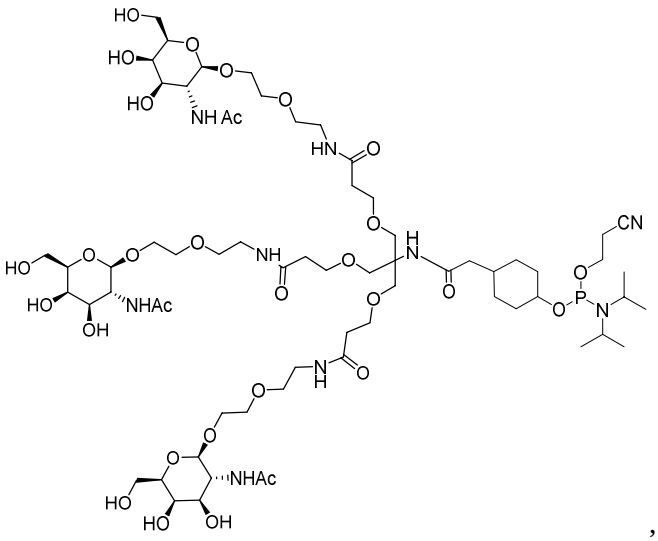
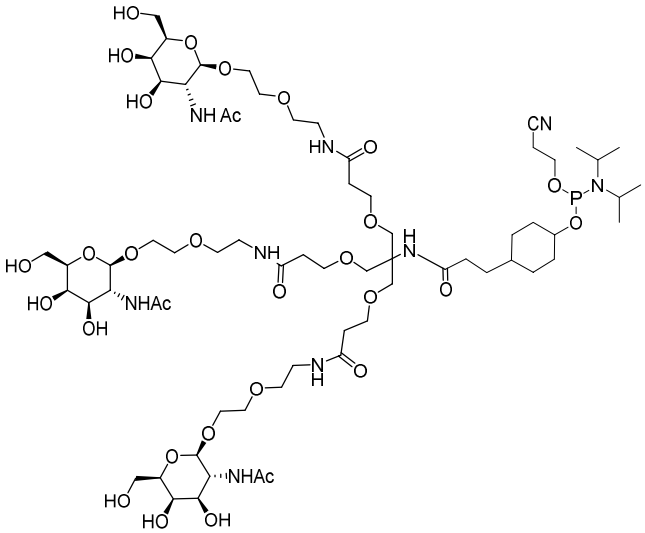
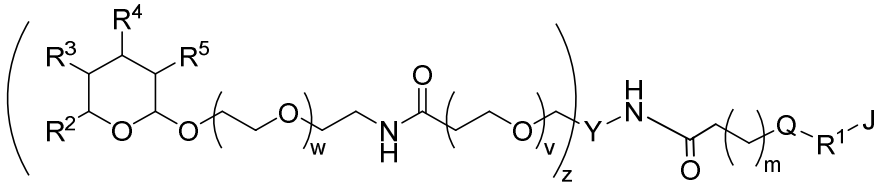


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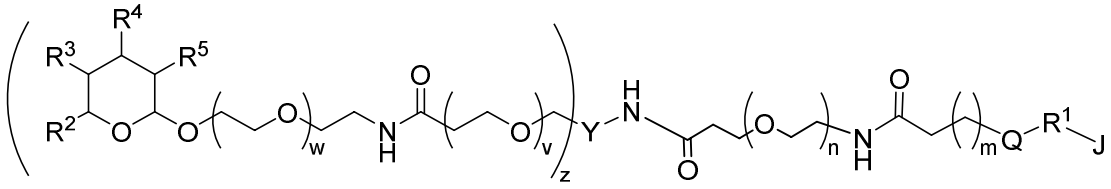


.

[0007a] In one aspect, provided 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 0 to 20;

z is 3;

Y is C;

Q is a C_{3-10} carbocycle;

R^1 is -OP(O)(OR^7)O- -OP(S)(OR^7)O-, or -OP(O)(SR^7)O-;

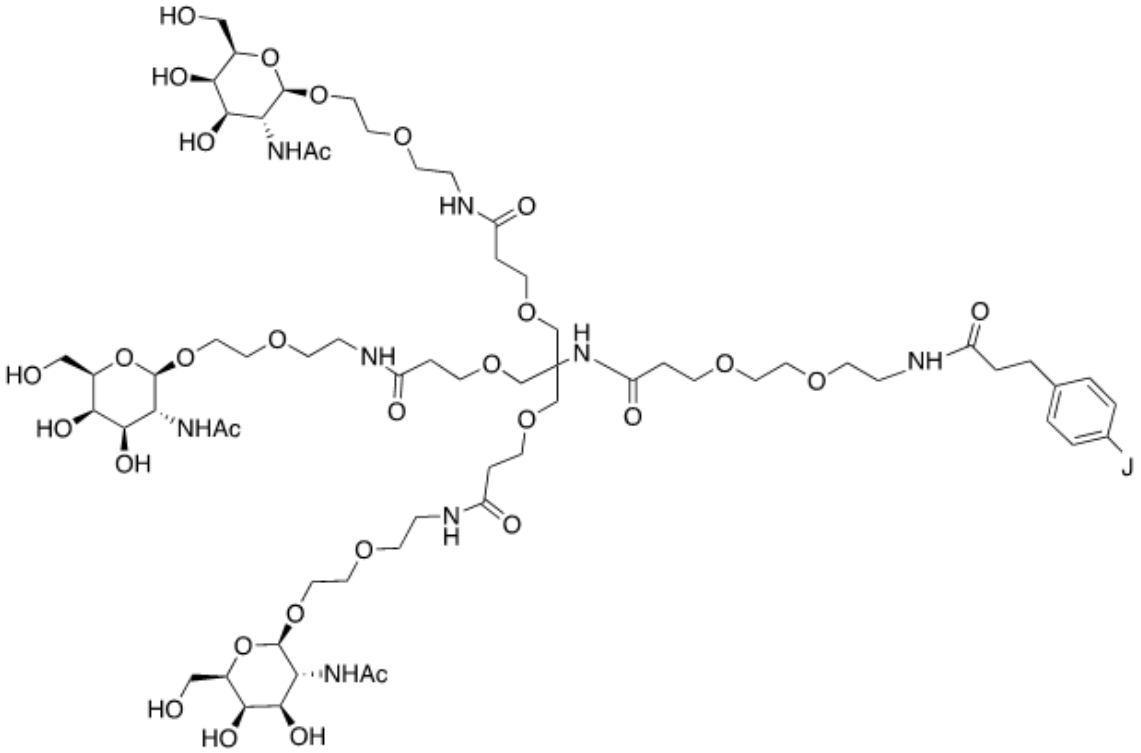
each R^2 is independently C_{1-6} alkyl substituted with -OH or -OC(O)CH_3;

R^3 and R^4 are each independently -OH or -OC(O)CH_3;

each R^5 is -NHC(O)CH_3; and

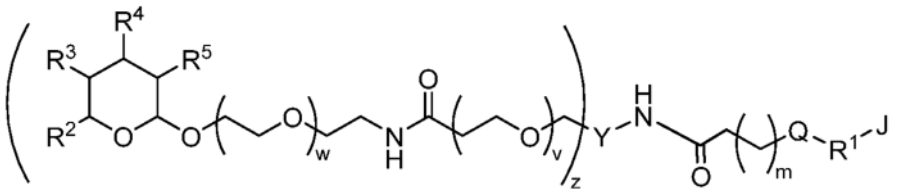
each R^7 is hydrogen.

[0007b] In another aspect, provided herein is a compound having the structure:

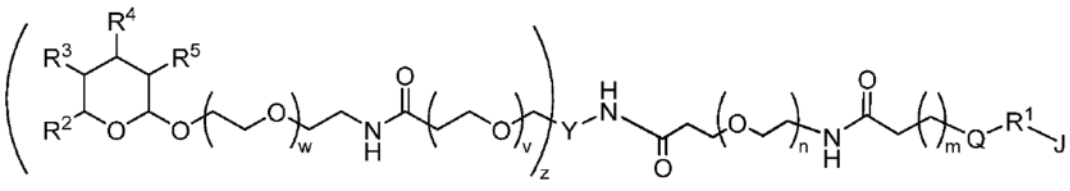


wherein J comprises an oligonucleotide.

[0007c] In another aspect, provided herein is use of an effective amount of a compound represented by Formula (I) or (II) in the manufacture of a medicament for decreasing a target mRNA or target protein and treating a disorder in a subject in need thereof, wherein the compound is 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 0 to 20;

z is 3;

Y is C;

Q is a C_{3-10} carbocycle;

R^1 is -OP(O)(OR^7)O-,-OP(O)(SR^7)O-, or -OP(S)(OR^7)O-;

each R^2 is C_{1-6} alkyl substituted with -OH or $-OC(O)CH_3$;

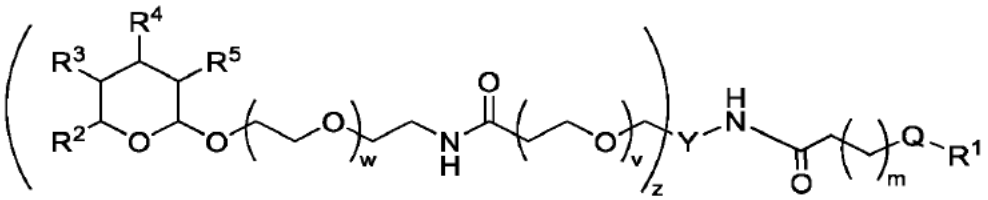
R^3 and R^4 are each independently -OH or $-OC(O)CH_3$;

each R^5 is $-NHC(O)CH_3$; and

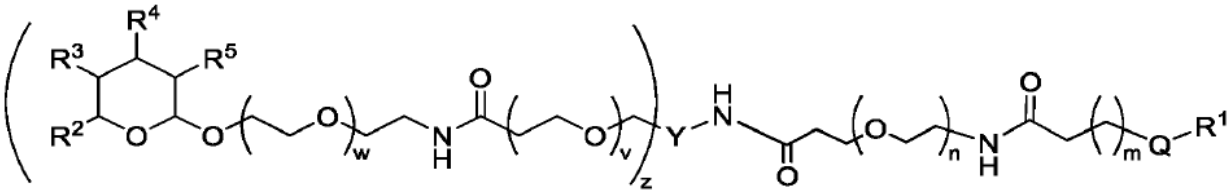
each R^7 is hydrogen,

wherein the disorder comprises a metabolic disorder or a liver disorder.

[0007d] In another aspect, provided 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 0 to 20;

z is 3;

Q is a C_{3-10} carbocycle;

R^1 is selected from: -OP(O)(OR^7)$_2$ or -OP(S)(OR^7)$_2$;

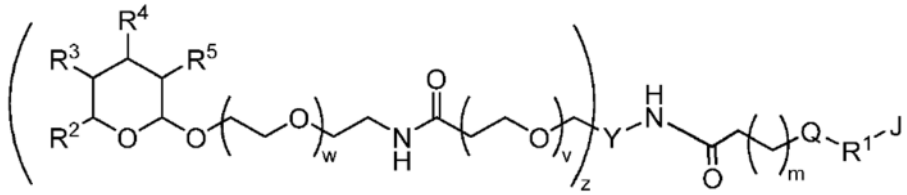
each R^2 is independently C_{1-6} alkyl substituted with -OH or $-CO(O)CH_3$;

R^3 and R^4 are each independently -OH or $-CO(O)CH_3$;

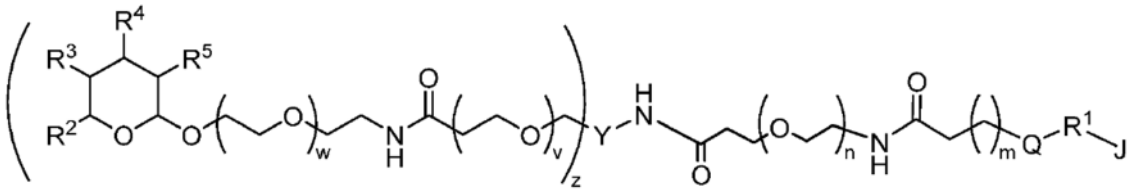
each R^5 is $-NHC(O)CH_3$; and

each R^7 is hydrogen.

[0007e] In another aspect, provided herein is a method of synthesizing 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 0 to 20;

z is 3;

Q is C_{3-10} carbocycle;

R^1 is -OP(O)(OR^7)O-, -OP(S)(OR^7)O-, or -OP(O)(SR^7)O-;;

each R^2 is independently C_{1-6} alkyl substituted with-OH or $OC(O)CH_3$;

R^3 and R^4 are each independently -OH or $OC(O)CH_3$;

each R^5 is $-NHC(O)CH_3$; and

each R^7 is hydrogen;

comprising reacting a compound of Formula (A) or (B) as described herein with an oligonucleotide.

[0007f] In another aspect, provided herein is the compound as described herein for use in therapy.

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.

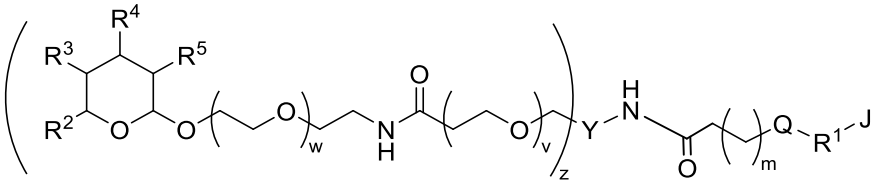
I. COMPOSITIONS

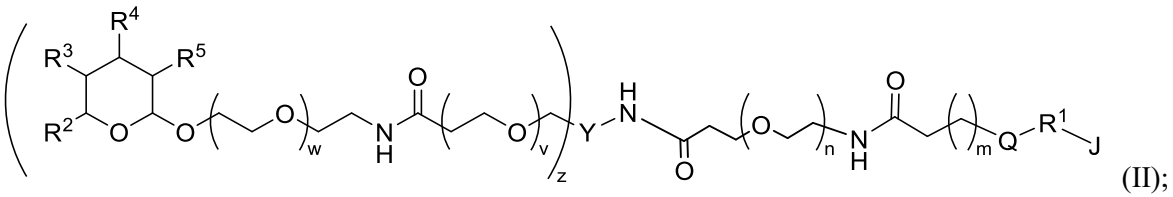
[0010] Provided herein, in some embodiments, are compositions comprising an oligonucleotide and an N-Acetylgalactosamine (GalNAc) moiety. In some embodiments, the composition comprises an oligonucleotide. The oligonucleotide may inhibit a target gene or oligonucleotide. The oligonucleotide may bind a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

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 0 to 20;

z is 3;

Y is C;

Q is a C_{3-10} carbocycle;

R^1 is -OP(O)(OR^7)O- -OP(S)(OR^7)O-, or -OP(O)(SR^7)O-;

each R^2 is independently C_{1-6} alkyl substituted with -OH or -$OC(O)CH_3$;

R^3 and R^4 are each independently -OH or -$OC(O)CH_3$;

each R^5 is -$NHC(O)CH_3$; and

each R^7 is hydrogen.

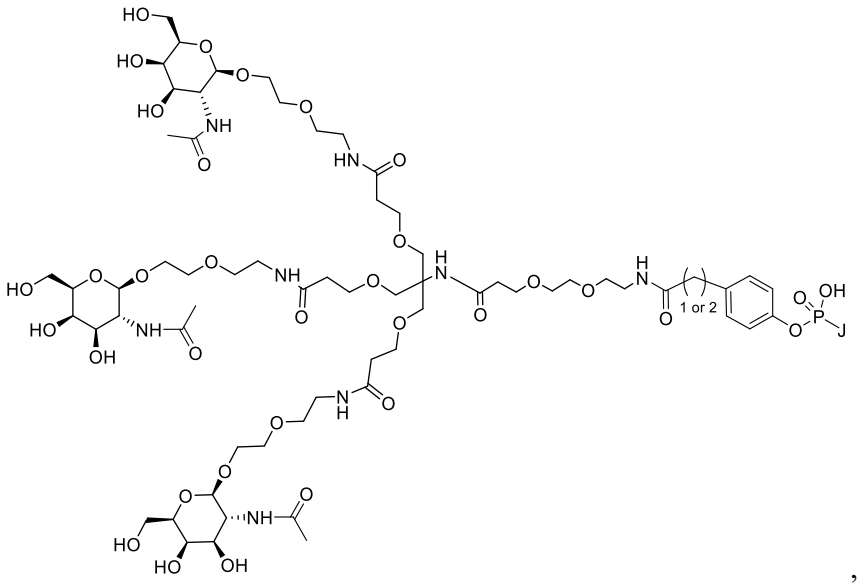
2. The compound or salt of claim 1, wherein each w, v, n and m is independently selected from any value from 1 to 5.

3. The compound or salt of claim 1, wherein each w is 1, v is 1, n is 1 or 2, and m is 1 or 2.

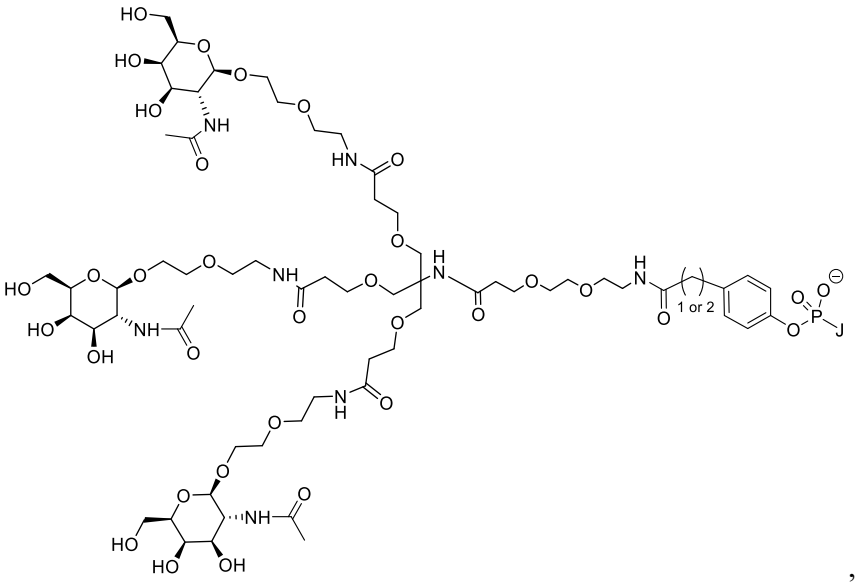
4. The compound or salt of claim 1, wherein Q is selected from C_{5-6} carbocycle.

5. The compound or salt of claim 1, wherein R^2 is selected from C_{1-3} alkyl substituted with -OH or -$OC(O)CH_3$.

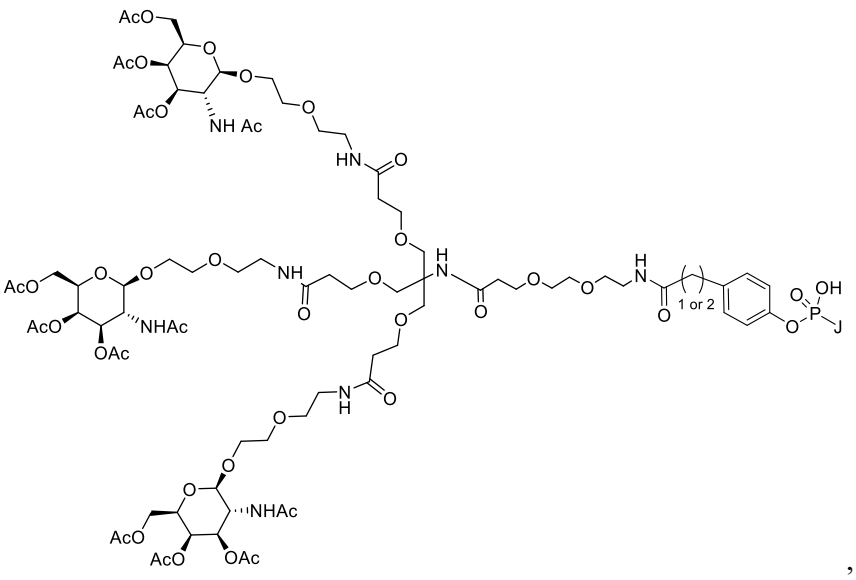
6. The compound or salt of claim 1, wherein the compound is selected from:



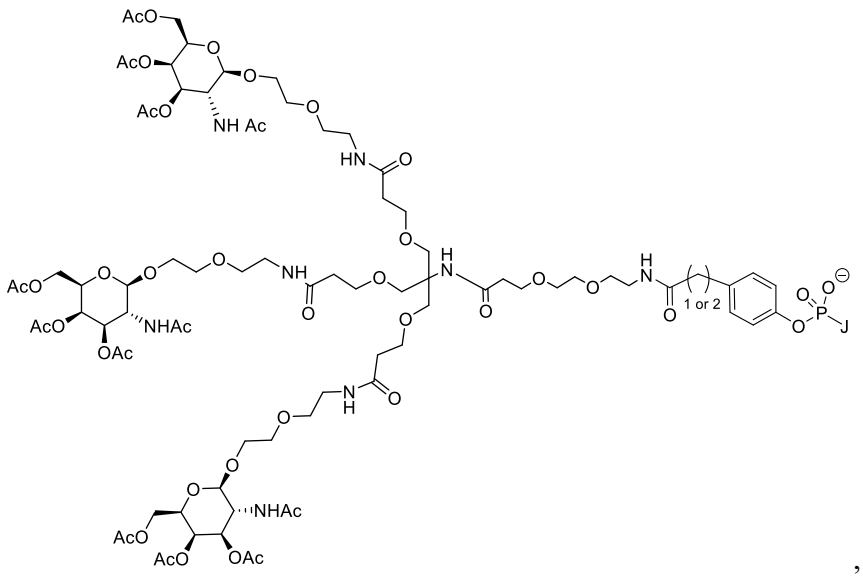
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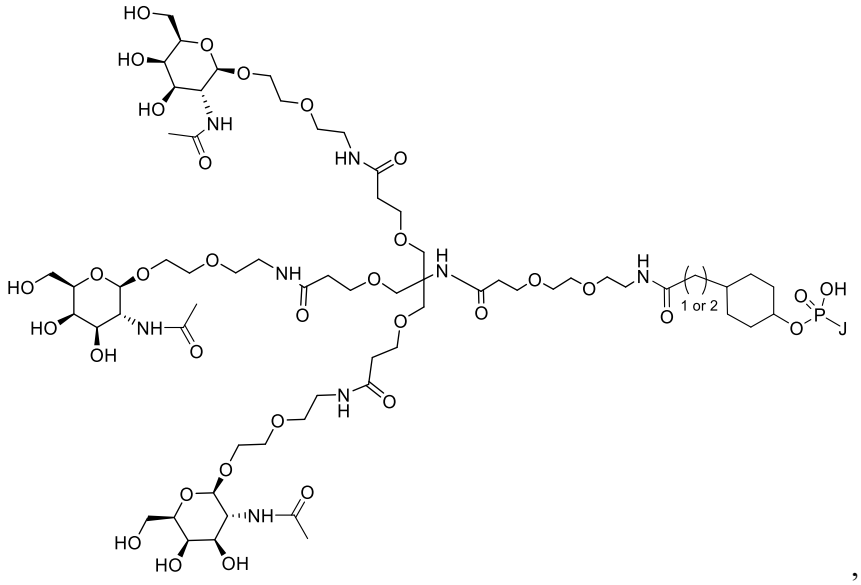
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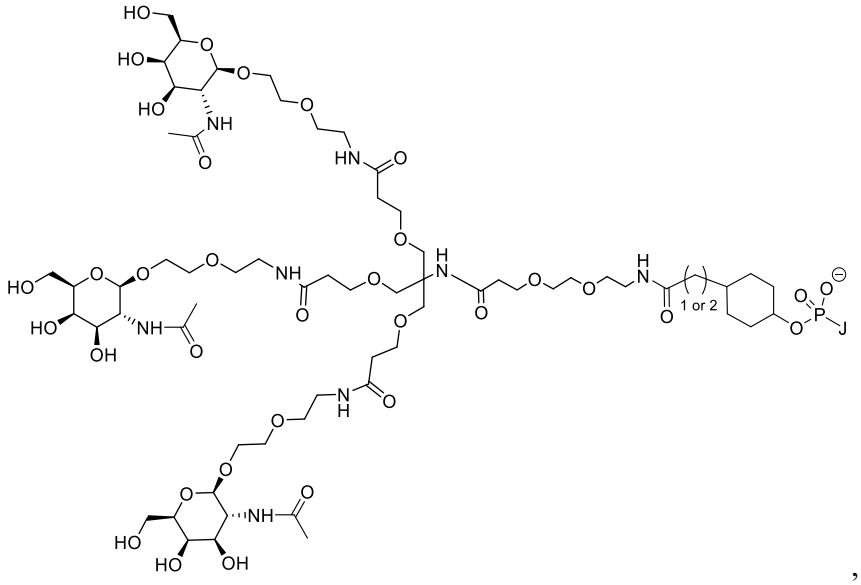
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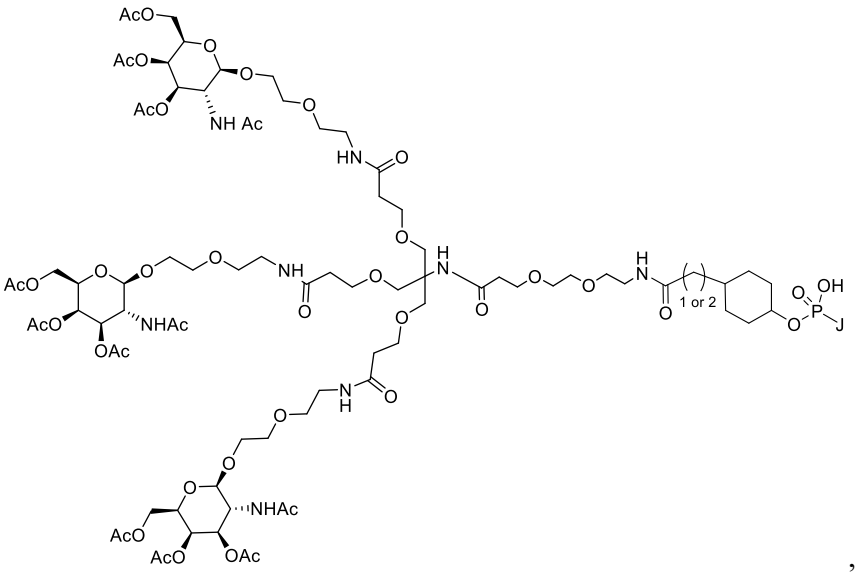
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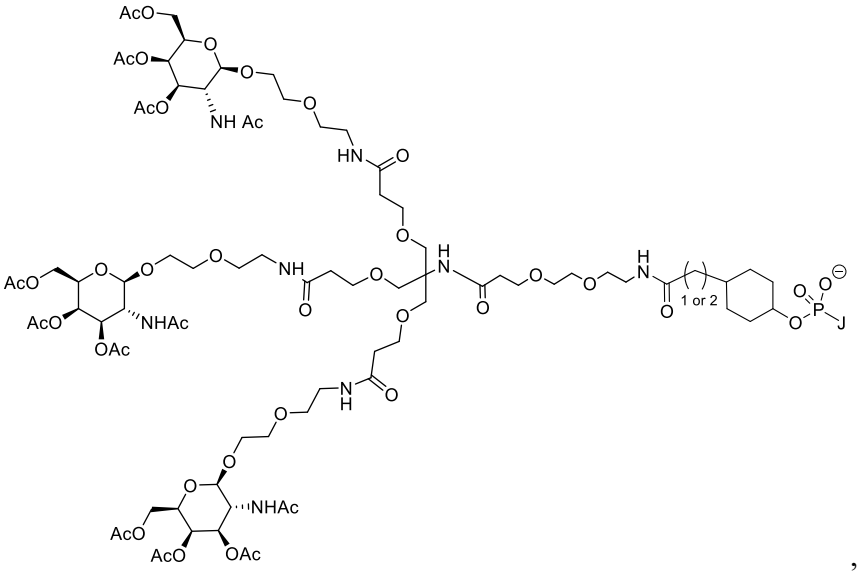
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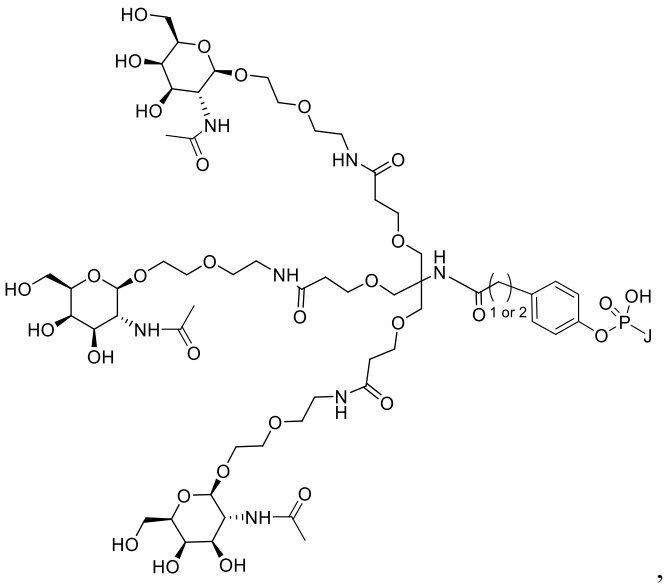
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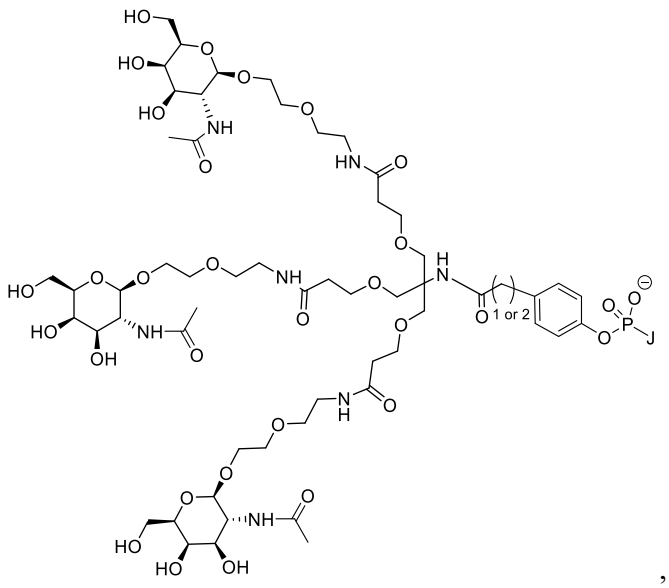
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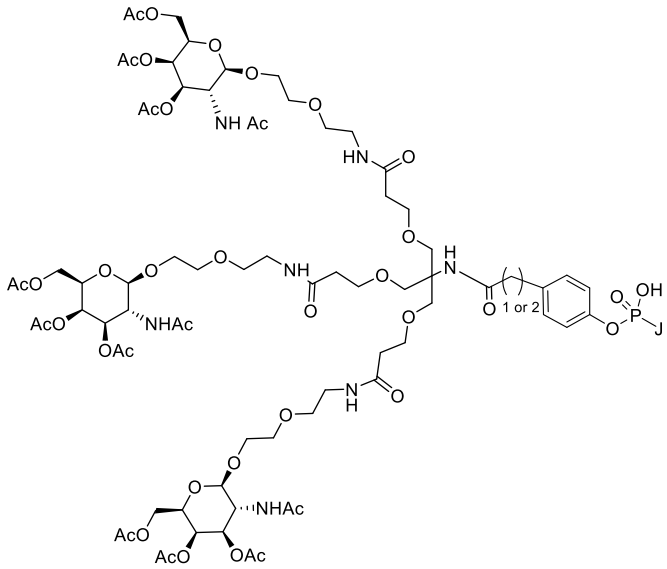
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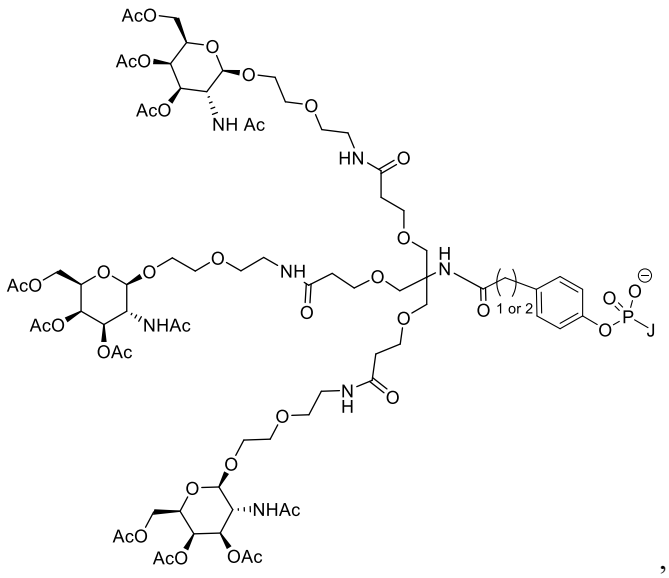
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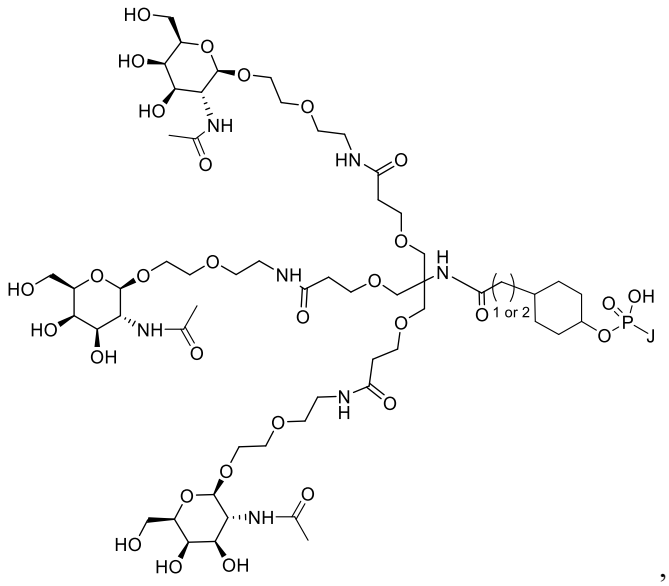
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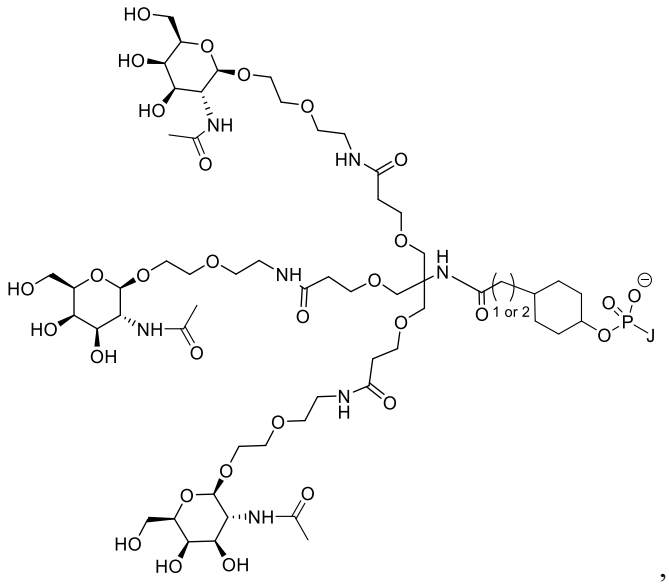
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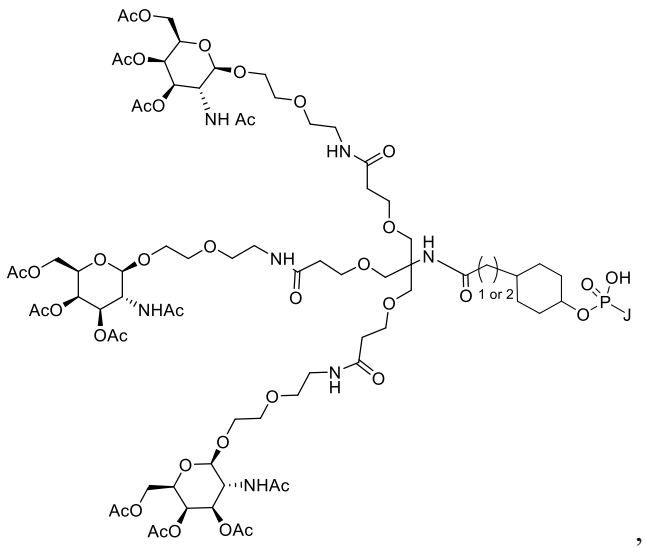
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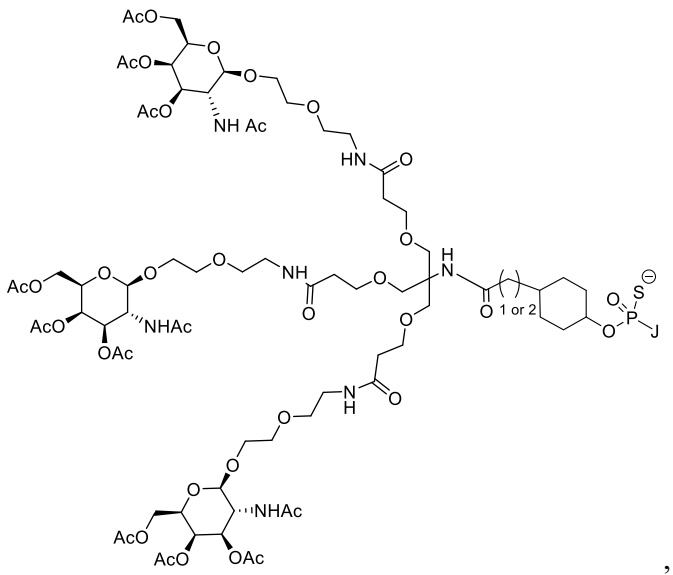
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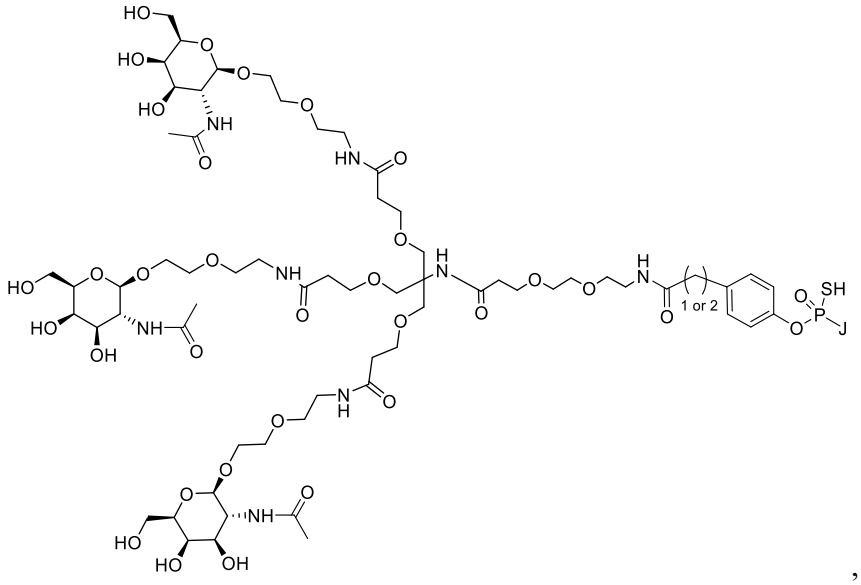
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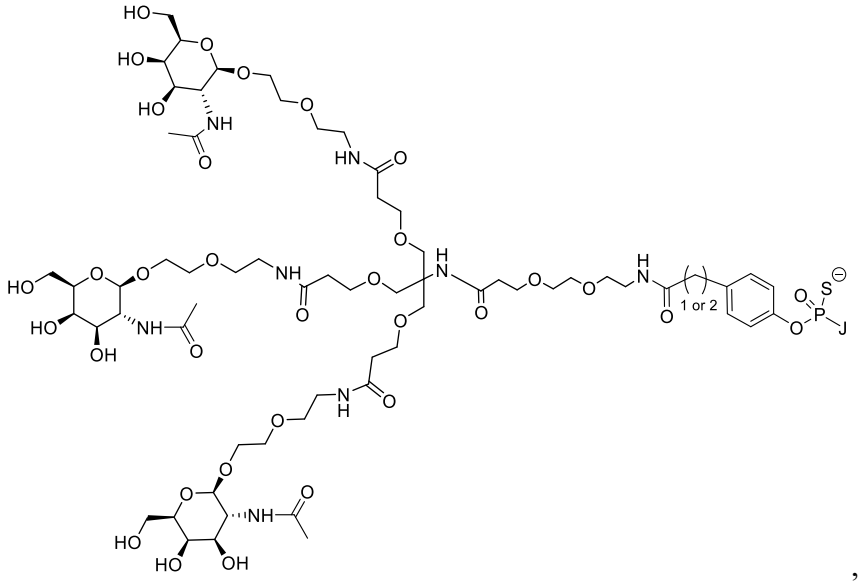
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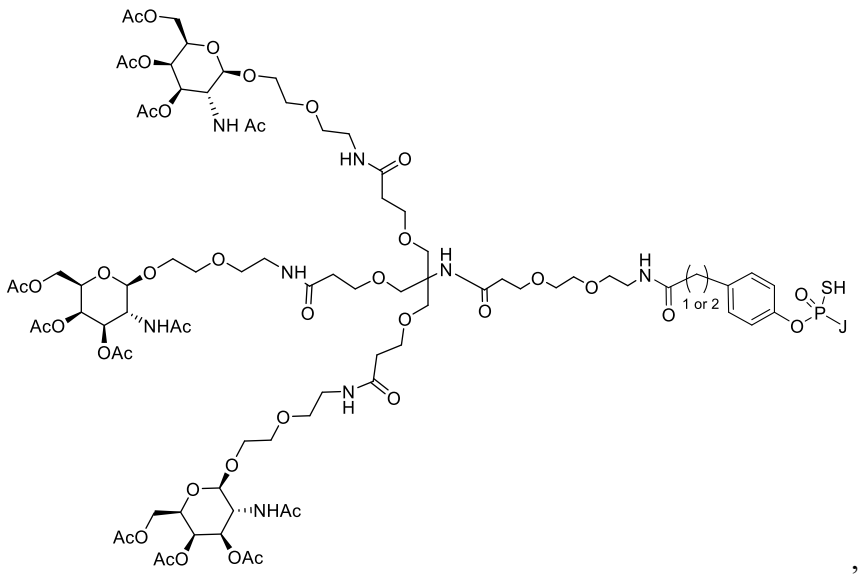
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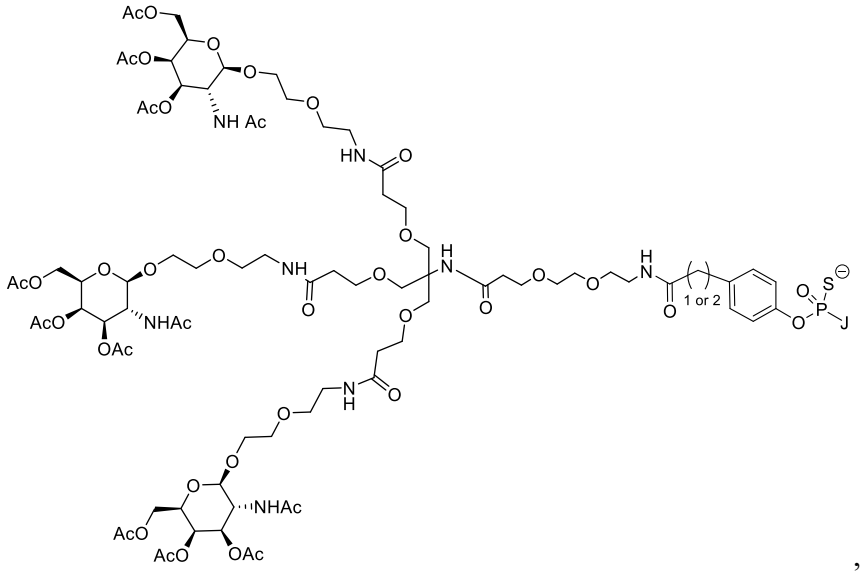
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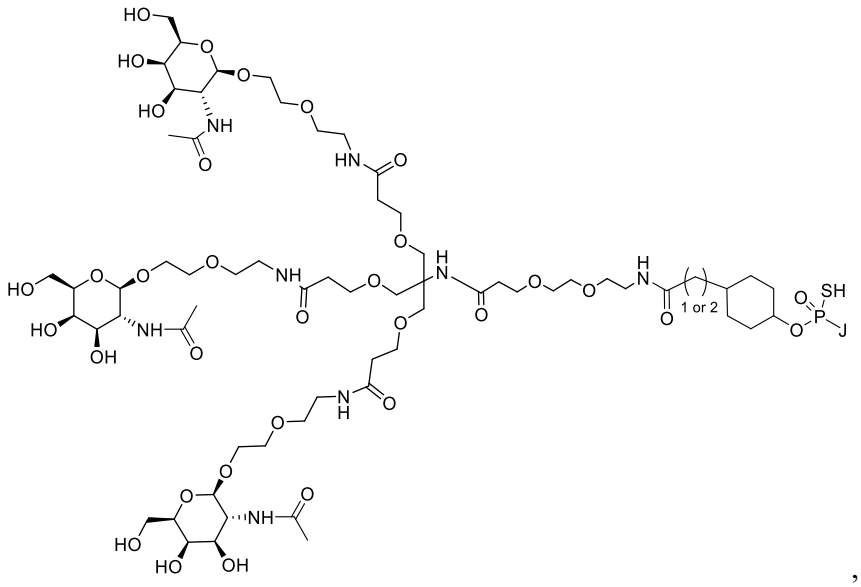
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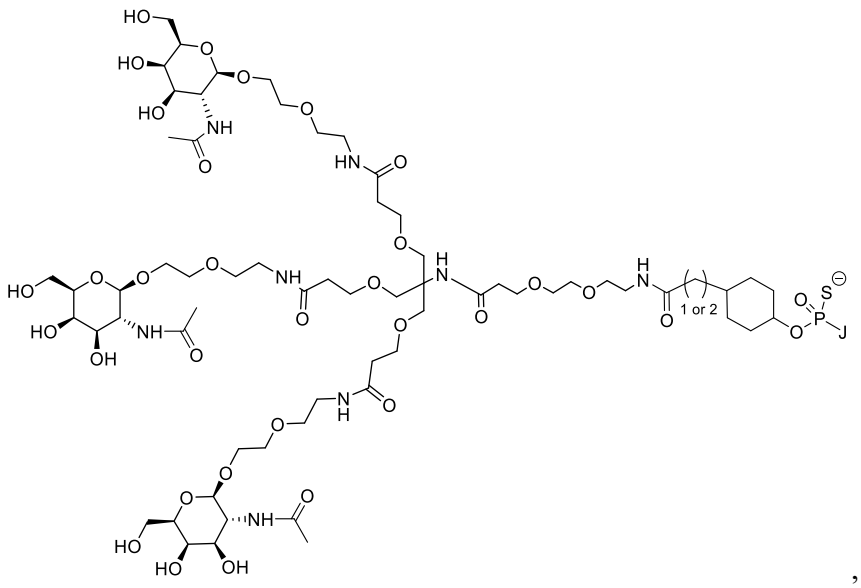
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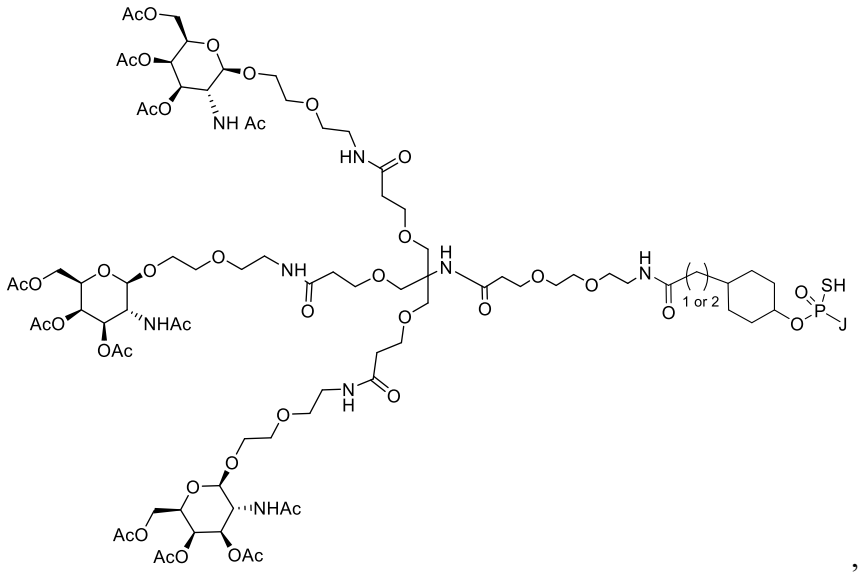
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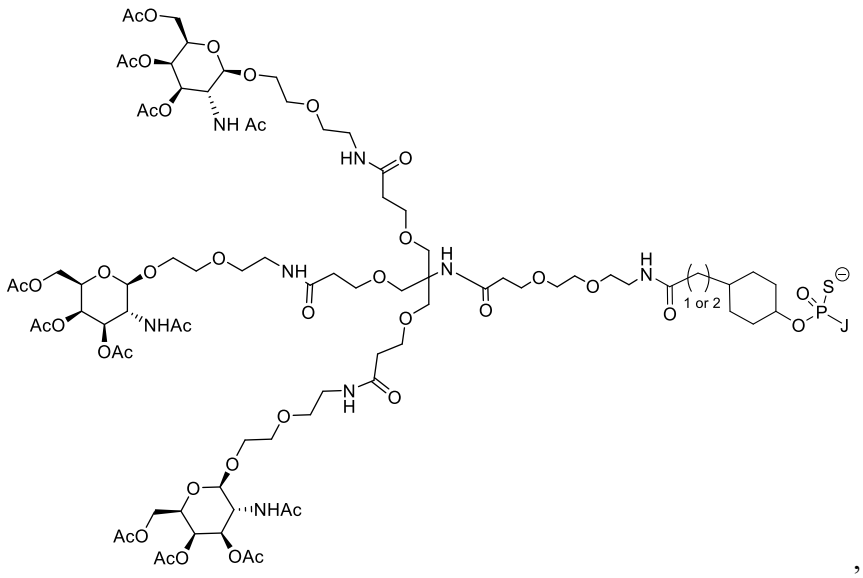
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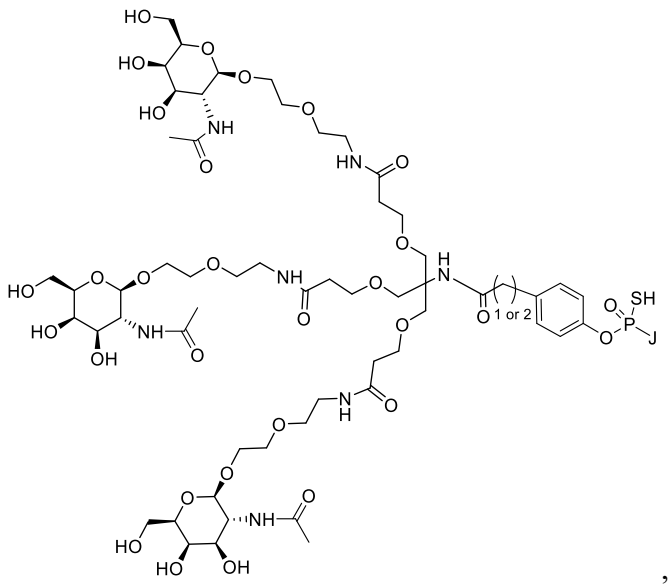
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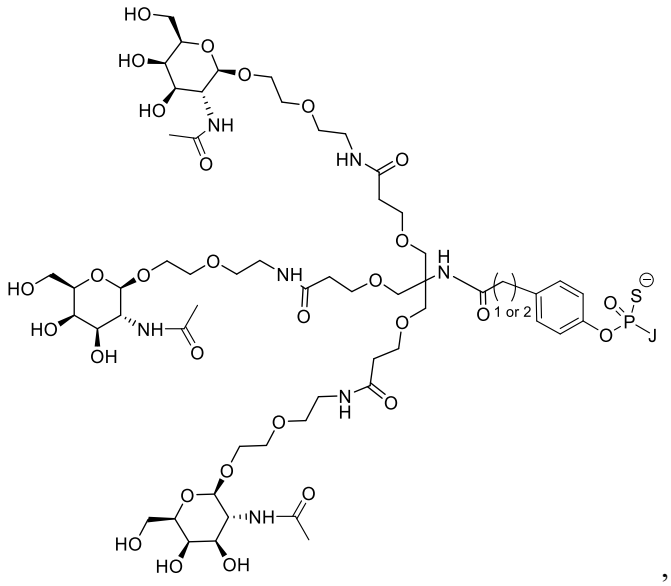
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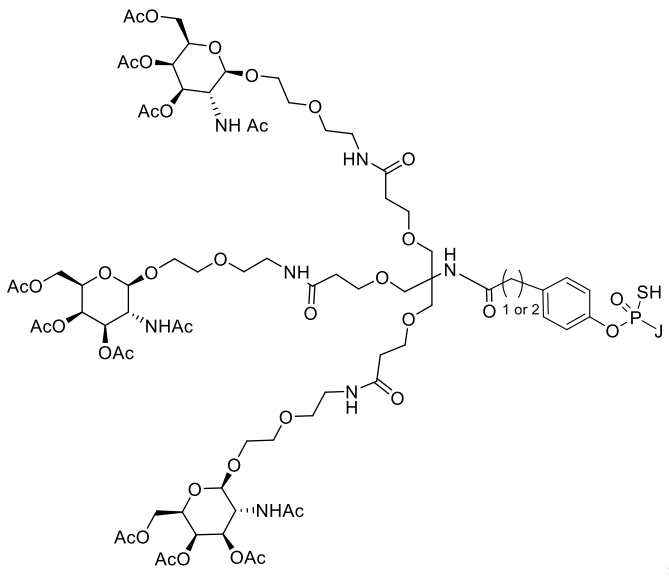
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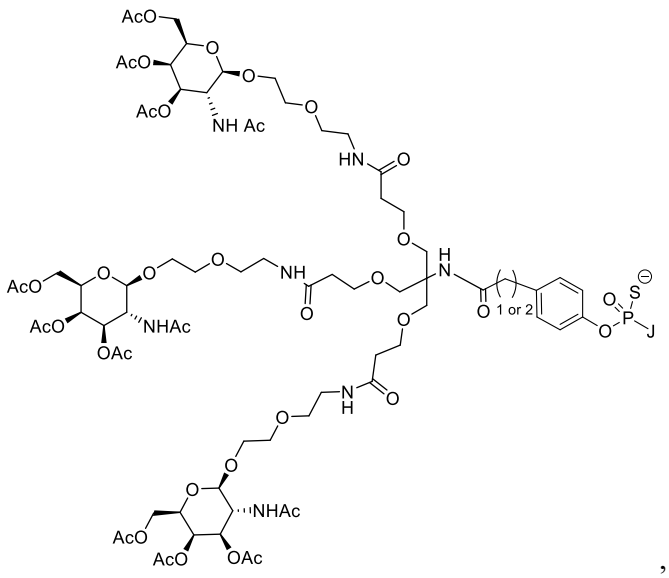
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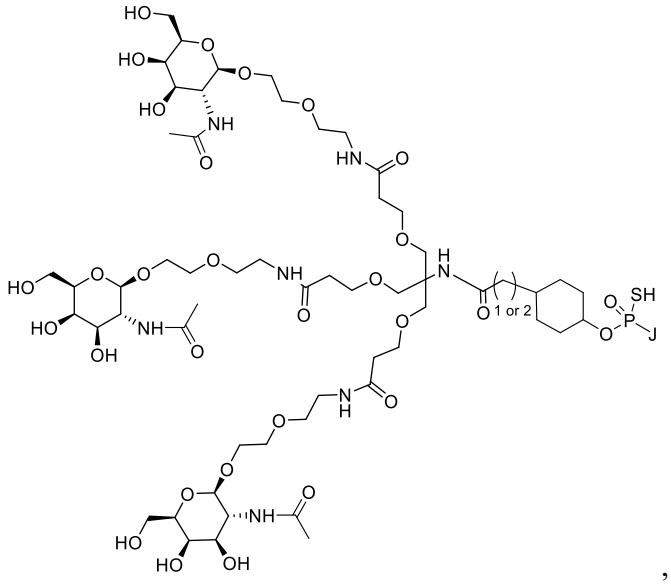
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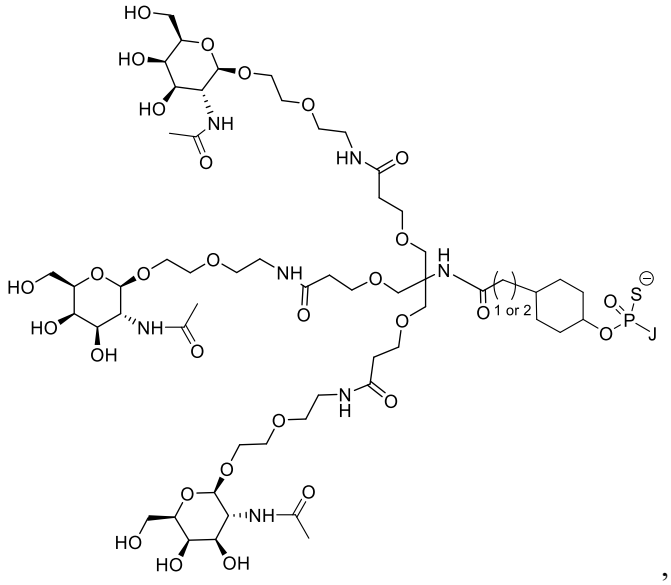
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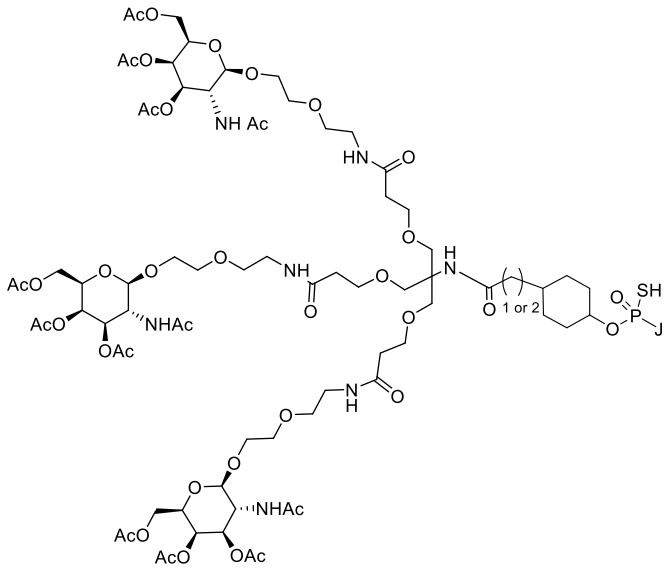
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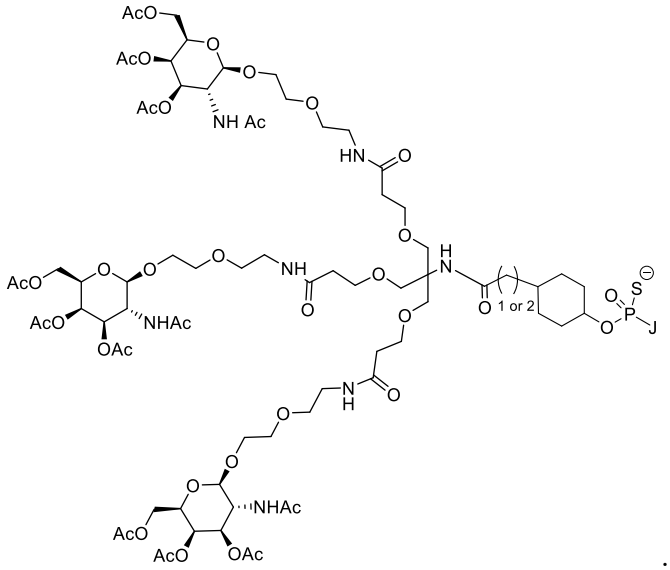
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7. The compound of claim 1, wherein the oligonucleotide (J) is attached to R^1 at a 5’ end of the oligonucleotide.

8. The compound of claim 7, wherein the 5’ end of the oligonucleotide comprises a phosphate.

9. The compound of claim 7, wherein the 5’ end of the oligonucleotide comprises a phosphorothioate.

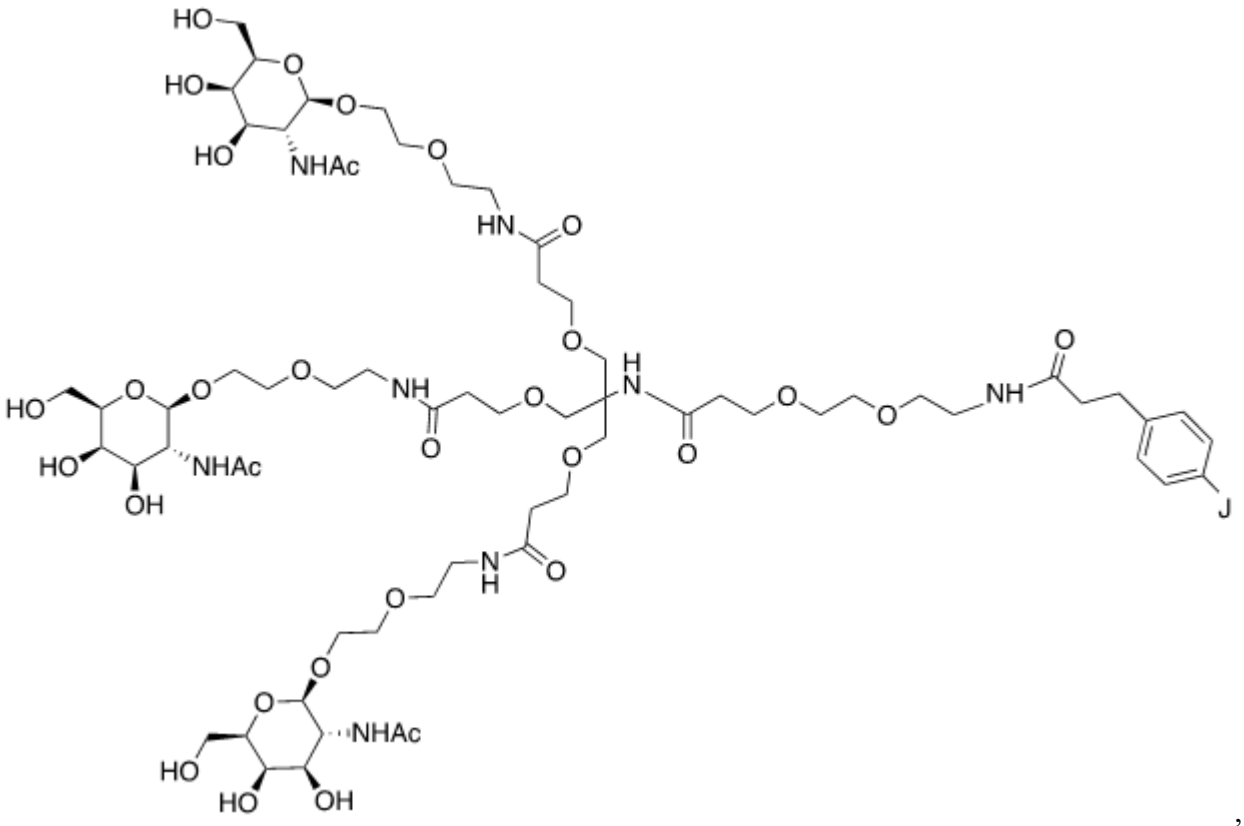
10. The compound of claim 1, wherein the oligonucleotide comprises a phosphorothioate linkage.

11. The compound of claim 1, wherein the oligonucleotide comprises a 2'-O-methyl or 2’fluoro modified nucleoside.

12. The compound of claim 1, wherein the oligonucleotide comprises a small interfering RNA (siRNA).

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

14. A compound having the structure:

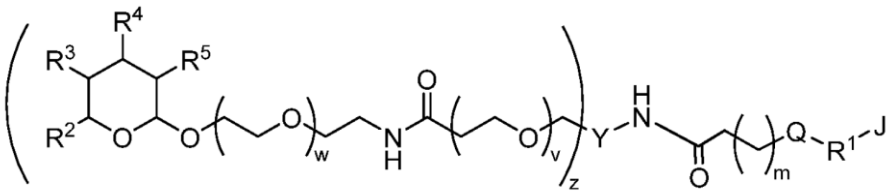


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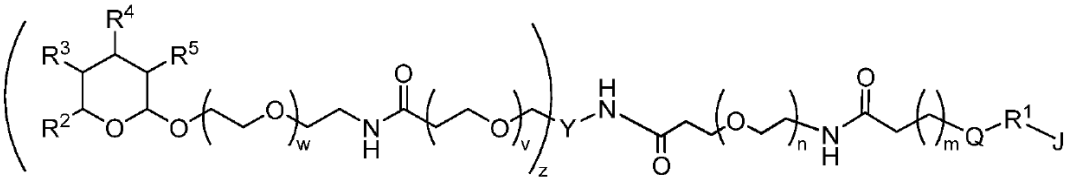
wherein J comprises an oligonucleotide.

15. The compound of claim 14, wherein the oligonucleotide comprises a siRNA.

16. Use of an effective amount of a compound represented by Formula (I) or (II) in the manufacture of a medicament for decreasing a target mRNA or target protein and treating a disorder in a subject in need thereof, wherein the compound is 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 0 to 20;

z is 3;

Y is C;

Q is a C_{3-10} carbocycle;

R^1 is -OP(O)(OR^7)O-,-OP(O)(SR^7)O-, or -OP(S)(OR^7)O-;

each R^2 is C_{1-6} alkyl substituted with -OH or $-OC(O)CH_3$;

R^3 and R^4 are each independently -OH or $-OC(O)CH_3$;

each R^5 is $-NHC(O)CH_3$; and

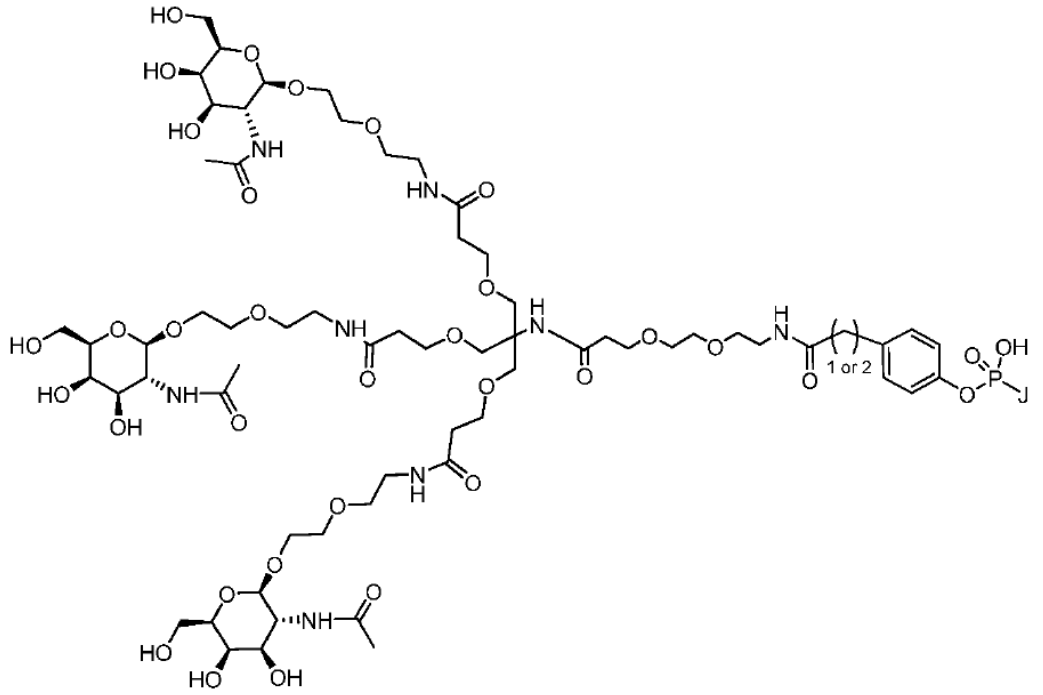
each R^7 is hydrogen,

wherein the disorder comprises a metabolic disorder or a liver disorder.

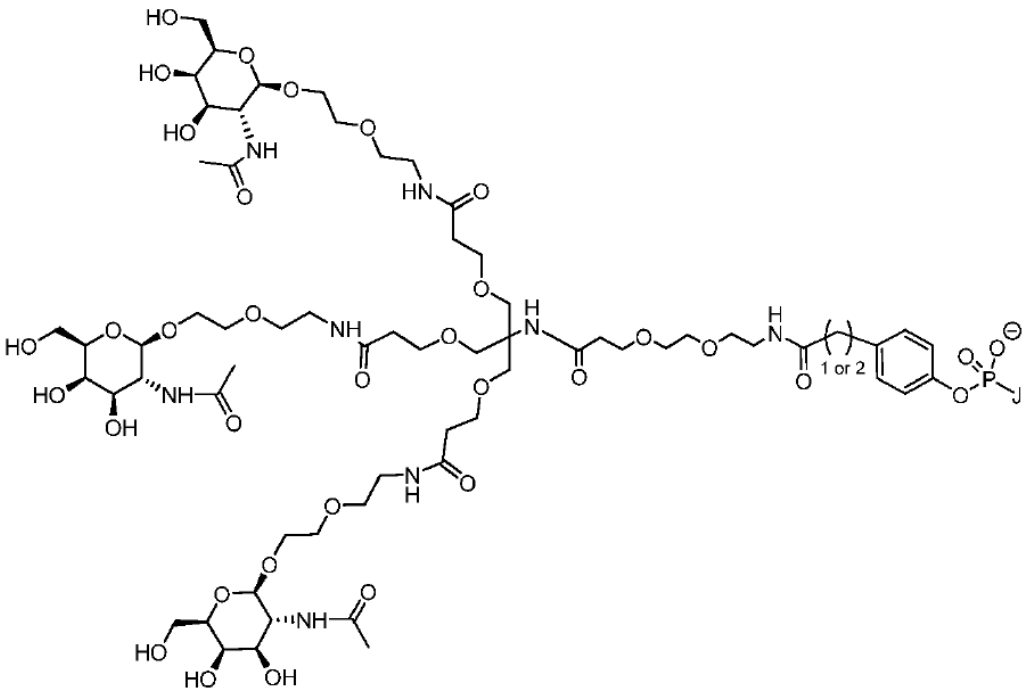
17. The use of claim 16, wherein each w, v, n, and m is independently selected from any value from 1 to 5.

18. The use of claim 16, wherein Q is selected from C_{5-6} carbocycle.

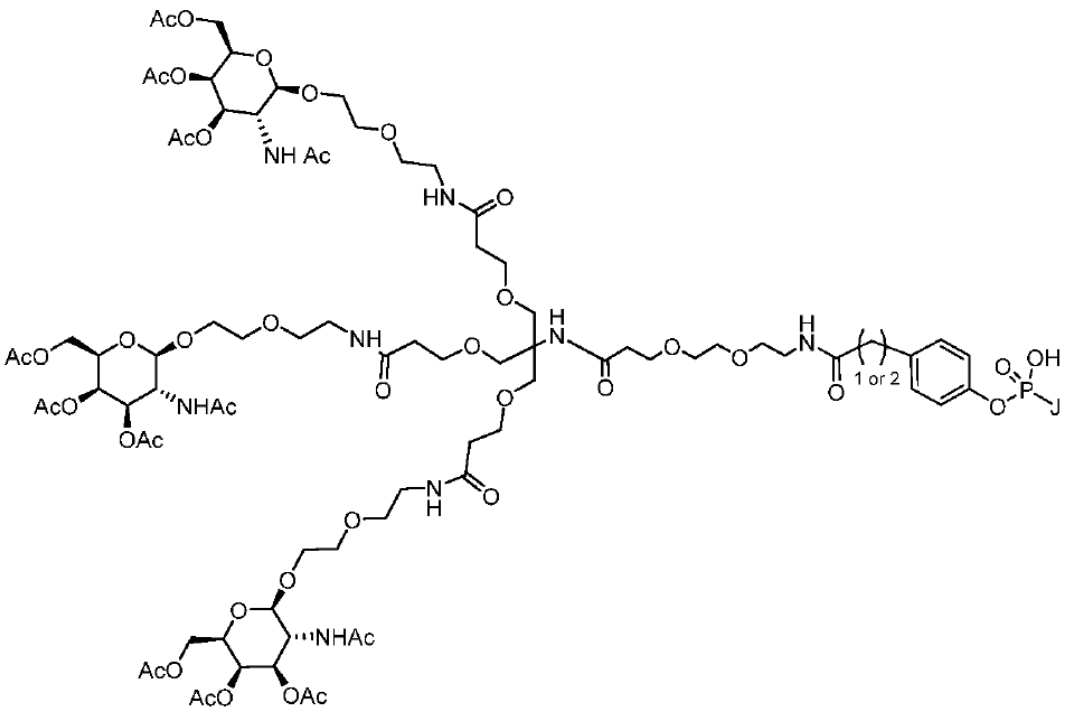
19. The use of claim 16, wherein the compound is selected from:



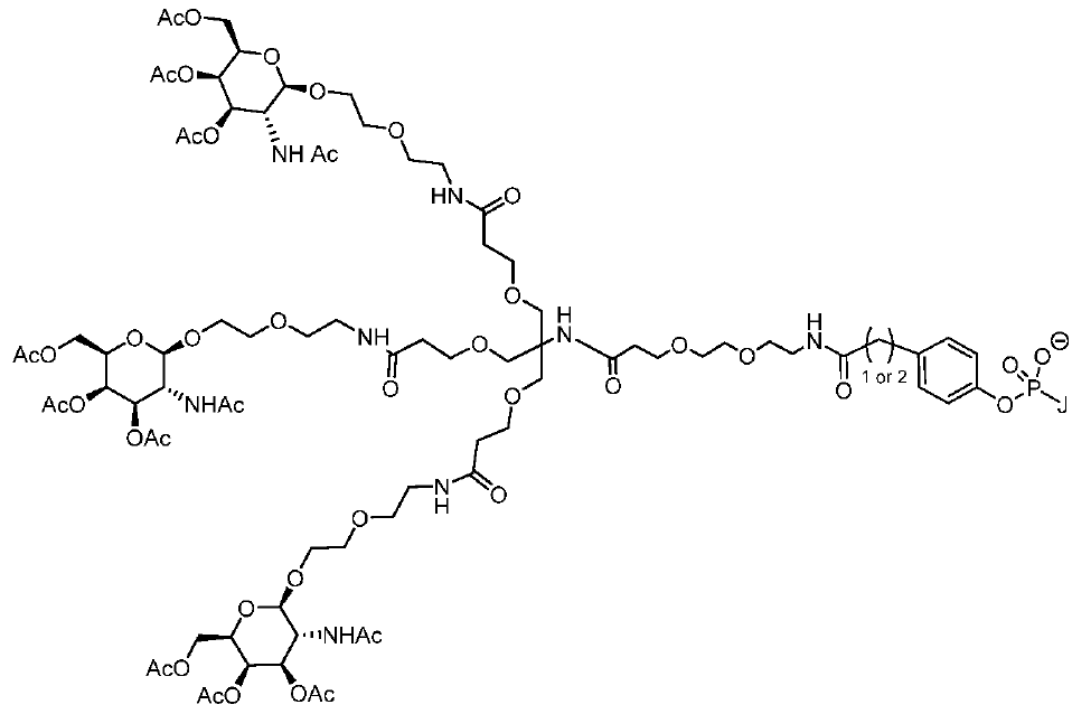
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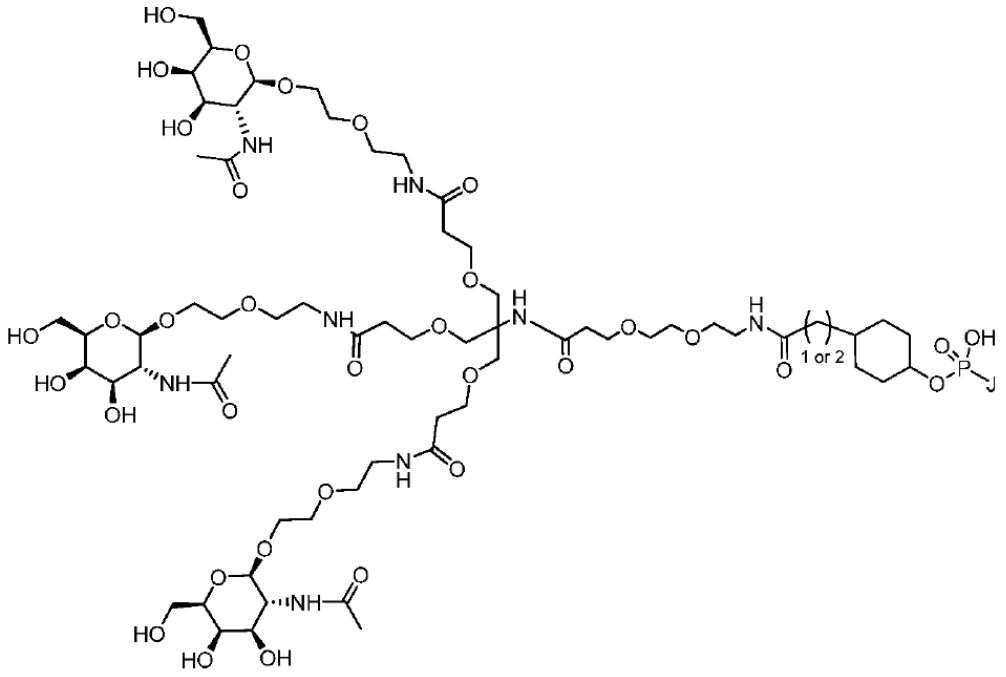
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AcO
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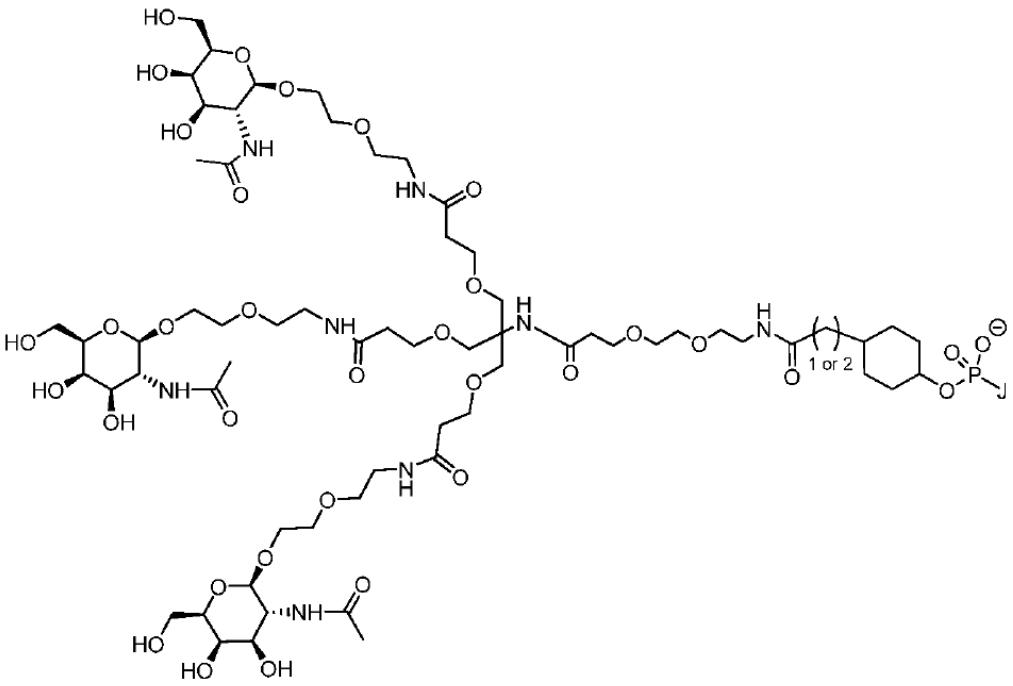
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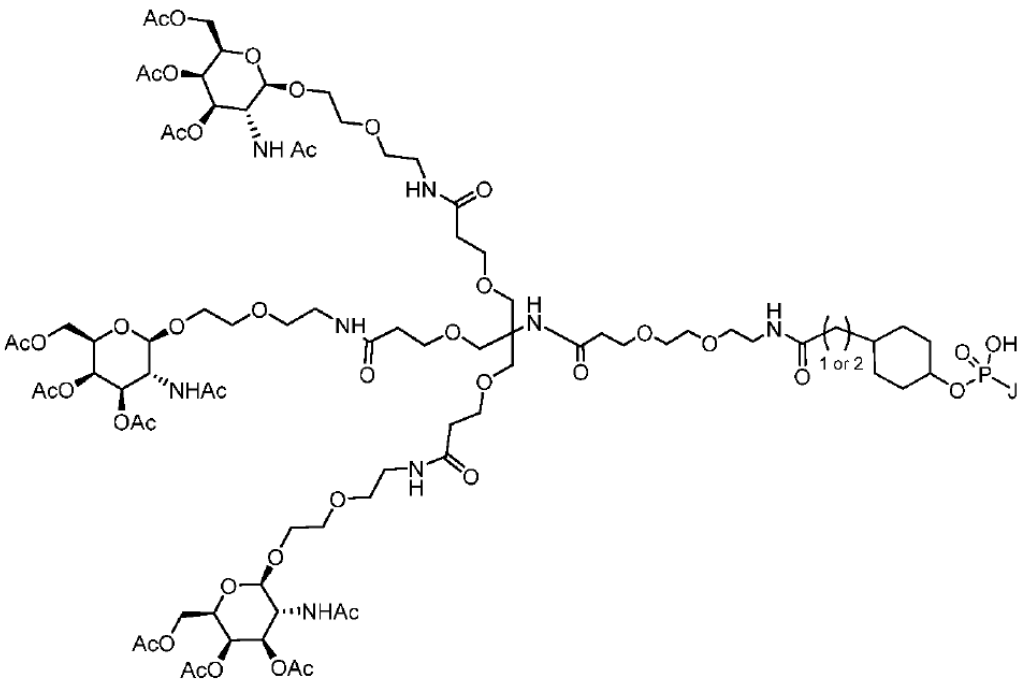
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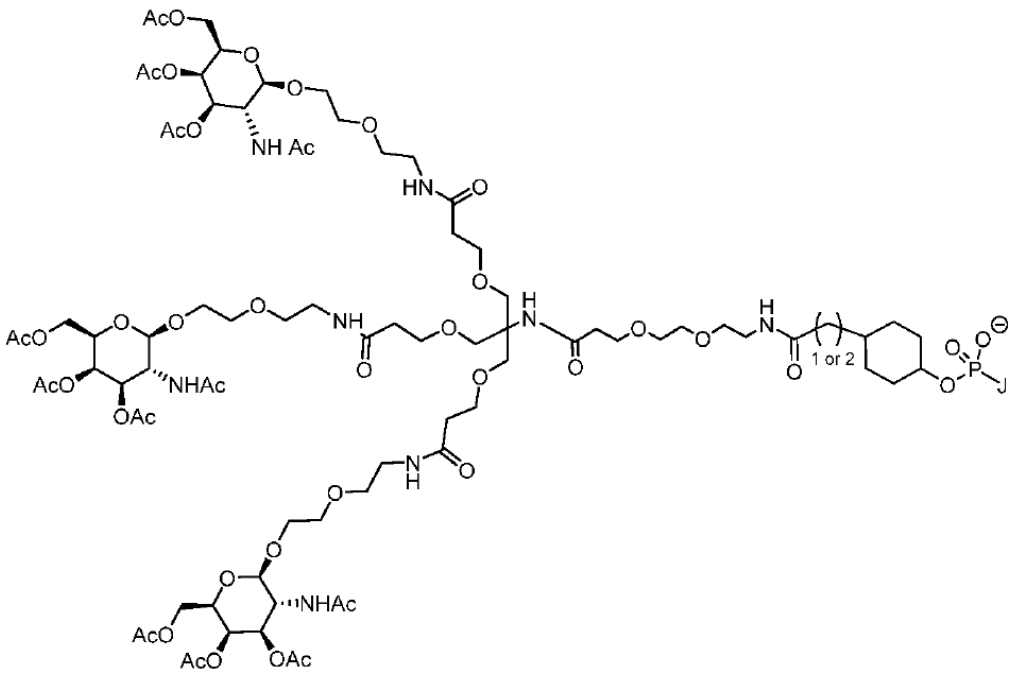
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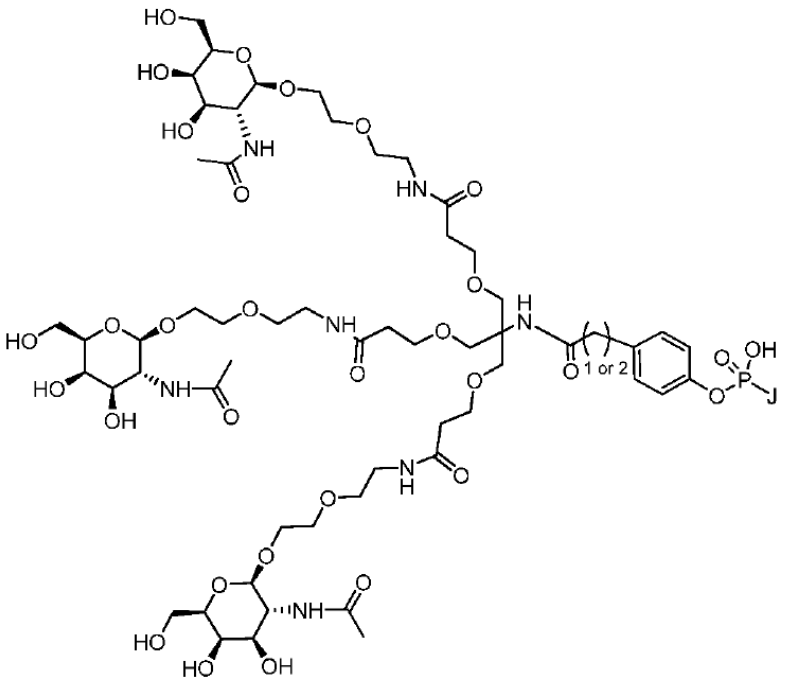
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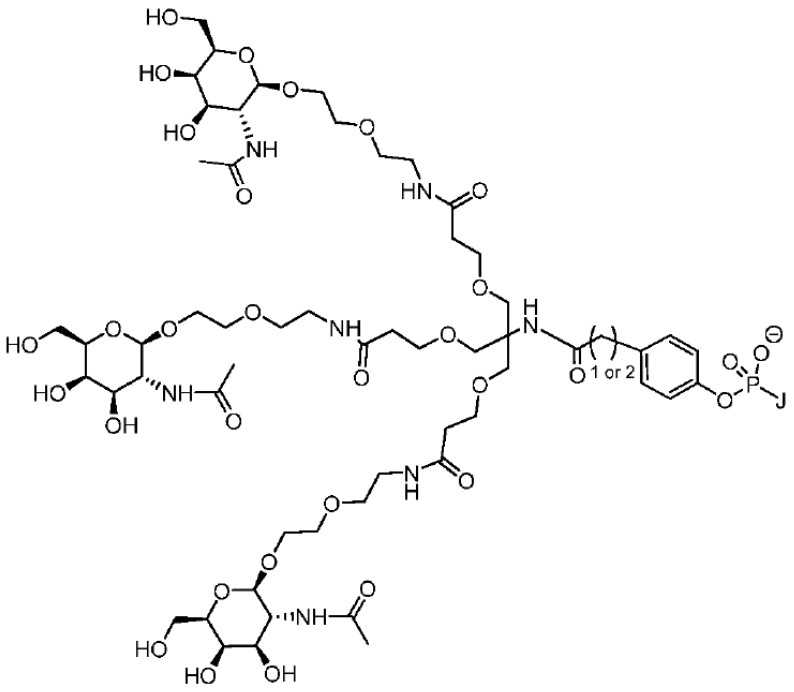
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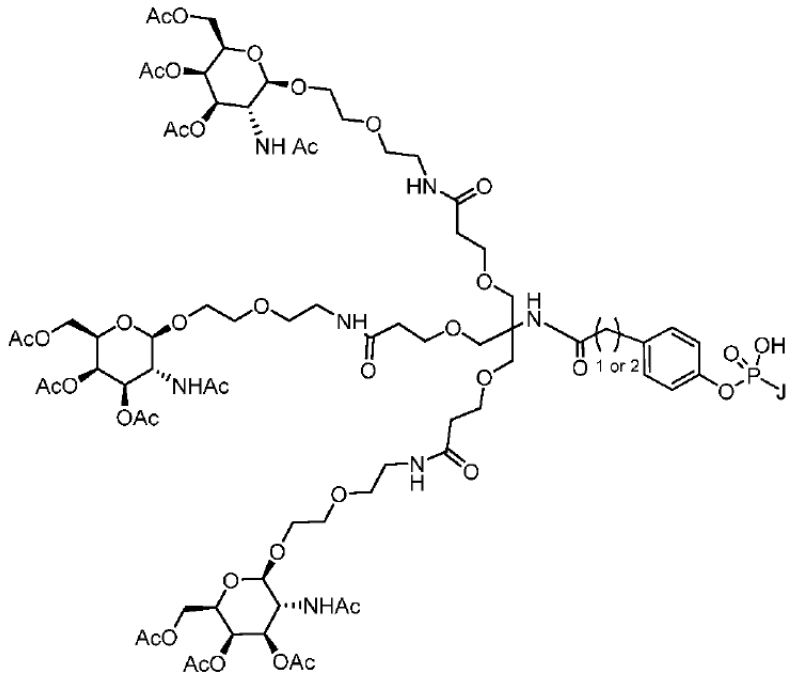
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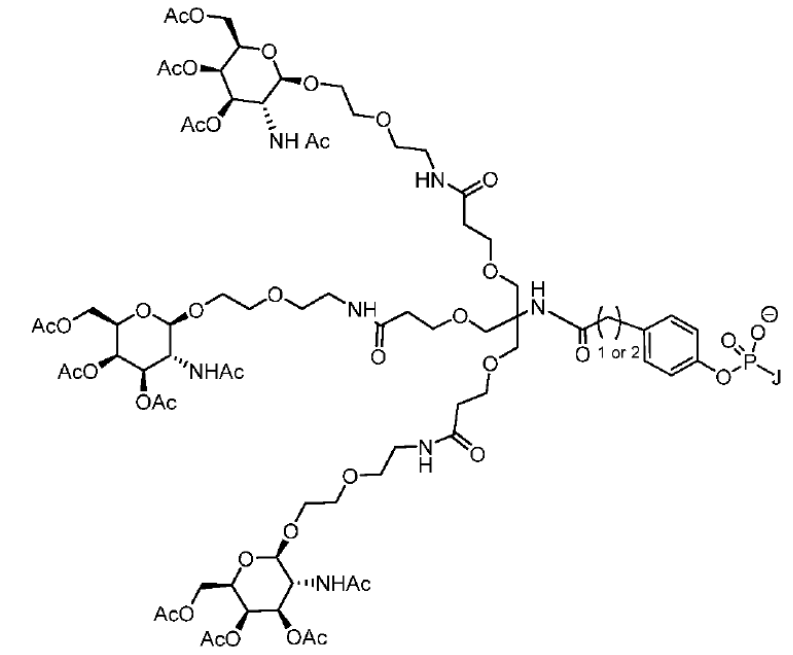
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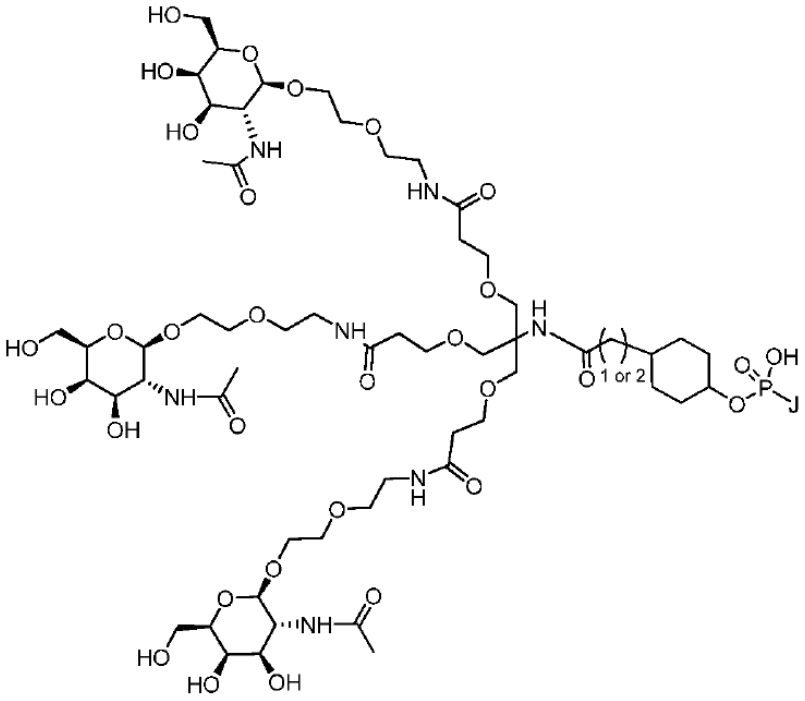
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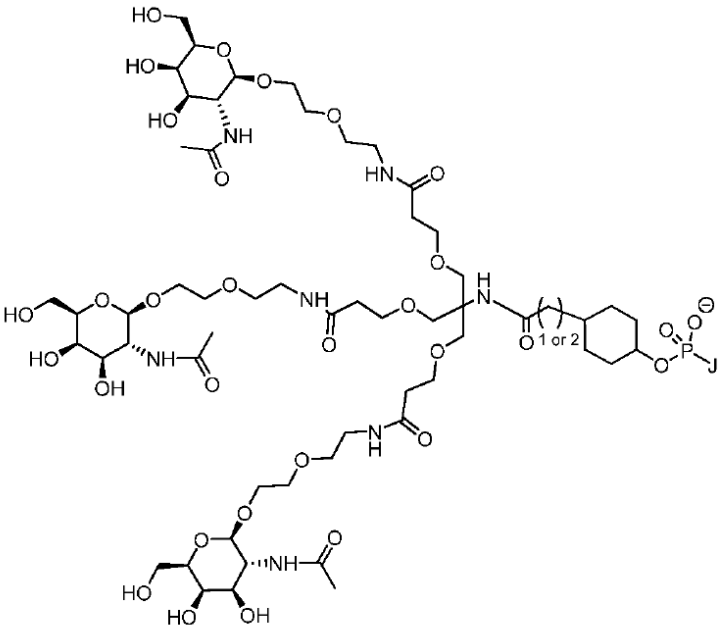
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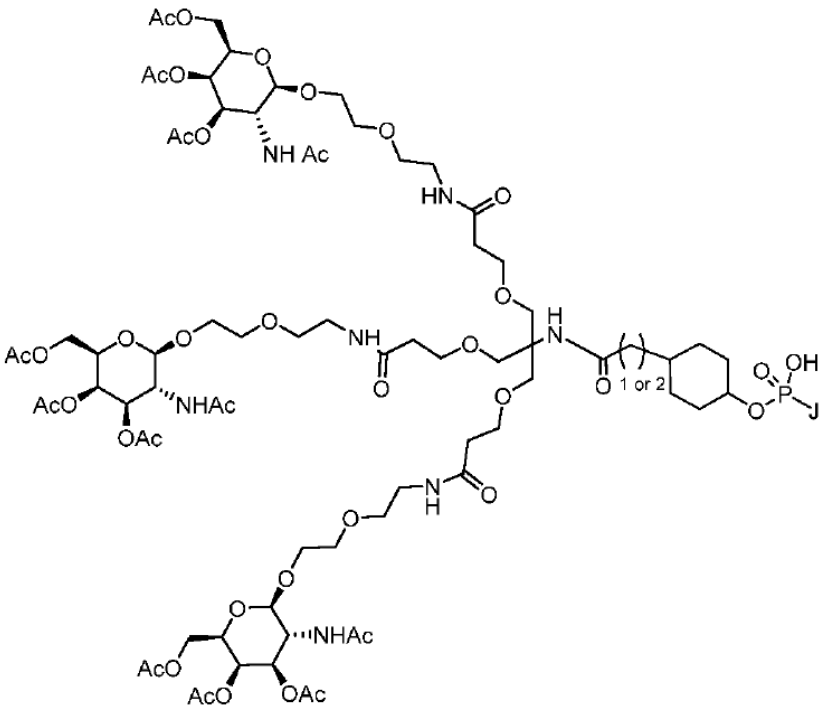
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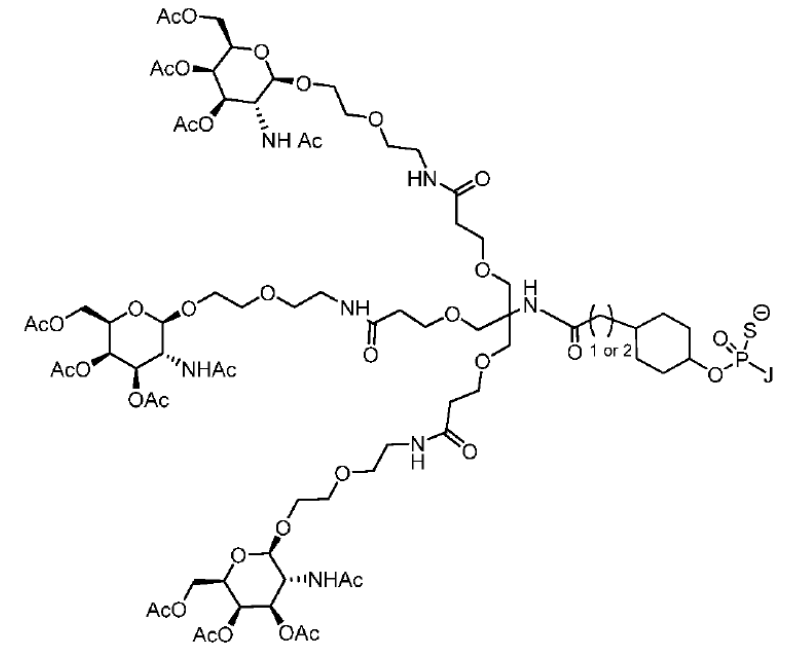
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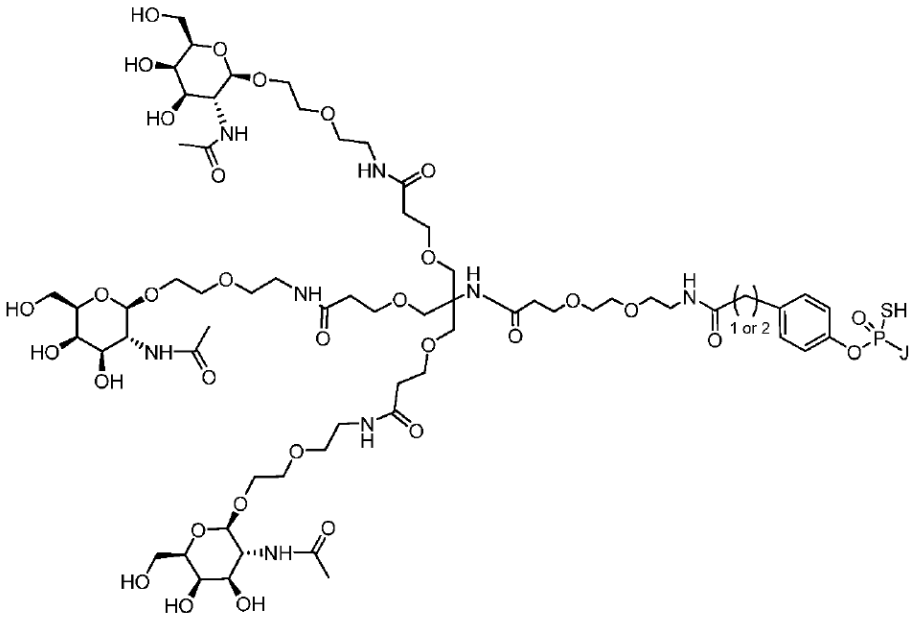
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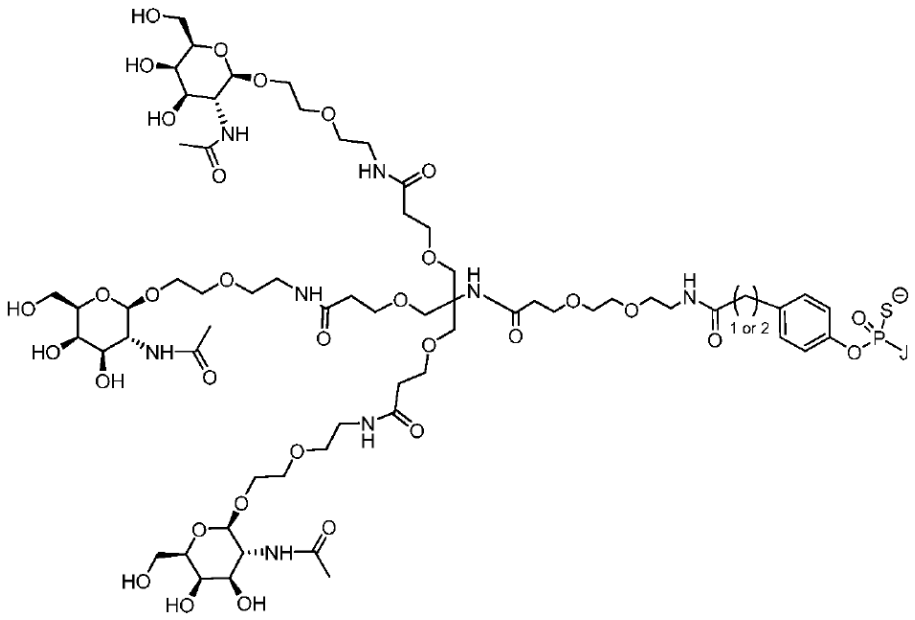
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AcO
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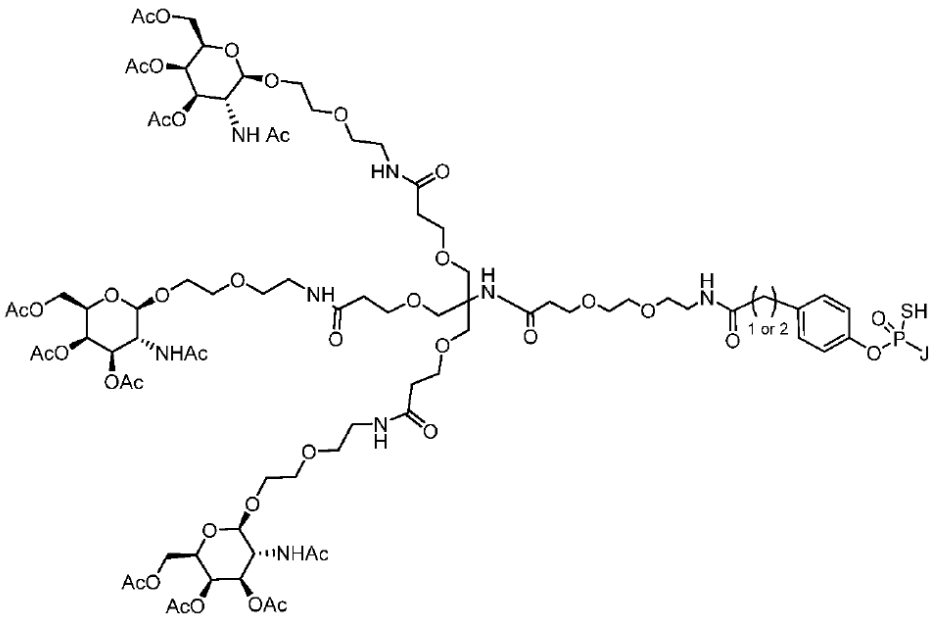
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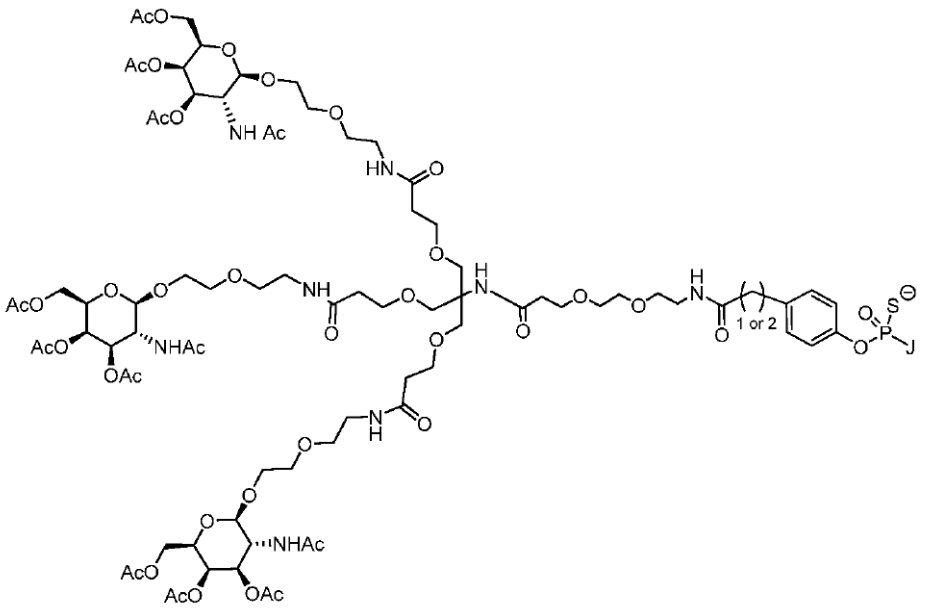
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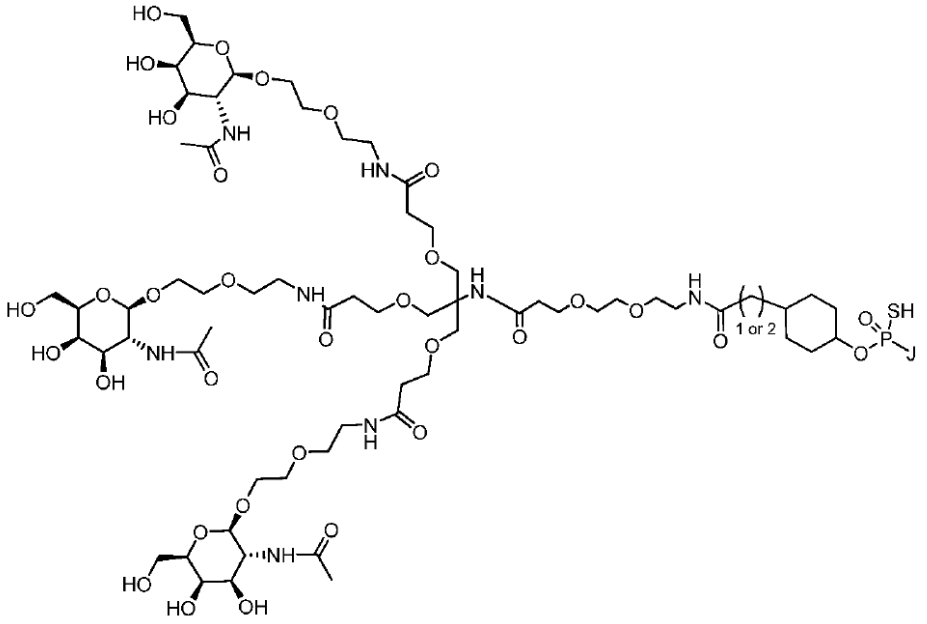
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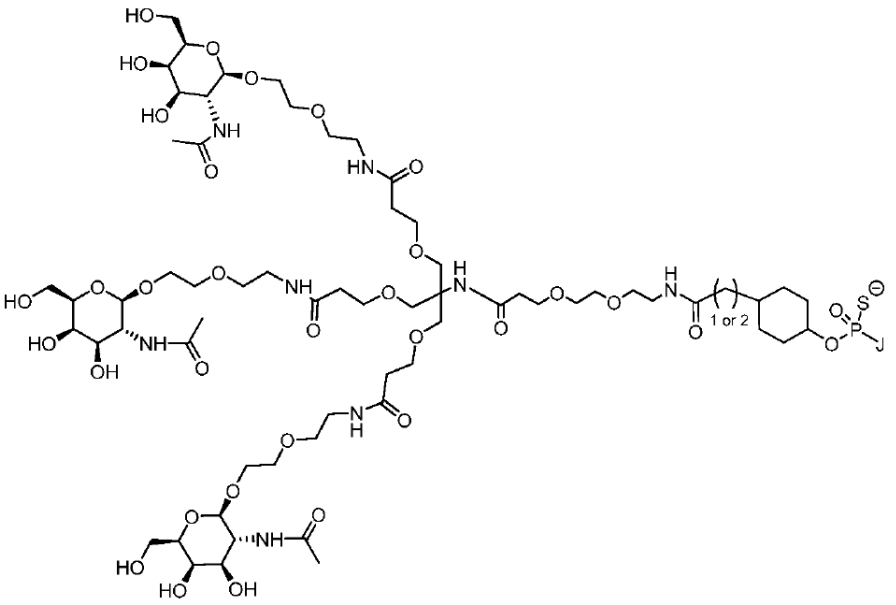
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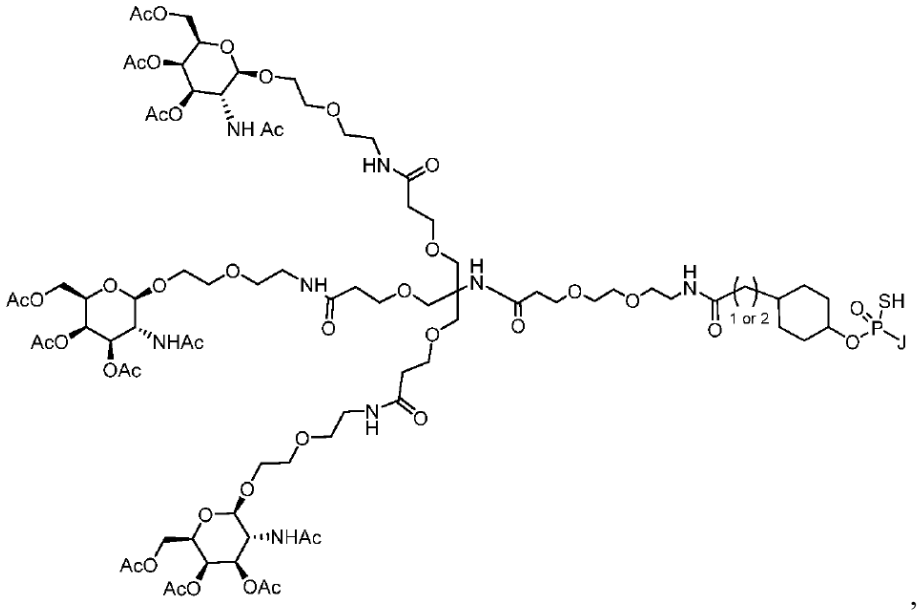
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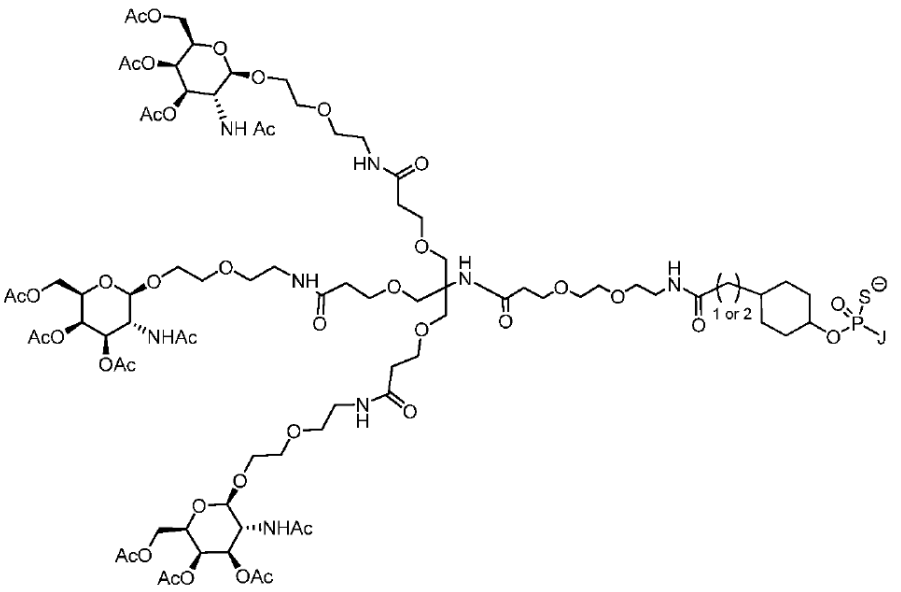
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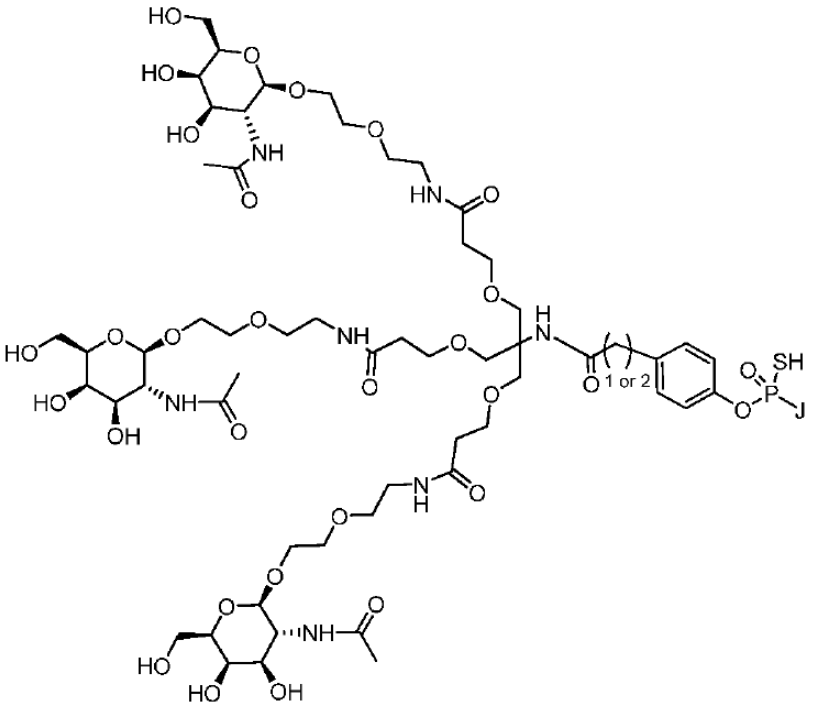
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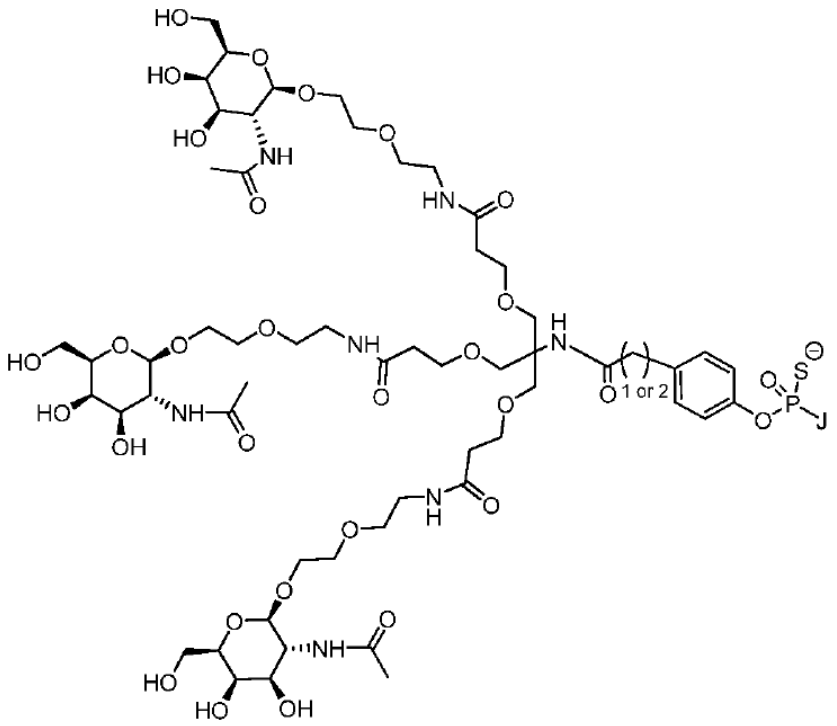
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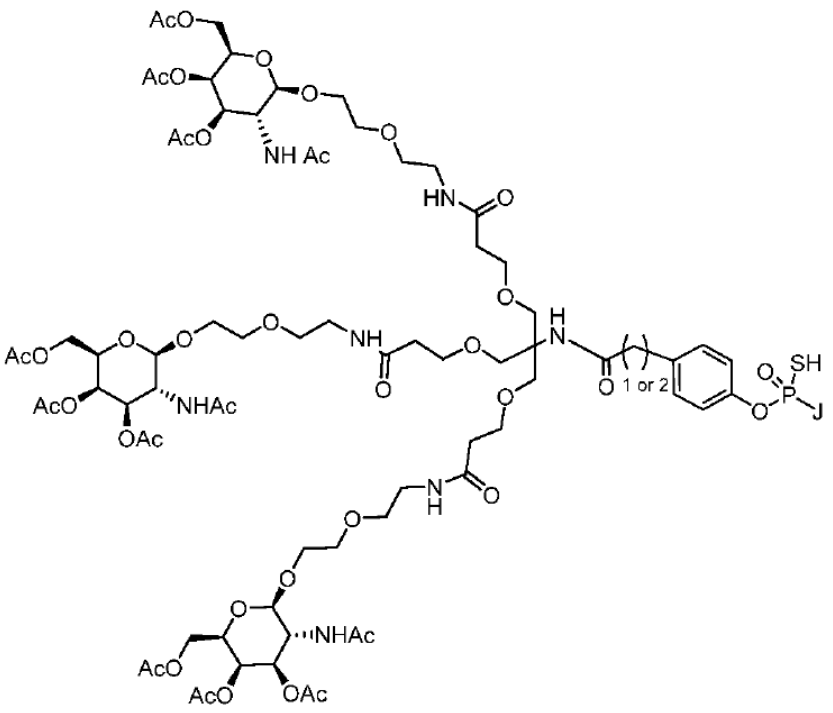
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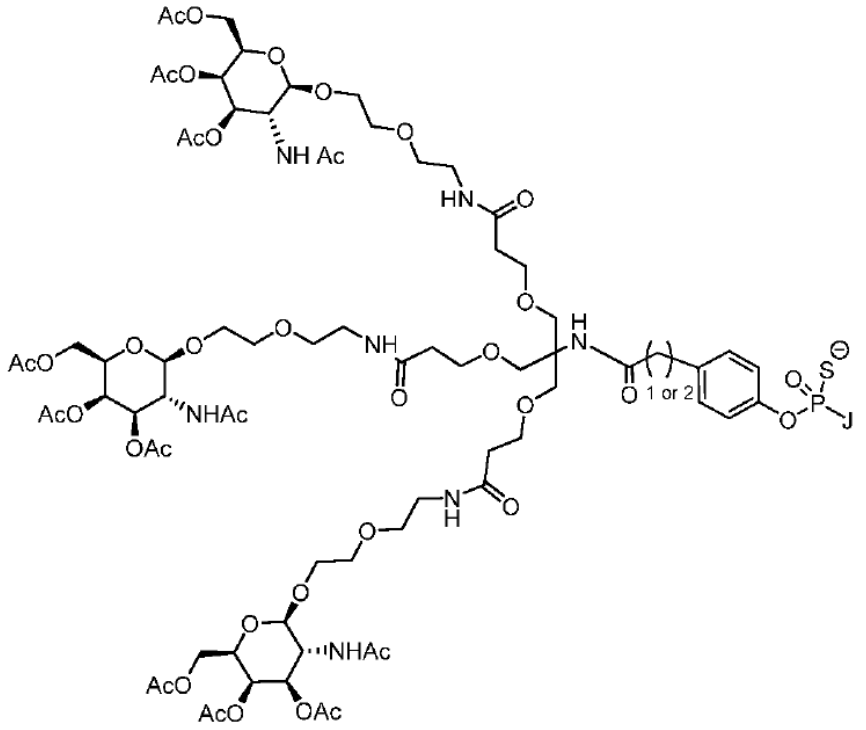
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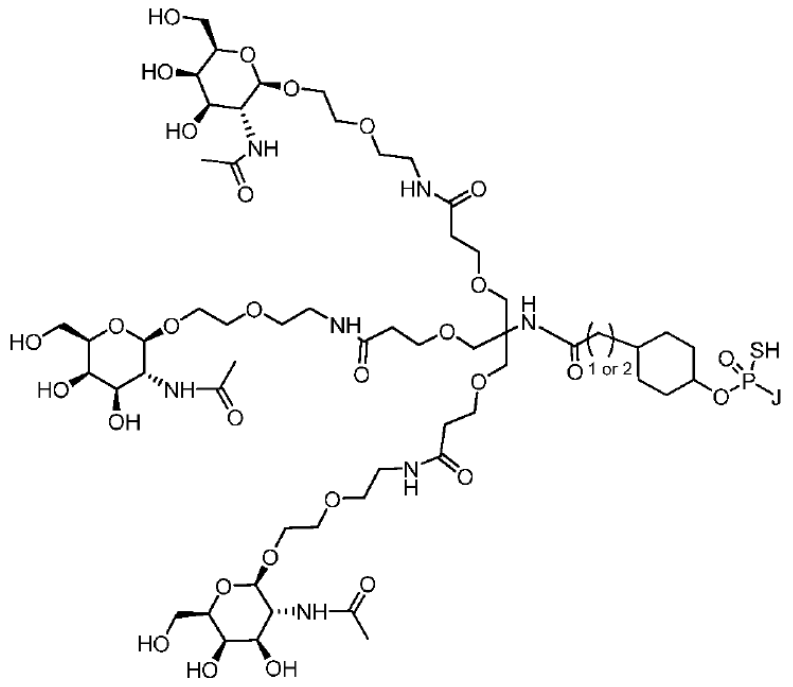
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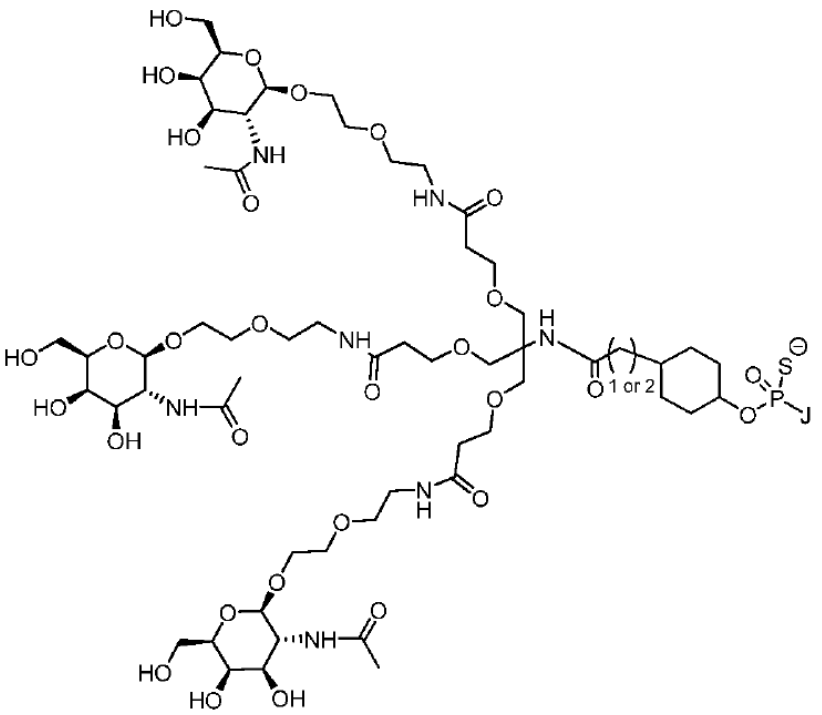
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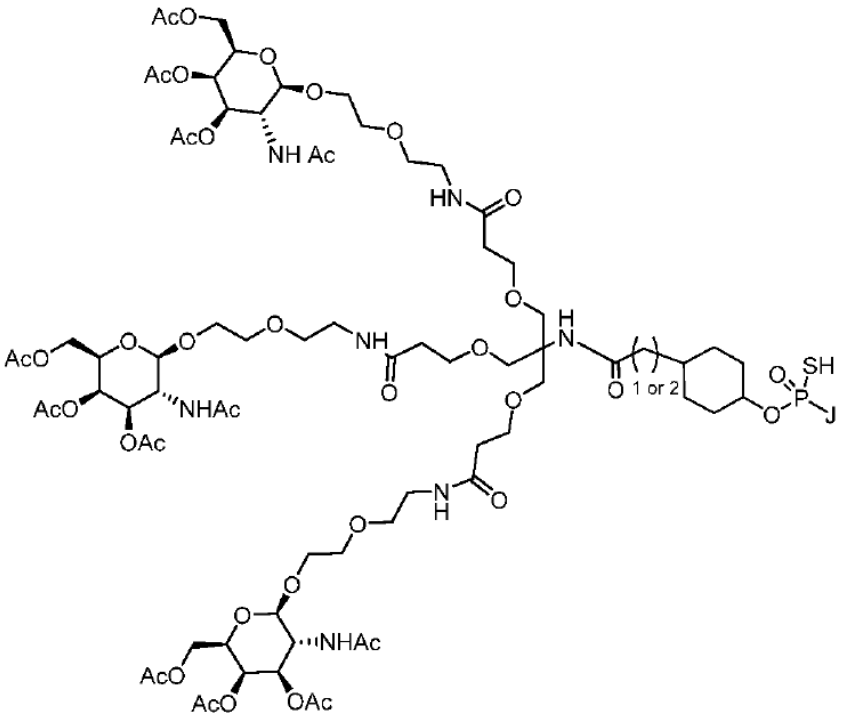
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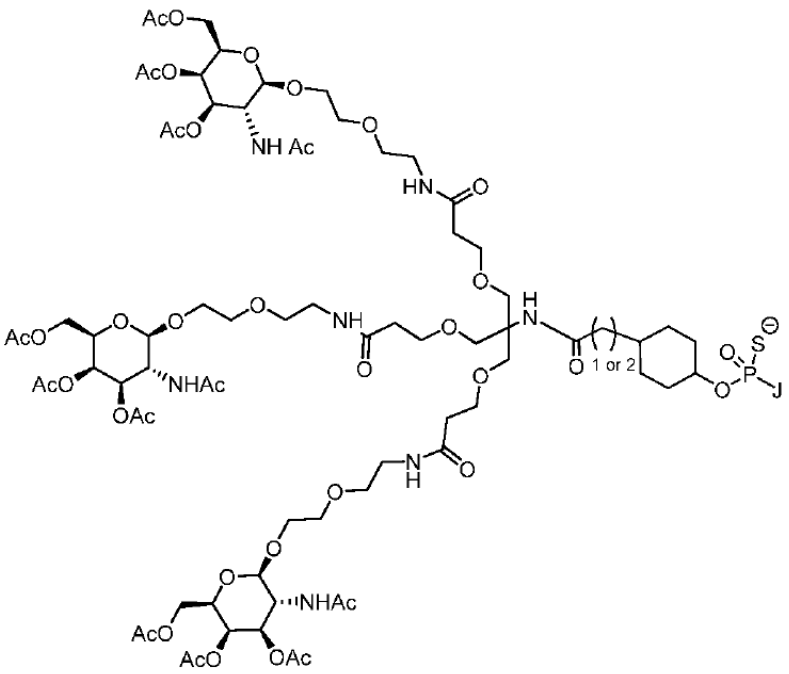
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, or



20. The use of claim 16, wherein the oligonucleotide (J) is attached to R^1 at a 5' end of the oligonucleotide.

21. The use of claim 16, wherein the oligonucleotide comprises at least one phosphorothioate linkage, 2'-O-methyl modified nucleoside, or 2'-fluoro modified nucleoside.

22. The use of claim 16, 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.

23. The use of claim 16, 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.

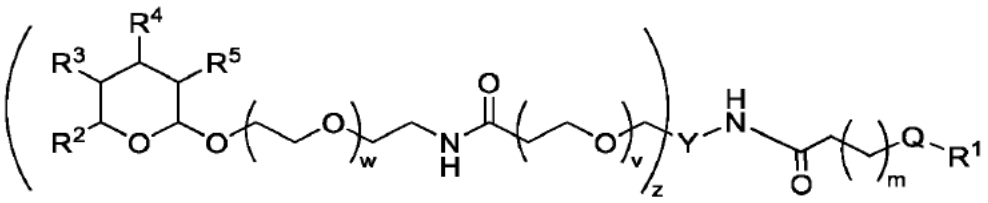
24. The use of claim 23, wherein the measurement of the symptom or the parameter related to the disorder in the subject is decreased for at least 10 days.

25. The use of claim 16, wherein the liver disorder is selected from the group consisting of liver inflammation, liver cancer, liver fibrosis, cholestasis, a gall bladder disease, a biliary tree disease, alcoholic liver disease, non-alcoholic steatohepatitis, or an inherited liver disorder, and liver infection.

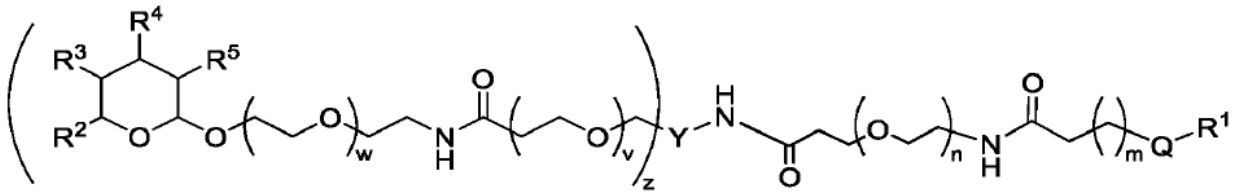
26. The use of claim 25, wherein the liver infection comprises hepatitis A, hepatitis B, or hepatitis C.

27. The use of claim 25, wherein the inherited liver disorder comprises hemochromatosis or Wilson disease.

28. 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 0 to 20;

z is 3;

Q is a C_{3-10} carbocycle;

R^1 is selected from: $-OP(O)(OR^7)_2$, or $-OP(S)(OR^7)_2$;

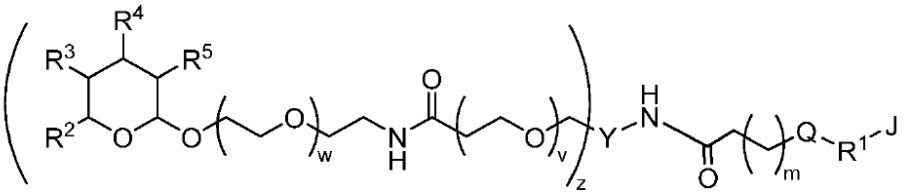
each R^2 is independently C_{1-6} alkyl substituted with -OH or $-CO(O)CH_3$;

R^3 and R^4 are each independently -OH or $-CO(O)CH_3$;

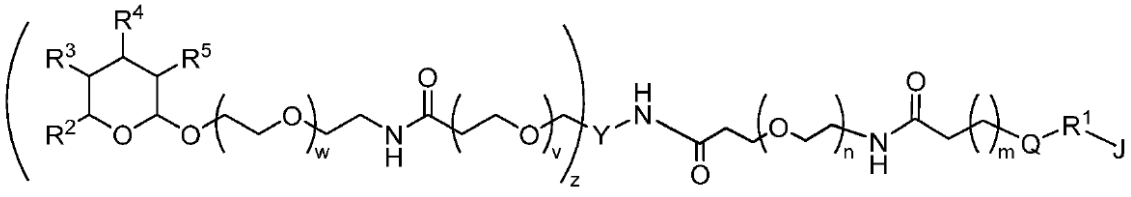
each R^5 is $-NHC(O)CH_3$; and

each R^7 is hydrogen.

29. A method of synthesizing 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 0 to 20;

z is 3;

Q is C_{3-10} carbocycle;

R^1 is $-OP(O)(OR^7)O-$, $-OP(S)(OR^7)O-$, or $-OP(O)(SR^7)O-$;

each R^2 is independently C_{1-6} alkyl substituted with -OH or $OC(O)CH_3$;

R^3 and R^4 are each independently -OH or $OC(O)CH_3$;

each R^5 is $-NHC(O)CH_3$; and

each R^7 is hydrogen;

comprising reacting a compound of Formula (A) or (B) of claim 28 with an oligonucleotide.

30. The compound of claim 1 for use in therapy.