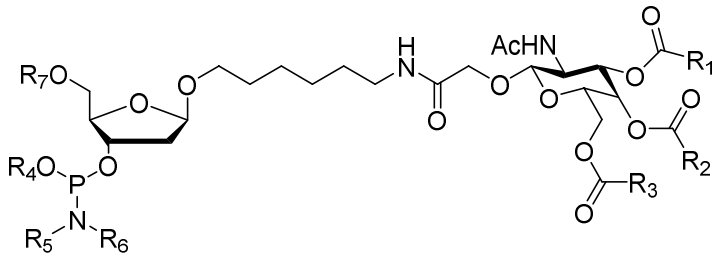
Claims

1. A N-Acetyl-Galactosamine (GalNAc) monomer comprising a structure selected from the group consisting of

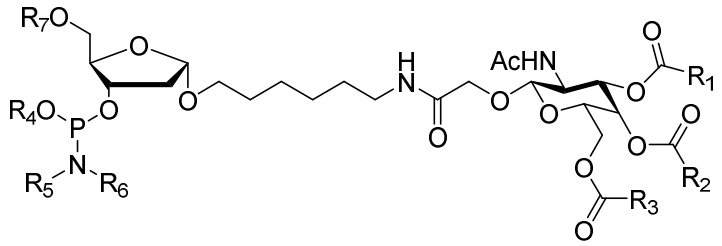


(M1'), wherein R1, R2, and R3 can be the same or different, and wherein R1, R2, and R3 are independently selected from an alkyl, aryl, and alkenyl group,

wherein R4 is a suitable protecting group or a C1-6 straight or branched alkyl group,

wherein R5 and R6 are each independently a C1-6 straight or branched alkyl group, and

wherein R7 is a suitable protecting group;

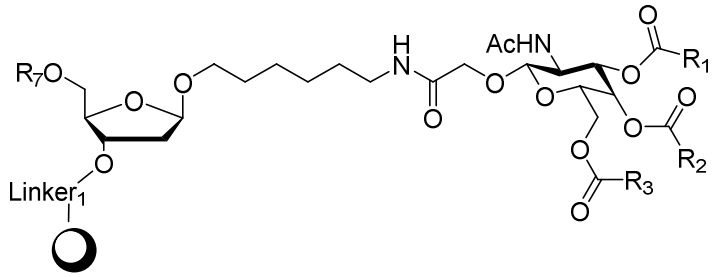


(M2'), wherein R1, R2, and R3 can be the same or different, and wherein R1, R2, and R3 are independently selected from an alkyl, aryl, and alkenyl group;

wherein R4 is a protecting group or a C1-6 straight or branched alkyl group,

wherein R5 and R6 are each independently C1-6 straight or branched alkyl; and

wherein R7 is a suitable protecting group;

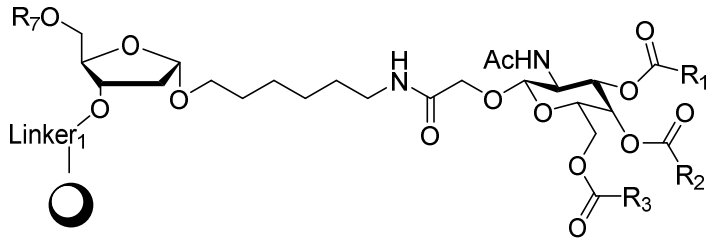


(M4', which is a monomer on solid support), wherein R1, R2, and R3 can be the same or different, and wherein R1, R2, and R3 are independently selected from an alkyl, aryl, and alkenyl group,

wherein R7 is a suitable protecting group, and

wherein Linker1 is a cleavable linker;

and

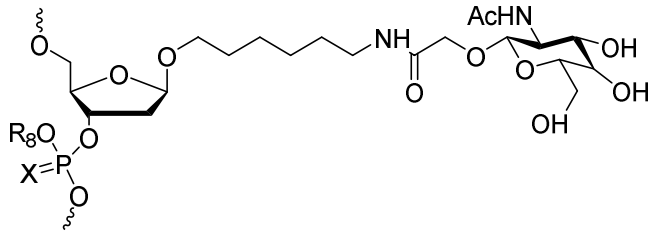


(M5', which is a monomer on solid support), wherein R1, R2, and R3 can be the same or different, and wherein R1, R2, and R3 are independently selected from the group consisting of an alkyl, aryl, and alkenyl group,

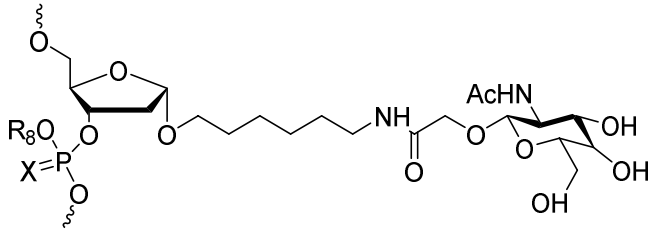
wherein R7 is a suitable protecting group, and

wherein Linker1 is a cleavable linker.

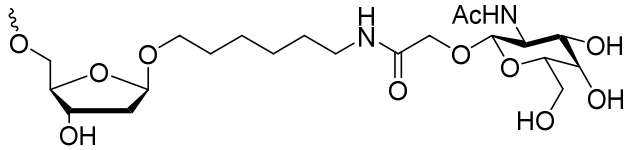
2. A GalNAc moiety comprising at least one GalNAc monomer, wherein the GalNAc monomers are selected from the group consisting of



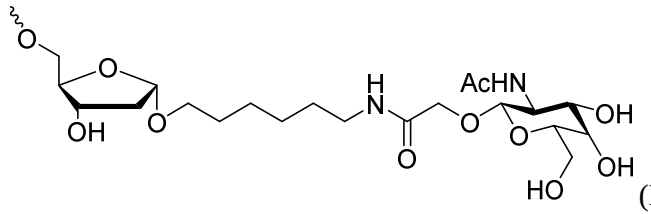
(M1), wherein R_8 is -H or a C1-6 straight or branched alkyl group;



(M2), wherein R_8 is -H or a C1-6 straight or branched alkyl group, and wherein X is O or S;



(M4);



(M5).

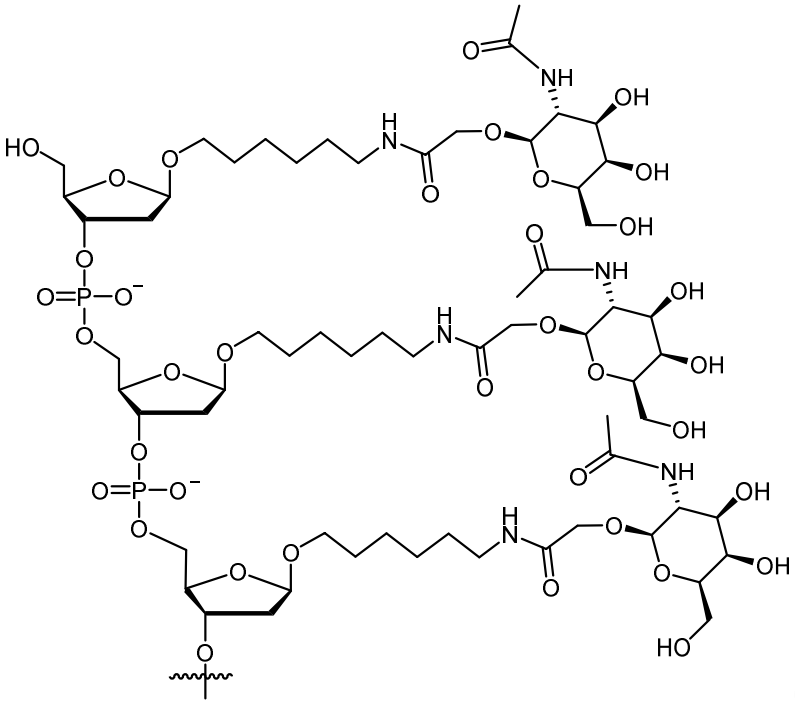
3. The GalNAc moiety of claim 2, wherein the GalNAc moiety comprises a spacer comprising a structure of hexaethylene glycol (HEG), C12 spacer (C12), abasic spacer (ab), a triethylene glycol (TEG), or C3 spacer (C3).

4. The GalNAc moiety of claim 2, wherein the GalNAc moiety comprises two or three GalNAc monomers.

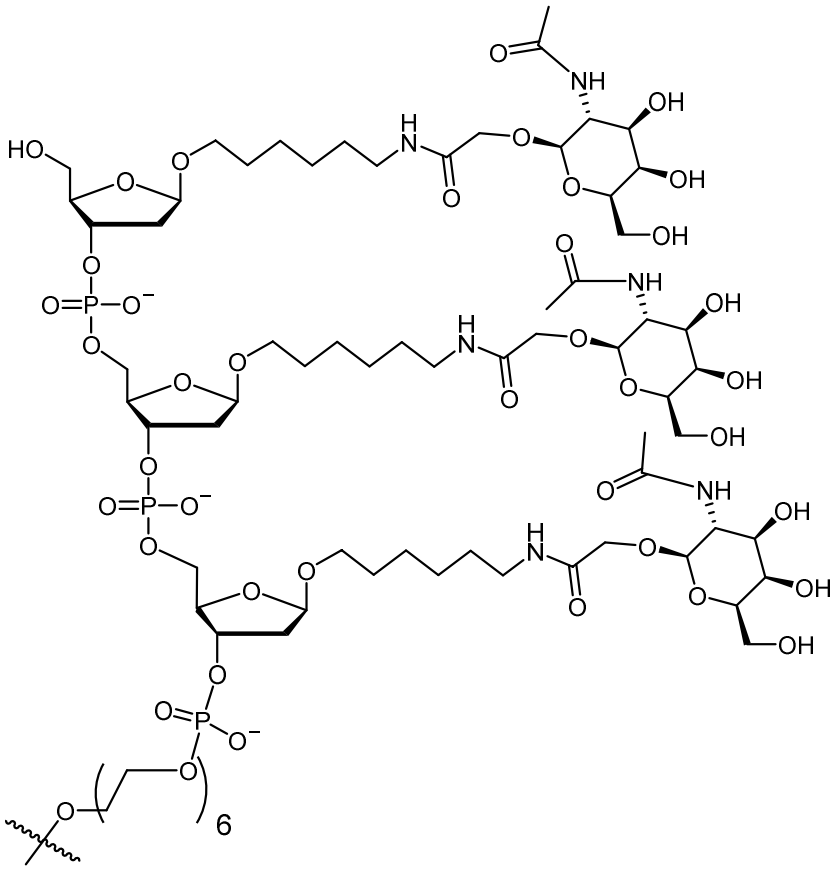
5. The GalNAc moiety of claim 2, wherein the GalNAc moiety comprises three M1 or M2 monomers.

6. The GalNAc moiety of claim 5, wherein the GalNAc moiety comprises three M1 monomers.

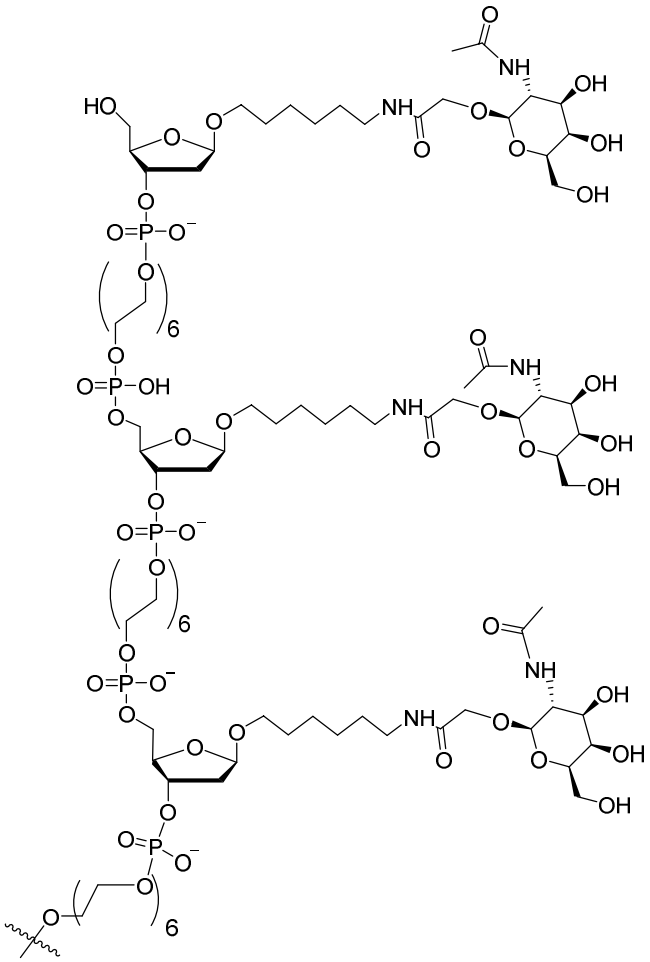
7. The GalNAc moiety of claim 2, comprising a cluster of GalNAc monomers comprising a structure of



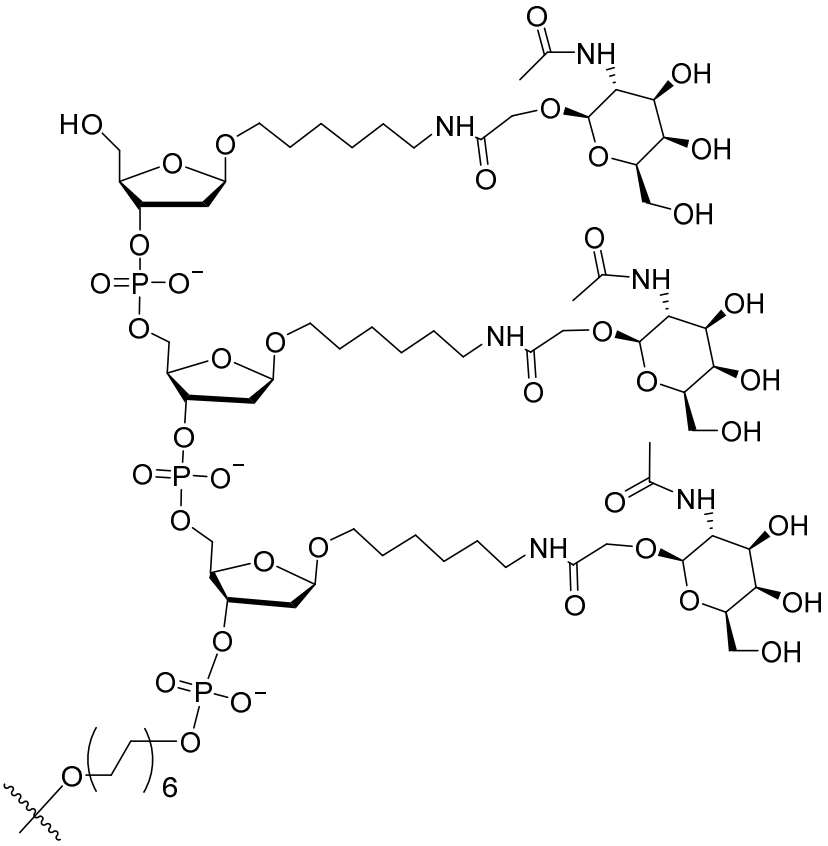
(G7);



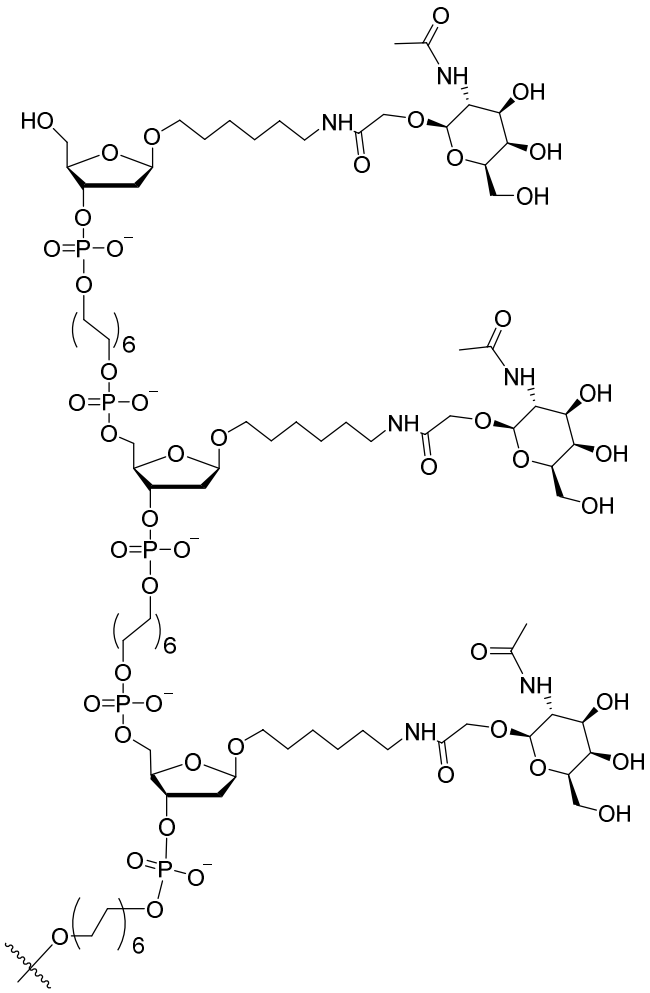
(G8);



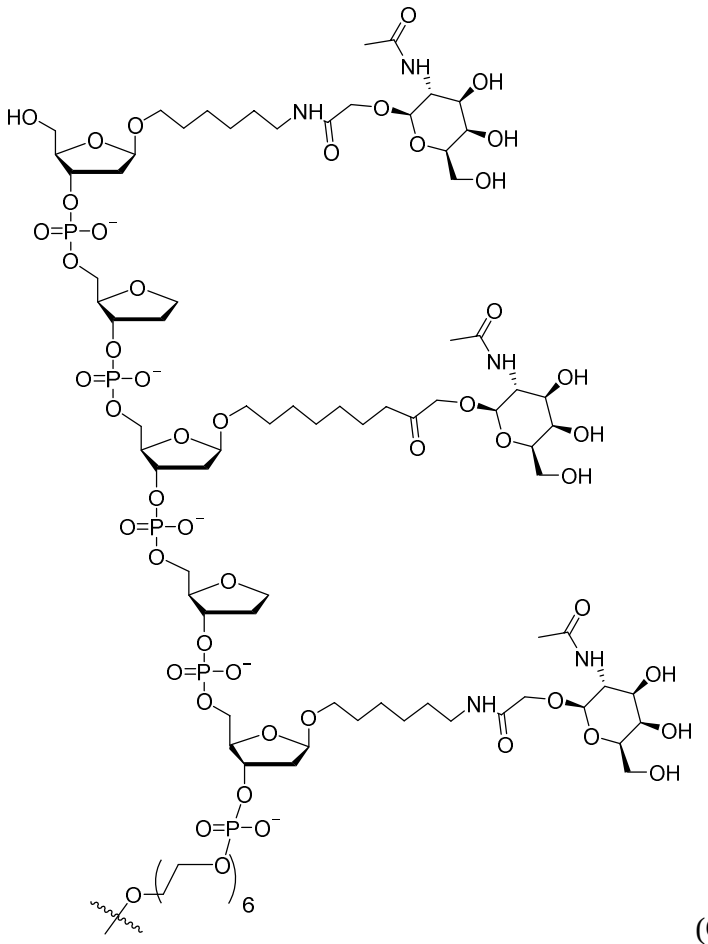
(G9);



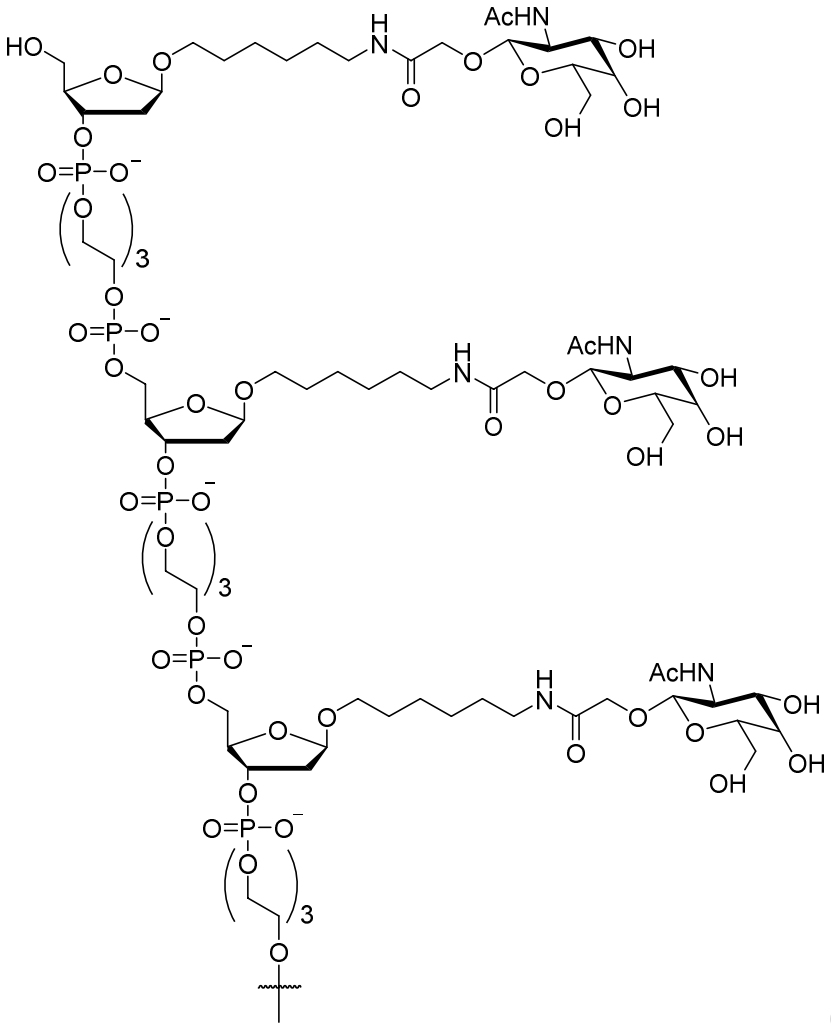
(G10);



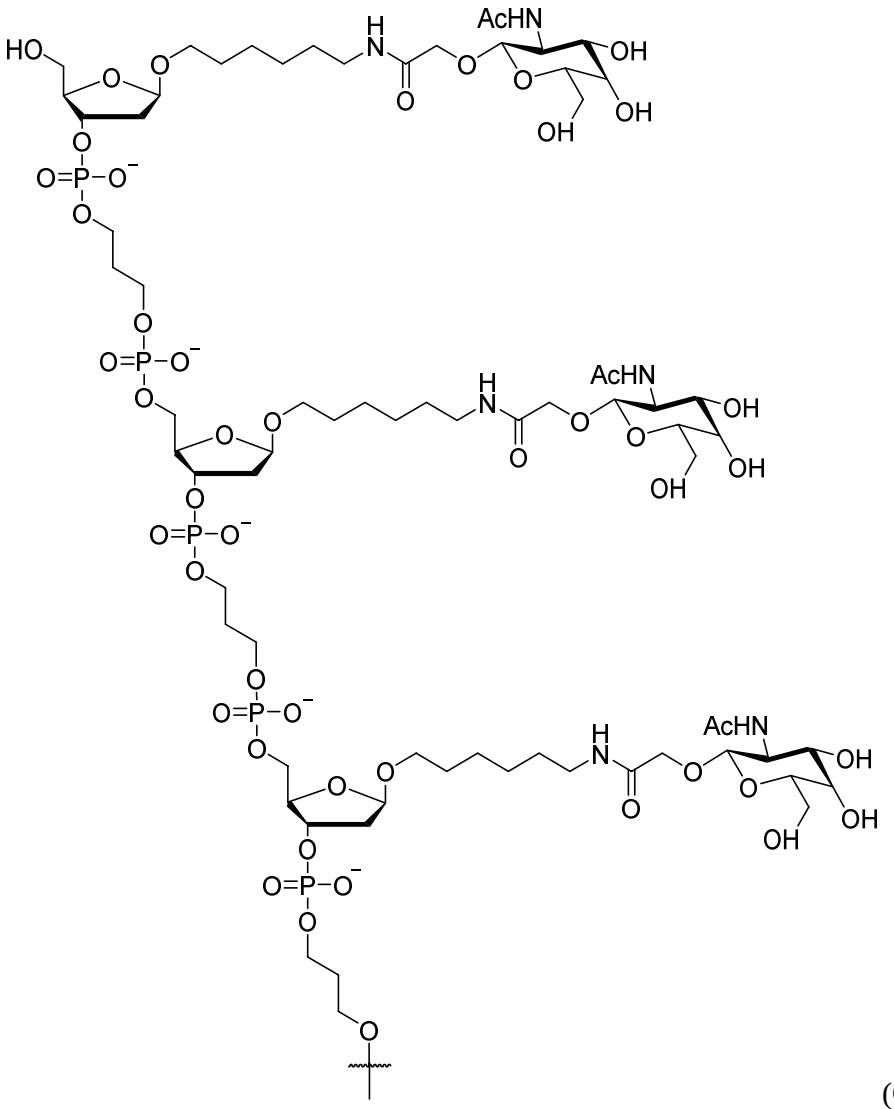
(G11);



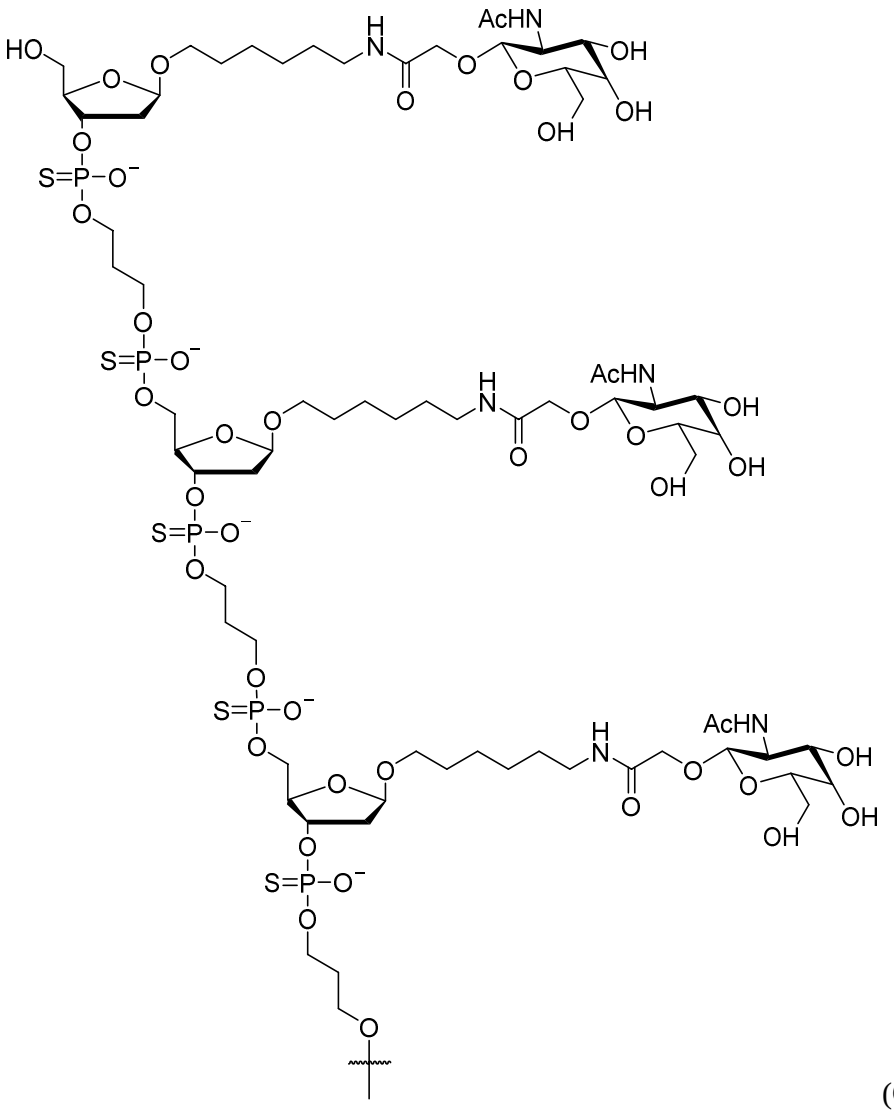
(G12);



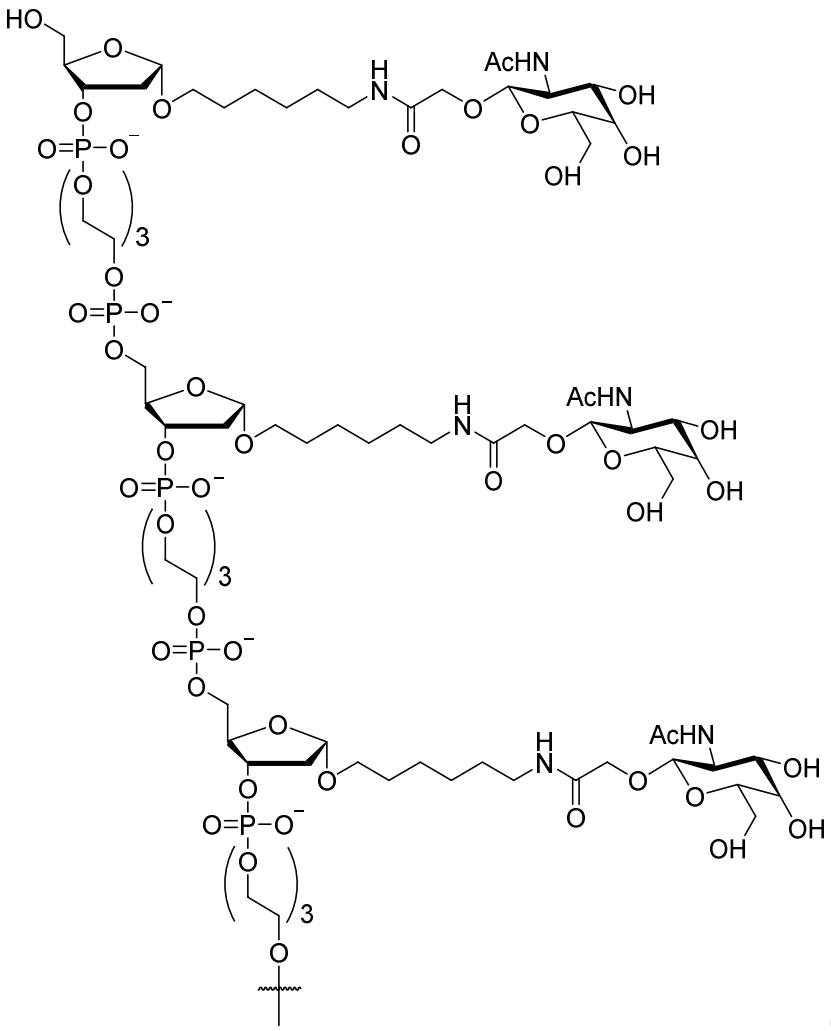
(G13);



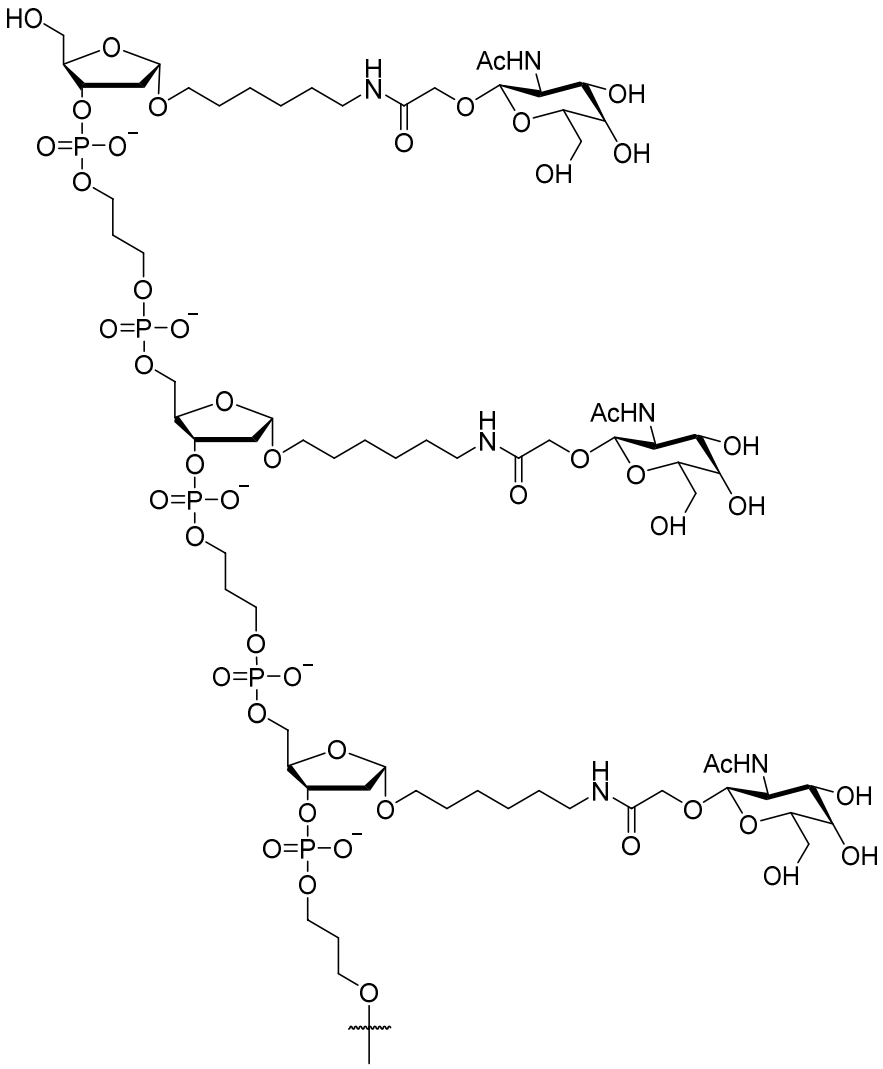
(G14);



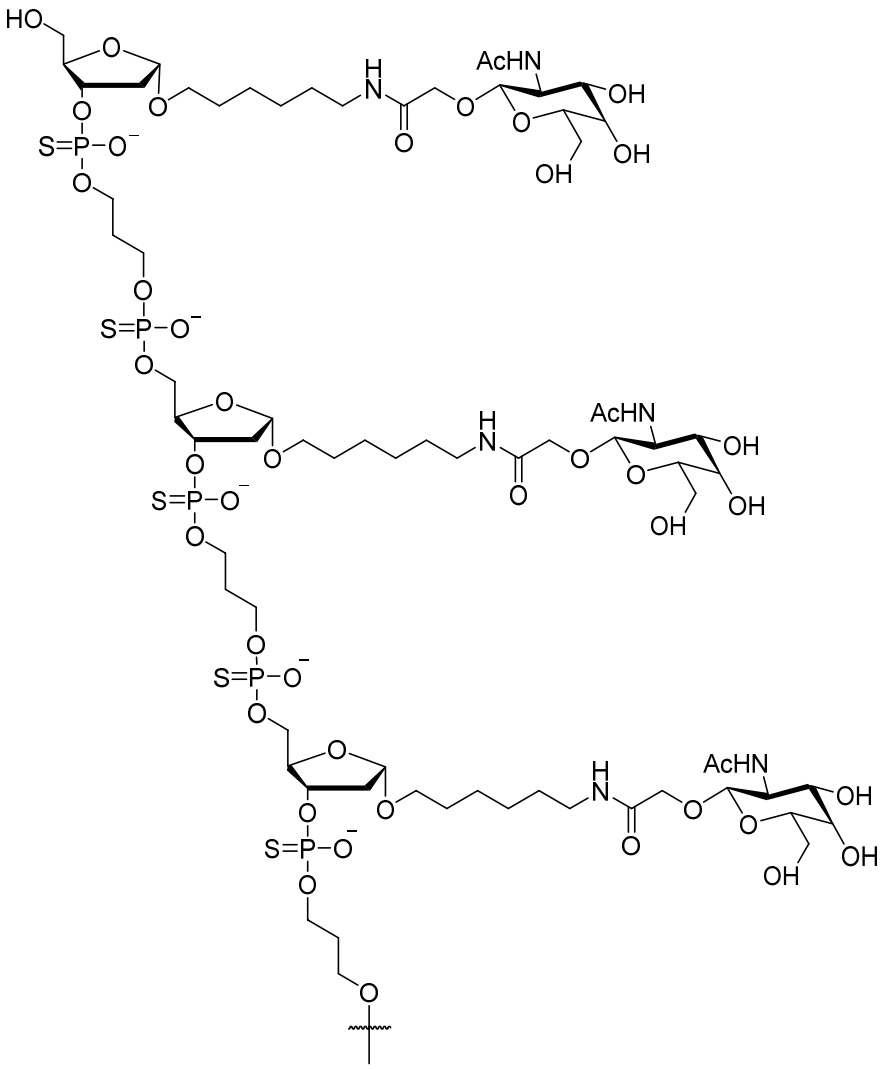
(G15);



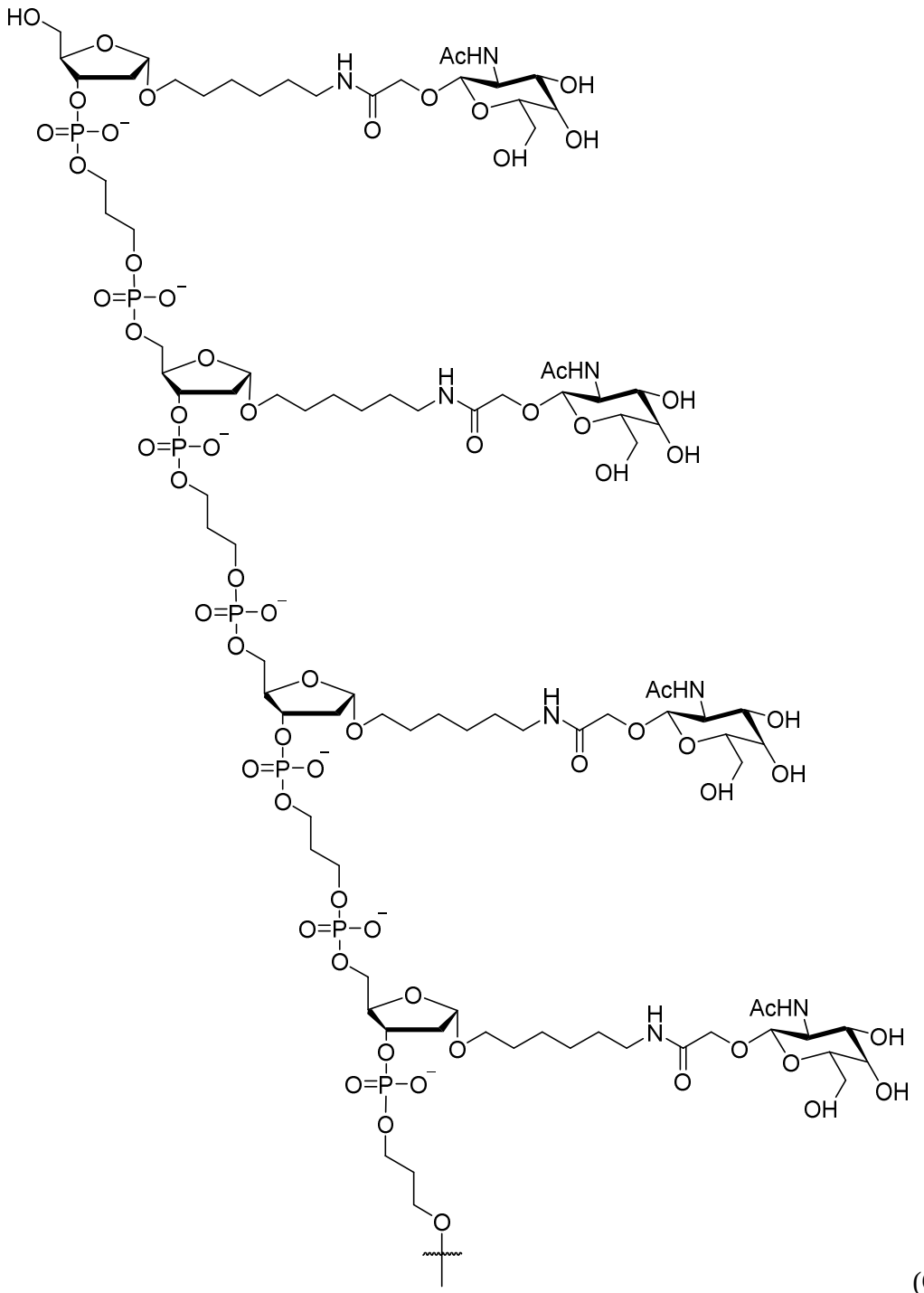
(G16);



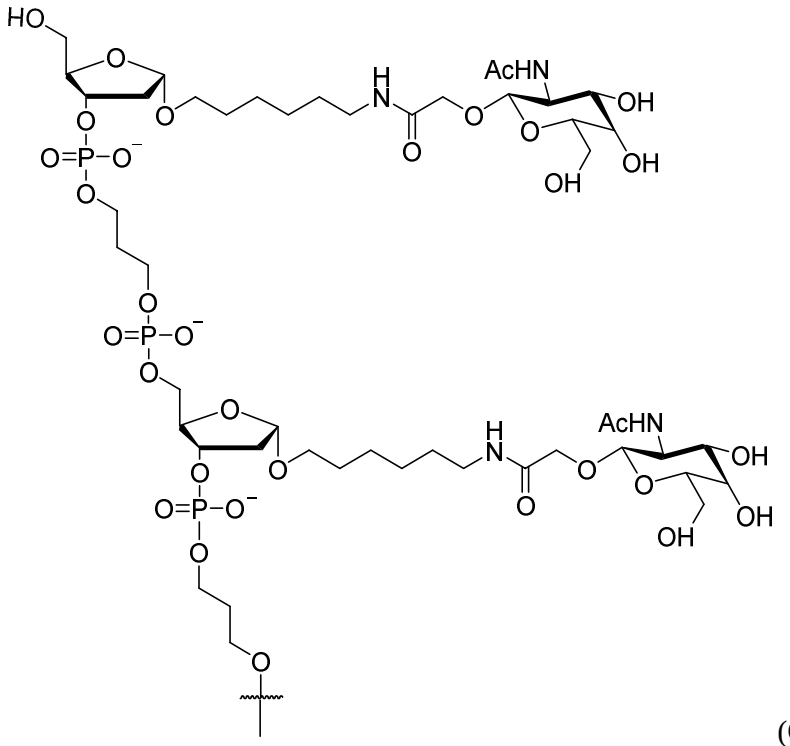
(G17);



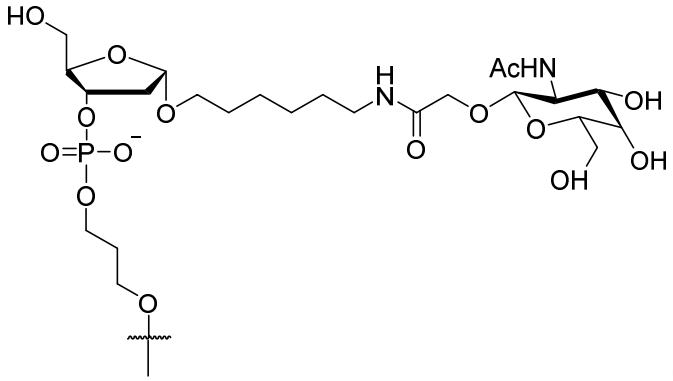
(G18);



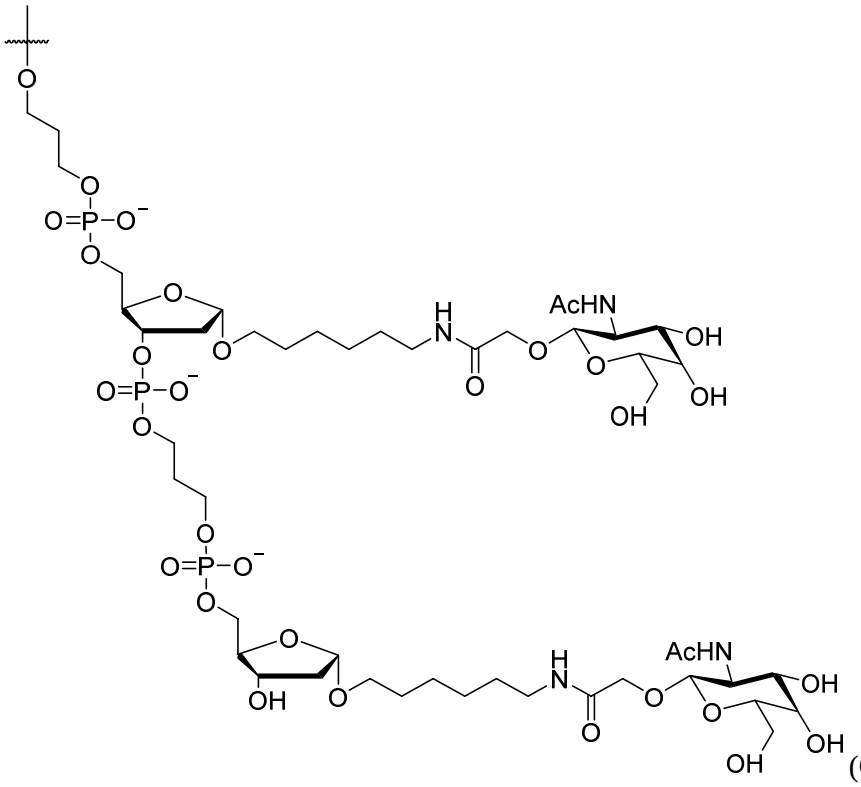
(G19);

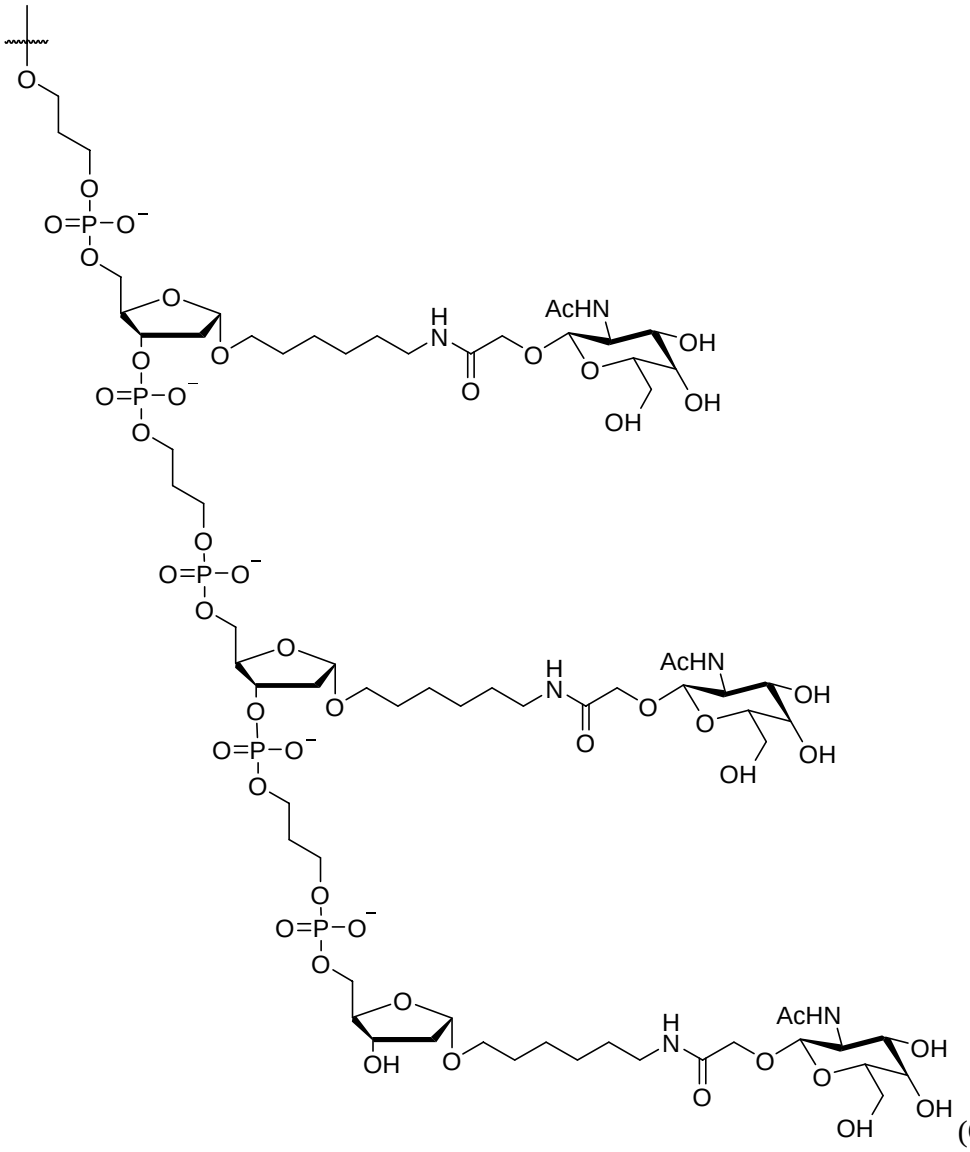


(G20);



(G21);


(G22);


O
O=P−O⁻
O
O
O=P−O⁻
O
O
O=P−O⁻
O
O
O=P−O⁻
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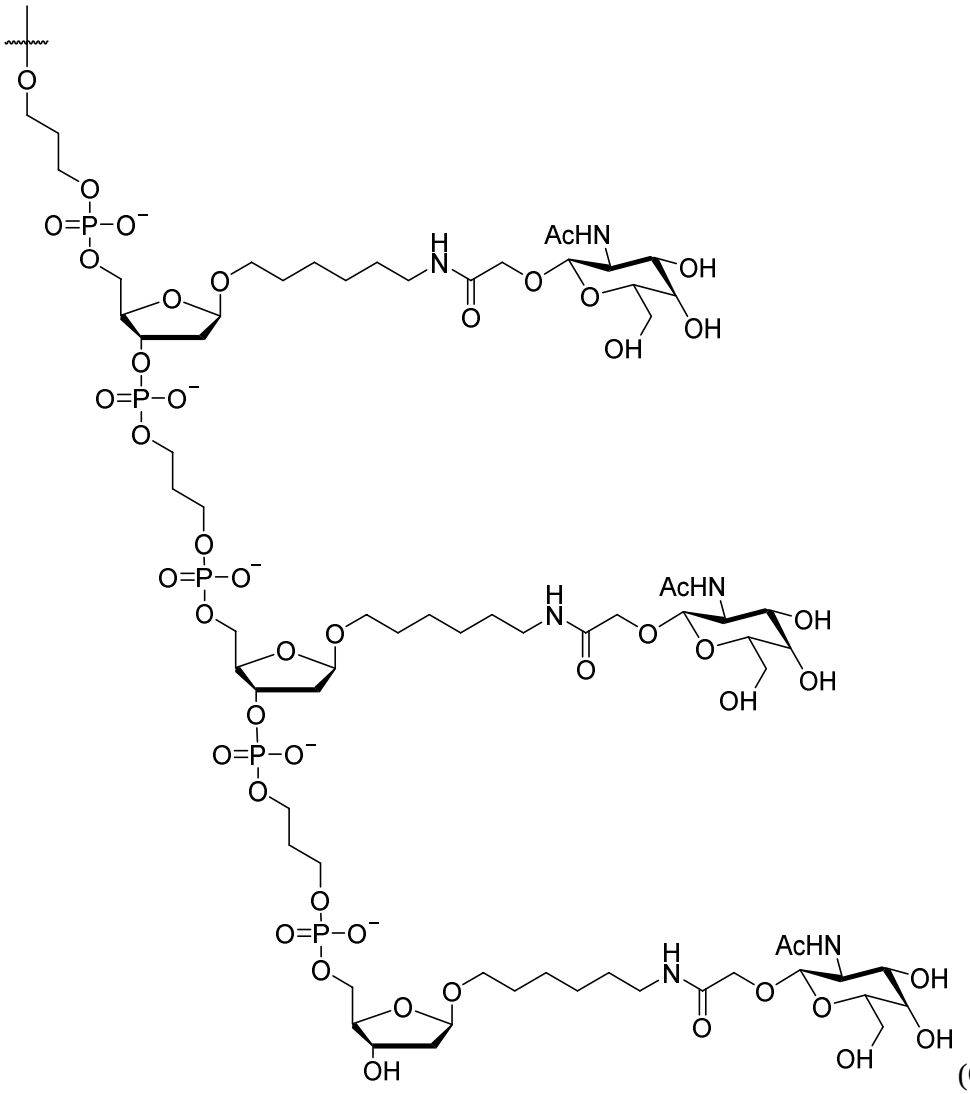
OH
OH
OH
O
O
O



(G24).

8. A conjugate comprising an oligonucleotide and the GalNAc moiety of anyone of claims 2-7, wherein the oligonucleotide regulates the expression of a target gene, and wherein the oligonucleotide and the GalNAc moiety are connected by a bond or a cleavable linker.

9. The conjugate of claim 8, wherein the oligonucleotide and the GalNAc moiety are connected by a cleavable linker.

10. The conjugate of claim 9, wherein the linker is C6ssC6 or dT.

11. The conjugate of claim 8, wherein the oligonucleotide and the GalNAc moiety are connected by a bond, wherein the bond is a phosphodiester bond or a phosphorothioate bond.

12. The conjugate of claim 8, wherein the conjugate comprises a structure of CJ7, CJ8, CJ9, CJ10, CJ11, CJ12, CJ13, CJ14, CJ15, CJ16, CJ17, CJ18, CJ19, CJ20, CJ21, CJ22, CJ23, CJ24, or CJ25.

13. The conjugate of any of claims 8-12, wherein the oligonucleotide is a synthetic isolated small activating RNA (saRNA).

14. The conjugate of claim 13, wherein the target gene is CEBPA.

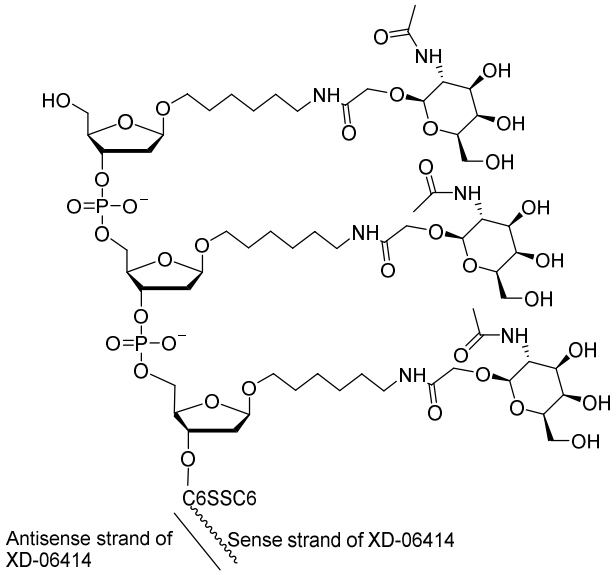
15. The conjugate of claim 13, wherein saRNA is a double-stranded saRNA.

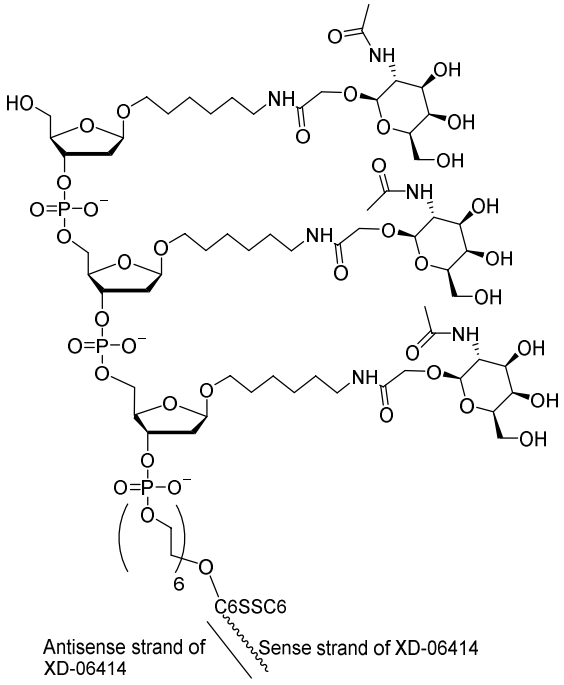
16. The conjugate claim 15, wherein a GalNAc cluster comprising two or more GalNAc monomers is connected to the 5' or 3' end of the sense strand.

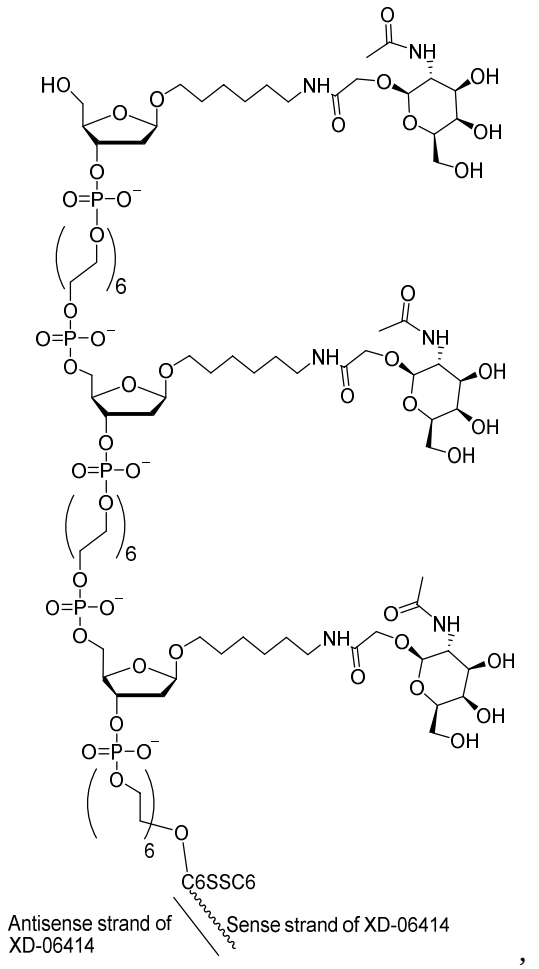
17. The conjugate of claim 15, wherein the double-stranded saRNA is selected from the group consisting of XD-03302 (SEQ ID NO: 2 and SEQ ID NO: 3), S1 (XD-06409) (SEQ ID NO: 4 and SEQ ID NO: 5), S2 (XD-06410) (SEQ ID NO: 6 and SEQ ID NO: 7), S3 (XD-06411) (SEQ ID NO: 8 and SEQ ID NO: 9), S4 (XD-06412) (SEQ ID NO: 10 and SEQ ID NO: 11), S5 (XD-06413) (SEQ ID NO: 12 and SEQ ID NO: 13), S6 (XD-06414) (SEQ ID NO: 14 and SEQ ID NO: 15), S7 (XD-06415) (SEQ ID NO: 16 and SEQ ID NO: 17), S8 (SEQ ID NO: 18 and SEQ ID NO: 19), XD-07139 (SEQ ID NO: 20 and SEQ ID NO: 21), XD-03934 (SEQ ID NO: 22 and SEQ ID NO: 23), and XD-14369K1(SEQ ID NO: 24 and SEQ ID NO: 25).

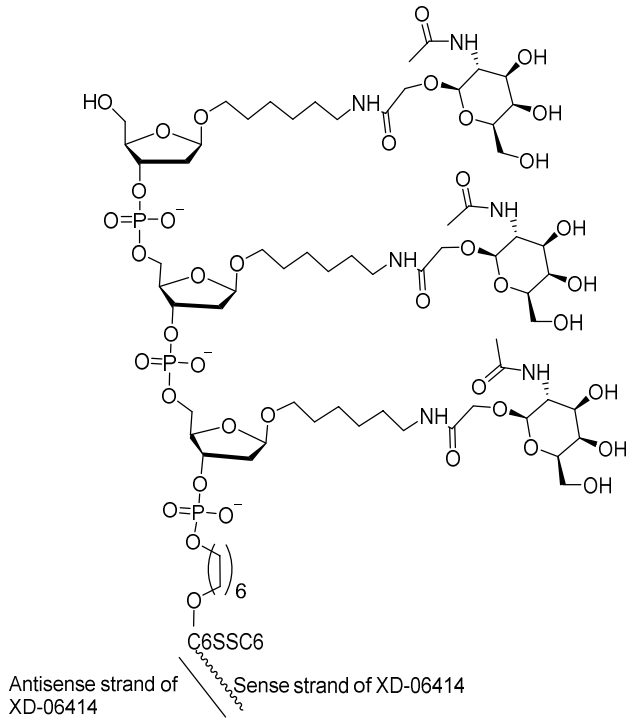
18. The conjugate of claim 15, wherein the saRNA is XD-06414 having an antisense strand comprising SEQ ID NO: 15 and a sense strand comprising SEQ ID NO: 14.

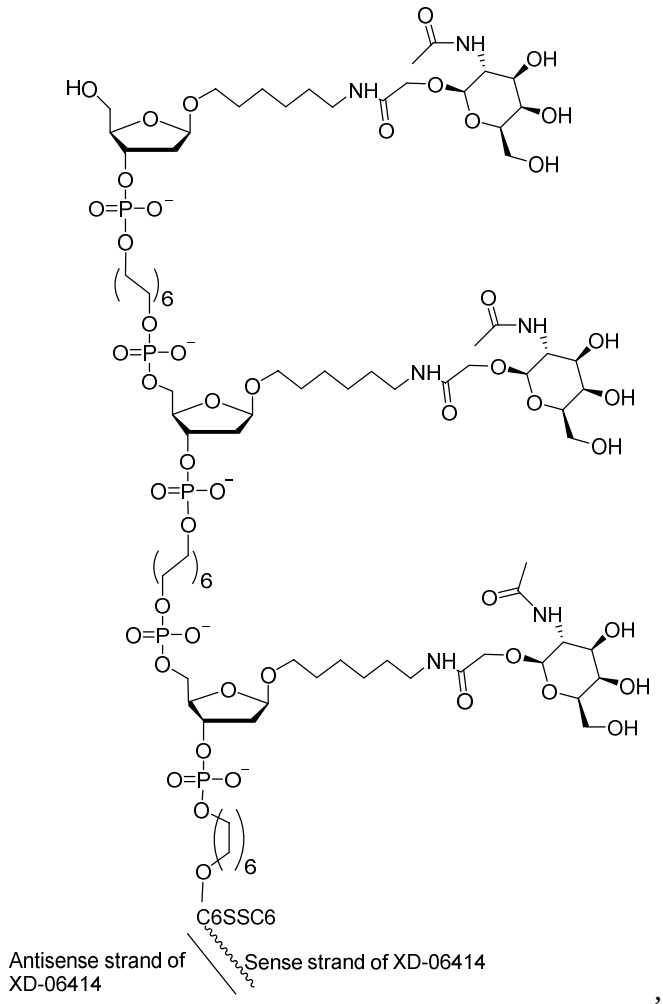
19. The conjugate of claim 18, wherein the conjugate is selected from the group consisting of,

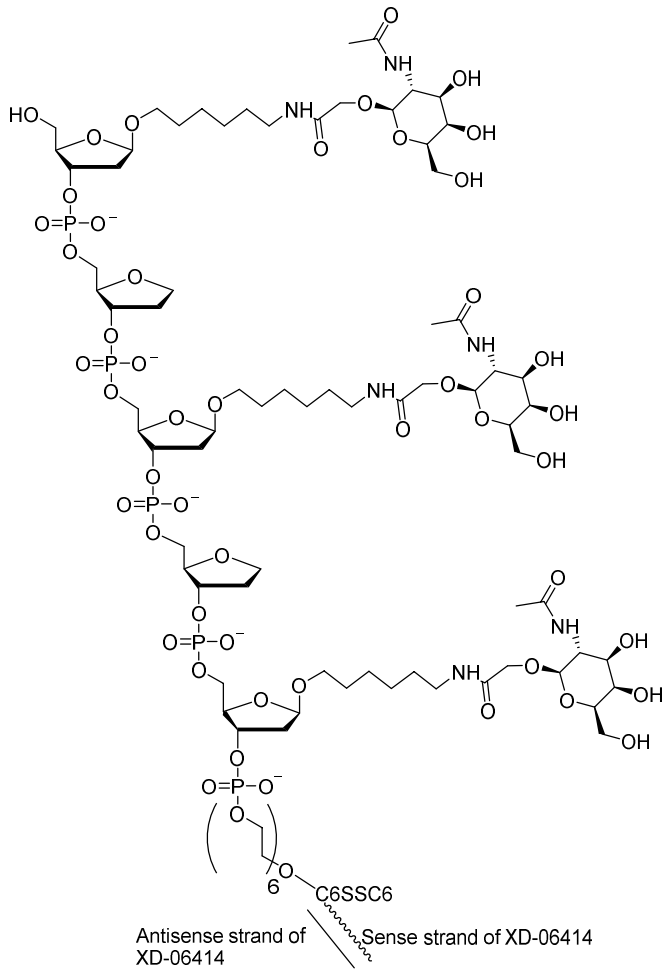
L14: 
C6SSC6
Antisense strand of XD-06414
Sense strand of XD-06414
,

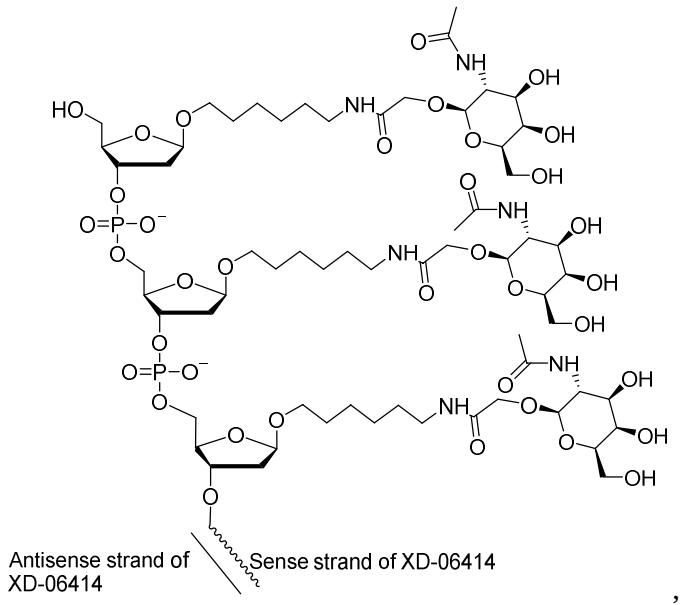
L15: 
6
C6SSC6
Antisense strand of XD-06414
Sense strand of XD-06414
,

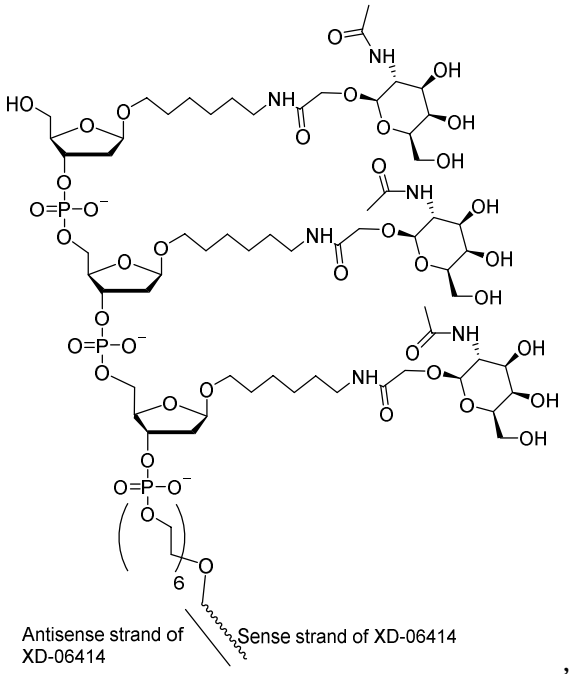
L16: 
Antisense strand of XD-06414
Sense strand of XD-06414
C6SSC6
,

L17: 
Antisense strand of XD-06414
Sense strand of XD-06414
C6SSC6
,

L18: 
C6SSC6
Antisense strand of XD-06414
Sense strand of XD-06414
,

L19: 
Antisense strand of XD-06414
Sense strand of XD-06414
C6SSC6
,

L53: 
Antisense strand of XD-06414
Sense strand of XD-06414
,

L54: 

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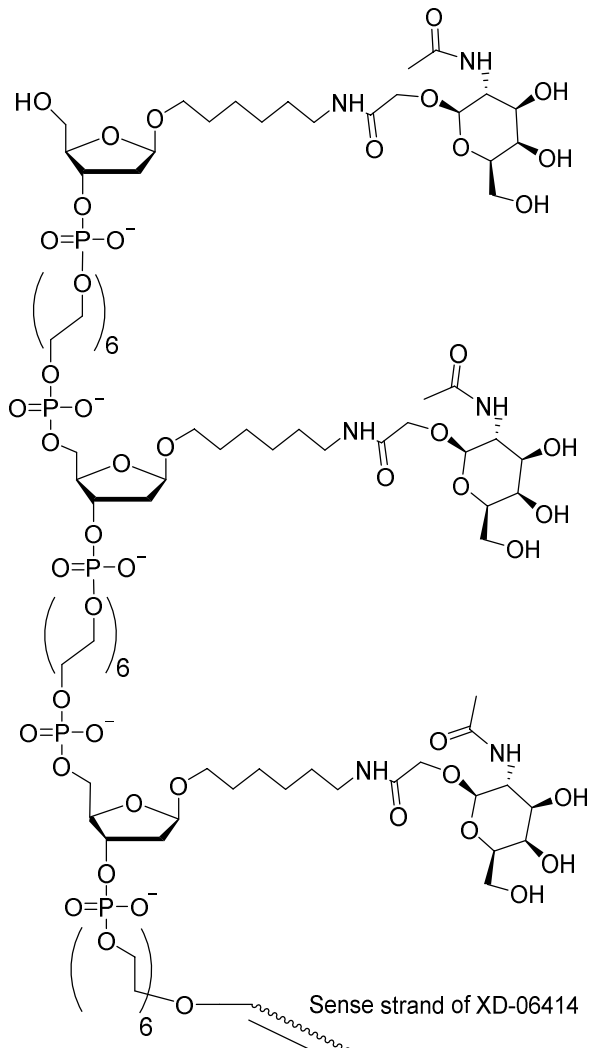
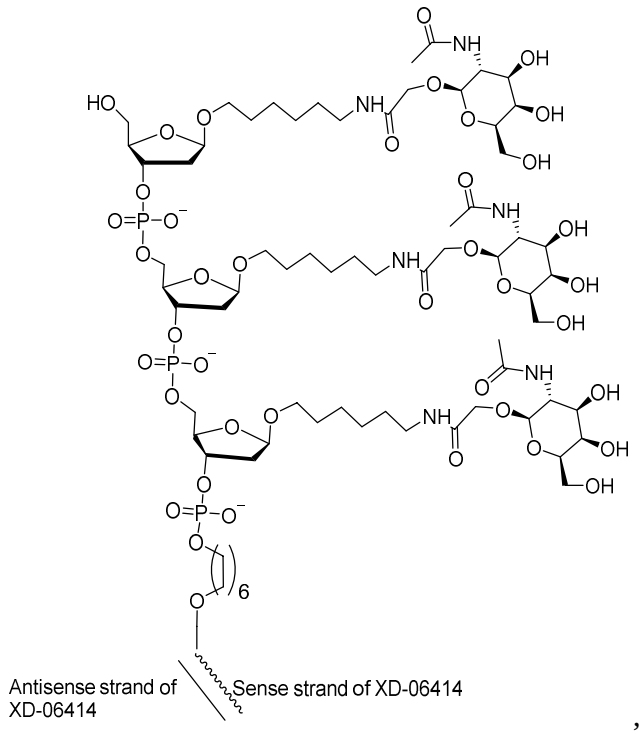
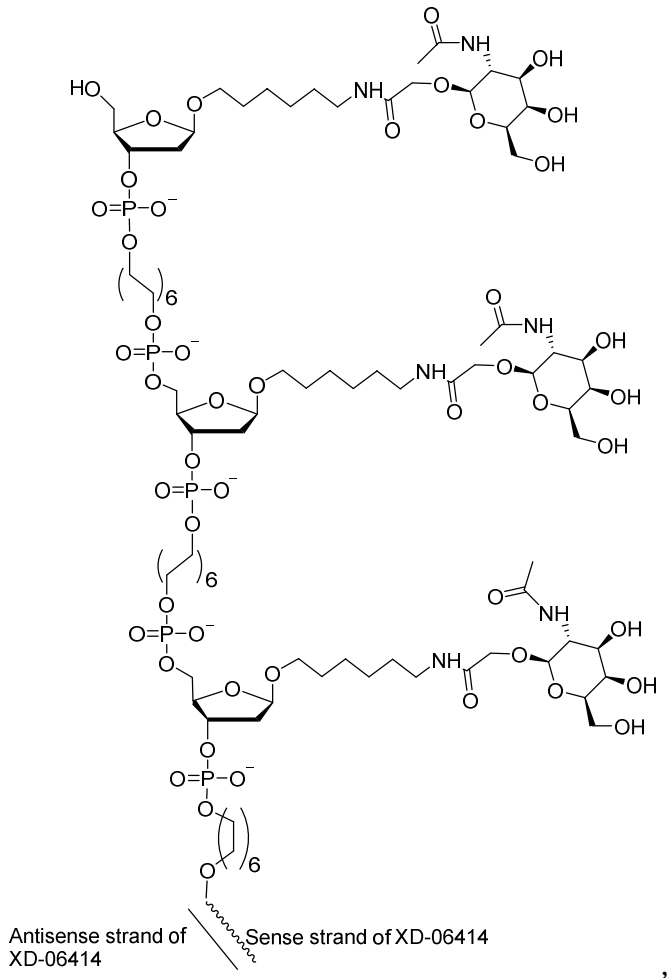
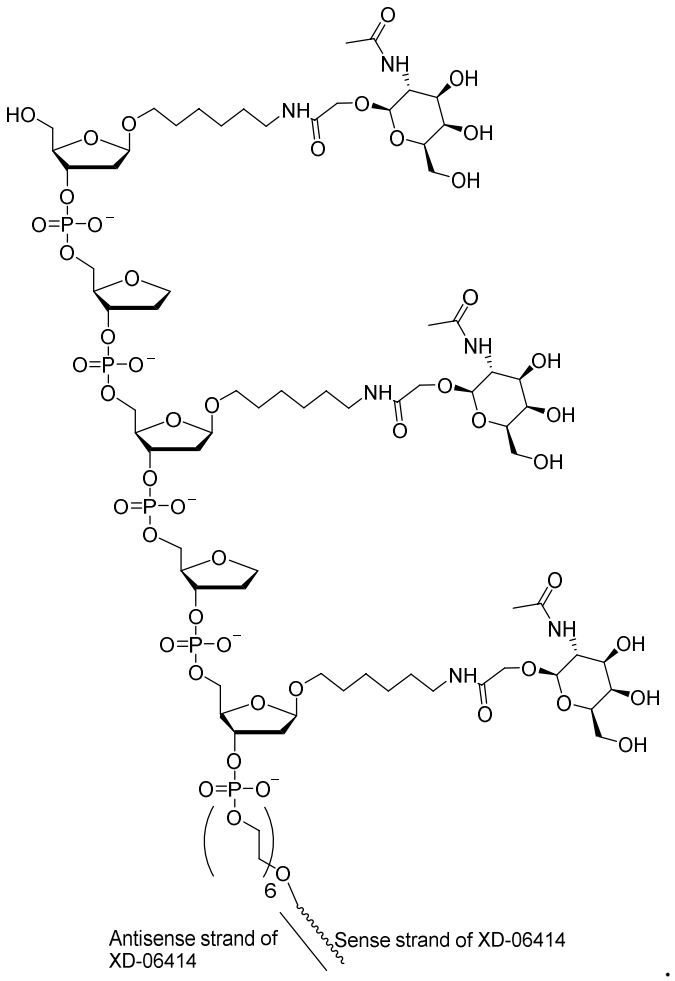

HO
O
NH
OH
O=P–O⁻
6
Sense strand of XD-06414
Antisense strand of XD-06414

L55: ,

L56: 
Antisense strand of XD-06414
Sense strand of XD-06414
,

L57: 
Antisense strand of XD-06414
Sense strand of XD-06414
, and

L58: 

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20. The conjugate of claim 18, wherein the conjugate is L53.

21. The conjugate of claim 18, wherein the conjugate is L55.

22. The conjugate of any of claims 8-12, wherein the oligonucleotide is a synthetic isolated small inhibiting RNA (siRNA).

23. The conjugate of claim 22, wherein siRNA is a double-stranded siRNA.

24. The conjugate of claim 23, wherein a GalNAc cluster comprising two or more GalNAc monomers is connected to the 5’ or 3’ end of the sense strand.

25. A method for preparing a conjugate according to any one of claims 8 to 24, comprising the steps of:
1). providing at least one GalNAc monomer selected from the group consisting of M1', M2', M4' and M5' ; optionally adding at least one spacer;
2). providing at least one oligonucleotide; optionally adding at least one linker;
and
3). synthesizing the conjugate from the GalNAc monomer(s) in step 1) and the oligonucleotide(s) in step 2), optionally removing the protecting groups.

26. The conjugate of claim 25, wherein the oligonucleotide is an saRNA.

27. The conjugate of claim 26, wherein the saRNA is selected from the group consisting of XD-03302 (SEQ ID NO: 2 and SEQ ID NO: 3), S1 (XD-06409) (SEQ ID NO: 4 and SEQ ID NO: 5), S2 (XD-06410) (SEQ ID NO: 6 and SEQ ID NO: 7), S3 (XD-06411) (SEQ ID NO: 8 and SEQ ID NO: 9), S4 (XD-06412) (SEQ ID NO: 10 and SEQ ID NO: 11), S5 (XD-06413) (SEQ ID NO: 12 and SEQ ID NO: 13), S6 (XD-06414) (SEQ ID NO: 14 and SEQ ID NO: 15), S7 (XD-06415) (SEQ ID NO: 16 and SEQ ID NO: 17), S8 (SEQ ID NO: 18 and SEQ ID NO: 19), XD-07139 (SEQ ID NO: 20 and SEQ ID NO: 21), XD-03934 (SEQ ID NO: 22 and SEQ ID NO: 23), and XD-14369K1 (SEQ ID NO: 24 and SEQ ID NO: 25).

28. The conjugate of claim 25, wherein the oligonucleotide is an siRNA.

29. A pharmaceutical composition comprising the conjugate of any one of claims 8-28 and at least one pharmaceutically acceptable excipient.

30. The pharmaceutical composition of claim 29, wherein the conjugate comprises an saRNA.

31. The pharmaceutical composition of claim 29, wherein the conjugate comprises an siRNA.

32. The conjugate of any one of claims 8-28 for use as a medicament.