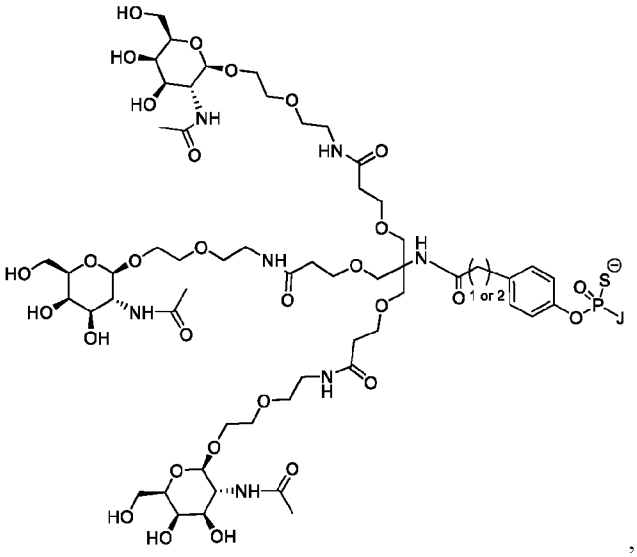

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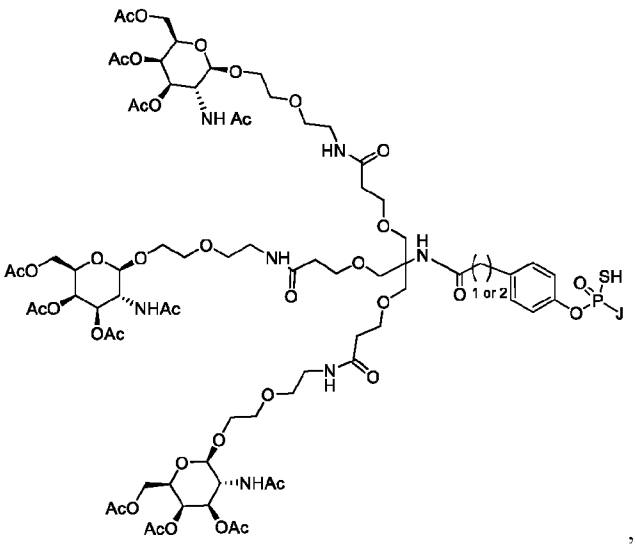

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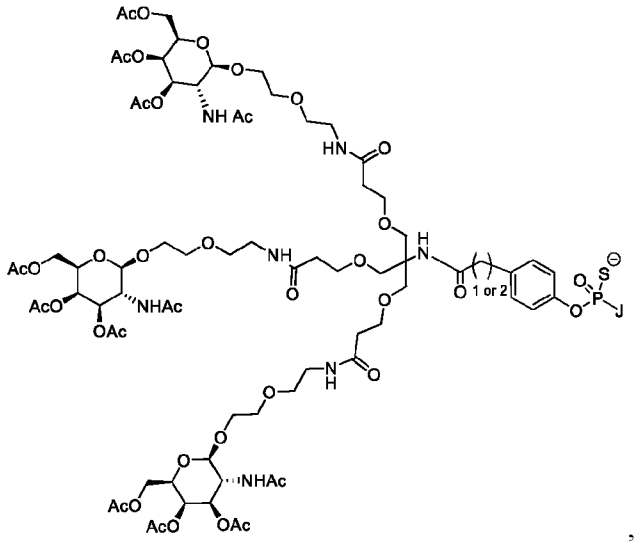

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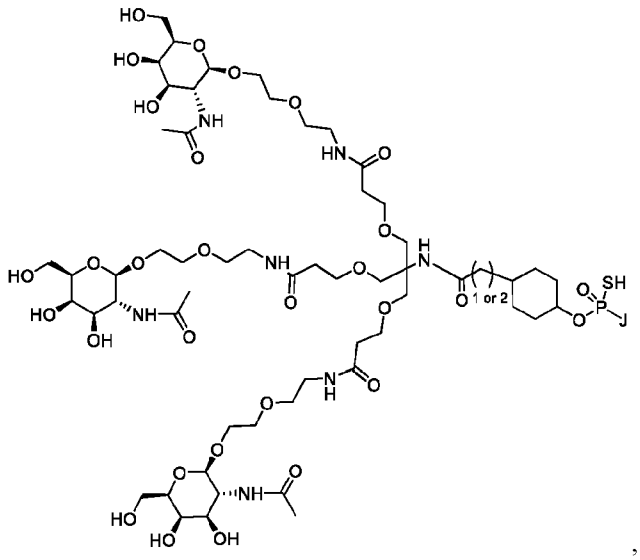

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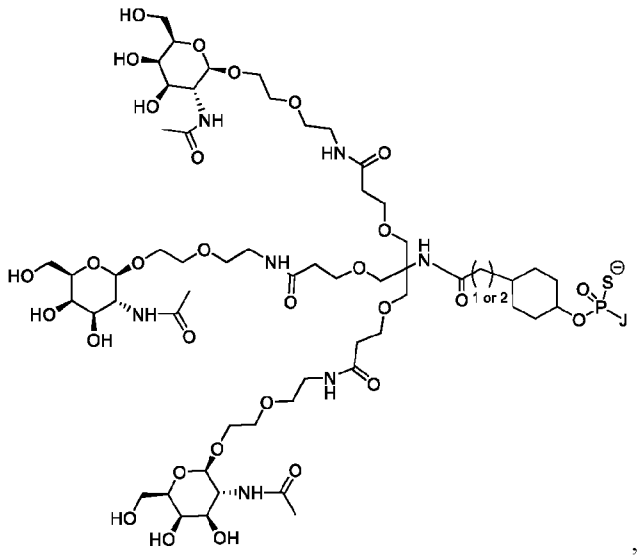

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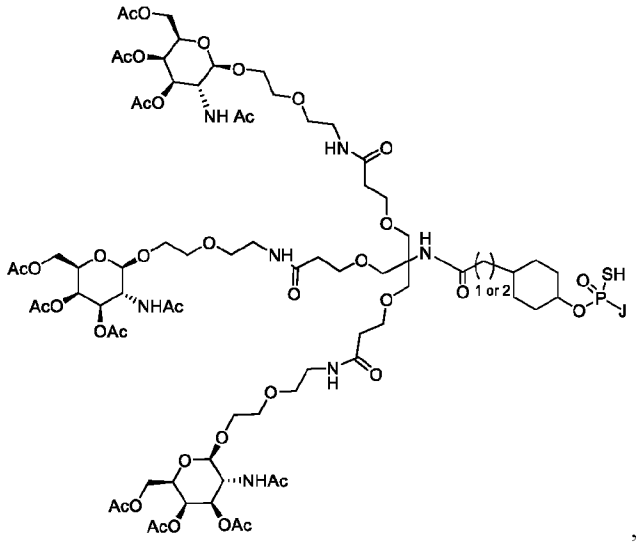

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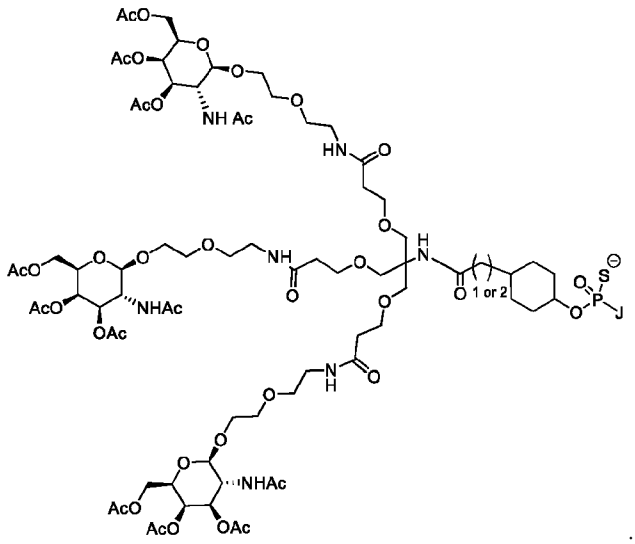


40. The compound of claim 1, **wherein the oligonucleotide (J) is attached at a 5' end or a 3' end** of the oligonucleotide.

41. The compound of claim 1, wherein the oligonucleotide comprises DNA.

42. The compound of claim 1, wherein the oligonucleotide comprises RNA.

43. The compound of claim 1, wherein the oligonucleotide comprises one or more modified internucleoside linkages.

44. The compound of claim 43, wherein the one or more modified internucleoside linkages comprise alkylphosphonate, phosphorothioate, methylphosphonate, phosphorodithioate, alkylphosphonothioate, phosphoramidate, carbamate, carbonate, phosphate triester, acetamidate, or carboxymethyl ester, or a combination thereof.

45. The compound of claim 1, wherein the oligonucleotide comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 modified internucleoside linkages.

46. The compound of claim 1, wherein the oligonucleotide comprises one or more modified nucleosides.

47. The compound of claim 46, wherein the one or more modified nucleosides comprise a locked nucleic acid (LNA), hexitol nucleic acid (HLA), cyclohexene nucleic acid (CeNA), 2'- methoxyethyl, 2'-O-alkyl, 2'-O-allyl, 2'-O-allyl, 2'-fluoro, or 2'-deoxy, or a combination thereof.

48. The compound of claim 46, wherein the one or more modified nucleosides comprise a 2',4' constrained ethyl nucleoside, a 2'-O-methyl nucleoside, 2'-deoxyfluoro nucleoside, 2'-O-N-methylacetamido (2'-O-NMA) nucleoside, a 2'-O- dimethylaminoethoxyethyl (2'-O-DMAEOE) nucleoside, 2'-O-aminopropyl (2'-O-AP) nucleoside, 2'-ara-F, 2'fluoro, or 2' O-alkyl, or a combination thereof.

49. The compound of claim 1, wherein the oligonucleotide comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, or more modified nucleosides.

50. The compound of claim 1, wherein the oligonucleotide comprises a lipid attached at a 3' or 5' terminus of the oligonucleotide.

51. The compound of claim 50, wherein the lipid comprises cholesterol, myristoyl, palmitoyl, stearoyl, lithocholoyl, docosanoyl, docosahexaenoyl, myristyl, palmityl stearyl, or α-tocopherol, or a combination thereof.

52. The compound of claim 1, wherein the oligonucleotide comprises an arginine-glycine-aspartic acid (RGD) peptide attached at a 3' or 5' terminus of the oligonucleotide.

53. The compound of claim 52, wherein the RGD peptide comprises Cyclo(-Arg-Gly-Asp-D-Phe-Cys), Cyclo(-Arg-Gly-Asp-D-Phe-Lys), Cyclo(-Arg-Gly-Asp-D-Phe-azido), an amino benzoic acid derived RGD, or a combination thereof.

54. The compound of claim 1, wherein the oligonucleotide comprises a small interfering RNA (siRNA) comprising a sense strand and an antisense strand.

55. The compound of claim 54, wherein the sense strand is 12-30 nucleosides in length.

56. The compound of claim 54, wherein the antisense strand is 12-30 nucleosides in length.

57. The compound of claim 54, wherein the sense strand and the antisense strand form a double-stranded RNA duplex.

58. The compound of claim 57, wherein a first base pair of the double-stranded RNA duplex is an AU base pair.

59. The compound of claim 54, wherein the sense strand or the antisense strand comprises a 3' overhang.

60. The compound of claim 59, wherein the 3' overhang comprises 1, 2, or more nucleosides.

61. The compound of claim 1, wherein the oligonucleotide comprises an antisense oligonucleotide (ASO).

62. The compound of claim 61, wherein the ASO is 12-30 nucleosides in length.

63. The compound of claim 1, wherein the compound binds to an asialoglycoprotein receptor.

64. The compound of claim 1, wherein the compound targets a hepatocyte.

65. A pharmaceutical composition comprising the compound of claim 1, and a pharmaceutically acceptable carrier, excipient, or diluent.

66. The pharmaceutical composition of claim 65, wherein the pharmaceutical composition is sterile.

67. The pharmaceutical composition of claim 65, wherein the pharmaceutical composition comprises a pharmaceutically acceptable carrier.

68. The pharmaceutical composition of claim 67, wherein the pharmaceutically acceptable carrier comprises water, a buffer, or a saline solution.

69. The pharmaceutical composition of claim 65, wherein the oligonucleotide targets a target mRNA and when administered to a subject in an effective amount decreases the target mRNA or a target protein by at least 10%.

70. A method of decreasing a target mRNA or target protein in a subject in need thereof, comprising administering an effective amount of the pharmaceutical composition of claim 65 to the subject.

71. The method of claim 70, wherein the effective amount decreases a measurement of the target mRNA or target protein in the subject, relative to a baseline target mRNA or target protein measurement.

72. The method of claim 70, wherein the effective amount treats a disorder in the subject.

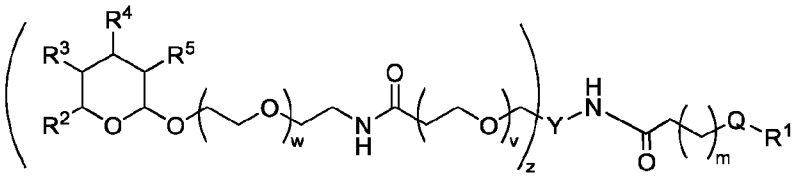
73. The method of claim 72, wherein the effective amount decreases a measurement of a symptom or parameter related to the disorder in the subject, relative to a baseline symptom or parameter measurement.

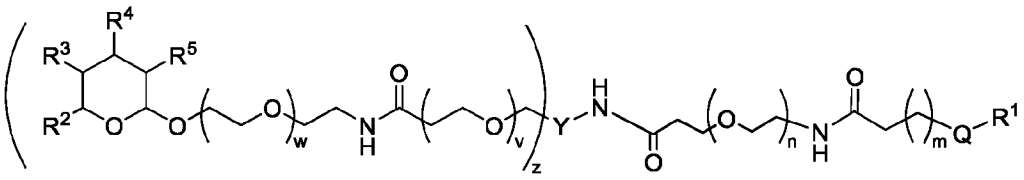
74. The method of claim 72, wherein the measurement of the symptom or the parameter related to the disorder in the subject is decreased for at least 10 days.

75. The method of claim 72, wherein the disorder comprises a metabolic disorder.

76. The method of claim 72, wherein the disorder comprises a liver disorder.

77. A compound represented by Formula (A) or (B):


(A), or


(B);

or a salt thereof, wherein

each w is independently selected from any value from 1 to 20;

each v is independently selected from any value from 1 to 20;

n is selected from any value from 1 to 20;

m is selected from any value from 1 to 20;

z is selected from any value from 1 to 3, wherein

if z is 3, Y is C

if z is 2, Y is CR^6, or

if z is 1, Y is $C(R^6)_2$;

Q is selected from:

C_{3-10} carbocycle optionally substituted with one or more substituents independently selected from halogen, -CN, $-NO_2$, $-OR^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, $-C(O)N(R^7)_2$, $-N(R^7)C(O)R^7$, $-N(R^7)C(O)N(R^7)_2$, $-OC(O)N(R^7)_2$, $-N(R^7)C(O)OR^7$, $-C(O)OR^7$, $-OC(O)R^7$, $-S(O)R^7$, and C_{1-6} alkyl, wherein the C_{1-6} alkyl, is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, $-NO_2$, and $-NH_2$;

R^1 is selected from:

$-OR^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, $-C(O)N(R^7)_2$, $-N(R^7)C(O)R^7$, $-N(R^7)C(O)N(R^7)_2$, $-OC(O)N(R^7)_2$, $-N(R^7)C(O)OR^7$, $-C(O)OR^7$, $-OC(O)R^7$, $-S(O)R^7$, $-S(O)_2R^7$, $-OS(O)_2R^7$, $-OP(O)(OR^7)_2$, $-OP(S)(OR^7)_2$, $-SP(O)(OR^7)_2$, $-OP(O)(SR^7)(OR^7)$, $-OP(O)(OR^7)N(R^7)_2$, $-OP(S)(OR^7)N(R^7)_2$, $-SP(O)(OR^7)N(R^7)_2$, $-OP(O)(SR^7)N(R^7)_2$, $-OP(O)(N(R^7)_2)_2$, $-OP(S)(N(R^7)_2)_2$, $-SP(O)(N(R^7)_2)_2$, $-OP(OR^7)_2$, $-SP(OR^7)_2$, $-OP(OR^7)(SR^7)$,$-OP(OR^7)N(R^7)_2$, $-OP(SR^7)N(R^7)_2$, $-SP(OR^7)N(R^7)_2$, $-OP(N(R^7)_2)_2$, and $-SP(N(R^7)_2)_2$;

each R^2 is independently selected from:

C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, $-OR^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, $-C(O)N(R^7)_2$, $-N(R^7)C(O)R^7$, $-N(R^7)C(O)N(R^7)_2$, $-OC(O)N(R^7)_2$, $-N(R^7)C(O)OR^7$, $-C(O)OR^7$, $-OC(O)R^7$, and $-S(O)R^7$;

R^3 and R^4 are each independently selected from:

$-OR^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, $-C(O)N(R^7)_2$, $-N(R^7)C(O)R^7$, $-N(R^7)C(O)N(R^7)_2$, $-OC(O)N(R^7)_2$, $-N(R^7)C(O)OR^7$, $-C(O)OR^7$, $-OC(O)R^7$, and $-S(O)R^7$;

each R^5 is independently selected from:

$-OC(O)R^7$, $-OC(O)N(R^7)_2$, $-N(R^7)C(O)R^7$, $-N(R^7)C(O)N(R^7)_2$, $-N(R^7)C(O)OR^7$, $-C(O)R^7$, $-C(O)OR^7$, and $-C(O)N(R^7)_2$;

each R^6 is independently selected from:

hydrogen;

halogen, -CN, $-NO_2$, $-OR^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, $-C(O)N(R^7)_2$, $-N(R^7)C(O)R^7$, $-N(R^7)C(O)N(R^7)_2$, $-OC(O)N(R^7)_2$, $-N(R^7)C(O)OR^7$, $-C(O)OR^7$, $-OC(O)R^7$, and $-S(O)R^7$; and

C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, -CN, $-NO_2$, $-OR^7$, $-SR^7$, $-N(R^7)_2$, $-C(O)R^7$, $-C(O)N(R^7)_2$, $-N(R^7)C(O)R^7$, $-N(R^7)C(O)N(R^7)_2$, $-OC(O)N(R^7)_2$, $-N(R^7)C(O)OR^7$, $-C(O)OR^7$, $-OC(O)R^7$, and $-S(O)R^7$;

each R^7 is independently selected from:

hydrogen;

C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, $-NO_2$, $-NH_2$, =O, =S, $-O-C_{1-6}$ alkyl, $-S-C_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)_2$, $-NH(C_{1-6}$ alkyl), C_{3-10} carbocycle, and 3- to 10-membered heterocycle; and

C_{3-10} carbocycle, and 3- to 10-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, -NO_2, -NH_2, =O, =S, -O-C_{1-6} alkyl, -S-C_{1-6} alkyl, -N(C_{1-6} alkyl)$_2$, -NH(C_{1-6} alkyl), C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, and C_{1-6} haloalkyl.

78. The compound or salt of claim 77, wherein each w is independently selected from any value from 1 to 10.

79. The compound or salt of claim 77, wherein each w is independently selected from any value from 1 to 5.

80. The compound or salt of claim 77, wherein each w is 1.

81. The compound or salt of claim 77, wherein each v is independently selected from any value from 1 to 10.

82. The compound or salt of claim 77, wherein each v is independently selected from any value from 1 to 5.

83. The compound or salt of claim 77, wherein each v is 1.

84. The compound or salt of claim 77, wherein n is selected from any value from 1 to 10.

85. The compound or salt of claim 77, wherein n is selected from any value from 1 to 5.

86. The compound or salt of claim 77, wherein n is 2.

87. The compound or salt of claim 77, wherein m is selected from any value from 1 to 10.

88. The compound or salt of claim 77, wherein m is selected from any value from 1 to 5.

89. The compound or salt of claim 77, wherein m is selected from 1 and 2.

90. The compound or salt of claim 77, wherein z is 3 and Y is C.

91. The compound or salt of claim 77, wherein Q is selected from C_{5-6} carbocycle optionally substituted with one or more substituents independently selected from halogen, -CN, -NO_2, -OR^7, -SR^7, -$N(R^7)_2$, -$C(O)R^7$, -$C(O)N(R^7)_2$, -$N(R^7)C(O)R^7$, -$N(R^7)C(O)N(R^7)_2$, -$OC(O)N(R^7)_2$, -$N(R^7)C(O)OR^7$, -$C(O)OR^7$, -$OC(O)R^7$, and -$S(O)R^7$.

92. The compound or salt of claim 77, wherein Q is selected from C_{5-6} carbocycle optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, -NO_2, and -NH_2.

93. The compound or salt of claim 77, wherein Q is selected from phenyl and cyclohexyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, -NO_2, and -NH_2.

94. The compound or salt of claim 77, wherein Q is selected from phenyl.

95. The compound or salt of claim 77, wherein Q is selected from cyclohexyl.

96. The compound or salt of claim 77, wherein R^1 is selected from -$OP(O)(OR^7)_2$, -$OP(O)(OR^7)N(R^7)_2$, -$OP(O)(N(R^7)_2)_2$, -$OP(OR^7)_2$, -$OP(OR^7)N(R^7)_2$, and -$OP((NR^7)_2)_2$.

97. The compound or salt of claim 77, wherein R^1 is selected from -$OP(O)(OR^7)_2$ and -$OP(OR^7)N(R^7)_2$.

98. The compound or salt of claim 77, wherein R^1 is selected from -OP(O)(OCH_2CH_3)OH and -OP(OCH_2CH_2CN)N($CH(CH_3)_2$)$_2$.

99. The compound or salt of claim 77, wherein R^1 is -OP(OCH_2CH_2CN)N($CH(CH_3)_2$)$_2$.

100. The compound or salt of claim 77, wherein R^2 is selected from C_{1-3} alkyl substituted with one or more substituents independently selected from halogen, -OR^7, -OC(O)R^7, -SR^7, -N(R^7)$_2$, -C(O)R^7, and -S(O)R^7.

101. The compound or salt of claim 77, wherein R^2 is selected from C_{1-3} alkyl substituted with one or more substituents independently selected from -OR^7, -OC(O)R^7, -SR^7, and -N(R^7)$_2$.

102. The compound or salt of claim 77, wherein R^2 is selected from C_{1-3} alkyl substituted with one or more substituents independently selected from -OR^7 and -OC(O)R^7.

103. The compound or salt of claim 77, wherein R^3 is selected from halogen, -OR^7, -SR^7, -N(R^7)$_2$, -C(O)R^7, -OC(O)R^7, and -S(O)R^7.

104. The compound or salt of claim 77, wherein R^3 is selected from -OR^7 -SR^7, -OC(O)R^7, and -N(R^7)$_2$.

105. The compound or salt of claim 77, wherein R^3 is selected from -OR^7 - and -OC(O)R^7.

106. The compound or salt of claim 77, wherein R^4 is selected from halogen, -OR^7, -SR^7, -N(R^7)$_2$, -C(O)R^7, -OC(O)R^7, and -S(O)R^7.

107. The compound or salt of claim 77, wherein R^4 is selected from -OR^7 -SR^7, -OC(O)R^7, and -N(R^7)$_2$.

108. The compound or salt of claim 77, wherein R^4 is selected from -OR^7 - and -OC(O)R^7.

109. The compound or salt of claim 77, wherein R^5 is selected from -OC(O)R^7, -OC(O)N(R^7)$_2$, -N(R^7)C(O)R^7, -N(R^7)C(O)N(R^7)$_2$, and -N(R^7)C(O)OR^7.

110. The compound or salt of claim 77, wherein R^5 is selected from -OC(O)R^7 and -N(R^7)C(O)R^7.

111. The compound or salt of claim 77, wherein each R^7 is independently selected from:

hydrogen; and

C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, -NO_2, -NH_2, =O, =S, -O-C_{1-6} alkyl, -S-C_{1-6} alkyl, -N(C_{1-6} alkyl)$_2$, -NH(C_{1-6} alkyl), C_{3-10} carbocycle, or 3- to 10-membered heterocycle.

112. The compound or salt of claim 77, wherein each R^7 is independently selected from C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, -NO_2, -NH_2, =O, =S, -O-C_{1-6} alkyl, -S-C_{1-6} alkyl, -N(C_{1-6} alkyl)$_2$, and -NH(C_{1-6} alkyl).

113. The compound or salt of claim 77, wherein each R^7 is independently selected from C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, and -SH.

114. The compound or salt of claim 113, wherein

w is 1;

v is 1;

n is 2;

m is 1 or 2;

z is 3 and Y is C;

Q is phenyl or cyclohexyl, each of which is optionally substituted with one or more substituents independently selected from halogen, -CN, -OH, -SH, $-NO_2$, $-NH_2$, and C_{1-3} alkyl;

R^1 is selected from $-OP(O)(OR^7)_2$ and $-OP(OR^7)N(R^7)_2$;

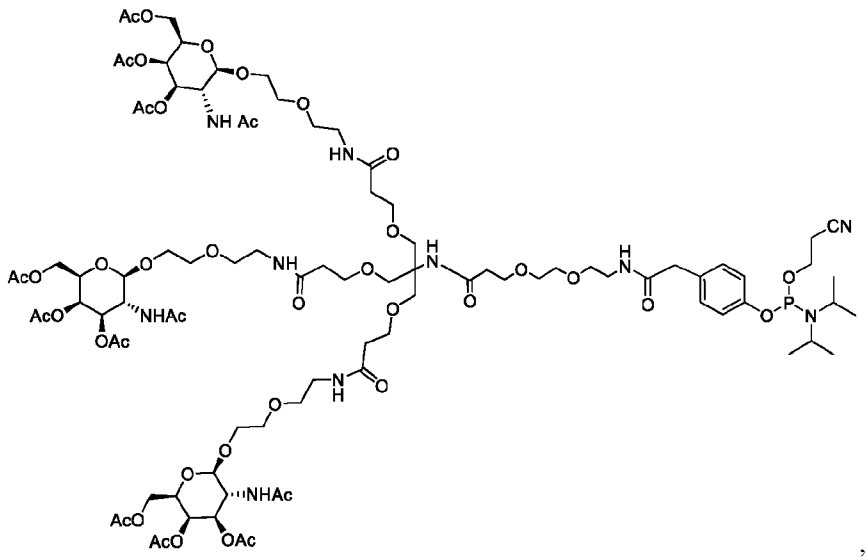
R^2 is C_1 alkyl substituted with -OH or $-OC(O)CH_3$;

R^3 is -OH or $-OC(O)CH_3$;

R^4 is -OH or $-OC(O)CH_3$; and

R^5 is $-NH(O)CH_3$.

115. The compound of claim 77, wherein the compound comprises:



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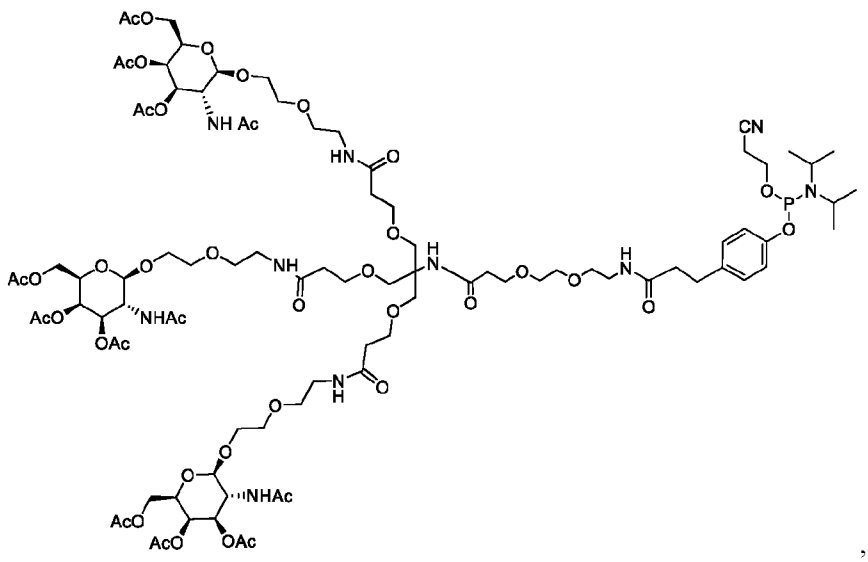

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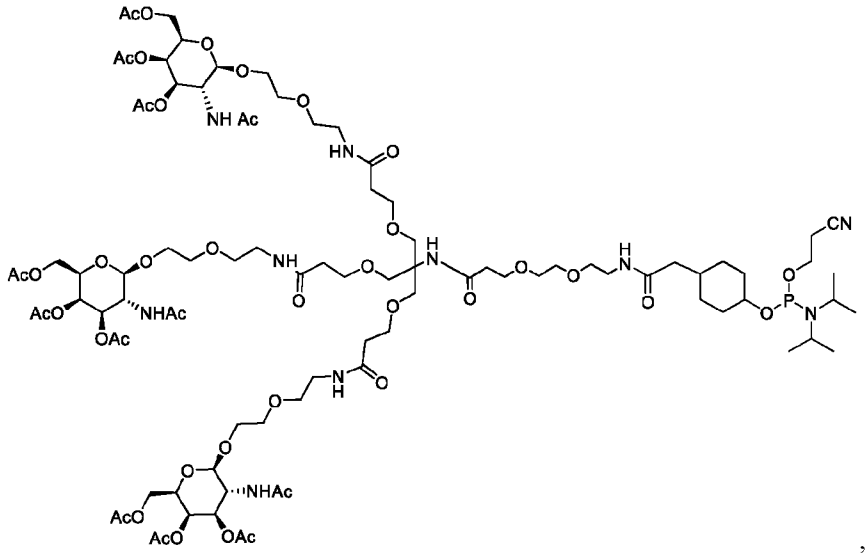

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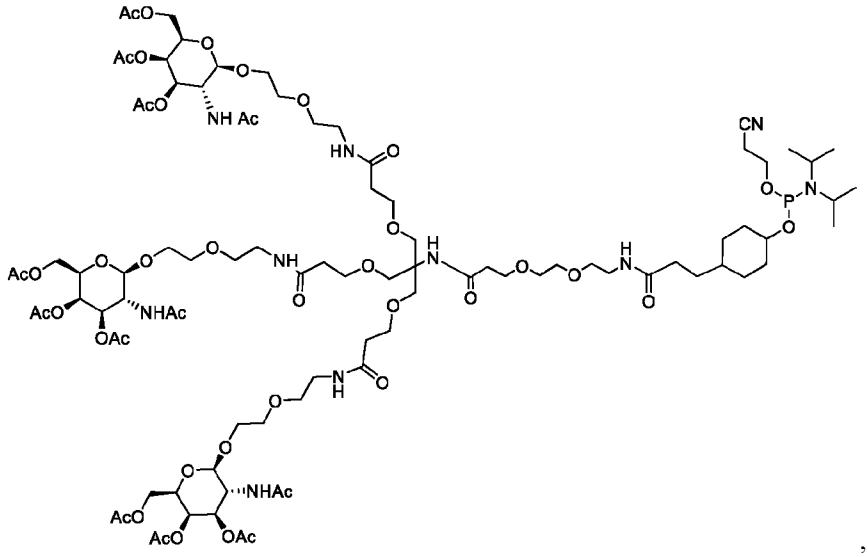

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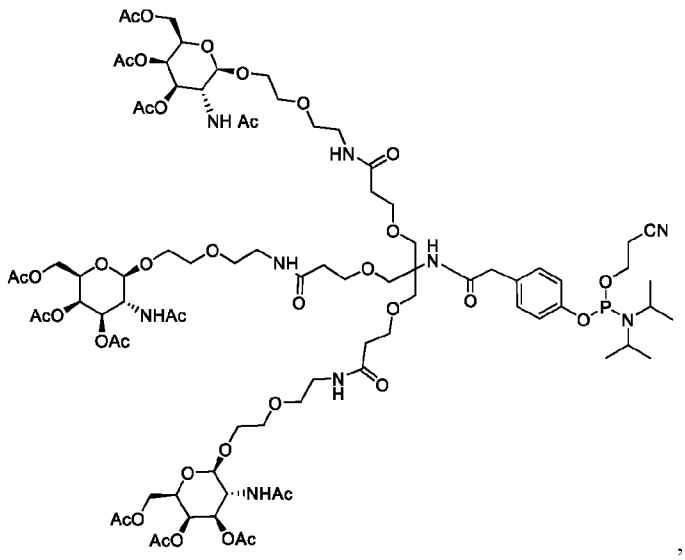

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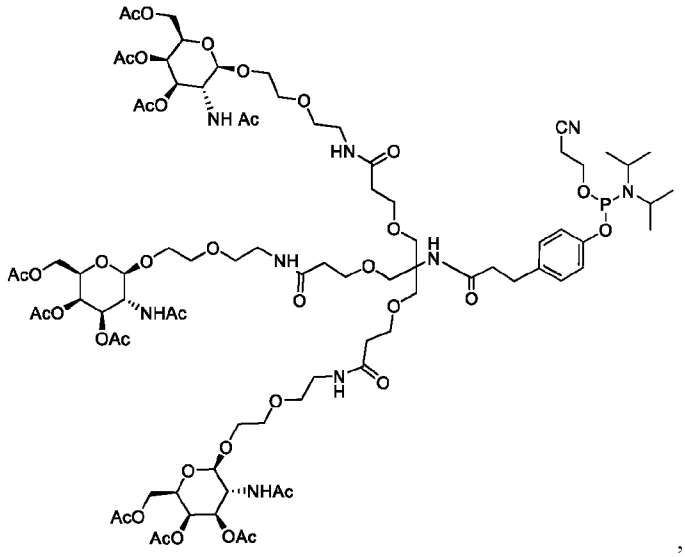

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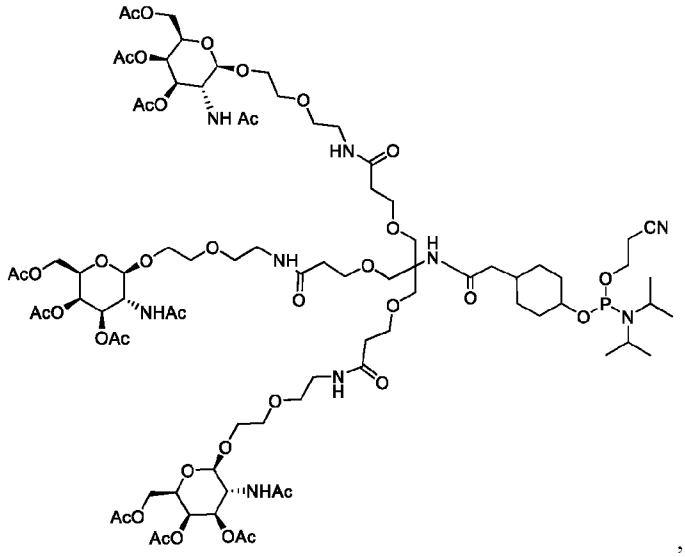

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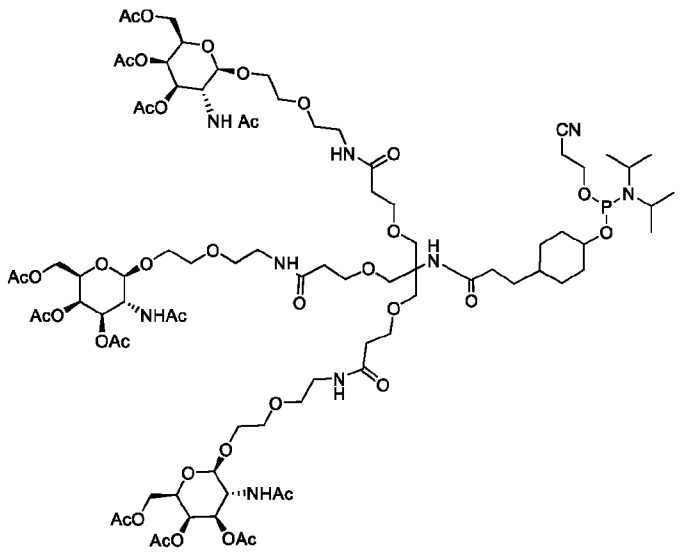

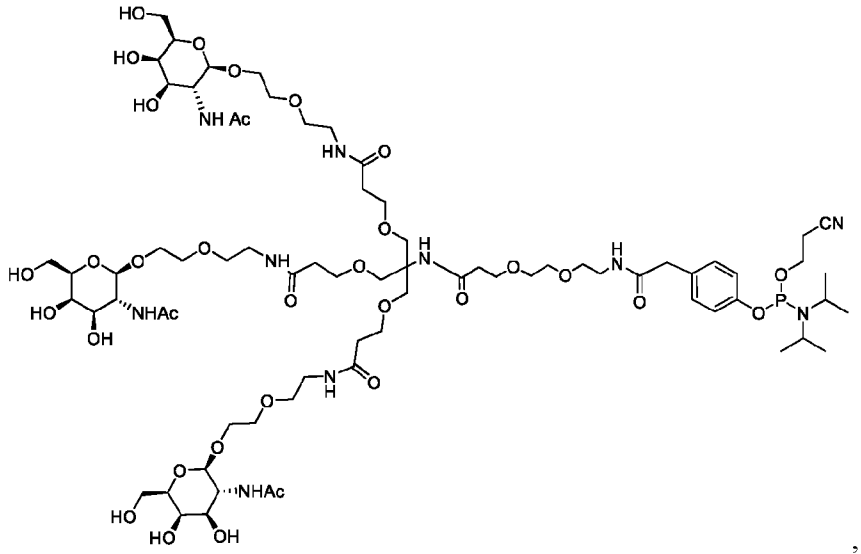

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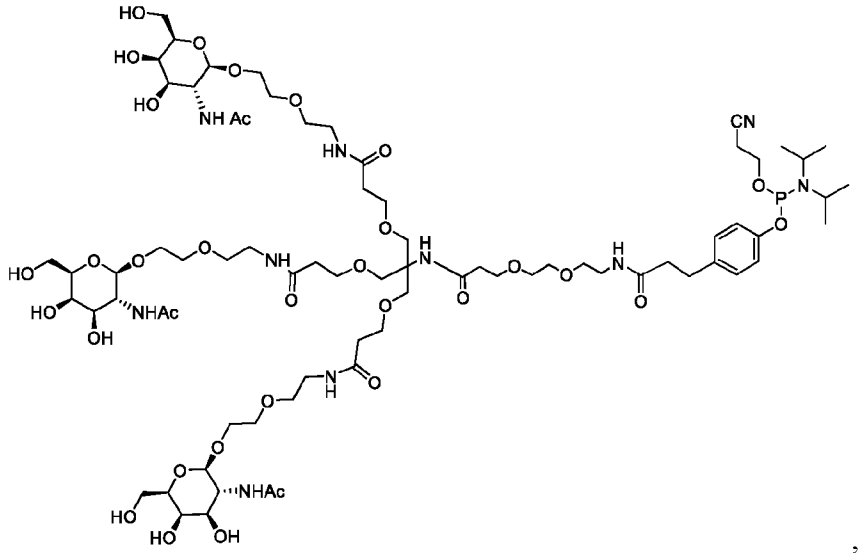

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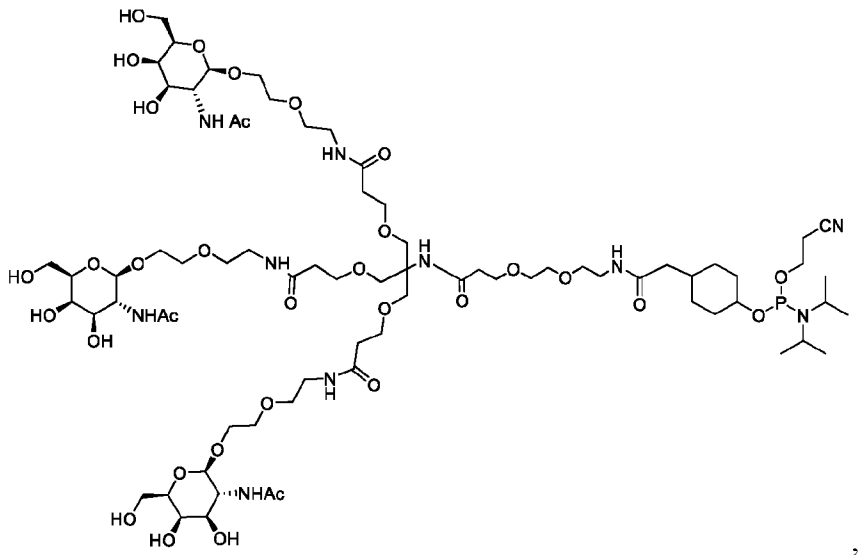

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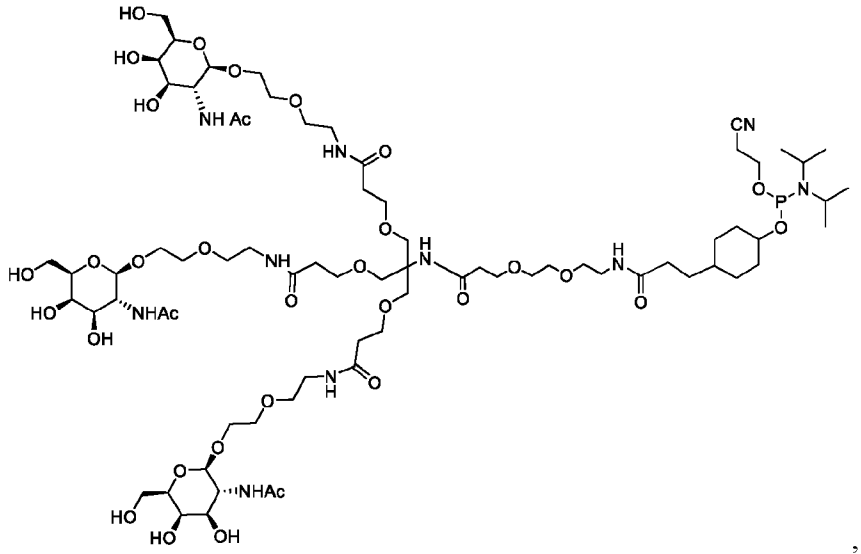

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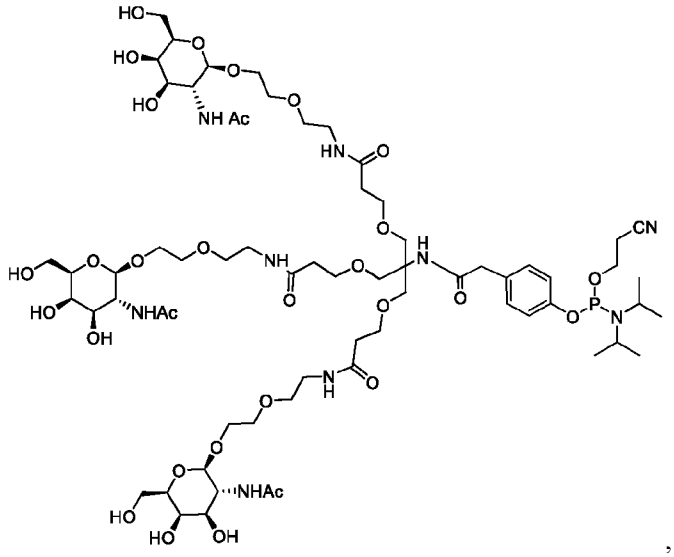

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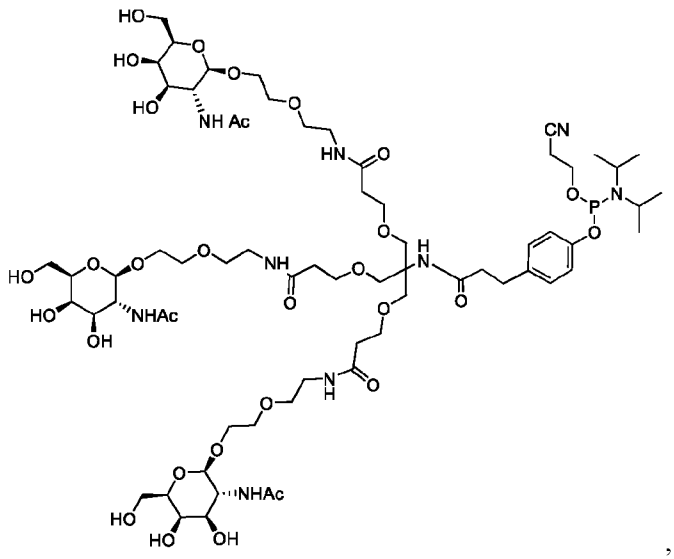

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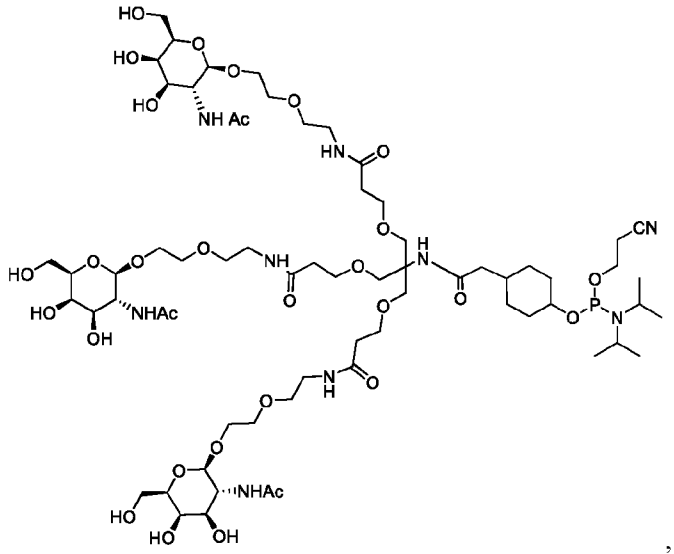
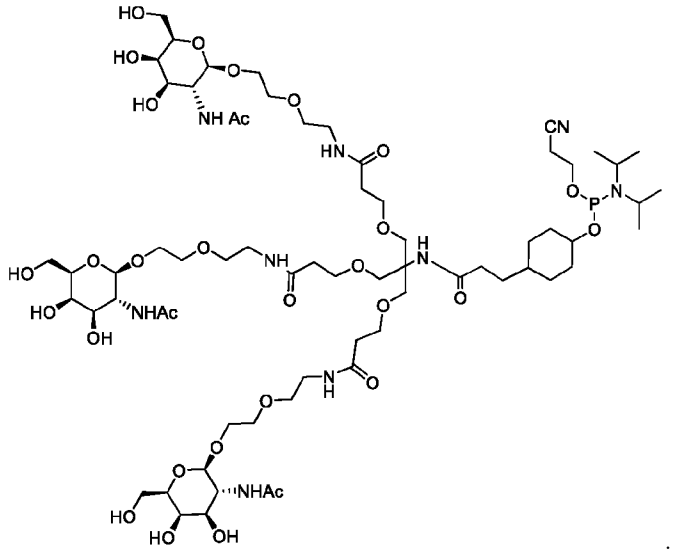
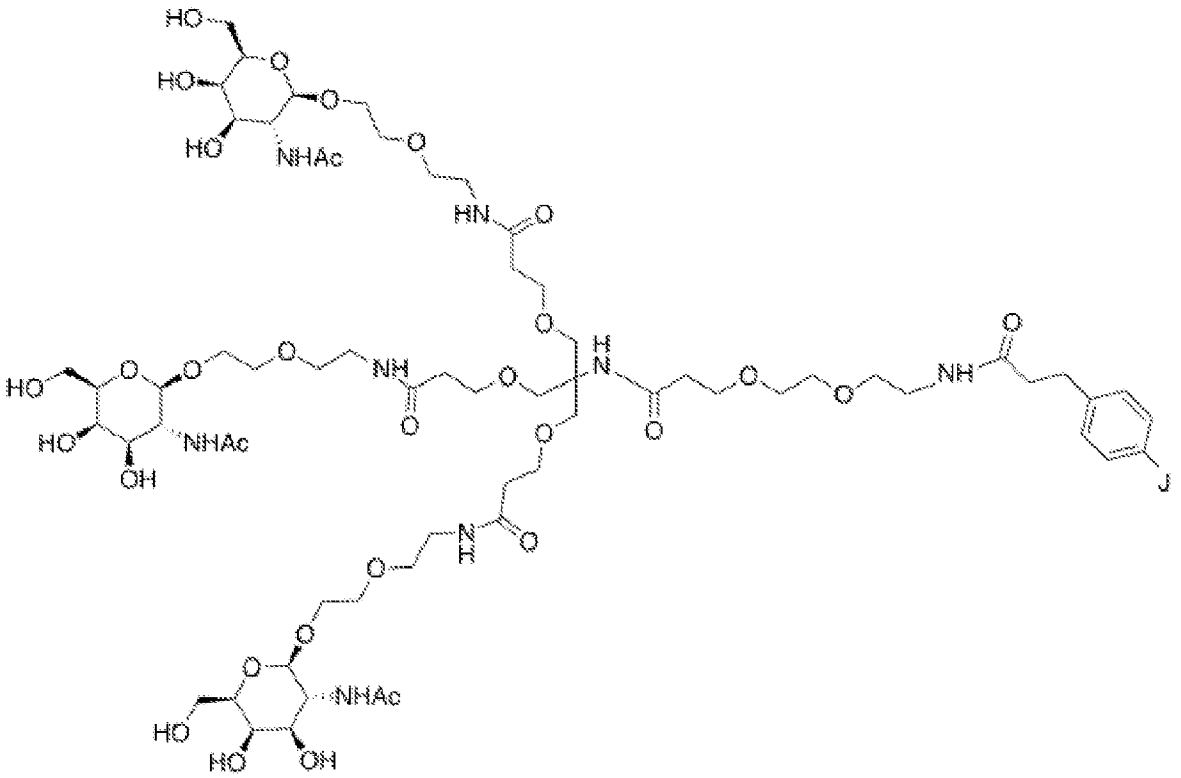


, or



.

116. A compound comprising:



wherein J comprises an oligonucleotide, or comprises a connection to the oligonucleotide.

117. The compound of claim 116, wherein J further comprises one or more phosphate groups linking the structure to the oligonucleotide.

118. The compound of claim 116, wherein J further comprises one or more phosphorothioate groups linking the structure to the oligonucleotide.

119. **The compound of claim 116, wherein the oligonucleotide comprises a 5' end, and J comprises a connection to the 5' end of the oligo**nucleotide.

120. The compound of claim 116, wherein the oligonucleotide comprises an siRNA.

Sequence Listing

1	**Sequence Listing Information**	
1-1	File Name	54462-735601_PCT.xml
1-2	DTD Version	V1_3
1-3	Software Name	WIPO Sequence
1-4	Software Version	2.2.0
1-5	Production Date	2023-03-10
1-6	Original free text language code	en
1-7	Non English free text language code	
2	**General Information**	
2-1	Current application: IP Office	WO
2-2	Current application: Application number	
2-3	Current application: Filing date	
2-4	Current application: Applicant file reference	54462-735.601
2-5	Earliest priority application: IP Office	US
2-6	Earliest priority application: Application number	63/320,431
2-7	Earliest priority application: Filing date	2022-03-16
2-8en	Applicant name	EMPIRICO INC.
2-8	Applicant name: Name Latin	
2-9en	Inventor name	Darren H. WAKEFIELD
2-9	Inventor name: Name Latin	
2-10en	Invention title	GALNAC COMPOSITIONS FOR IMPROVING SIRNA BIOAVAILABILITY
2-11	Sequence Total Quantity	64

3-1	**Sequences**	
3-1-1	Sequence Number [ID]	1
3-1-2	Molecule Type	RNA
3-1-3	Length	21
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		note=GalNAc moiety-ETL17
		organism=synthetic construct
		modified_base 1
		mod_base=OTHER
		note=phosphorothioate linkage
		note=2-O-methyl modified nucleoside
		modified_base 19^20
		mod_base=OTHER
		note=phosphorothioate linkage
		modified_base 20^21
		mod_base=OTHER
		note=phosphorothioate linkage
		modified_base 11
		mod_base=OTHER
		note=2-fluoro-modified nucleoside
		modified_base 6
		mod_base=OTHER
		note=2-O-methyl modified nucleoside
		modified_base 12
		mod_base=OTHER
		note=2-O-methyl modified nucleoside
		modified_base 13
		mod_base=OTHER
		note=2-O-methyl modified nucleoside
		modified_base 2
		mod_base=OTHER
		note=2-O-methyl modified nucleoside
		modified_base 3
		mod_base=OTHER
		note=2-O-methyl modified nucleoside
		modified_base 4
		mod_base=OTHER
		note=2-O-methyl modified nucleoside
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		note=2-O-methyl modified nucleoside
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		modified_base 8
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		modified_base 9
		mod_base=OTHER
		note=2-fluoro-modified nucleoside
		modified_base 10
		mod_base=OTHER
		note=2-O-methyl modified nucleoside
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		note=2-O-methyl modified nucleoside
		modified_base 15
		mod_base=OTHER
		note=2-O-methyl modified nucleoside
		modified_base 16
		mod_base=OTHER
		note=2-O-methyl modified nucleoside
		modified_base 17
		mod_base=OTHER

		note=2-O-methyl modified nucleoside **modified_base 18** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 19** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 21** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 20** mod_base=OTHER note=2-O-methyl modified nucleoside	
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3-1-5	Residues	cagtttttaa gggacaccat t	21
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3-2-1	Sequence Number [ID]	2	
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3-2-4	Features Location/ Qualifiers	**source 1..21** mol_type=other RNA note=GalNAc moiety-ETL17 organism=synthetic construct **modified_base 1** mod_base=OTHER note=phosphorothioate linkage note=2-O-methyl modified nucleoside **modified_base 19^20** mod_base=OTHER note=phosphorothioate linkage **modified_base 20^21** mod_base=OTHER note=phosphorothioate linkage **modified_base 8** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 9** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 10** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 17** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 2** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 3** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 4** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 5** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 6** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 7** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 12** mod_base=OTHER	

		note=2-O-methyl modified nucleoside **modified_base 11** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 13** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 14** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 15** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 16** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 18** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 19** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 20** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 21** mod_base=OTHER note=2-O-methyl modified nucleoside	
	NonEnglishQualifier Value		
3-2-5	Residues	`tttttaaggg acaccagaat t`	21
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3-3-1	Sequence Number [ID]	3	
3-3-2	Molecule Type	RNA	
3-3-3	Length	21	
3-3-4	Features Location/ Qualifiers	**source 1..21** mol_type=other RNA note=GalNAc moiety-ETL17 organism=synthetic construct **modified_base 1** mod_base=OTHER note=2-O-methyl modified nucleoside note=phosphorothioate linkage **modified_base 2** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 3** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 4** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 5** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 6** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 7** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 8** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 9** mod_base=OTHER	

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3-5-4	Features Location/ Qualifiers	**source 1..21** mol_type=other RNA note=GalNAc moiety-ETL17 organism=synthetic construct **modified_base 1** mod_base=OTHER note=phosphorothioate linkage note=2-O-methyl modified nucleoside **modified_base 2** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 3** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 4** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 5** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 6** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 7** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 8** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 9** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 10** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 11** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 12** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 13** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 14** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 15** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 16** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 17** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 18** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 19** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 20** mod_base=OTHER note=2-O-methyl modified nucleoside

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3-6-3	Length	21	
3-6-4	Features Location/ Qualifiers	**source 1..21** mol_type=other RNA note=GalNAc moiety-ETL17 organism=synthetic construct **modified_base 1** mod_base=OTHER note=2-O-methyl modified nucleoside note=phosphorothioate linkage **modified_base 2** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 3** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 4** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 5** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 6** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 7** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 8** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 9** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 10** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 11** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 12** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 13** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 14** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 15** mod_base=OTHER note=2-O-methyl modified nucleoside	

		modified_base 16 mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 17** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 18** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 19** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 20** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 21** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 19^20** mod_base=OTHER note=phosphorothioate linkage **modified_base 20^21** mod_base=OTHER note=phosphorothioate linkage	
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3-7-1	Sequence Number [ID]	7	
3-7-2	Molecule Type	RNA	
3-7-3	Length	21	
3-7-4	Features Location/ Qualifiers	**source 1..21** mol_type=other RNA note=GalNAc moiety-ETL17 organism=synthetic construct **modified_base 1** mod_base=OTHER note=phosphorothioate linkage note=2-O-methyl modified nucleoside **modified_base 2** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 3** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 4** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 5** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 6** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 7** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 8** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 9** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 10** mod_base=OTHER note=2-O-methyl modified nucleoside	

		modified_base 11 mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 12** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 13** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 14** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 15** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 16** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 17** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 18** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 19** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 20** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 21** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 19^20** mod_base=OTHER note=phosphorothioate linkage **modified_base 20^21** mod_base=OTHER note=phosphorothioate linkage	
	NonEnglishQualifier Value		
3-7-5	Residues	`aactactgca taatatggat t`	21
3-8	**Sequences**		
3-8-1	Sequence Number [ID]	8	
3-8-2	Molecule Type	RNA	
3-8-3	Length	21	
3-8-4	Features Location/ Qualifiers	**source 1..21** mol_type=other RNA organism=synthetic construct **modified_base 1^2** mod_base=OTHER note=phosphorothioate linkage **modified_base 1** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 2** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 3** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 4** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 5** mod_base=OTHER	

		note=2-O-methyl modified nucleoside	
		modified_base 6	
		mod_base=OTHER	
		note=2-fluoro-modified nucleoside	
		modified_base 7	
		mod_base=OTHER	
		note=2-O-methyl modified nucleoside	
		modified_base 8	
		mod_base=OTHER	
		note=2-fluoro-modified nucleoside	
		modified_base 9	
		mod_base=OTHER	
		note=2-O-methyl modified nucleoside	
		modified_base 10	
		mod_base=OTHER	
		note=2-fluoro-modified nucleoside	
		modified_base 11	
		mod_base=OTHER	
		note=2-O-methyl modified nucleoside	
		modified_base 12	
		mod_base=OTHER	
		note=2-fluoro-modified nucleoside	
		modified_base 13	
		mod_base=OTHER	
		note=2-O-methyl modified nucleoside	
		modified_base 14	
		mod_base=OTHER	
		note=2-fluoro-modified nucleoside	
		modified_base 15	
		mod_base=OTHER	
		note=2-O-methyl modified nucleoside	
		modified_base 16	
		mod_base=OTHER	
		note=2-fluoro-modified nucleoside	
		modified_base 17	
		mod_base=OTHER	
		note=2-O-methyl modified nucleoside	
		modified_base 18	
		mod_base=OTHER	
		note=2-fluoro-modified nucleoside	
		modified_base 19	
		mod_base=OTHER	
		note=2-O-methyl modified nucleoside	
		modified_base 20	
		mod_base=OTHER	
		note=2-O-methyl modified nucleoside	
		modified_base 21	
		mod_base=OTHER	
		note=2-O-methyl modified nucleoside	
		modified_base 19^20	
		mod_base=OTHER	
		note=phosphorothioate linkage	
		modified_base 20^21	
		mod_base=OTHER	
		note=phosphorothioate linkage	
		modified_base 2^3	
		mod_base=OTHER	
		note=phosphorothioate linkage	
	NonEnglishQualifier Value		
3-8-5	Residues	`tggtgtccct taaaaactgt t`	21
3-9	**Sequences**		
3-9-1	Sequence Number [ID]	9	
3-9-2	Molecule Type	RNA	
3-9-3	Length	21	

3-9-4	Features Location/ Qualifiers	**source 1..21** mol_type=other RNA organism=synthetic construct **modified_base 1^2** mod_base=OTHER note=phosphorothioate linkage **modified_base 1** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 3** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 5** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 7** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 9** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 11** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 13** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 15** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 17** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 19** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 20** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 21** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 2** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 4** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 6** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 8** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 10** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 12** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 14** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 16** mod_base=OTHER

		note=2-fluoro-modified nucleoside **modified_base 18** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 19^20** mod_base=OTHER note=phosphorothioate linkage **modified_base 20^21** mod_base=OTHER note=phosphorothioate linkage **modified_base 2^3** mod_base=OTHER note=phosphorothioate linkage	
3-9-5	NonEnglishQualifier Value Residues	ttctggtgtc ccttaaaaat t	21
3-10	**Sequences**		
3-10-1	Sequence Number [ID]	10	
3-10-2	Molecule Type	RNA	
3-10-3	Length	21	
3-10-4	Features Location/ Qualifiers	**source 1..21** mol_type=other RNA organism=synthetic construct **modified_base 1^2** mod_base=OTHER note=phosphorothioate linkage **modified_base 1** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 3** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 5** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 7** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 9** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 11** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 13** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 15** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 17** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 19** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 20** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 21** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 2** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 4**	

		mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 6** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 8** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 10** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 12** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 14** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 16** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 18** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 19^20** mod_base=OTHER note=phosphorothioate linkage **modified_base 20^21** mod_base=OTHER note=phosphorothioate linkage **modified_base 2^3** mod_base=OTHER note=phosphorothioate linkage	
	NonEnglishQualifier Value		
3-10-5	Residues	`tgctaagaat gtgtcaaaat t`	21
3-11	**Sequences**		
3-11-1	Sequence Number [ID]	11	
3-11-2	Molecule Type	RNA	
3-11-3	Length	21	
3-11-4	Features Location/ Qualifiers	**source 1..21** mol_type=other RNA organism=synthetic construct **modified_base 1^2** mod_base=OTHER note=phosphorothioate linkage **modified_base 1** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 3** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 5** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 7** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 9** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 11** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 13** mod_base=OTHER note=2-O-methyl modified nucleoside	

		modified_base 15 mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 17** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 19** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 20** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 21** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 2** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 4** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 6** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 8** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 10** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 12** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 14** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 16** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 18** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 19^20** mod_base=OTHER note=phosphorothioate linkage **modified_base 20^21** mod_base=OTHER note=phosphorothioate linkage **modified_base 2^3** mod_base=OTHER note=phosphorothioate linkage	
	NonEnglishQualifier Value		
3-11-5	Residues	`tgtgctaaga atgtgtcaat t`	21
3-12	**Sequences**		
3-12-1	Sequence Number [ID]	12	
3-12-2	Molecule Type	RNA	
3-12-3	Length	21	
3-12-4	Features Location/ Qualifiers	**source 1..21** mol_type=other RNA organism=synthetic construct **modified_base 1^2** mod_base=OTHER note=phosphorothioate linkage **modified_base 1** mod_base=OTHER	

note=2-O-methyl modified nucleoside
modified_base 3
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 5
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 7
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 9
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 11
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 13
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 15
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 17
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 19
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 20
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 21
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 2
mod_base=OTHER
note=2-fluoro-modified nucleoside
modified_base 4
mod_base=OTHER
note=2-fluoro-modified nucleoside
modified_base 6
mod_base=OTHER
note=2-fluoro-modified nucleoside
modified_base 8
mod_base=OTHER
note=2-fluoro-modified nucleoside
modified_base 10
mod_base=OTHER
note=2-fluoro-modified nucleoside
modified_base 12
mod_base=OTHER
note=2-fluoro-modified nucleoside
modified_base 14
mod_base=OTHER
note=2-fluoro-modified nucleoside
modified_base 16
mod_base=OTHER
note=2-fluoro-modified nucleoside
modified_base 18
mod_base=OTHER
note=2-fluoro-modified nucleoside
modified_base 20^21
mod_base=OTHER
note=phosphorothioate linkage
modified_base 19^20

		mod_base=OTHER note=phosphorothioate linkage **modified_base 2^3** mod_base=OTHER note=phosphorothioate linkage	
	NonEnglishQualifier Value		
3-12-5	Residues	`tgttcagtgc taagaatgtt t`	21
3-13	**Sequences**		
3-13-1	Sequence Number [ID]	13	
3-13-2	Molecule Type	RNA	
3-13-3	Length	21	
3-13-4	Features Location/ Qualifiers	**source 1..21** mol_type=other RNA organism=synthetic construct **modified_base 1^2** mod_base=OTHER note=phosphorothioate linkage **modified_base 1** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 3** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 5** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 7** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 9** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 11** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 13** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 15** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 17** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 19** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 21** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 20** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 19^20** mod_base=OTHER note=phosphorothioate linkage **modified_base 20^21** mod_base=OTHER note=phosphorothioate linkage **modified_base 2** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 4** mod_base=OTHER note=2-fluoro-modified nucleoside	

		modified_base 6 mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 8** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 10** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 12** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 14** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 16** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 18** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 2^3** mod_base=OTHER note=phosphorothioate linkage
3-13-5	NonEnglishQualifier Value Residues	`tcaaaagagt gactatgcat t` 21
3-14	**Sequences**	
3-14-1	Sequence Number [ID]	14
3-14-2	Molecule Type	RNA
3-14-3	Length	21
3-14-4	Features Location/ Qualifiers	**source 1..21** mol_type=other RNA organism=synthetic construct **modified_base 1^2** mod_base=OTHER note=phosphorothioate linkage **modified_base 1** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 3** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 5** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 7** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 9** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 11** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 13** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 15** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 17** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 19** mod_base=OTHER

		note=2-O-methyl modified nucleoside **modified_base 20** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 21** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 2** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 4** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 6** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 8** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 10** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 12** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 14** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 16** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 18** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 19^20** mod_base=OTHER note=phosphorothioate linkage **modified_base 20^21** mod_base=OTHER note=phosphorothioate linkage **modified_base 2^3** mod_base=OTHER note=phosphorothioate linkage	
3-14-5	NonEnglishQualifier Value Residues	`tccatattat gcagtagttt t`	21
3-15	**Sequences**		
3-15-1	Sequence Number [ID]	15	
3-15-2	Molecule Type	RNA	
3-15-3	Length	21	
3-15-4	Features Location/ Qualifiers	**source 1..21** mol_type=other RNA note=GalNAc moiety-ETL17 organism=synthetic construct **modified_base 1** mod_base=OTHER note=2-O-methyl modified nucleoside note=phosphorothioate linkage **modified_base 2** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 3** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 4** mod_base=OTHER	

		note=2-O-methyl modified nucleoside **modified_base 5** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 6** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 7** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 8** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 9** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 10** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 11** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 12** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 13** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 14** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 15** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 16** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 17** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 18** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 19** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 20** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 21** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 19^20** mod_base=OTHER note=phosphorothioate linkage **modified_base 20^21** mod_base=OTHER note=phosphorothioate linkage
	NonEnglishQualifier Value	
3-15-5	Residues	`ggtcctggaa ggaattatat t` 21
3-16	**Sequences**	
3-16-1	Sequence Number [ID]	16
3-16-2	Molecule Type	RNA
3-16-3	Length	22

3-16-4	Features Location/ Qualifiers	**source 1..22** mol_type=other RNA note=GalNAc moiety-ETL17 organism=synthetic construct **modified_base 1** mod_base=OTHER note=phosphorothioate linkage note=2-fluoro-modified nucleoside **modified_base 3** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 5** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 7** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 10** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 12** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 16** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 18** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 2** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 4** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 6** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 8** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 11** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 13** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 14** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 15** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 17** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 19** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 20** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 21** mod_base=OTHER note=2-O-methyl modified nucleoside

		modified_base 22 mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 20^21** mod_base=OTHER note=phosphorothioate linkage **modified_base 21^22** mod_base=OTHER note=phosphorothioate linkage	
3-16-5	NonEnglishQualifier Value Residues	`aacttcttdg tcagacataa tt`	22
3-17	**Sequences**		
3-17-1	Sequence Number [ID]	17	
3-17-2	Molecule Type	RNA	
3-17-3	Length	21	
3-17-4	Features Location/ Qualifiers	**source 1..21** mol_type=other RNA note=GalNAc moiety-ETL17 organism=synthetic construct **modified_base 1** mod_base=OTHER note=2-O-methyl modified nucleoside note=phosphorothioate linkage **modified_base 2** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 3** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 4** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 5** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 6** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 7** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 8** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 9** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 10** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 11** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 12** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 13** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 14** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 15** mod_base=OTHER note=2-O-methyl modified nucleoside	

		modified_base 16 mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 17** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 18** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 19** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 20** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 21** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 19^20** mod_base=OTHER note=phosphorothioate linkage **modified_base 20^21** mod_base=OTHER note=phosphorothioate linkage	
3-17-5	NonEnglishQualifier Value Residues	`cttcttgtca gacataaaat t`	21
3-18	**Sequences**		
3-18-1	Sequence Number [ID]	18	
3-18-2	Molecule Type	RNA	
3-18-3	Length	21	
3-18-4	Features Location/ Qualifiers	**source 1..21** mol_type=other RNA note=GalNAc moiety-ETL17 organism=synthetic construct **modified_base 1** mod_base=OTHER note=2-O-methyl modified nucleoside note=phosphorothioate linkage **modified_base 2** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 3** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 4** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 5** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 6** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 7** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 8** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 9** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 10** mod_base=OTHER note=2-fluoro-modified nucleoside	

		modified_base 11 mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 12** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 13** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 14** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 15** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 16** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 17** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 18** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 19** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 20** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 21** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 19^20** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 20^21** mod_base=OTHER note=2-O-methyl modified nucleoside	
	NonEnglishQualifier Value		
3-18-5	Residues	caaccaggag tgtaacatat t	21
3-19	**Sequences**		
3-19-1	Sequence Number [ID]	19	
3-19-2	Molecule Type	RNA	
3-19-3	Length	21	
3-19-4	Features Location/ Qualifiers	**source 1..21** mol_type=other RNA organism=synthetic construct **modified_base 1^2** mod_base=OTHER note=phosphorothioate linkage **modified_base 1** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 3** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 5** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 7** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 9** mod_base=OTHER	

		note=2-O-methyl modified nucleoside **modified_base 11** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 13** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 15** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 17** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 19** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 20** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 21** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 2** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 4** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 6** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 8** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 10** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 12** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 14** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 16** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 18** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 19^20** mod_base=OTHER note=phosphorothioate linkage **modified_base 20^21** mod_base=OTHER note=phosphorothioate linkage **modified_base 2^3** mod_base=OTHER note=phosphorothioate linkage
	NonEnglishQualifier Value	
3-19-5	Residues	`tataattcct tccaggacct t` 21
3-20	**Sequences**	
3-20-1	Sequence Number [ID]	20
3-20-2	Molecule Type	RNA
3-20-3	Length	21

3-20-4	Features Location/ Qualifiers	**source 1..21** mol_type=other RNA organism=synthetic construct **modified_base 1^2** mod_base=OTHER note=phosphorothioate linkage **modified_base 1** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 3** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 5** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 7** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 9** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 11** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 13** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 15** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 17** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 19** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 20** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 21** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 2** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 4** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 6** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 8** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 10** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 12** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 14** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 16** mod_base=OTHER

		note=2-fluoro-modified nucleoside **modified_base 18** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 19^20** mod_base=OTHER note=phosphorothioate linkage **modified_base 20^21** mod_base=OTHER note=phosphorothioate linkage **modified_base 2^3** mod_base=OTHER note=phosphorothioate linkage	
	NonEnglishQualifier Value		
3-20-5	Residues	ttatgtctga caagaagttt t	21
3-21	**Sequences**		
3-21-1	Sequence Number [ID]	21	
3-21-2	Molecule Type	RNA	
3-21-3	Length	21	
3-21-4	Features Location/ Qualifiers	**source 1..21** mol_type=other RNA organism=synthetic construct **modified_base 1^2** mod_base=OTHER note=phosphorothioate linkage **modified_base 1** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 3** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 5** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 7** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 9** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 11** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 13** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 15** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 17** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 19** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 20** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 21** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 2** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 4**	

		mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 6** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 8** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 10** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 12** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 14** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 16** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 18** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 19^20** mod_base=OTHER note=phosphorothioate linkage **modified_base 20^21** mod_base=OTHER note=phosphorothioate linkage **modified_base 2^3** mod_base=OTHER note=phosphorothioate linkage	
	NonEnglishQualifier Value		
3-21-5	Residues	`ttttatgtct gacaagaagt t`	21
3-22	**Sequences**		
3-22-1	Sequence Number [ID]	22	
3-22-2	Molecule Type	RNA	
3-22-3	Length	21	
3-22-4	Features Location/ Qualifiers	**source 1..21** mol_type=other RNA organism=synthetic construct **modified_base 1^2** mod_base=OTHER note=phosphorothioate linkage **modified_base 1** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 3** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 5** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 7** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 9** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 11** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 13** mod_base=OTHER note=2-O-methyl modified nucleoside	

		modified_base 15 mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 17** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 19** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 20** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 21** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 2** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 4** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 6** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 8** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 10** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 12** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 14** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 16** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 18** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 19^20** mod_base=OTHER note=phosphorothioate linkage **modified_base 20^21** mod_base=OTHER note=phosphorothioate linkage **modified_base 2^3** mod_base=OTHER note=phosphorothioate linkage	
	NonEnglishQualifier Value		
3-22-5	Residues	`tatgttacac tcctggttgt t`	21
3-23	**Sequences**		
3-23-1	Sequence Number [ID]	23	
3-23-2	Molecule Type	RNA	
3-23-3	Length	21	
3-23-4	Features Location/ Qualifiers	**source 1..21** mol_type=other RNA note=GalNAc moiety-ETL17 organism=synthetic construct **modified_base 1** mod_base=OTHER note=phosphorothioate linkage note=2-O-methyl modified nucleoside	

modified_base 2
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 3
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 4
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 5
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 6
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 7
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 8
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 9
mod_base=OTHER
note=2-fluoro-modified nucleoside
modified_base 10
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 11
mod_base=OTHER
note=2-fluoro-modified nucleoside
modified_base 12
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 13
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 14
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 15
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 16
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 17
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 18
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 19
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 20
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 21
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 19^20
mod_base=OTHER
note=phosphorothioate linkage
modified_base 20^21
mod_base=OTHER

		note=phosphorothioate linkage	
	NonEnglishQualifier Value		
3-23-5	Residues	gtatctccag aatgttatat t	21
3-24	**Sequences**		
3-24-1	Sequence Number [ID]	24	
3-24-2	Molecule Type	RNA	
3-24-3	Length	21	
3-24-4	Features Location/	**source 1..21**	
	Qualifiers	mol_type=other RNA	
		note=GalNAc moiety-ETL17	
		organism=synthetic construct	
		modified_base 1	
		mod_base=OTHER	
		note=2-O-methyl modified nucleoside	
		note=phosphorothioate linkage	
		modified_base 2	
		mod_base=OTHER	
		note=2-O-methyl modified nucleoside	
		modified_base 3	
		mod_base=OTHER	
		note=2-O-methyl modified nucleoside	
		modified_base 4	
		mod_base=OTHER	
		note=2-O-methyl modified nucleoside	
		modified_base 5	
		mod_base=OTHER	
		note=2-O-methyl modified nucleoside	
		modified_base 6	
		mod_base=OTHER	
		note=2-O-methyl modified nucleoside	
		modified_base 7	
		mod_base=OTHER	
		note=2-O-methyl modified nucleoside	
		modified_base 8	
		mod_base=OTHER	
		note=2-fluoro-modified nucleoside	
		modified_base 9	
		mod_base=OTHER	
		note=2-fluoro-modified nucleoside	
		modified_base 10	
		mod_base=OTHER	
		note=2-fluoro-modified nucleoside	
		modified_base 11	
		mod_base=OTHER	
		note=2-fluoro-modified nucleoside	
		modified_base 12	
		mod_base=OTHER	
		note=2-O-methyl modified nucleoside	
		modified_base 13	
		mod_base=OTHER	
		note=2-O-methyl modified nucleoside	
		modified_base 14	
		mod_base=OTHER	
		note=2-O-methyl modified nucleoside	
		modified_base 15	
		mod_base=OTHER	
		note=2-O-methyl modified nucleoside	
		modified_base 16	
		mod_base=OTHER	
		note=2-O-methyl modified nucleoside	
		modified_base 17	
		mod_base=OTHER	
		note=2-O-methyl modified nucleoside	
		modified_base 18	
		mod_base=OTHER	

		note=2-O-methyl modified nucleoside **modified_base 19** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 20** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 21** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 19^20** mod_base=OTHER note=phosphorothioate linkage **modified_base 20^21** mod_base=OTHER note=phosphorothioate linkage	
3-24-5	NonEnglishQualifier Value Residues	`acttcctgga atcgatacat t`	21
3-25	**Sequences**		
3-25-1	Sequence Number [ID]	25	
3-25-2	Molecule Type	RNA	
3-25-3	Length	21	
3-25-4	Features Location/ Qualifiers	**source 1..21** mol_type=other RNA note=GalNAc moiety-ETL17 organism=synthetic construct **modified_base 1** mod_base=OTHER note=phosphorothioate linkage note=2-O-methyl modified nucleoside **modified_base 2** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 3** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 4** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 5** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 6** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 7** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 8** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 9** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 10** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 11** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 12** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 13** mod_base=OTHER	

		note=2-O-methyl modified nucleoside **modified_base 14** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 15** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 16** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 17** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 18** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 19** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 20** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 21** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 19^20** mod_base=OTHER note=phosphorothioate linkage **modified_base 20^21** mod_base=OTHER note=phosphorothioate linkage
	NonEnglishQualifier Value	
3-25-5	Residues	`cttcctggaa tcgatactat t` 21
3-26	**Sequences**	
3-26-1	Sequence Number [ID]	26
3-26-2	Molecule Type	RNA
3-26-3	Length	21
3-26-4	Features Location/ Qualifiers	**source 1..21** mol_type=other RNA note=GalNAc moiety-ETL17 organism=synthetic construct **modified_base 1** mod_base=OTHER note=2-O-methyl modified nucleoside note=phosphorothioate linkage **modified_base 2** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 3** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 4** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 5** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 6** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 7** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 8** mod_base=OTHER

		note=2-O-methyl modified nucleoside **modified_base 9** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 10** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 11** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 12** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 13** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 14** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 15** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 16** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 17** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 18** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 19** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 20** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 21** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 19^20** mod_base=OTHER note=phosphorothioate linkage **modified_base 20^21** mod_base=OTHER note=phosphorothioate linkage
	NonEnglishQualifier Value	
3-26-5	Residues	`ctggaatcga tacttgtaat t` 21
3-27	**Sequences**	
3-27-1	Sequence Number [ID]	27
3-27-2	Molecule Type	RNA
3-27-3	Length	21
3-27-4	Features Location/ Qualifiers	**source 1..21** mol_type=other RNA note=GalNAc moiety-ETL17 organism=synthetic construct **modified_base 1** mod_base=OTHER note=phosphorothioate linkage note=2-O-methyl modified nucleoside **modified_base 2** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 3** mod_base=OTHER

		note=2-O-methyl modified nucleoside **modified_base 4** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 5** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 6** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 7** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 8** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 9** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 10** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 11** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 12** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 13** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 14** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 16** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 15** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 17** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 18** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 19** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 20** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 21** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 19^20** mod_base=OTHER note=phosphorothioate linkage **modified_base 20^21** mod_base=OTHER note=phosphorothioate linkage
	NonEnglishQualifier Value	
3-27-5	Residues	`ggaatcgata cttgtattat t` 21
3-28	**Sequences**	
3-28-1	Sequence Number [ID]	28

3-28-2	Molecule Type	RNA
3-28-3	Length	21
3-28-4	Features Location/ Qualifiers	**source 1..21** mol_type=other RNA note=GalNAc moiety-ETL17 organism=synthetic construct **modified_base 1** mod_base=OTHER note=phosphorothioate linkage note=2-O-methyl modified nucleoside **modified_base 2** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 3** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 4** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 5** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 6** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 7** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 8** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 9** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 10** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 11** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 12** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 13** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 14** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 15** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 16** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 17** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 18** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 19** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 20**

		mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 21** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 19^20** mod_base=OTHER note=phosphorothioate linkage **modified_base 20^21** mod_base=OTHER note=phosphorothioate linkage	
	NonEnglishQualifier Value		
3-28-5	Residues	`gatgctttct acaaaggtat t`	21
3-29	**Sequences**		
3-29-1	Sequence Number [ID]	29	
3-29-2	Molecule Type	RNA	
3-29-3	Length	21	
3-29-4	Features Location/ Qualifiers	**source 1..21** mol_type=other RNA note=GalNAc moiety-ETL17 organism=synthetic construct **modified_base 1** mod_base=OTHER note=2-O-methyl modified nucleoside note=phosphorothioate linkage **modified_base 2** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 3** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 4** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 5** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 6** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 7** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 8** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 9** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 10** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 11** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 12** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 13** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 14** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 15**	

		mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 16** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 17** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 18** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 19** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 20** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 21** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 19^20** mod_base=OTHER note=phosphorothioate linkage **modified_base 20^21** mod_base=OTHER note=phosphorothioate linkage	
	NonEnglishQualifier Value		
3-29-5	Residues	agaaaagcag aacggtgaat t	21
3-30	**Sequences**		
3-30-1	Sequence Number [ID]	30	
3-30-2	Molecule Type	RNA	
3-30-3	Length	22	
3-30-4	Features Location/ Qualifiers	**source 1..22** mol_type=other RNA note=GalNAc moiety-ETL17 organism=synthetic construct **modified_base 1** mod_base=OTHER note=phosphorothioate linkage note=2-O-methyl modified nucleoside **modified_base 2** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 3** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 4** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 5** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 6** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 7** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 8** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 10** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 11**	

		mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 12** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 13** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 14** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 15** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 16** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 17** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 18** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 19** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 20** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 21** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 21^22** mod_base=OTHER note=phosphorothioate linkage **modified_base 20^21** mod_base=OTHER note=phosphorothioate linkage **modified_base 22** mod_base=OTHER note=2-O-methyl modified nucleoside
	NonEnglishQualifier Value	
3-30-5	Residues	`aagcagaadc ggtgaaagta tt` 22
3-31	**Sequences**	
3-31-1	Sequence Number [ID]	31
3-31-2	Molecule Type	RNA
3-31-3	Length	21
3-31-4	Features Location/ Qualifiers	**source 1..21** mol_type=other RNA note=GalNAc moiety-ETL17 organism=synthetic construct **modified_base 1** mod_base=OTHER note=2-O-methyl modified nucleoside note=phosphorothioate linkage **modified_base 2** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 3** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 4** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 5**

		mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 6** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 7** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 8** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 9** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 10** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 11** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 12** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 13** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 14** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 15** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 16** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 17** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 18** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 19** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 20** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 21** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 19^20** mod_base=OTHER note=phosphorothioate linkage **modified_base 20^21** mod_base=OTHER note=phosphorothioate linkage	
	NonEnglishQualifier Value		
3-31-5	Residues	`agtgggagat acattggaat t`	21
3-32	**Sequences**		
3-32-1	Sequence Number [ID]	32	
3-32-2	Molecule Type	RNA	
3-32-3	Length	21	
3-32-4	Features Location/	**source 1..21**	
	Qualifiers	mol_type=other RNA note=GalNAc moiety-ETL17	

organism=synthetic construct
modified_base 1
mod_base=OTHER
note=2-O-methyl modified nucleoside
note=phosphorothioate linkage
modified_base 2
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 3
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 4
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 5
mod_base=OTHER
note=2-fluoro-modified nucleoside
modified_base 6
mod_base=OTHER
note=2-fluoro-modified nucleoside
modified_base 7
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 8
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 9
mod_base=OTHER
note=2-fluoro-modified nucleoside
modified_base 10
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 11
mod_base=OTHER
note=2-fluoro-modified nucleoside
modified_base 12
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 13
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 14
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 15
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 16
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 17
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 18
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 19
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 20
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 21
mod_base=OTHER
note=2-O-methyl modified nucleoside

		modified_base 19^20 mod_base=OTHER note=phosphorothioate linkage **modified_base 20^21** mod_base=OTHER note=phosphorothioate linkage	
	NonEnglishQualifier Value		
3-32-5	Residues	tgggagatac attggatcat t	21
3-33	**Sequences**		
3-33-1	Sequence Number [ID]	33	
3-33-2	Molecule Type	RNA	
3-33-3	Length	21	
3-33-4	Features Location/ Qualifiers	**source 1..21** mol_type=other RNA organism=synthetic construct **modified_base 1^2** mod_base=OTHER note=phosphorothioate linkage **modified_base 1** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 3** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 5** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 7** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 9** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 11** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 13** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 15** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 17** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 19** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 20** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 21** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 2** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 4** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 6** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 8** mod_base=OTHER	

		note=2-fluoro-modified nucleoside **modified_base 10** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 12** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 14** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 16** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 18** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 19^20** mod_base=OTHER note=phosphorothioate linkage **modified_base 20^21** mod_base=OTHER note=phosphorothioate linkage **modified_base 2^3** mod_base=OTHER note=phosphorothioate linkage
	NonEnglishQualifier Value	
3-33-5	Residues	`tataacattc tggagatact t` 21
3-34	**Sequences**	
3-34-1	Sequence Number [ID]	34
3-34-2	Molecule Type	RNA
3-34-3	Length	21
3-34-4	Features Location/ Qualifiers	**source 1..21** mol_type=other RNA organism=synthetic construct **modified_base 1^2** mod_base=OTHER note=phosphorothioate linkage **modified_base 1** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 3** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 5** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 7** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 9** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 11** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 13** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 15** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 17** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 19**

		mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 20** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 21** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 2** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 4** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 6** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 8** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 10** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 12** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 14** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 16** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 18** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 19^20** mod_base=OTHER note=phosphorothioate linkage **modified_base 20^21** mod_base=OTHER note=phosphorothioate linkage **modified_base 2^3** mod_base=OTHER note=phosphorothioate linkage
	NonEnglishQualifier Value	
3-34-5	Residues	`tgtatcgatt ccaggaagtt t` 21
3-35	**Sequences**	
3-35-1	Sequence Number [ID]	35
3-35-2	Molecule Type	RNA
3-35-3	Length	21
3-35-4	Features Location/ Qualifiers	**source 1..21** mol_type=other RNA organism=synthetic construct **modified_base 1^2** mod_base=OTHER note=phosphorothioate linkage **modified_base 1** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 3** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 5** mod_base=OTHER note=2-O-methyl modified nucleoside

		modified_base 7 mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 9** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 11** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 13** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 15** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 17** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 19** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 20** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 21** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 2** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 4** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 6** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 8** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 10** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 12** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 14** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 16** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 18** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 19^20** mod_base=OTHER note=phosphorothioate linkage **modified_base 20^21** mod_base=OTHER note=phosphorothioate linkage **modified_base 2^3** mod_base=OTHER note=phosphorothioate linkage	
3-35-5	NonEnglishQualifier Value Residues	`tagtatcgat tccaggaagt t`	21

3-36	**Sequences**	
3-36-1	Sequence Number [ID]	36
3-36-2	Molecule Type	RNA
3-36-3	Length	21
3-36-4	Features Location/	**source 1..21**
	Qualifiers	mol_type=other RNA
		organism=synthetic construct
		modified_base 1^2
		mod_base=OTHER
		note=phosphorothioate linkage
		modified_base 1
		mod_base=OTHER
		note=2-O-methyl modified nucleoside
		modified_base 3
		mod_base=OTHER
		note=2-O-methyl modified nucleoside
		modified_base 5
		mod_base=OTHER
		note=2-O-methyl modified nucleoside
		modified_base 7
		mod_base=OTHER
		note=2-O-methyl modified nucleoside
		modified_base 9
		mod_base=OTHER
		note=2-O-methyl modified nucleoside
		modified_base 11
		mod_base=OTHER
		note=2-O-methyl modified nucleoside
		modified_base 13
		mod_base=OTHER
		note=2-O-methyl modified nucleoside
		modified_base 15
		mod_base=OTHER
		note=2-O-methyl modified nucleoside
		modified_base 17
		mod_base=OTHER
		note=2-O-methyl modified nucleoside
		modified_base 19
		mod_base=OTHER
		note=2-O-methyl modified nucleoside
		modified_base 20
		mod_base=OTHER
		note=2-O-methyl modified nucleoside
		modified_base 21
		mod_base=OTHER
		note=2-O-methyl modified nucleoside
		modified_base 2
		mod_base=OTHER
		note=2-fluoro-modified nucleoside
		modified_base 4
		mod_base=OTHER
		note=2-fluoro-modified nucleoside
		modified_base 6
		mod_base=OTHER
		note=2-fluoro-modified nucleoside
		modified_base 8
		mod_base=OTHER
		note=2-fluoro-modified nucleoside
		modified_base 10
		mod_base=OTHER
		note=2-fluoro-modified nucleoside
		modified_base 12
		mod_base=OTHER
		note=2-fluoro-modified nucleoside
		modified_base 14

		mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 16** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 18** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 19^20** mod_base=OTHER note=phosphorothioate linkage **modified_base 20^21** mod_base=OTHER note=phosphorothioate linkage **modified_base 2^3** mod_base=OTHER note=phosphorothioate linkage	
3-36-5	NonEnglishQualifier Value Residues	`ttacaagtat cgattccagt t`	21
3-37	**Sequences**		
3-37-1	Sequence Number [ID]	37	
3-37-2	Molecule Type	RNA	
3-37-3	Length	21	
3-37-4	Features Location/ Qualifiers	**source 1..21** mol_type=other RNA organism=synthetic construct **modified_base 1^2** mod_base=OTHER note=phosphorothioate linkage **modified_base 1** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 3** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 5** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 7** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 9** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 11** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 13** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 15** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 17** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 19** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 20** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 21** mod_base=OTHER note=2-O-methyl modified nucleoside	

		modified_base 2 mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 4** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 6** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 8** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 10** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 12** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 14** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 16** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 18** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 19^20** mod_base=OTHER note=phosphorothioate linkage **modified_base 20^21** mod_base=OTHER note=phosphorothioate linkage **modified_base 2^3** mod_base=OTHER note=phosphorothioate linkage	
3-37-5	NonEnglishQualifier Value Residues	`taatacaagt atcgattcct t`	21
3-38	**Sequences**		
3-38-1	Sequence Number [ID]	38	
3-38-2	Molecule Type	RNA	
3-38-3	Length	21	
3-38-4	Features Location/ Qualifiers	**source 1..21** mol_type=other RNA organism=synthetic construct **modified_base 1^2** mod_base=OTHER note=phosphorothioate linkage **modified_base 1** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 3** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 5** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 7** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 9** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 11** mod_base=OTHER	

		note=2-O-methyl modified nucleoside **modified_base 13** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 15** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 17** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 19** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 21** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 2** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 4** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 6** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 8** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 10** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 12** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 14** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 16** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 18** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 20** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 19^20** mod_base=OTHER note=phosphorothioate linkage **modified_base 20^21** mod_base=OTHER note=phosphorothioate linkage **modified_base 2^3** mod_base=OTHER note=phosphorothioate linkage
	NonEnglishQualifier Value	
3-38-5	Residues	`tacctttgta gaaagcatct t` 21
3-39	**Sequences**	
3-39-1	Sequence Number [ID]	39
3-39-2	Molecule Type	RNA
3-39-3	Length	21
3-39-4	Features Location/ Qualifiers	**source 1..21** mol_type=other RNA organism=synthetic construct **modified_base 1^2**

mod_base=OTHER
note=phosphorothioate linkage
modified_base 1
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 3
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 5
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 7
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 9
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 11
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 13
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 15
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 17
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 19
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 20
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 21
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 2
mod_base=OTHER
note=2-fluoro-modified nucleoside
modified_base 4
mod_base=OTHER
note=2-fluoro-modified nucleoside
modified_base 6
mod_base=OTHER
note=2-fluoro-modified nucleoside
modified_base 8
mod_base=OTHER
note=2-fluoro-modified nucleoside
modified_base 10
mod_base=OTHER
note=2-fluoro-modified nucleoside
modified_base 12
mod_base=OTHER
note=2-fluoro-modified nucleoside
modified_base 14
mod_base=OTHER
note=2-fluoro-modified nucleoside
modified_base 16
mod_base=OTHER
note=2-fluoro-modified nucleoside
modified_base 18
mod_base=OTHER
note=2-fluoro-modified nucleoside

		modified_base 19^20 mod_base=OTHER note=phosphorothioate linkage **modified_base 20^21** mod_base=OTHER note=phosphorothioate linkage **modified_base 2^3** mod_base=OTHER note=phosphorothioate linkage	
	NonEnglishQualifier Value		
3-39-5	Residues	ttcaccgttc tgcttttctt t	21
3-40	**Sequences**		
3-40-1	Sequence Number [ID]	40	
3-40-2	Molecule Type	RNA	
3-40-3	Length	21	
3-40-4	Features Location/ Qualifiers	**source 1..21** mol_type=other RNA organism=synthetic construct **modified_base 1^2** mod_base=OTHER note=phosphorothioate linkage **modified_base 1** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 3** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 5** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 7** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 9** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 11** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 13** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 15** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 17** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 19** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 21** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 20** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 2** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 4** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 6** mod_base=OTHER	

		note=2-fluoro-modified nucleoside **modified_base 8** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 10** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 12** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 14** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 16** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 18** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 19^20** mod_base=OTHER note=phosphorothioate linkage **modified_base 20^21** mod_base=OTHER note=phosphorothioate linkage **modified_base 2^3** mod_base=OTHER note=phosphorothioate linkage	
	NonEnglishQualifier Value		
3-40-5	Residues	tactttcacc gttctgcttt t	21
3-41	**Sequences**		
3-41-1	Sequence Number [ID]	41	
3-41-2	Molecule Type	RNA	
3-41-3	Length	21	
3-41-4	Features Location/ Qualifiers	**source 1..21** mol_type=other RNA organism=synthetic construct **modified_base 1^2** mod_base=OTHER note=phosphorothioate linkage **modified_base 1** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 3** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 5** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 7** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 9** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 11** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 13** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 15** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 17**	

		mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 19** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 20** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 21** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 2** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 4** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 6** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 8** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 10** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 12** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 14** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 16** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 18** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 19^20** mod_base=OTHER note=phosphorothioate linkage **modified_base 20^21** mod_base=OTHER note=phosphorothioate linkage **modified_base 2^3** mod_base=OTHER note=phosphorothioate linkage	
	NonEnglishQualifier Value		
3-41-5	Residues	`ttccaatgta tctcccactt t`	21
3-42	**Sequences**		
3-42-1	Sequence Number [ID]	42	
3-42-2	Molecule Type	RNA	
3-42-3	Length	21	
3-42-4	Features Location/ Qualifiers	**source 1..21** mol_type=other RNA organism=synthetic construct **modified_base 1^2** mod_base=OTHER note=phosphorothioate linkage **modified_base 1** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 3** mod_base=OTHER note=2-O-methyl modified nucleoside	

modified_base 5
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 7
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 9
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 11
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 13
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 15
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 17
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 19
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 20
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 21
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 2
mod_base=OTHER
note=2-fluoro-modified nucleoside
modified_base 4
mod_base=OTHER
note=2-fluoro-modified nucleoside
modified_base 6
mod_base=OTHER
note=2-fluoro-modified nucleoside
modified_base 8
mod_base=OTHER
note=2-fluoro-modified nucleoside
modified_base 10
mod_base=OTHER
note=2-fluoro-modified nucleoside
modified_base 12
mod_base=OTHER
note=2-fluoro-modified nucleoside
modified_base 14
mod_base=OTHER
note=2-fluoro-modified nucleoside
modified_base 16
mod_base=OTHER
note=2-fluoro-modified nucleoside
modified_base 18
mod_base=OTHER
note=2-fluoro-modified nucleoside
modified_base 19^20
mod_base=OTHER
note=phosphorothioate linkage
modified_base 20^21
mod_base=OTHER
note=phosphorothioate linkage
modified_base 2^3
mod_base=OTHER

		note=phosphorothioate linkage	
	NonEnglishQualifier Value		
3-42-5	Residues	tgatccaatg tatctcccat t	21
3-43	**Sequences**		
3-43-1	Sequence Number [ID]	43	
3-43-2	Molecule Type	RNA	
3-43-3	Length	21	
3-43-4	Features Location/	**source 1..21**	
	Qualifiers	mol_type=other RNA	
		note=GalNAc moiety-ETL17	
		organism=synthetic construct	
		modified_base 1	
		mod_base=OTHER	
		note=2-O-methyl modified nucleoside	
		note=phosphorothioate linkage	
		modified_base 2	
		mod_base=OTHER	
		note=2-O-methyl modified nucleoside	
		modified_base 3	
		mod_base=OTHER	
		note=2-O-methyl modified nucleoside	
		modified_base 4	
		mod_base=OTHER	
		note=2-O-methyl modified nucleoside	
		modified_base 5	
		mod_base=OTHER	
		note=2-fluoro-modified nucleoside	
		modified_base 6	
		mod_base=OTHER	
		note=2-O-methyl modified nucleoside	
		modified_base 7	
		mod_base=OTHER	
		note=2-O-methyl modified nucleoside	
		modified_base 8	
		mod_base=OTHER	
		note=2-fluoro-modified nucleoside	
		modified_base 9	
		mod_base=OTHER	
		note=2-fluoro-modified nucleoside	
		modified_base 10	
		mod_base=OTHER	
		note=2-O-methyl modified nucleoside	
		modified_base 11	
		mod_base=OTHER	
		note=2-O-methyl modified nucleoside	
		modified_base 12	
		mod_base=OTHER	
		note=2-O-methyl modified nucleoside	
		modified_base 13	
		mod_base=OTHER	
		note=2-O-methyl modified nucleoside	
		modified_base 14	
		mod_base=OTHER	
		note=2-O-methyl modified nucleoside	
		modified_base 15	
		mod_base=OTHER	
		note=2-O-methyl modified nucleoside	
		modified_base 16	
		mod_base=OTHER	
		note=2-O-methyl modified nucleoside	
		modified_base 17	
		mod_base=OTHER	
		note=2-O-methyl modified nucleoside	
		modified_base 18	
		mod_base=OTHER	

		note=2-O-methyl modified nucleoside **modified_base 19** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 20** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 21** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 19^20** mod_base=OTHER note=phosphorothioate linkage **modified_base 20^21** mod_base=OTHER note=phosphorothioate linkage	
3-43-5	NonEnglishQualifier Value Residues	tcttgtcaga cataaagcat t	21
3-44	**Sequences**		
3-44-1	Sequence Number [ID]	44	
3-44-2	Molecule Type	RNA	
3-44-3	Length	21	
3-44-4	Features Location/ Qualifiers	**source 1..21** mol_type=other RNA note=GalNAc moiety-ETL17 organism=synthetic construct **modified_base 1** mod_base=OTHER note=2-O-methyl modified nucleoside note=phosphorothioate linkage **modified_base 2** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 3** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 4** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 5** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 6** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 7** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 8** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 9** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 10** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 11** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 12** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 13** mod_base=OTHER	

		note=2-O-methyl modified nucleoside **modified_base 14** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 15** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 16** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 17** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 18** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 19** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 20** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 21** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 19^20** mod_base=OTHER note=phosphorothioate linkage **modified_base 20^21** mod_base=OTHER note=phosphorothioate linkage	
3-44-5	NonEnglishQualifier Value Residues	`tcttgtcaga cataaagcat t`	21
3-45	**Sequences**		
3-45-1	Sequence Number [ID]	45	
3-45-2	Molecule Type	RNA	
3-45-3	Length	21	
3-45-4	Features Location/ Qualifiers	**source 1..21** mol_type=other RNA note=GalNAc moiety-ETL17 organism=synthetic construct **modified_base 1** mod_base=OTHER note=phosphorothioate linkage note=2-O-methyl modified nucleoside **modified_base 2** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 3** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 4** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 5** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 6** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 7** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 8** mod_base=OTHER	

		note=2-fluoro-modified nucleoside	
		modified_base 9	
		mod_base=OTHER	
		note=2-fluoro-modified nucleoside	
		modified_base 10	
		mod_base=OTHER	
		note=2-O-methyl modified nucleoside	
		modified_base 11	
		mod_base=OTHER	
		note=2-O-methyl modified nucleoside	
		modified_base 12	
		mod_base=OTHER	
		note=2-O-methyl modified nucleoside	
		modified_base 13	
		mod_base=OTHER	
		note=2-O-methyl modified nucleoside	
		modified_base 14	
		mod_base=OTHER	
		note=2-O-methyl modified nucleoside	
		modified_base 15	
		mod_base=OTHER	
		note=2-O-methyl modified nucleoside	
		modified_base 16	
		mod_base=OTHER	
		note=2-O-methyl modified nucleoside	
		modified_base 17	
		mod_base=OTHER	
		note=2-O-methyl modified nucleoside	
		modified_base 18	
		mod_base=OTHER	
		note=2-O-methyl modified nucleoside	
		modified_base 19	
		mod_base=OTHER	
		note=2-O-methyl modified nucleoside	
		modified_base 20	
		mod_base=OTHER	
		note=2-O-methyl modified nucleoside	
		modified_base 21	
		mod_base=OTHER	
		note=2-O-methyl modified nucleoside	
		modified_base 19^20	
		mod_base=OTHER	
		note=phosphorothioate linkage	
		modified_base 20^21	
		mod_base=OTHER	
		note=phosphorothioate linkage	
	NonEnglishQualifier Value		
3-45-5	Residues	`tcttgtcaga cataaagcat t`	21
3-46	**Sequences**		
3-46-1	Sequence Number [ID]	46	
3-46-2	Molecule Type	RNA	
3-46-3	Length	21	
3-46-4	Features Location/	**source 1..21**	
	Qualifiers	mol_type=other RNA	
		note=GalNAc moiety-ETL17	
		organism=synthetic construct	
		modified_base 1	
		mod_base=OTHER	
		note=phosphorothioate linkage	
		note=2-O-methyl modified nucleoside	
		modified_base 2	
		mod_base=OTHER	
		note=2-O-methyl modified nucleoside	
		modified_base 3	
		mod_base=OTHER	

		note=2-O-methyl modified nucleoside **modified_base 4** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 5** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 6** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 7** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 8** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 9** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 10** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 11** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 12** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 13** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 14** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 15** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 16** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 17** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 18** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 19** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 20** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 21** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 19^20** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 20^21** mod_base=OTHER note=2-O-methyl modified nucleoside	
	NonEnglishQualifier Value		
3-46-5	Residues	`tcttgtcaga cataaagcat t`	21
3-47	**Sequences**		
3-47-1	Sequence Number [ID]	47	

3-47-2	Molecule Type	RNA
3-47-3	Length	21
3-47-4	Features Location/ Qualifiers	**source 1..21** mol_type=other RNA note=GalNAc moiety-ETL17 organism=synthetic construct **modified_base 1** mod_base=OTHER note=2-O-methyl modified nucleoside note=phosphorothioate linkage **modified_base 2** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 3** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 4** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 5** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 6** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 7** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 8** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 9** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 10** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 11** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 12** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 13** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 14** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 15** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 16** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 17** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 18** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 19** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 20**

		mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 21** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 19^20** mod_base=OTHER note=phosphorothioate linkage **modified_base 20^21** mod_base=OTHER note=phosphorothioate linkage	
	NonEnglishQualifier Value		
3-47-5	Residues	`tcttgtcaga cataaagcat t`	21
3-48	**Sequences**		
3-48-1	Sequence Number [ID]	48	
3-48-2	Molecule Type	RNA	
3-48-3	Length	22	
3-48-4	Features Location/ Qualifiers	**source 1..22** mol_type=other RNA note=GalNAc moiety-ETL17 organism=synthetic construct **modified_base 1** mod_base=OTHER note=2-O-methyl modified nucleoside note=phosphorothioate linkage **modified_base 2** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 3** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 4** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 5** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 6** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 8** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 9** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 10** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 11** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 12** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 13** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 14** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 15** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 16**	

		mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 17** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 18** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 19** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 20** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 21** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 20^21** mod_base=OTHER note=phosphorothioate linkage **modified_base 21^22** mod_base=OTHER note=phosphorothioate linkage **modified_base 22** mod_base=OTHER note=2-O-methyl modified nucleoside	
	NonEnglishQualifier Value		
3-48-5	Residues	`ttgtcadgac ataaagccaa tt`	22
3-49	**Sequences**		
3-49-1	Sequence Number [ID]	49	
3-49-2	Molecule Type	RNA	
3-49-3	Length	22	
3-49-4	Features Location/ Qualifiers	**source 1..22** mol_type=other RNA note=GalNAc moiety-ETL17 organism=synthetic construct **modified_base 1** mod_base=OTHER note=phosphorothioate linkage note=2-O-methyl modified nucleoside **modified_base 2** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 3** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 4** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 5** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 6** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 7** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 8** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 9** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 11**	

		mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 12** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 13** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 14** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 15** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 16** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 17** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 18** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 19** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 20** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 21** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 22** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 20^21** mod_base=OTHER note=phosphorothioate linkage **modified_base 21^22** mod_base=OTHER note=phosphorothioate linkage
	NonEnglishQualifier Value	
3-49-5	Residues	`ttgtcagacd ataaagccaa tt` 22
3-50	**Sequences**	
3-50-1	Sequence Number [ID]	50
3-50-2	Molecule Type	RNA
3-50-3	Length	21
3-50-4	Features Location/ Qualifiers	**source 1..21** mol_type=other RNA note=GalNAc moiety-ETL17 organism=synthetic construct **modified_base 1** mod_base=OTHER note=2-O-methyl modified nucleoside note=phosphorothioate linkage **modified_base 2** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 3** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 4** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 5**

		mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 6** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 7** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 8** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 9** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 10** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 11** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 12** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 13** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 14** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 15** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 16** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 17** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 18** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 19** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 20** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 21** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 19^20** mod_base=OTHER note=phosphorothioate linkage **modified_base 20^21** mod_base=OTHER note=phosphorothioate linkage	
	NonEnglishQualifier Value		
3-50-5	Residues	`ttgtcagaca taaagccaat t`	21
3-51	**Sequences**		
3-51-1	Sequence Number [ID]	51	
3-51-2	Molecule Type	RNA	
3-51-3	Length	21	
3-51-4	Features Location/	**source 1..21**	
	Qualifiers	mol_type=other RNA note=GalNAc moiety-ETL17	

organism=synthetic construct
modified_base 1
mod_base=OTHER
note=2-O-methyl modified nucleoside
note=phosphorothioate linkage
modified_base 2
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 3
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 4
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 5
mod_base=OTHER
note=2-fluoro-modified nucleoside
modified_base 6
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 7
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 8
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 9
mod_base=OTHER
note=2-fluoro-modified nucleoside
modified_base 10
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 11
mod_base=OTHER
note=2-fluoro-modified nucleoside
modified_base 12
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 13
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 14
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 15
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 16
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 17
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 18
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 19
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 20
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 21
mod_base=OTHER
note=2-O-methyl modified nucleoside

		modified_base 19^20 mod_base=OTHER note=phosphorothioate linkage **modified_base 20^21** mod_base=OTHER note=phosphorothioate linkage	
	NonEnglishQualifier Value		
3-51-5	Residues	`ttgtcagaca taaagccaat t`	21
3-52	**Sequences**		
3-52-1	Sequence Number [ID]	52	
3-52-2	Molecule Type	RNA	
3-52-3	Length	21	
3-52-4	Features Location/ Qualifiers	**source 1..21** mol_type=other RNA note=GalNAc moiety-ETL17 organism=synthetic construct **modified_base 1** mod_base=OTHER note=2-O-methyl modified nucleoside note=phosphorothioate linkage **modified_base 2** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 3** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 4** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 5** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 6** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 7** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 8** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 9** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 10** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 11** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 12** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 13** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 14** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 15** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 16** mod_base=OTHER note=2-O-methyl modified nucleoside	

		modified_base 17 mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 18** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 19** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 20** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 21** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 19^20** mod_base=OTHER note=phosphorothioate linkage **modified_base 20^21** mod_base=OTHER note=phosphorothioate linkage	
	NonEnglishQualifier Value		
3-52-5	Residues	`ttgtcagaca taaagccaat t`	21
3-53	**Sequences**		
3-53-1	Sequence Number [ID]	53	
3-53-2	Molecule Type	RNA	
3-53-3	Length	21	
3-53-4	Features Location/ Qualifiers	**source 1..21** mol_type=other RNA note=GalNAc moiety-ETL17 organism=synthetic construct **modified_base 1** mod_base=OTHER note=2-O-methyl modified nucleoside note=phosphorothioate linkage **modified_base 2** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 3** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 4** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 5** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 6** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 7** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 8** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 9** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 10** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 11** mod_base=OTHER note=2-fluoro-modified nucleoside	

		modified_base 12 mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 13** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 14** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 15** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 16** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 17** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 18** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 19** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 20** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 21** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 19^20** mod_base=OTHER note=phosphorothioate linkage **modified_base 20^21** mod_base=OTHER note=phosphorothioate linkage	
3-53-5	NonEnglishQualifier Value Residues	`ttgtcagaca taaagccaat t`	21
3-54	**Sequences**		
3-54-1	Sequence Number [ID]	54	
3-54-2	Molecule Type	RNA	
3-54-3	Length	21	
3-54-4	Features Location/ Qualifiers	**source 1..21** mol_type=other RNA organism=synthetic construct **modified_base 1^2** mod_base=OTHER note=phosphorothioate linkage **modified_base 1** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 3** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 5** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 7** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 9** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 11** mod_base=OTHER	

		note=2-O-methyl modified nucleoside **modified_base 13** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 15** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 17** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 19** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 20** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 21** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 2** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 4** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 6** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 8** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 10** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 12** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 14** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 16** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 18** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 19^20** mod_base=OTHER note=phosphorothioate linkage **modified_base 20^21** mod_base=OTHER note=phosphorothioate linkage **modified_base 2^3** mod_base=OTHER note=phosphorothioate linkage
	NonEnglishQualifier Value	
3-54-5	Residues	`tgctttatgt ctgacaagat t` 21
3-55	**Sequences**	
3-55-1	Sequence Number [ID]	55
3-55-2	Molecule Type	RNA
3-55-3	Length	21
3-55-4	Features Location/ Qualifiers	**source 1..21** mol_type=other RNA organism=synthetic construct **modified_base 1^2**

mod_base=OTHER
note=phosphorothioate linkage
modified_base 1
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 3
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 4
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 5
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 7
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 9
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 11
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 13
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 15
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 17
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 19
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 20
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 21
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 2
mod_base=OTHER
note=2-fluoro-modified nucleoside
modified_base 6
mod_base=OTHER
note=2-fluoro-modified nucleoside
modified_base 8
mod_base=OTHER
note=2-fluoro-modified nucleoside
modified_base 10
mod_base=OTHER
note=2-fluoro-modified nucleoside
modified_base 12
mod_base=OTHER
note=2-fluoro-modified nucleoside
modified_base 14
mod_base=OTHER
note=2-fluoro-modified nucleoside
modified_base 16
mod_base=OTHER
note=2-fluoro-modified nucleoside
modified_base 18
mod_base=OTHER
note=2-fluoro-modified nucleoside

		modified_base 19^20 mod_base=OTHER note=phosphorothioate linkage **modified_base 20^21** mod_base=OTHER note=phosphorothioate linkage **modified_base 2^3** mod_base=OTHER note=phosphorothioate linkage	
	NonEnglishQualifier Value		
3-55-5	Residues	tgctttatgt ctgacaagat t	21
3-56	**Sequences**		
3-56-1	Sequence Number [ID]	56	
3-56-2	Molecule Type	RNA	
3-56-3	Length	21	
3-56-4	Features Location/ Qualifiers	**source 1..21** mol_type=other RNA organism=synthetic construct **modified_base 1^2** mod_base=OTHER note=phosphorothioate linkage **modified_base 1** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 3** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 4** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 5** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 7** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 8** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 9** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 11** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 13** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 15** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 17** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 19** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 20** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 21** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 2** mod_base=OTHER	

		note=2-fluoro-modified nucleoside **modified_base 6** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 10** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 12** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 14** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 16** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 18** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 19^20** mod_base=OTHER note=phosphorothioate linkage **modified_base 20^21** mod_base=OTHER note=phosphorothioate linkage **modified_base 2^3** mod_base=OTHER note=phosphorothioate linkage	
	NonEnglishQualifier Value		
3-56-5	Residues	`tgctttatgt ctgacaagat t`	21
3-57	**Sequences**		
3-57-1	Sequence Number [ID]	57	
3-57-2	Molecule Type	RNA	
3-57-3	Length	21	
3-57-4	Features Location/ Qualifiers	**source 1..21** mol_type=other RNA organism=synthetic construct **modified_base 1^2** mod_base=OTHER note=phosphorothioate linkage **modified_base 1** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 3** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 5** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 7** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 9** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 11** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 13** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 10** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 13**	

		mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 15** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 17** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 19** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 20** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 21** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 2** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 4** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 6** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 8** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 12** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 14** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 16** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 18** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 19^20** mod_base=OTHER note=phosphorothioate linkage **modified_base 20^21** mod_base=OTHER note=phosphorothioate linkage **modified_base 2^3** mod_base=OTHER note=phosphorothioate linkage	
3-57-5	NonEnglishQualifier Value Residues	`tgctttatgt ctgacaagat t`	21
3-58	**Sequences**		
3-58-1	Sequence Number [ID]	58	
3-58-2	Molecule Type	RNA	
3-58-3	Length	21	
3-58-4	Features Location/ Qualifiers	**source 1..21** mol_type=other RNA organism=synthetic construct **modified_base 1^2** mod_base=OTHER note=phosphorothioate linkage **modified_base 1** mod_base=OTHER note=2-O-methyl modified nucleoside	

modified_base 3
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 5
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 6
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 8
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 9
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 11
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 13
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 15
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 17
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 19
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 20
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 21
mod_base=OTHER
note=2-O-methyl modified nucleoside
modified_base 2
mod_base=OTHER
note=2-fluoro-modified nucleoside
modified_base 4
mod_base=OTHER
note=2-fluoro-modified nucleoside
modified_base 7
mod_base=OTHER
note=2-fluoro-modified nucleoside
modified_base 10
mod_base=OTHER
note=2-fluoro-modified nucleoside
modified_base 12
mod_base=OTHER
note=2-fluoro-modified nucleoside
modified_base 14
mod_base=OTHER
note=2-fluoro-modified nucleoside
modified_base 16
mod_base=OTHER
note=2-fluoro-modified nucleoside
modified_base 18
mod_base=OTHER
note=2-fluoro-modified nucleoside
modified_base 19^20
mod_base=OTHER
note=phosphorothioate linkage
modified_base 20^21
mod_base=OTHER

		note=phosphorothioate linkage	
		modified_base 2^3	
		mod_base=OTHER	
		note=phosphorothioate linkage	
	NonEnglishQualifier Value		
3-58-5	Residues	tgctttatgt ctgacaagat t	21
3-59	**Sequences**		
3-59-1	Sequence Number [ID]	59	
3-59-2	Molecule Type	RNA	
3-59-3	Length	21	
3-59-4	Features Location/	**source 1..21**	
	Qualifiers	mol_type=other RNA	
		organism=synthetic construct	
		modified_base 1^2	
		mod_base=OTHER	
		note=phosphorothioate linkage	
		modified_base 1	
		mod_base=OTHER	
		note=2-O-methyl modified nucleoside	
		modified_base 3	
		mod_base=OTHER	
		note=2-O-methyl modified nucleoside	
		modified_base 5	
		mod_base=OTHER	
		note=2-O-methyl modified nucleoside	
		modified_base 7	
		mod_base=OTHER	
		note=2-O-methyl modified nucleoside	
		modified_base 9	
		mod_base=OTHER	
		note=2-O-methyl modified nucleoside	
		modified_base 11	
		mod_base=OTHER	
		note=2-O-methyl modified nucleoside	
		modified_base 13	
		mod_base=OTHER	
		note=2-O-methyl modified nucleoside	
		modified_base 15	
		mod_base=OTHER	
		note=2-O-methyl modified nucleoside	
		modified_base 17	
		mod_base=OTHER	
		note=2-O-methyl modified nucleoside	
		modified_base 19	
		mod_base=OTHER	
		note=2-O-methyl modified nucleoside	
		modified_base 20	
		mod_base=OTHER	
		note=2-O-methyl modified nucleoside	
		modified_base 21	
		mod_base=OTHER	
		note=2-O-methyl modified nucleoside	
		modified_base 2	
		mod_base=OTHER	
		note=2-fluoro-modified nucleoside	
		modified_base 4	
		mod_base=OTHER	
		note=2-fluoro-modified nucleoside	
		modified_base 6	
		mod_base=OTHER	
		note=2-fluoro-modified nucleoside	
		modified_base 8	
		mod_base=OTHER	
		note=2-fluoro-modified nucleoside	
		modified_base 10	

		mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 12** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 14** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 16** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 18** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 19^20** mod_base=OTHER note=phosphorothioate linkage **modified_base 20^21** mod_base=OTHER note=phosphorothioate linkage **modified_base 2^3** mod_base=OTHER note=phosphorothioate linkage	
	NonEnglishQualifier Value		
3-59-5	Residues	`ttggctttat gtctgacaat t`	21
3-60	**Sequences**		
3-60-1	Sequence Number [ID]	60	
3-60-2	Molecule Type	RNA	
3-60-3	Length	21	
3-60-4	Features Location/ Qualifiers	**source 1..21** mol_type=other RNA organism=synthetic construct **modified_base 1^2** mod_base=OTHER note=phosphorothioate linkage **modified_base 1** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 3** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 5** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 7** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 9** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 11** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 13** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 15** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 17** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 19** mod_base=OTHER note=2-O-methyl modified nucleoside	

		modified_base 20 mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 21** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 2** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 4** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 6** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 8** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 10** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 12** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 14** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 16** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 18** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 19^20** mod_base=OTHER note=phosphorothioate linkage **modified_base 20^21** mod_base=OTHER note=phosphorothioate linkage **modified_base 2^3** mod_base=OTHER note=phosphorothioate linkage	
	NonEnglishQualifier Value		
3-60-5	Residues	`ttggctttat gtctgacaat t`	21
3-61	**Sequences**		
3-61-1	Sequence Number [ID]	61	
3-61-2	Molecule Type	RNA	
3-61-3	Length	21	
3-61-4	Features Location/ Qualifiers	**source 1..21** mol_type=other RNA organism=synthetic construct **modified_base 1^2** mod_base=OTHER note=phosphorothioate linkage **modified_base 1** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 3** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 4** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 5** mod_base=OTHER	

		note=2-O-methyl modified nucleoside **modified_base 7** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 9** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 11** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 13** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 15** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 17** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 19** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 21** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 2** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 6** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 8** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 10** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 12** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 14** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 18** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 16** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 20** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 19^20** mod_base=OTHER note=phosphorothioate linkage **modified_base 20^21** mod_base=OTHER note=phosphorothioate linkage **modified_base 2^3** mod_base=OTHER note=phosphorothioate linkage
	NonEnglishQualifier Value	
3-61-5	Residues	`ttggctttat gtctgacaat t` 21
3-62	**Sequences**	
3-62-1	Sequence Number [ID]	62

3-62-2	Molecule Type	RNA
3-62-3	Length	21
3-62-4	Features Location/ Qualifiers	**source 1..21** mol_type=other RNA organism=synthetic construct **modified_base 1^2** mod_base=OTHER note=phosphorothioate linkage **modified_base 1** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 3** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 5** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 7** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 9** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 10** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 11** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 13** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 15** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 17** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 20** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 21** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 20** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 2** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 4** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 6** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 8** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 12** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 14** mod_base=OTHER note=2-fluoro-modified nucleoside

		modified_base 16 mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 18** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 19^20** mod_base=OTHER note=phosphorothioate linkage **modified_base 20^21** mod_base=OTHER note=phosphorothioate linkage **modified_base 2^3** mod_base=OTHER note=phosphorothioate linkage	
	NonEnglishQualifier Value		
3-62-5	Residues	ttggctttat gtctgacaat t	21
3-63	**Sequences**		
3-63-1	Sequence Number [ID]	63	
3-63-2	Molecule Type	RNA	
3-63-3	Length	21	
3-63-4	Features Location/ Qualifiers	**source 1..21** mol_type=other RNA organism=synthetic construct **modified_base 1^2** mod_base=OTHER note=phosphorothioate linkage **modified_base 1** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 3** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 4** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 5** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 7** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 9** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 10** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 11** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 13** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 15** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 17** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 19** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 20** mod_base=OTHER	

		note=2-O-methyl modified nucleoside **modified_base 21** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 2** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 6** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 8** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 12** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 14** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 16** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 18** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 19^20** mod_base=OTHER note=phosphorothioate linkage **modified_base 20^21** mod_base=OTHER note=phosphorothioate linkage **modified_base 2^3** mod_base=OTHER note=phosphorothioate linkage
	NonEnglishQualifier Value	
3-63-5	Residues	`ttggctttat gtctgacaat t` 21
3-64	**Sequences**	
3-64-1	Sequence Number [ID]	64
3-64-2	Molecule Type	RNA
3-64-3	Length	21
3-64-4	Features Location/ Qualifiers	**source 1..21** mol_type=other RNA organism=synthetic construct **modified_base 1^2** mod_base=OTHER note=phosphorothioate linkage **modified_base 1** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 3** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 4** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 6** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 7** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 8** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 9**

		mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 11** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 13** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 15** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 17** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 19** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 2** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 5** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 10** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 12** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 14** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 16** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 18** mod_base=OTHER note=2-fluoro-modified nucleoside **modified_base 20** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 21** mod_base=OTHER note=2-O-methyl modified nucleoside **modified_base 19^20** mod_base=OTHER note=phosphorothioate linkage **modified_base 20^21** mod_base=OTHER note=phosphorothioate linkage **modified_base 2^3** mod_base=OTHER note=phosphorothioate linkage	
	NonEnglishQualifier Value		
3-64-5	Residues	`ttggctttat gtctgacaat t`	21