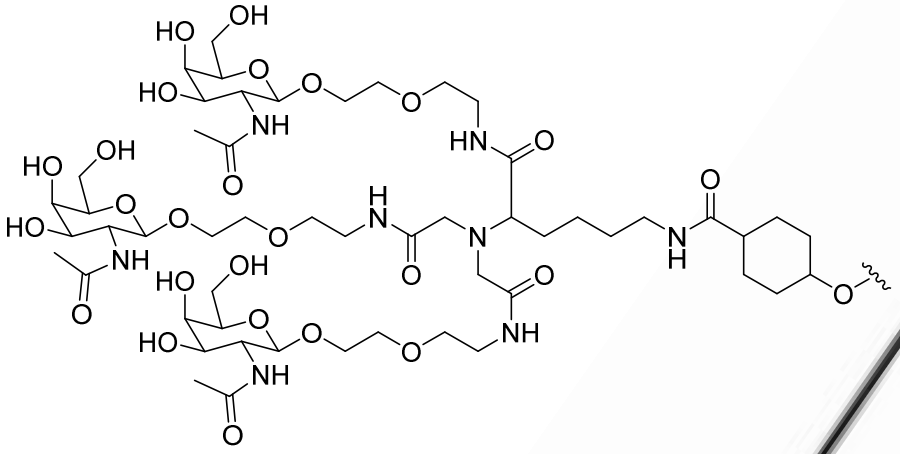
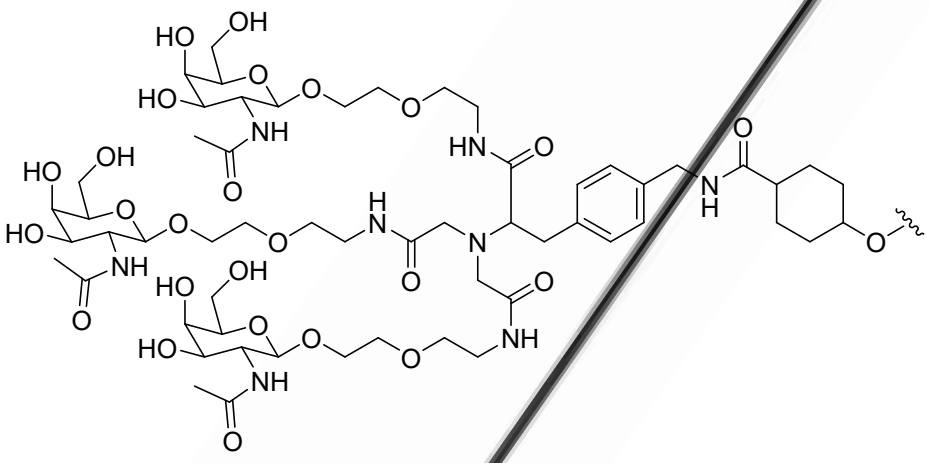
Claims

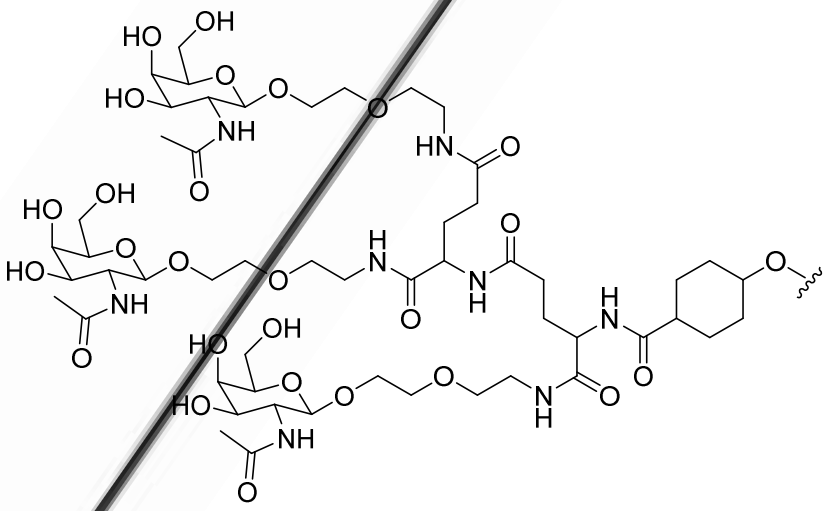
1. A targeting ligand comprising a structure selected from the group consisting of:



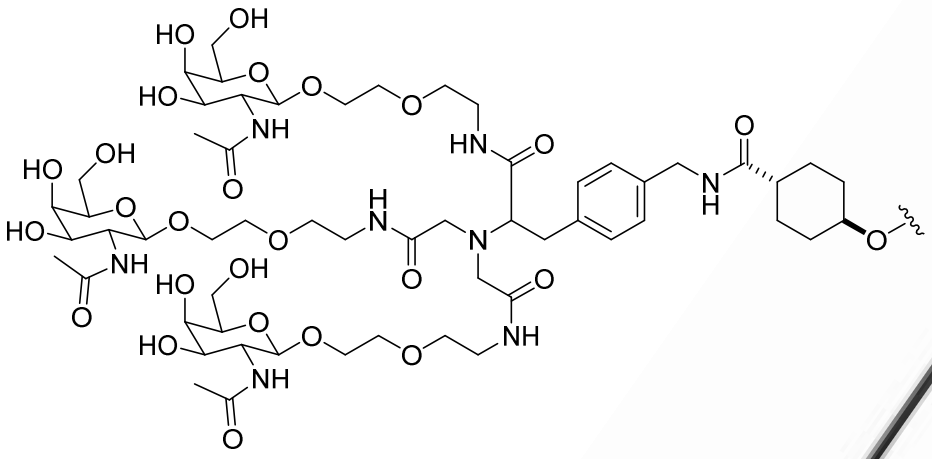
(Structure 1001);



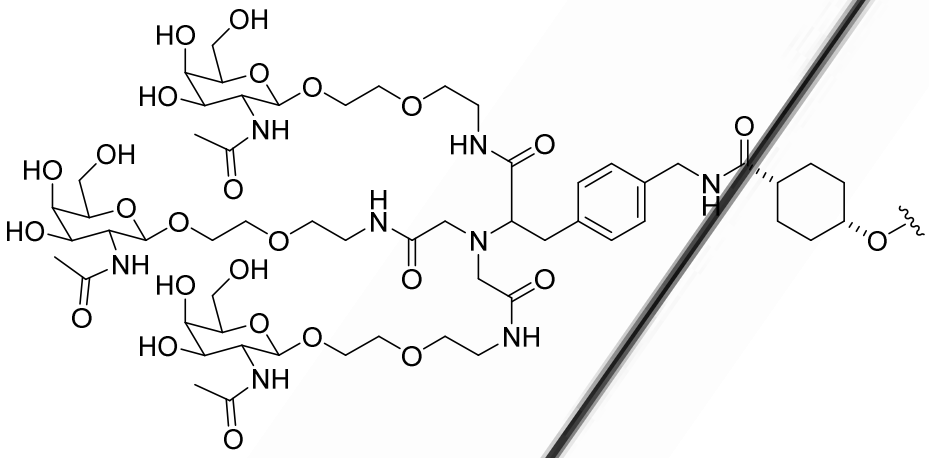
(Structure 1002);



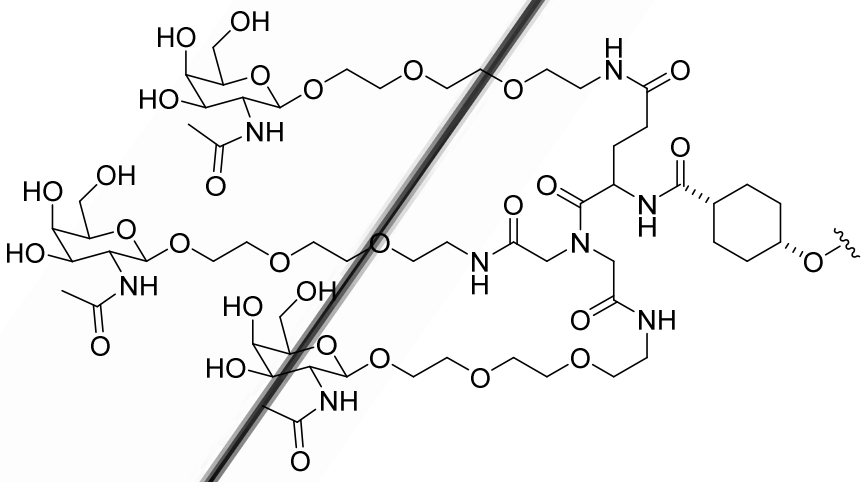
(Structure 1003);



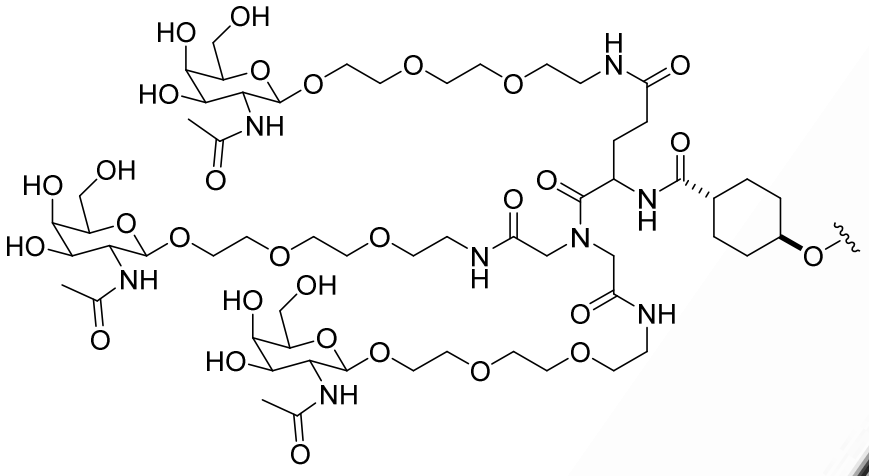
(Structure 1004);



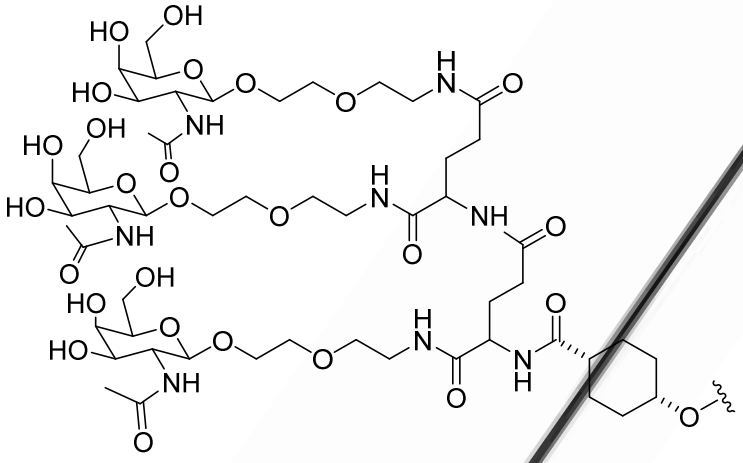
(Structure 1005);



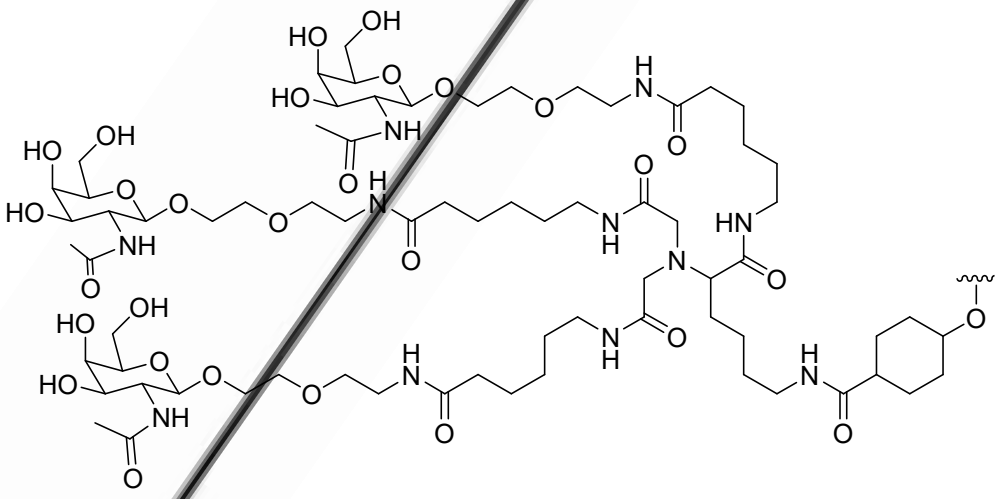
(Structure 1006);



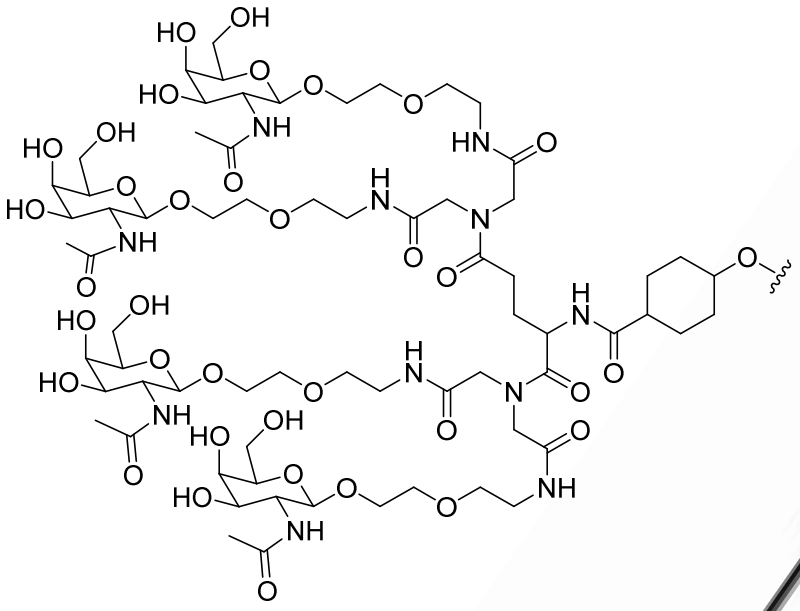
(Structure 1007);



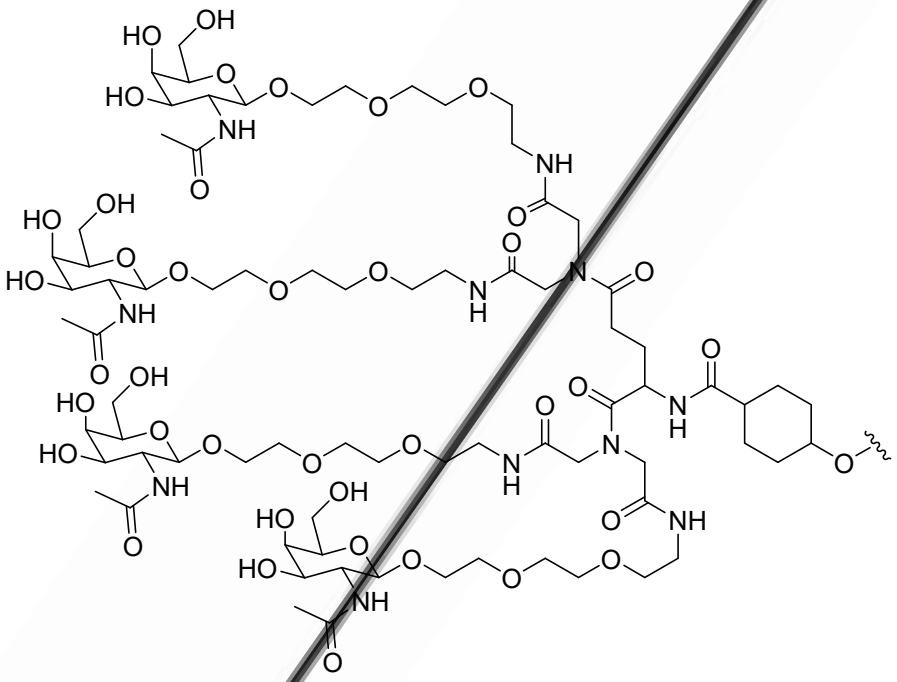
(Structure 1008);



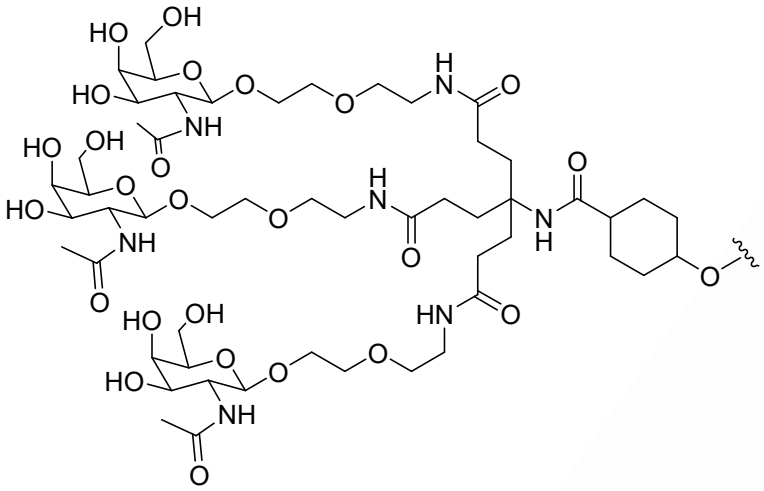
(Structure 1009);



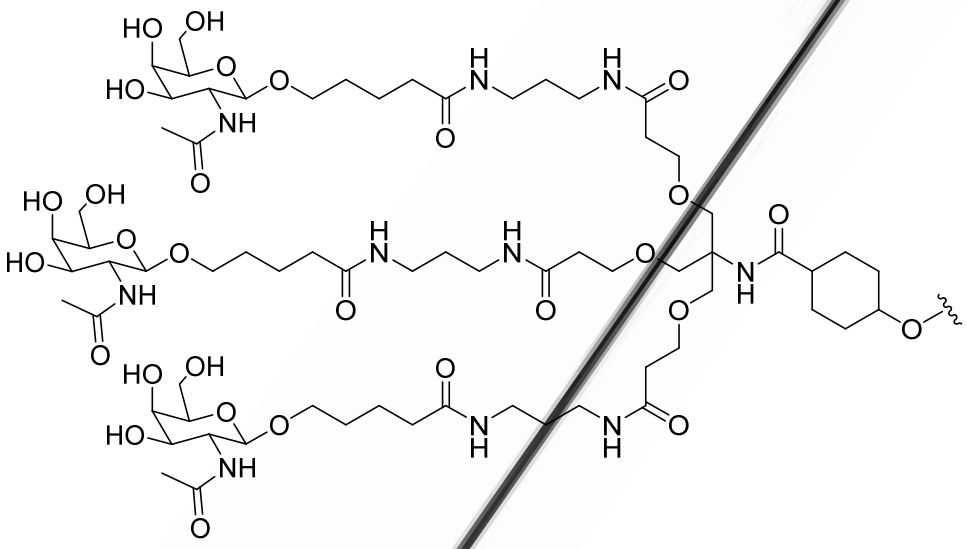
(Structure 1012);



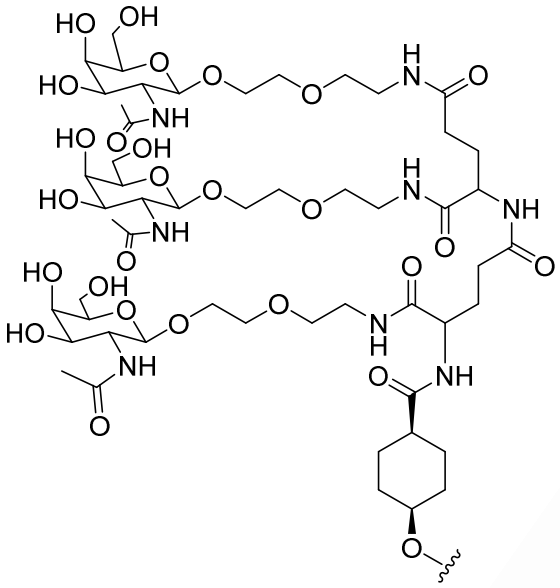
(Structure 1014);



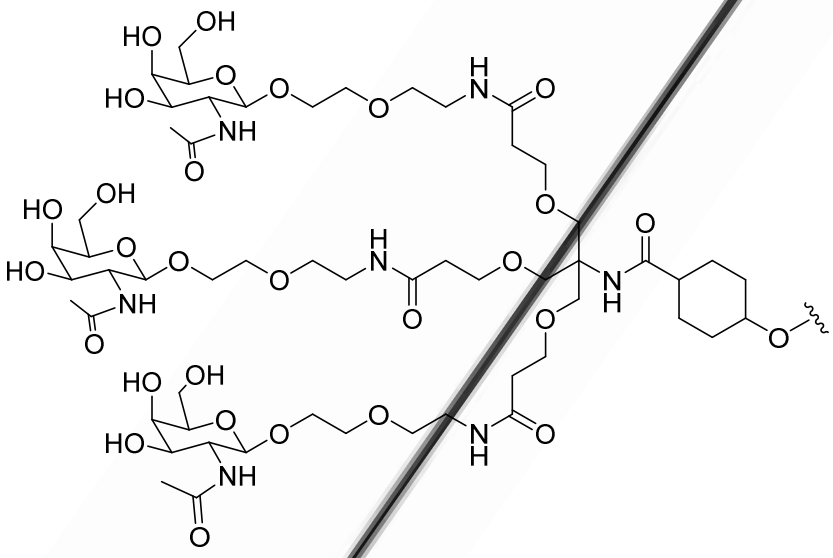
(Structure 1016);



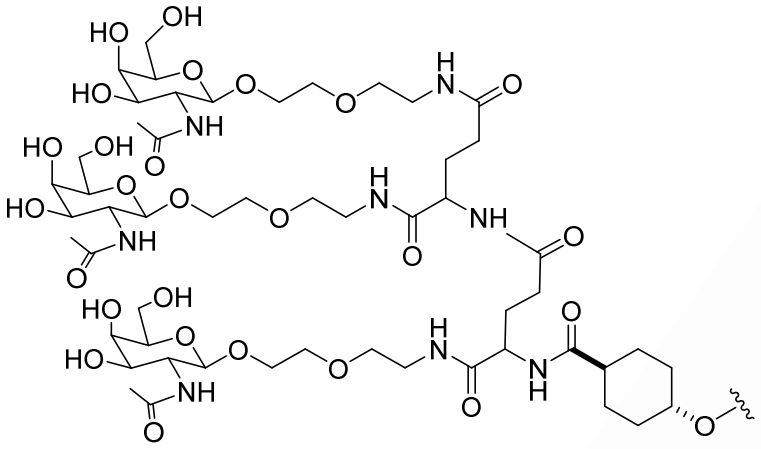
(Structure 1018);



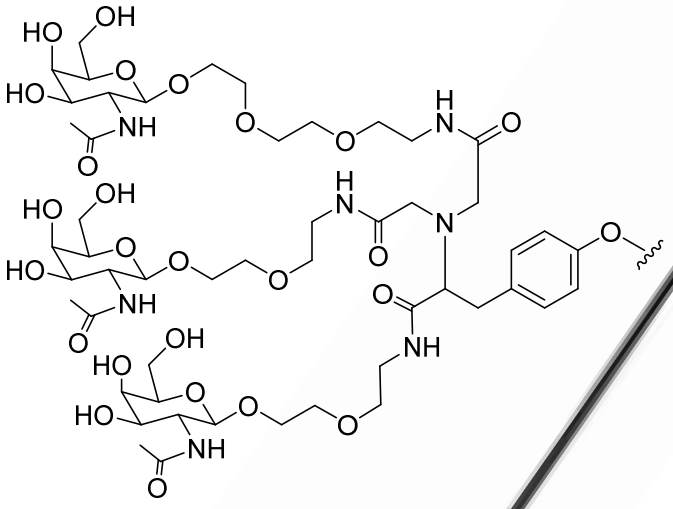
(Structure 1019);



(Structure 1021);



(Structure 1023); and



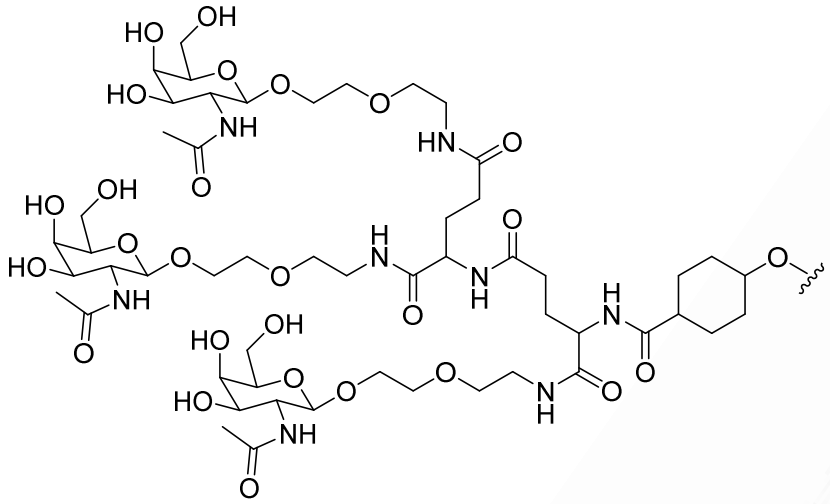
(Structure 1024),

wherein the targeting ligand is linked to an RNAi agent.

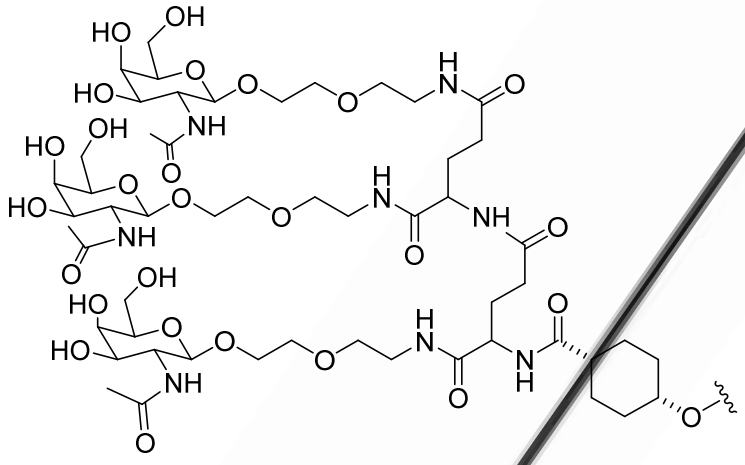
2. The targeting ligand of claim 1, wherein the RNAi agent is double-stranded.

3. The targeting ligand of claim 2, wherein the RNAi agent includes one or more modified nucleotides.

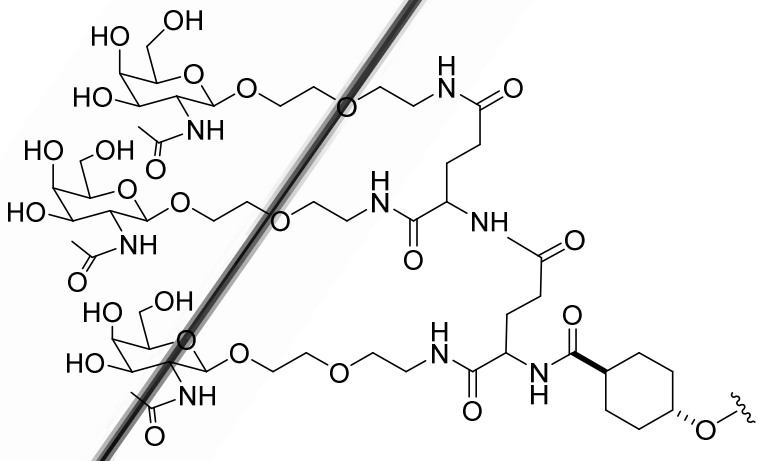
4. The targeting ligand of claim 1, wherein the structure is selected from the group consisting of:



(Structure 1003);



(Structure 1008); and

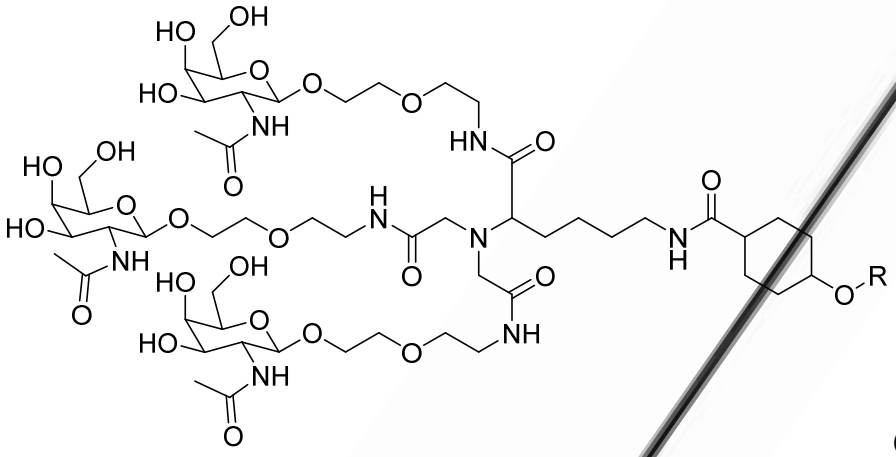


(Structure 1023).

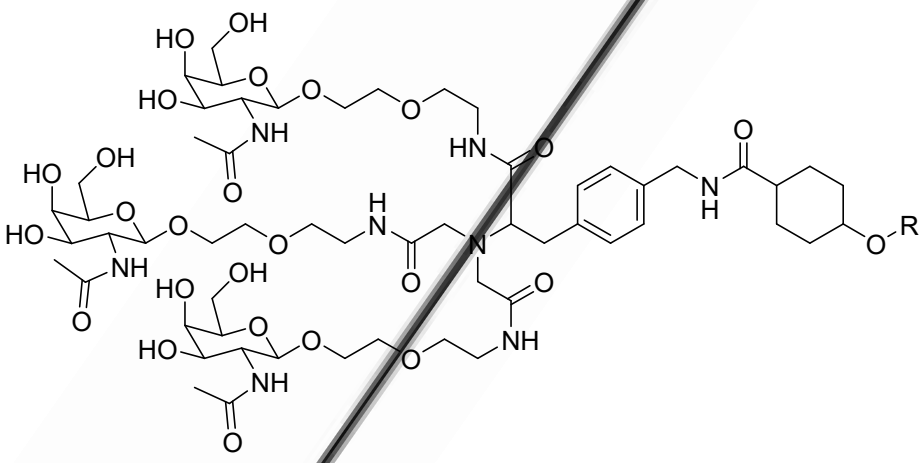
5. The targeting ligand of claim 2, wherein the double-stranded RNAi agent is linked to the targeting ligand at the 5' terminal end of the sense strand of an RNAi agent.

6. The targeting ligand of claim 5, wherein the RNAi agent is linked to the linker of the targeting ligand via a phosphate group, phosphorothioate group, or a phosphonate group.

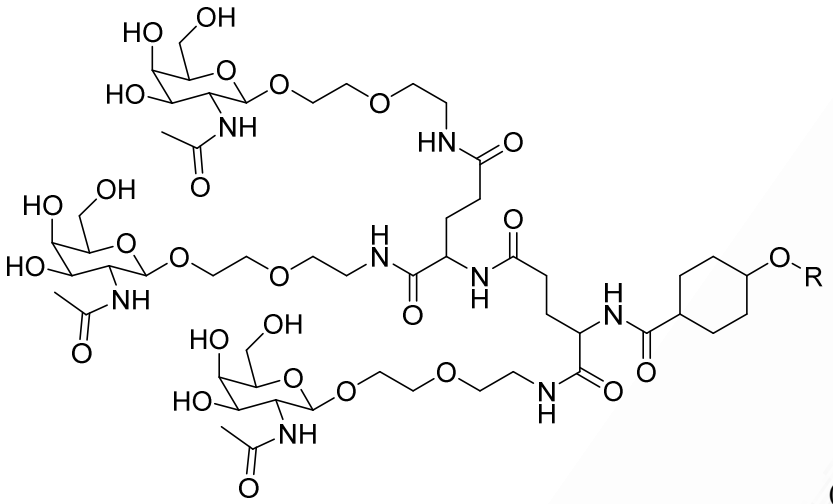
7. A composition comprising a targeting ligand linked to an expression-inhibiting oligomeric compound, wherein the structure of the targeting ligand and expression-inhibiting oligomeric compound is represented by the structure selected from the group consisting of:



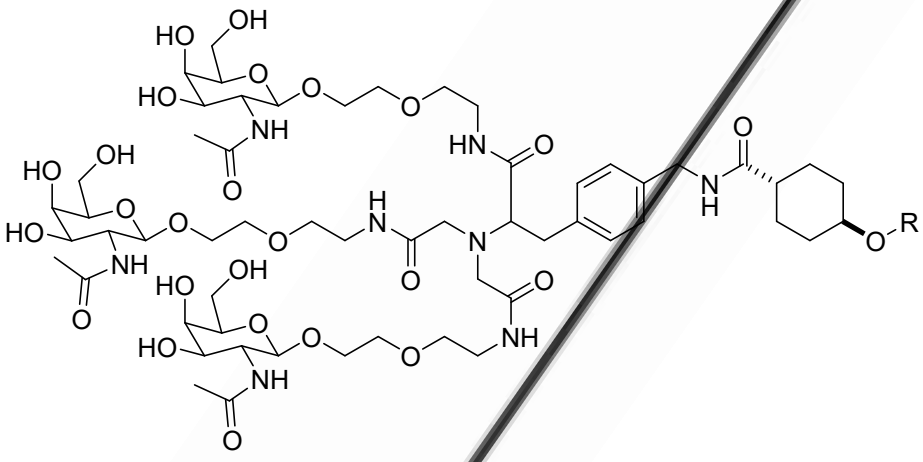
(Structure 1001a);



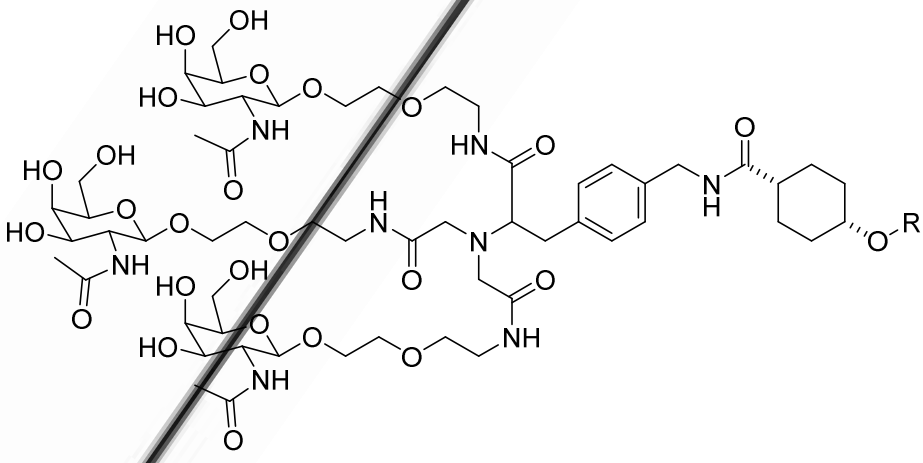
(Structure 1002a);



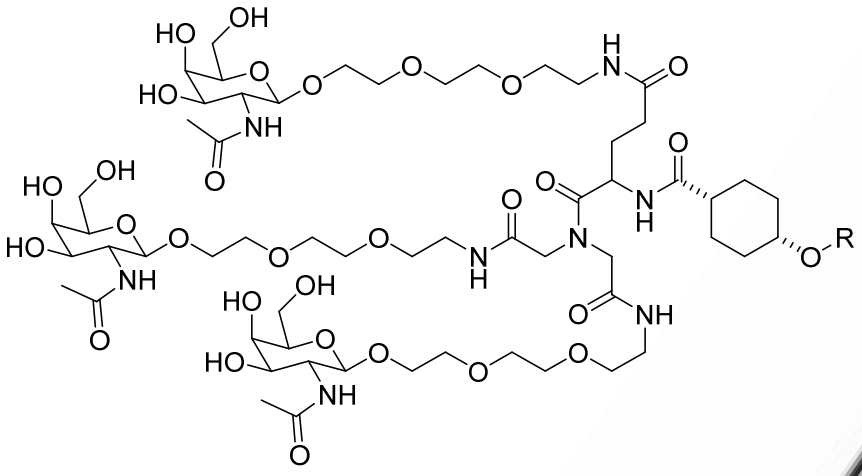
(Structure 1003a);



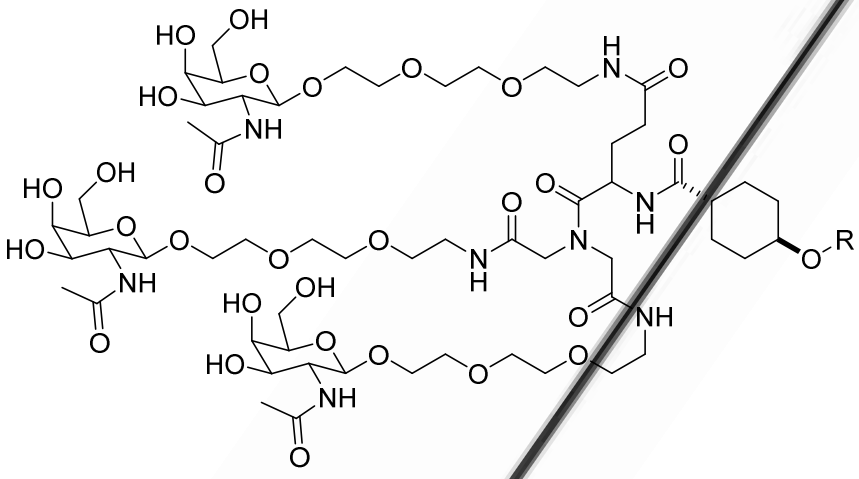
(Structure 1004a);



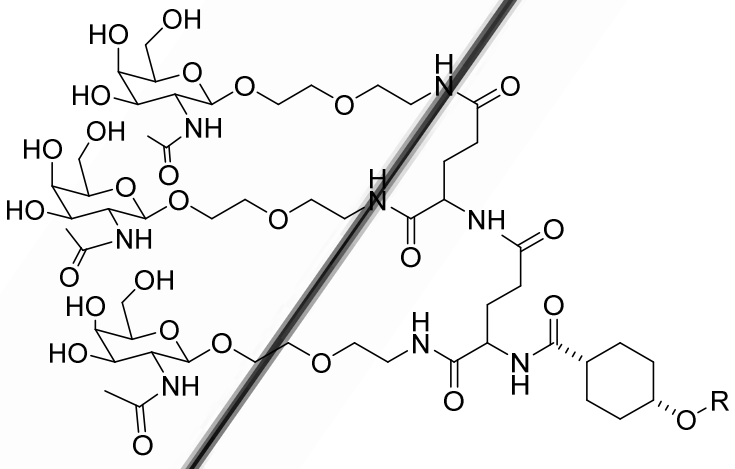
(Structure 1005a);



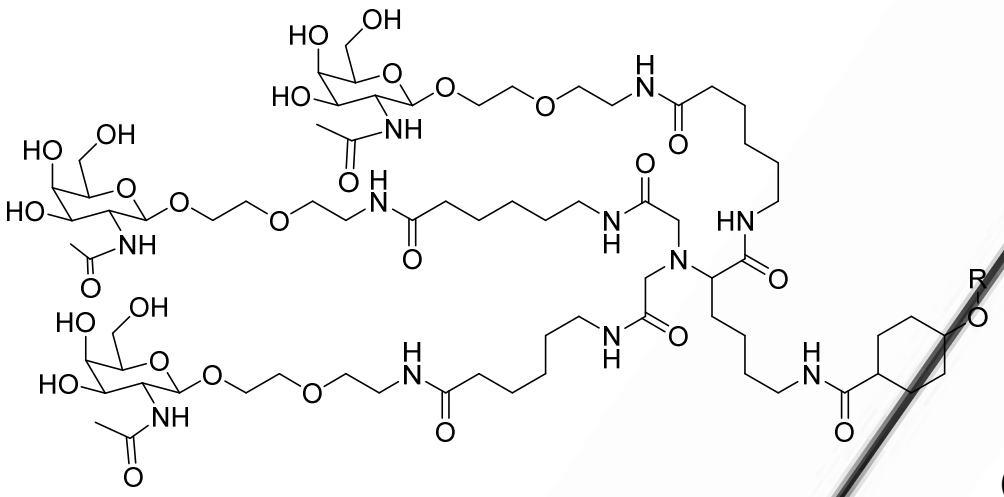
(Structure 1006a);



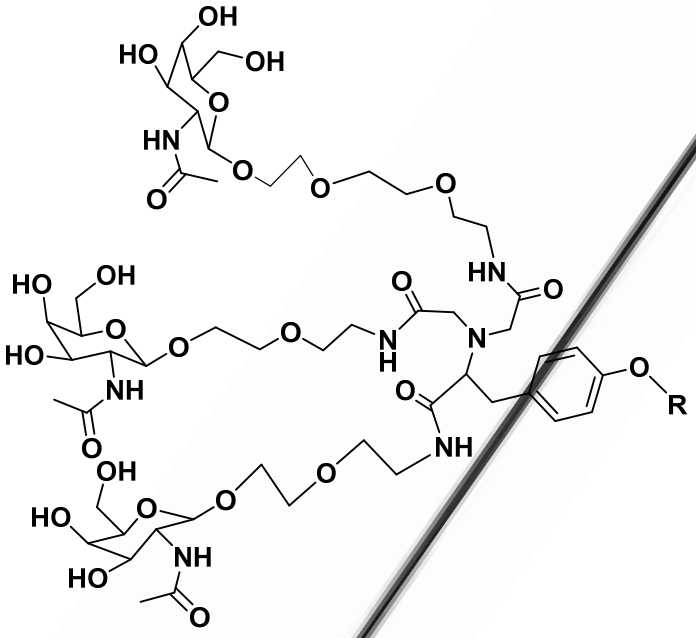
(Structure 1007a);



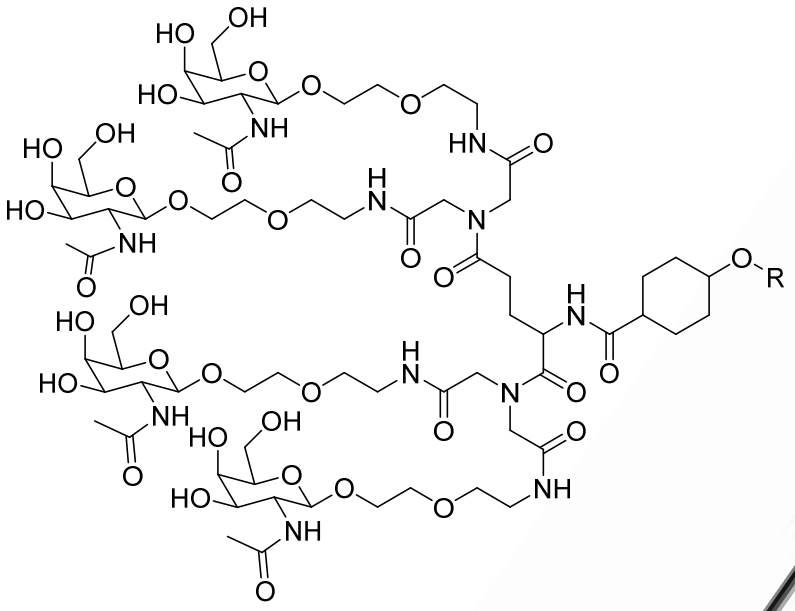
(Structure 1008a);



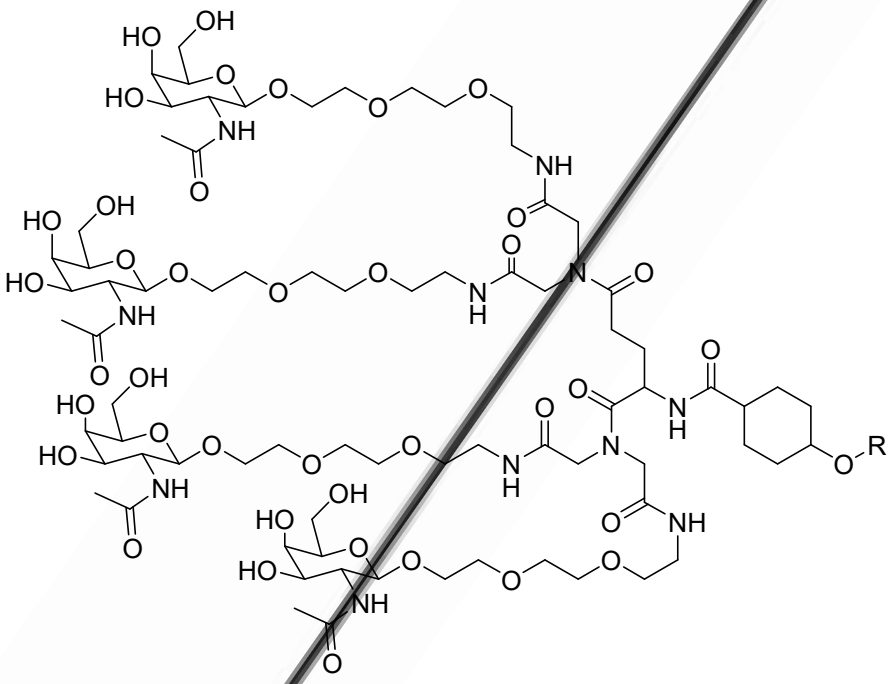
(Structure 1009a);



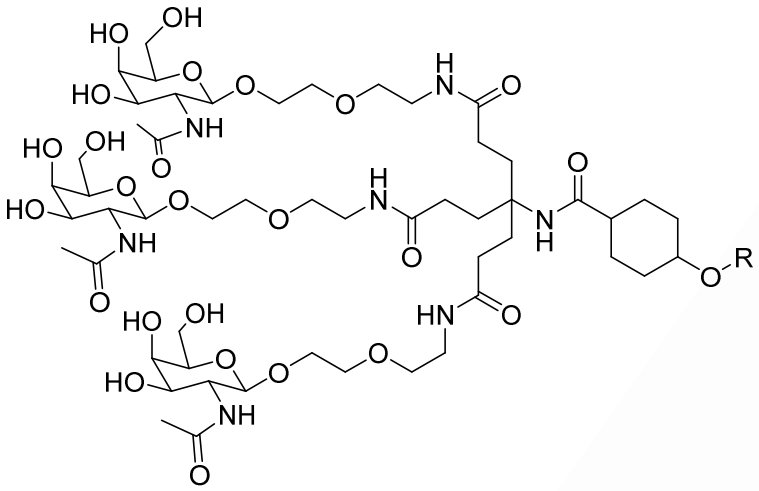
(Structure 1024a);



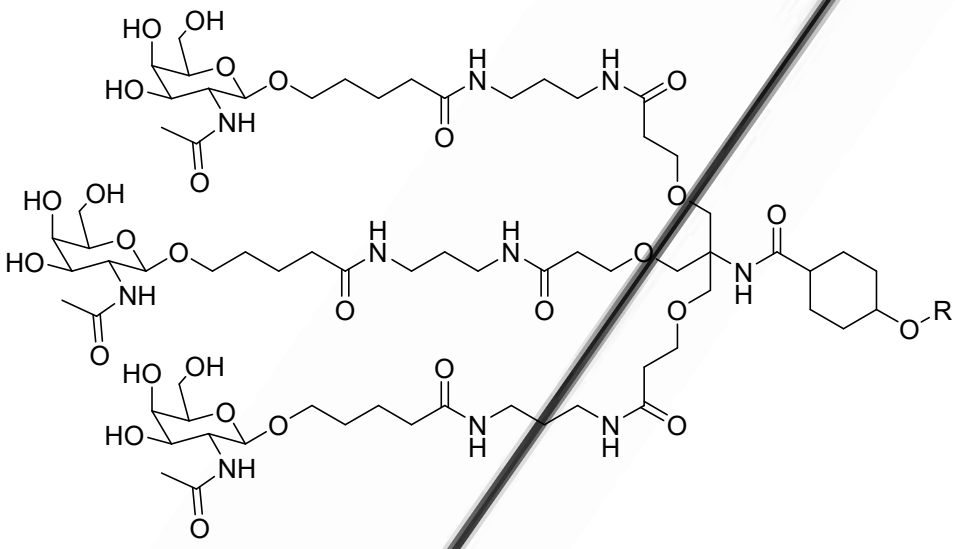
(Structure 1012a);



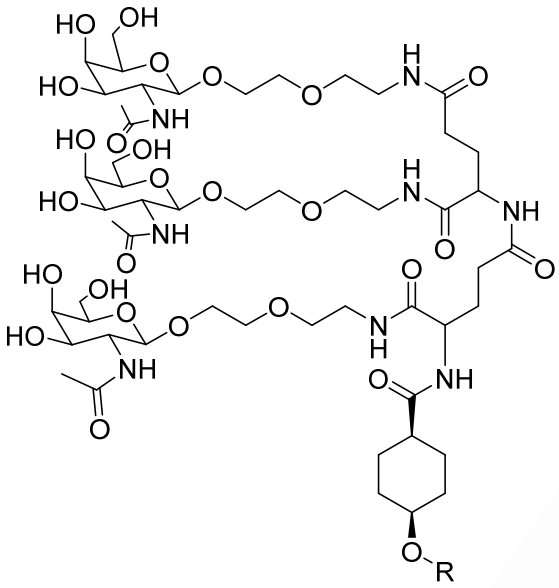
(Structure 1014a);



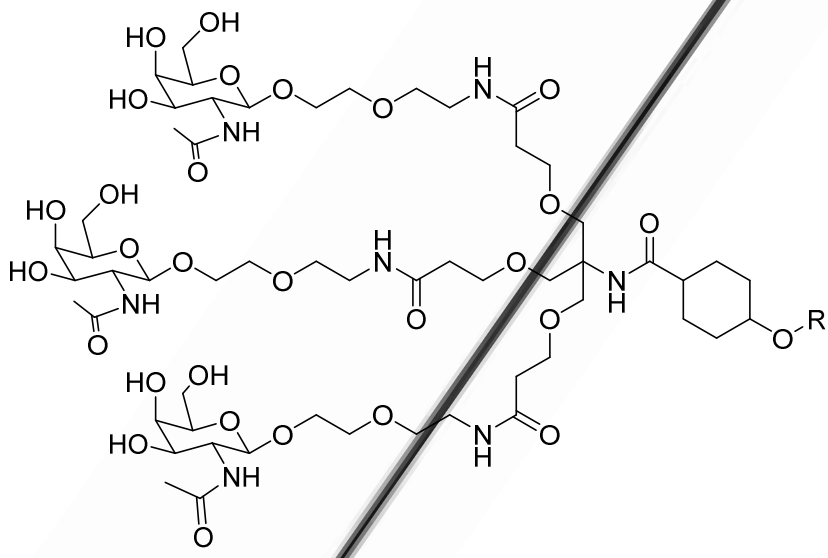
(Structure 1016a);



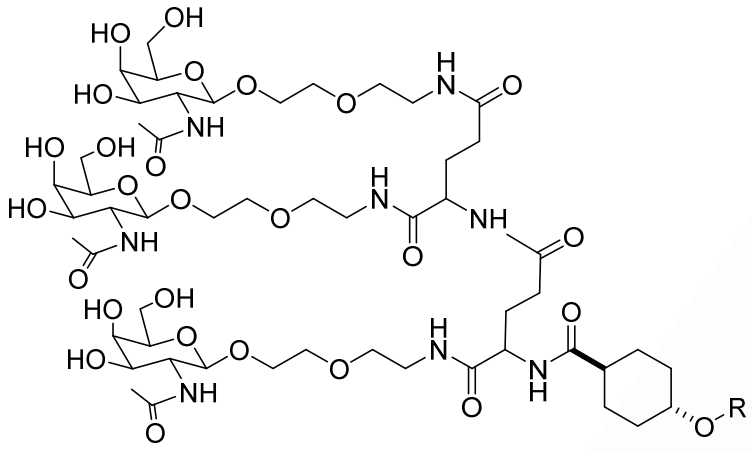
(Structure 1018a);



(Structure 1019a);



(Structure 1021a); and



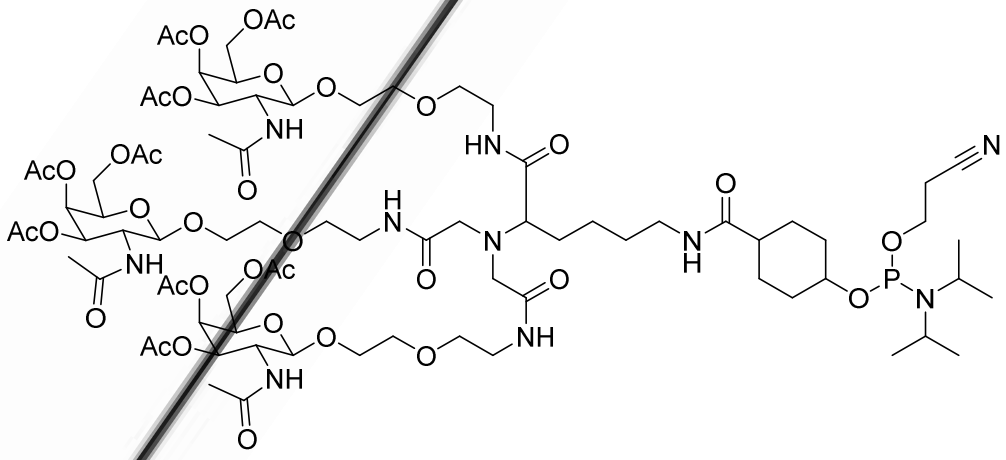
(Structure 1023a);

wherein R in each structure comprises the expression-inhibiting oligomeric compound, wherein the expression-inhibiting oligomeric compound comprises an RNAi agent, and wherein the targeting ligand is linked to the RNAi agent via a phosphate group, phosphorothioate group, or a phosphonate group.

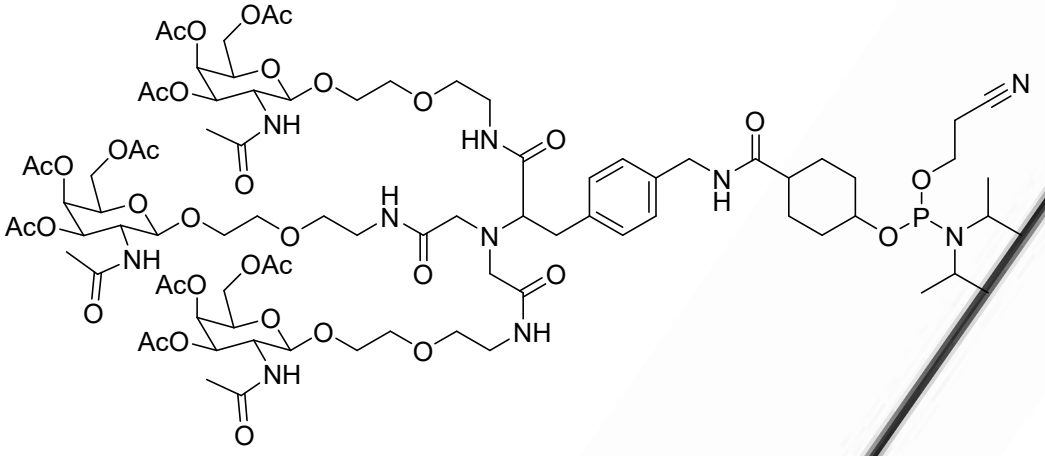
8. The composition of claim 7, wherein the RNAi agent is a double-stranded RNAi agent.

9. The composition of claim 8, wherein the targeting ligand is linked to the 5' terminal end of the sense strand of an RNAi agent.

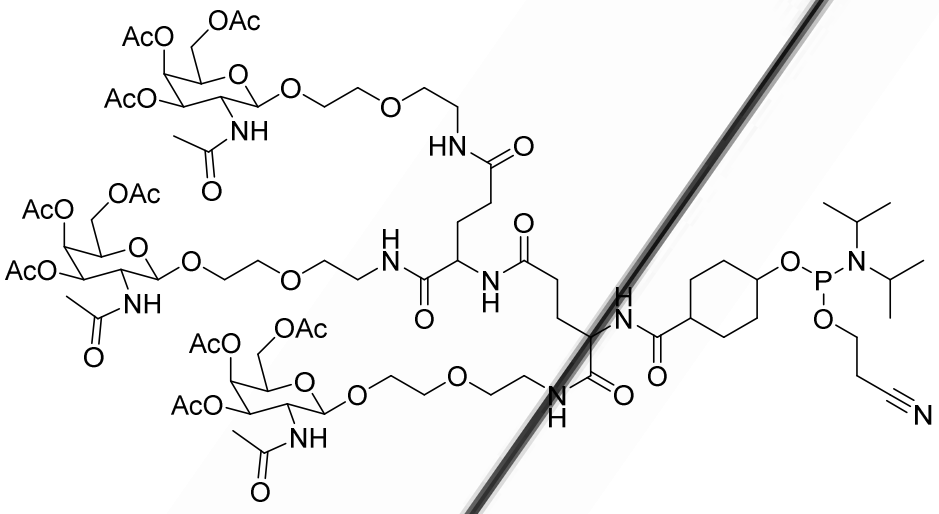
10. A compound having the structure selected from the group consisting of:



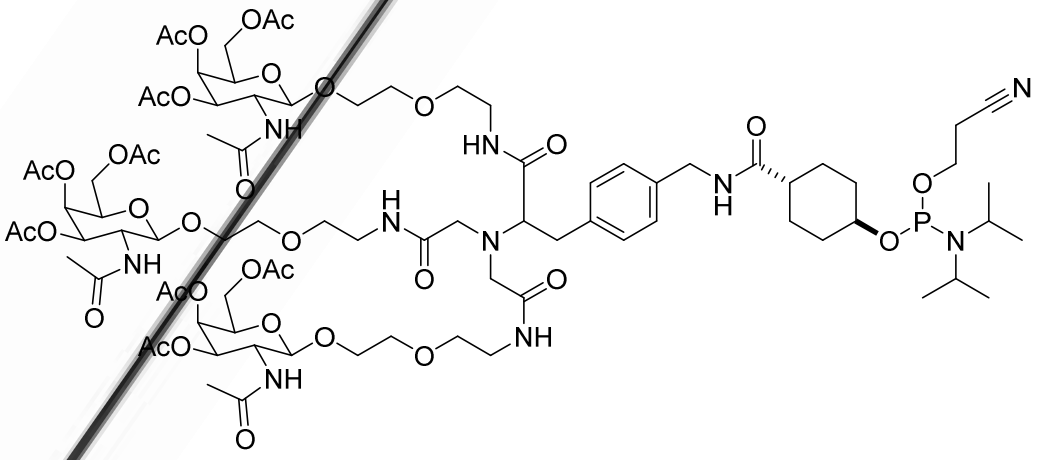
(Structure 1001b);



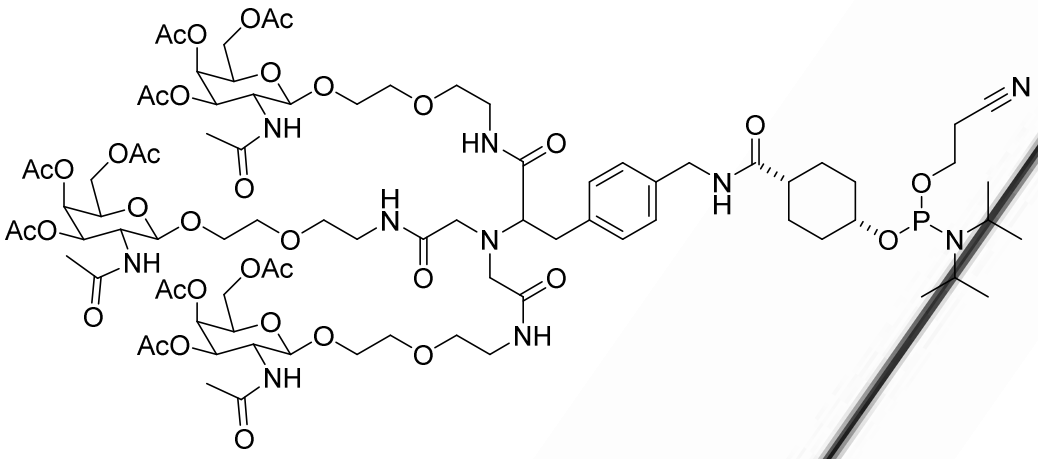
(Structure 1002b);



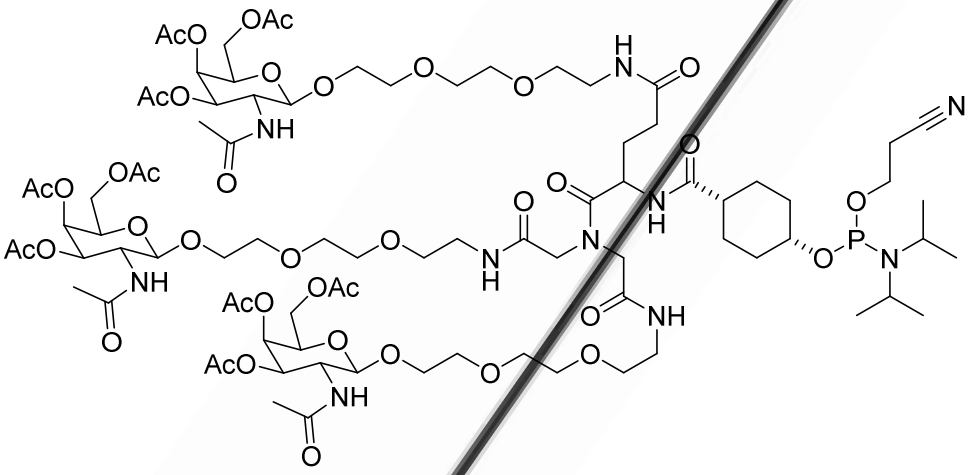
(Structure 1003b);



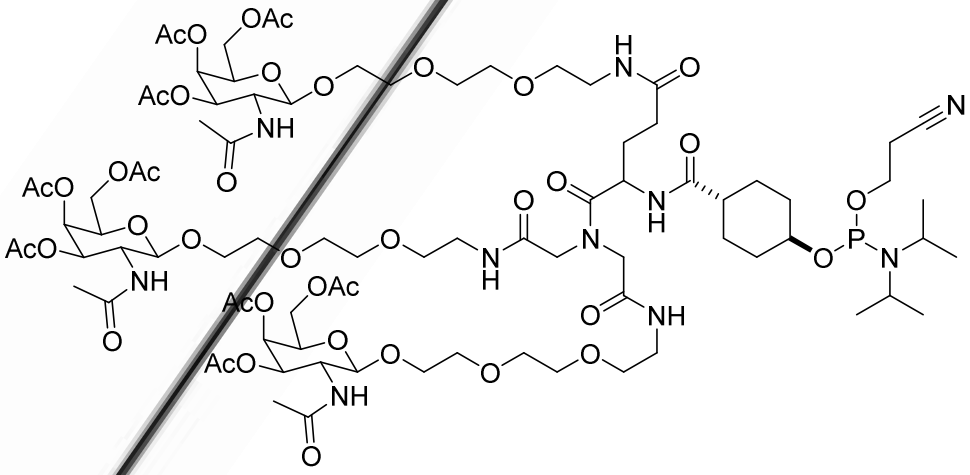
(Structure 1004b);



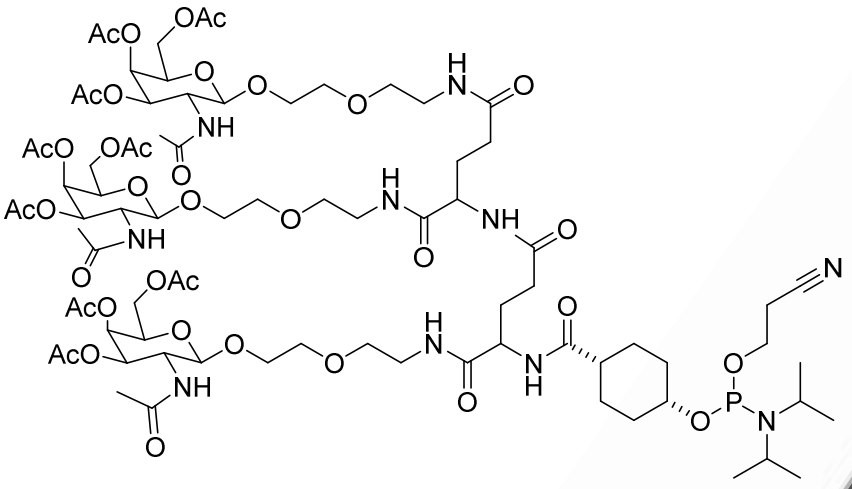
(Structure 1005b);



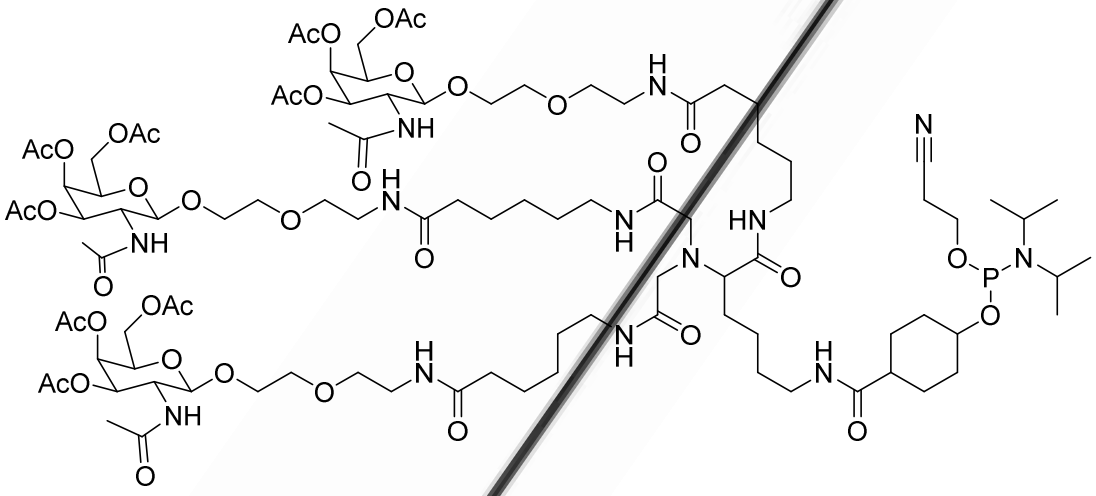
(Structure 1006b);



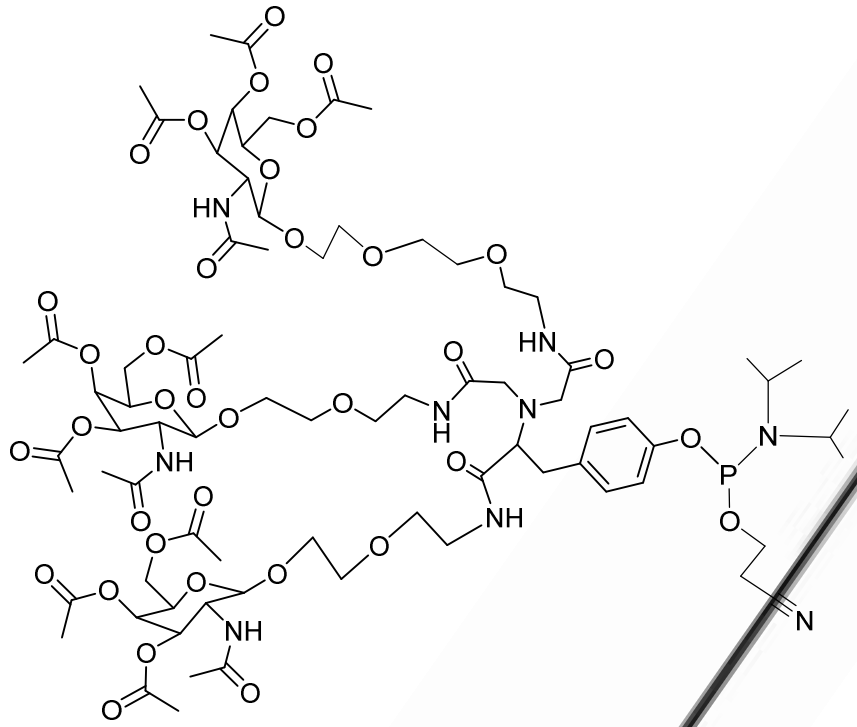
(Structure 1007b);



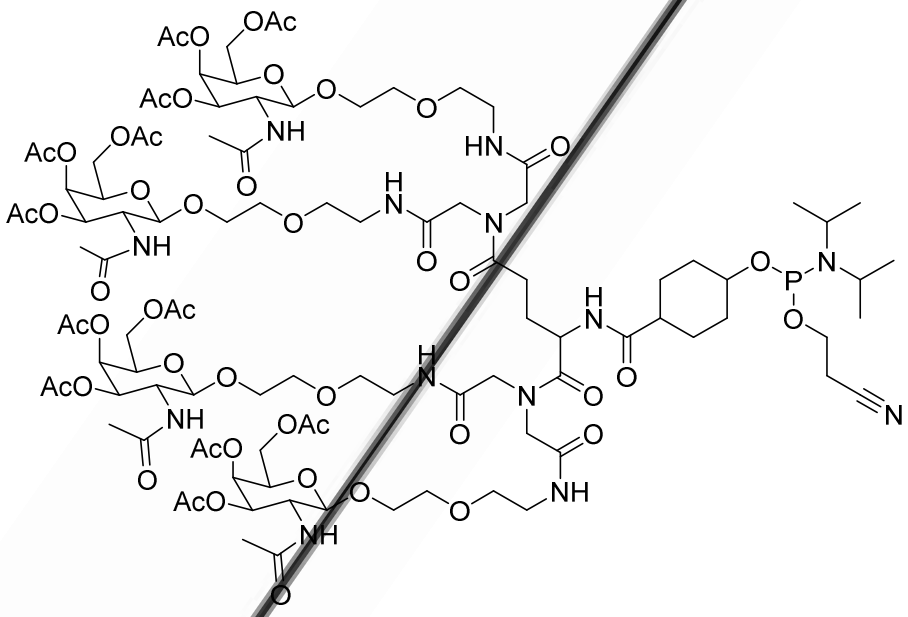
(Structure 1008b);



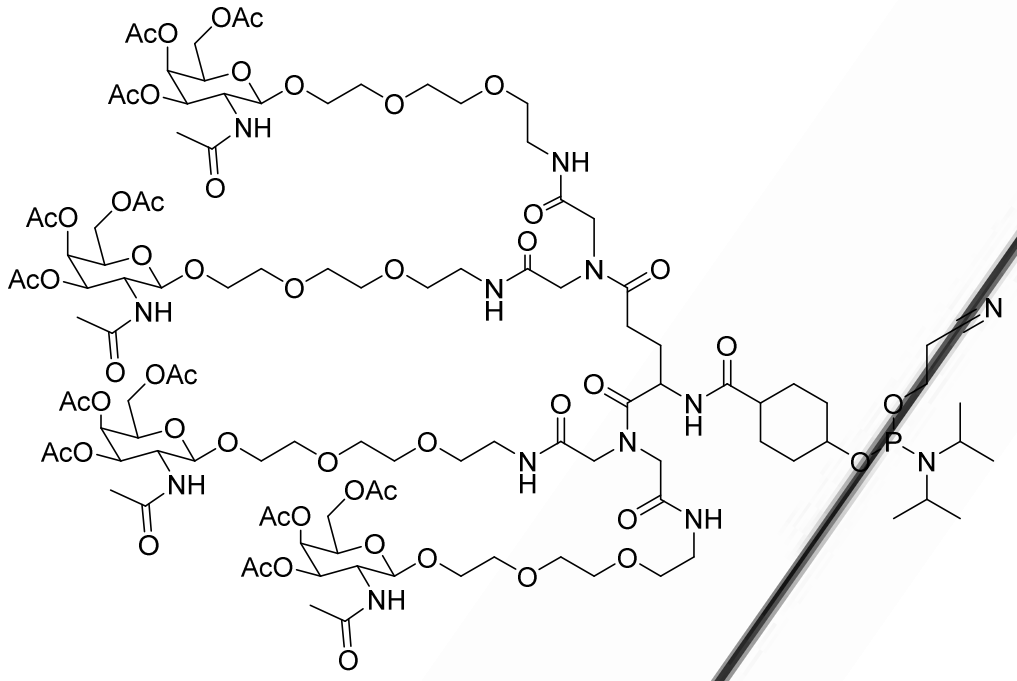
(Structure 1009b);



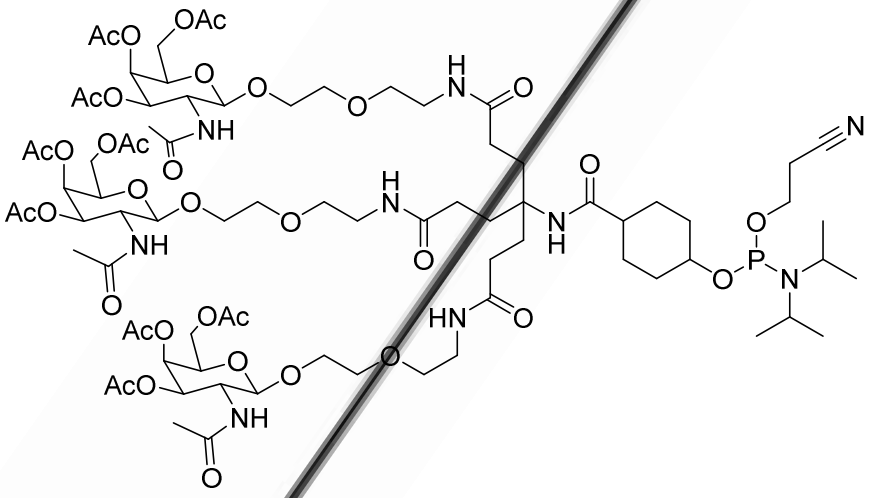
(Structure 1024b);



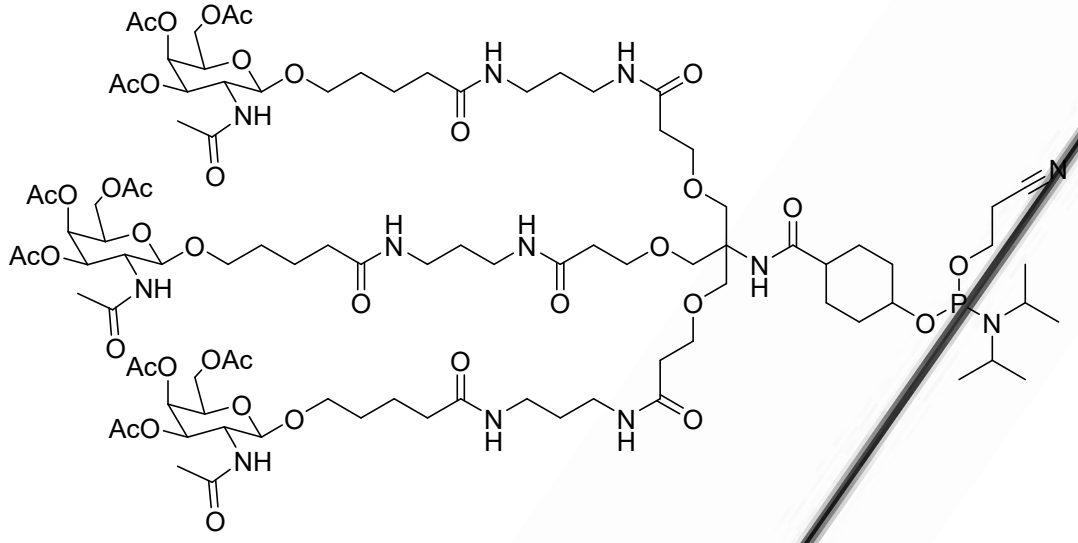
(Structure 1012b);



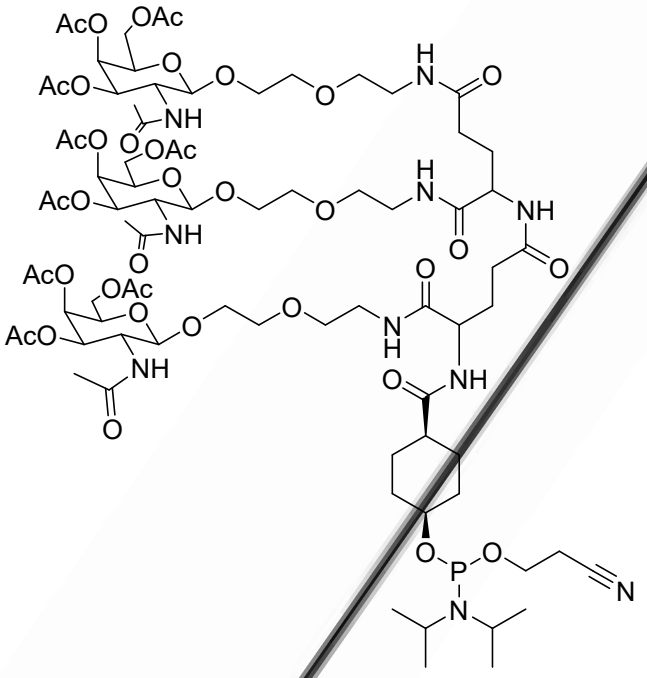
(Structure 1014b);



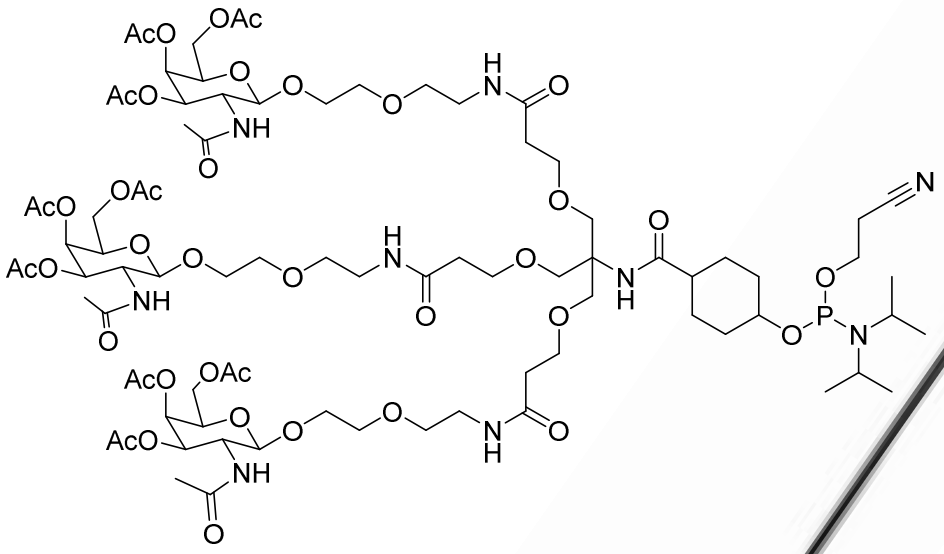
(Structure 1016b);



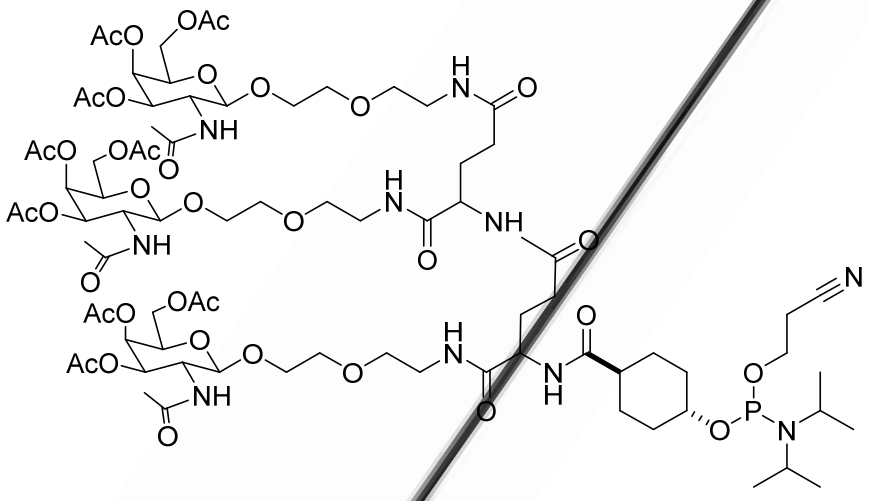
(Structure 1018b);



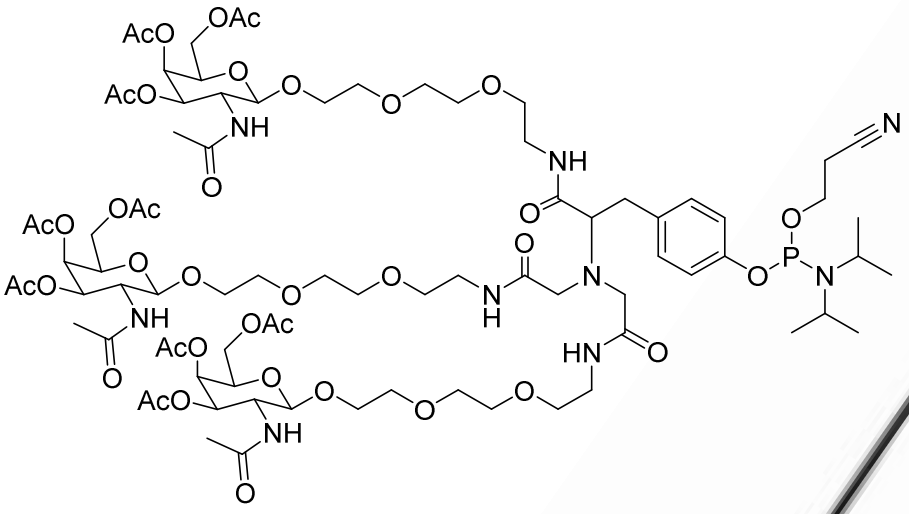
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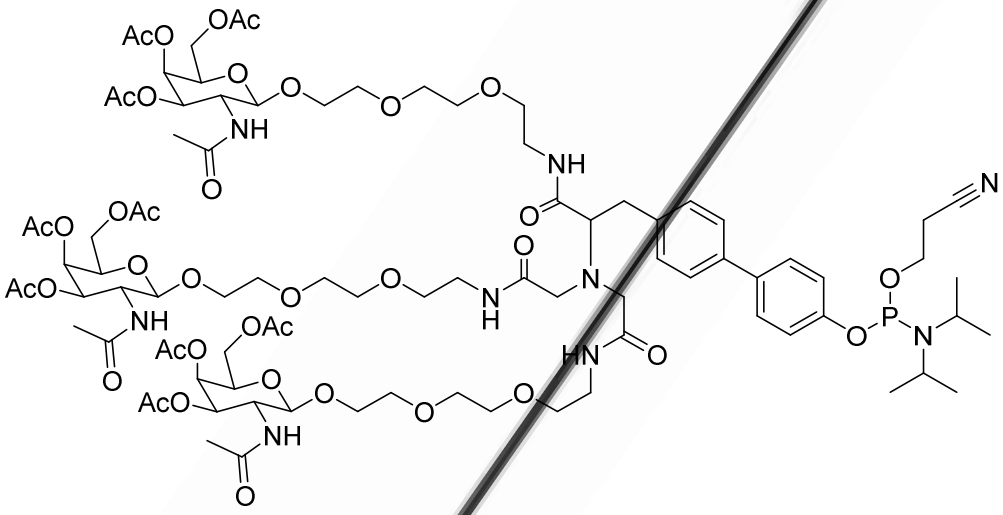
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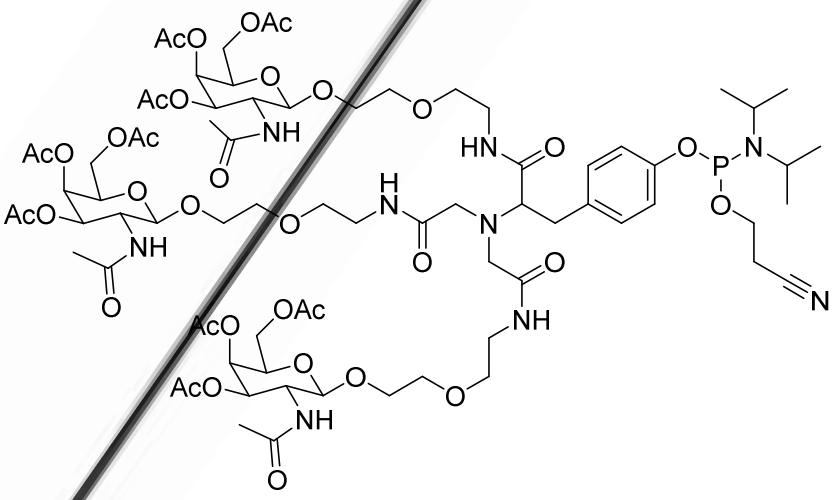
(Structure 1023b);



(Structure 1025b);

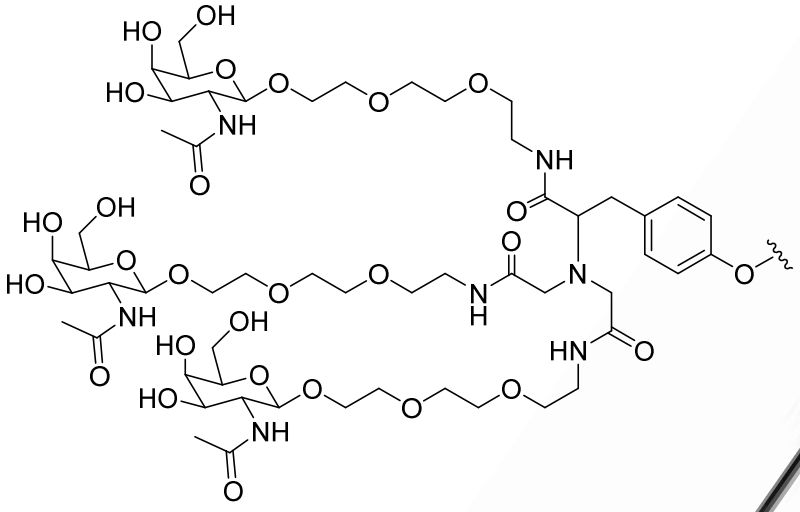


(Structure 1026b); and

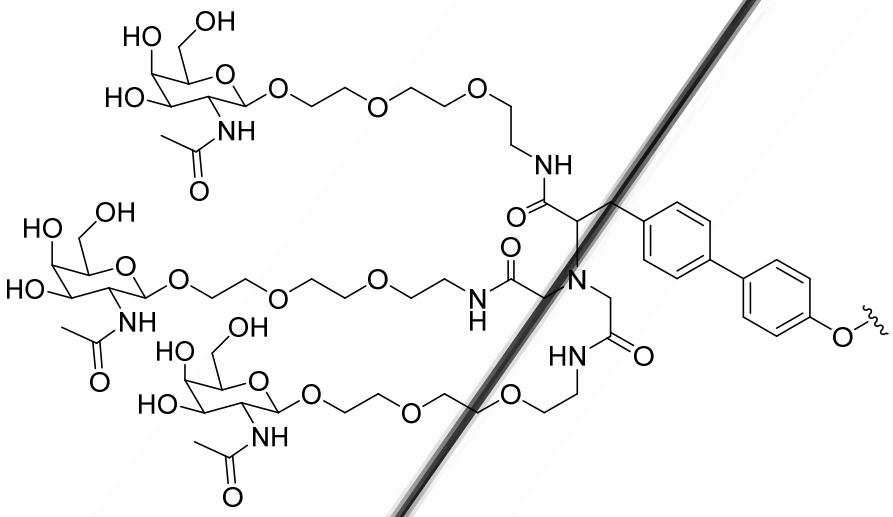


(Structure 1027b).

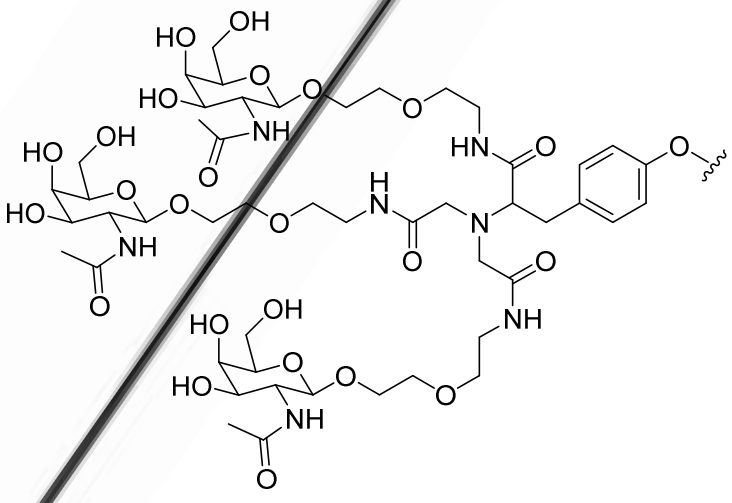
11. A targeting ligand comprising a structure selected from the group consisting of:



(Structure 1025);



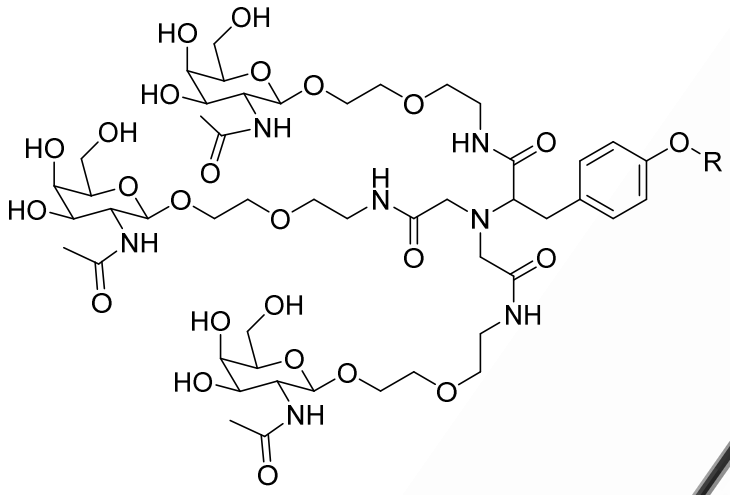
(Structure 1026); and



(Structure 1027),

wherein the targeting ligand is linked to an RNAi agent.

12. The targeting ligand of claim 11, wherein the targeting ligand linked to the RNAi agent has the following structure:



wherein R comprises the RNAi agent (Structure 1027a).

13. The targeting ligand of claim 11, wherein the RNAi agent is double stranded.

14. The targeting ligand of claim 13, wherein the RNAi agent includes one or more modified nucleotides.

15. Use of the targeting ligand of claim 1 in the manufacture of a medicament for inhibiting expression of a target nucleic acid in a subject.

16. Use of the targeting ligand of claim 11 in the manufacture of a medicament for inhibiting expression of a target nucleic acid in a subject.

17. An in vitro method of introducing a therapeutic agent into a mammalian cell, the method comprising contacting a mammalian cell with the targeting ligand of claim 1, wherein the therapeutic agent comprises the RNAi agent.

18. The method of claim 17, wherein the therapeutic agent is a double-stranded RNAi agent.

19. An in vitro method of introducing a therapeutic agent into a mammalian cell, the method comprising contacting a mammalian cell with the targeting ligand of claim 11, wherein the therapeutic agent comprises the RNAi agent.

20. The method of claim 19, wherein the therapeutic agent is a double-stranded RNAi agent.

21. Use of the targeting ligand of claim 1 in the manufacture of a medicament for treating a disease or disorder in a subject that would benefit from administration of a therapeutic compound.

22. Use of the targeting ligand of claim 11 in the manufacture of a medicament for treating a disease or disorder in a subject that would benefit from administration of a therapeutic compound.

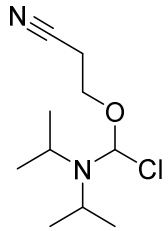
23. Use of the composition of claim 7 in the manufacture of a medicament for treating a disease or disorder in a subject that would benefit from administration of a therapeutic compound.

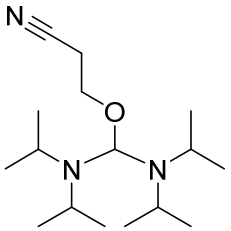
24. A method of manufacturing a phosphoramidite compound including the compound of claim 10, the method comprising:

(i) covalently linking the carboxylic acid moiety or its activated ester of the linker to a terminal amine located on the branch point group, and

(ii) linking the linker to a phosphorus atom of a phosphoramidite through a phosphitylation reaction with a phosphoramidite forming reagent; thereby forming a phosphoramidite compound that includes a targeting ligand.

25. The method of claim 24, wherein the phosphoramidite reagent is selected from the group consisting of:



and


.

26. The targeting ligand of claim 2, comprising Structure 1003.

27. The targeting ligand of claim 2, comprising Structure 1008.

28. The targeting ligand of claim 2, comprising Structure 1023.

29. The targeting ligand of claim 5, comprising Structure 1003.

30. The targeting ligand of claim 5, comprising Structure 1008.

31. The targeting ligand of claim 5, comprising Structure 1023.

32. The targeting ligand of claim 6, comprising Structure 1003.

33. The targeting ligand of claim 6, comprising Structure 1008.

34. The targeting ligand of claim 6, comprising Structure 1023.

35. The composition of claim 7, comprising Structure 1003a.

36. The composition of claim 7, comprising Structure 1008a.

37. The composition of claim 7, comprising Structure 1023a.

38. The composition of claim 8, comprising Structure 1003a.

39. The composition of claim 8, comprising Structure 1008a.

40. The composition of claim 8, comprising Structure 1023a.

41. The composition of claim 9, comprising Structure 1003a.

42. The composition of claim 9, comprising Structure 1008a.

43. The composition of claim 9, comprising Structure 1023a.

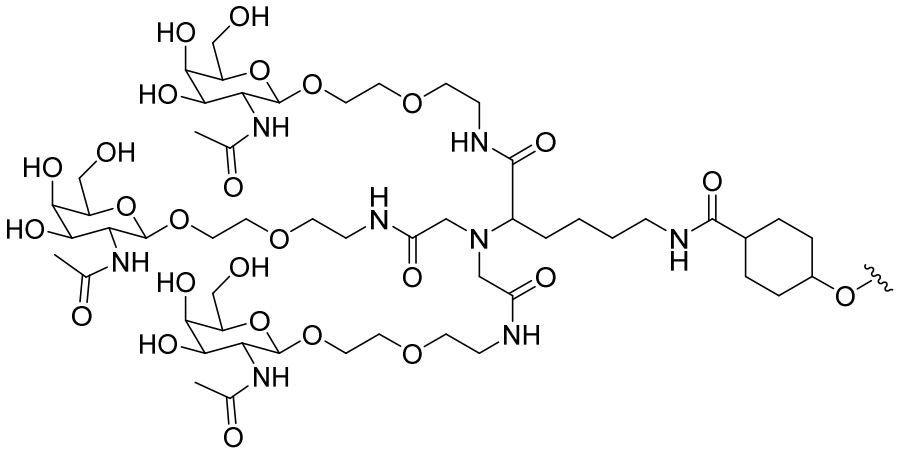
44. The compound of claim 10, comprising Structure 1003b.

45. The compound of claim 10, comprising Structure 1008b.

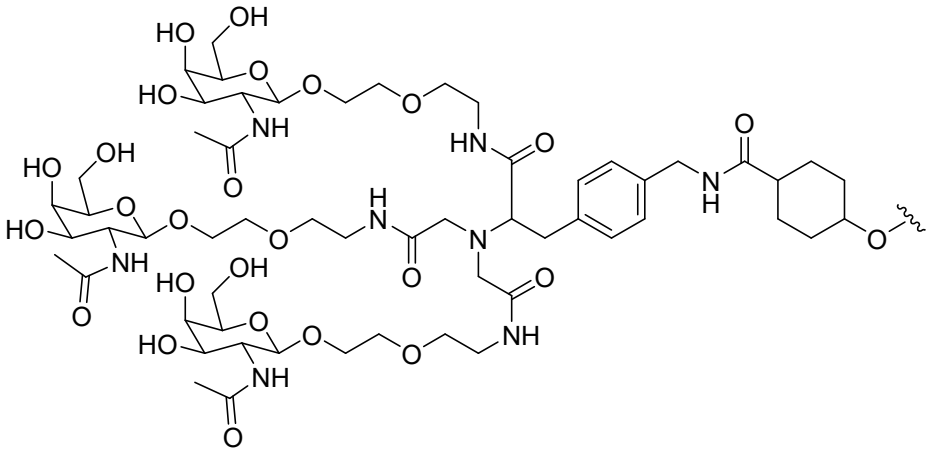
46. The compound of claim 10, comprising Structure 1023b.

Claims

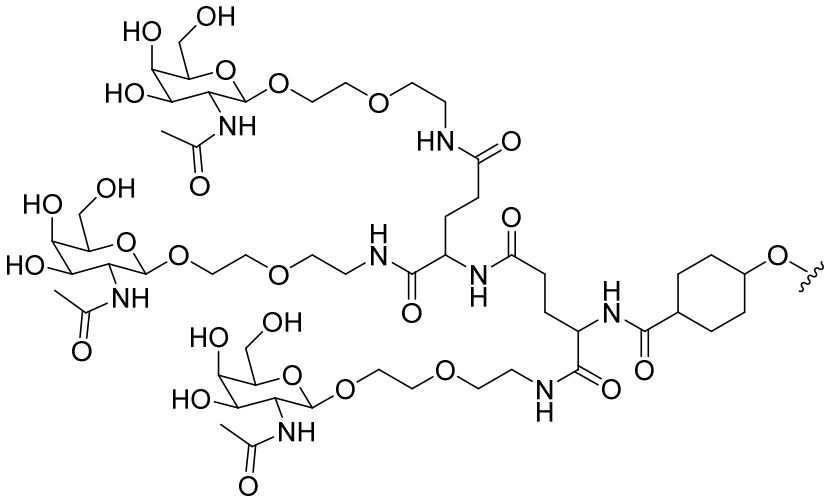
1. A targeting ligand comprising a structure selected from the group consisting of:



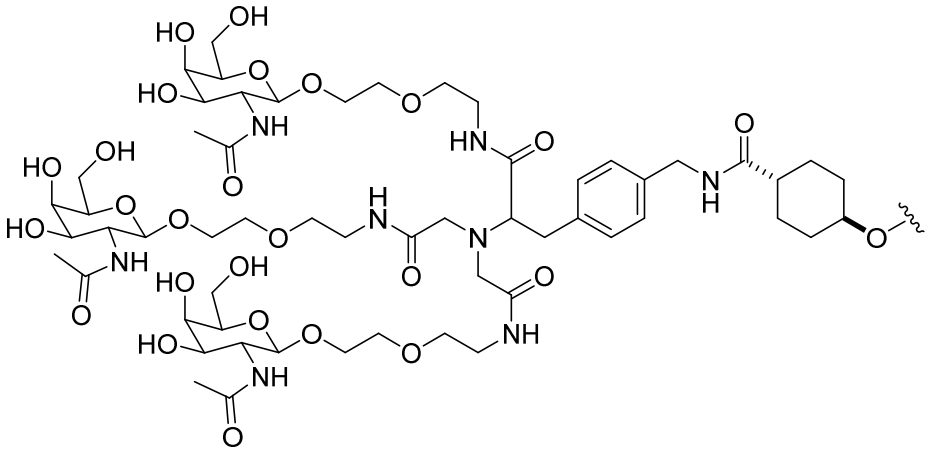
(Structure 1001);



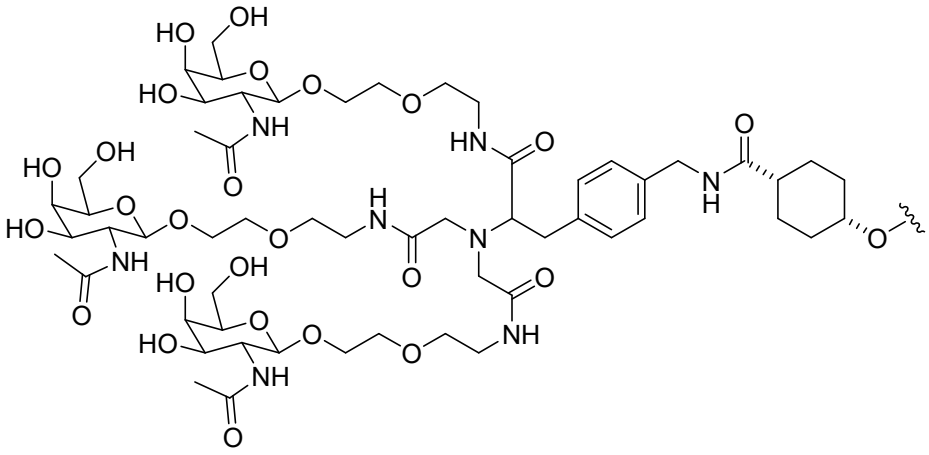
(Structure 1002);



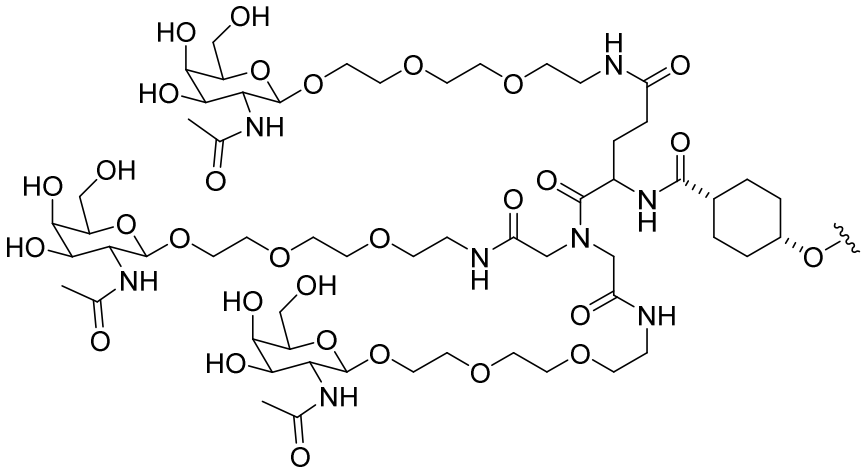
(Structure 1003);



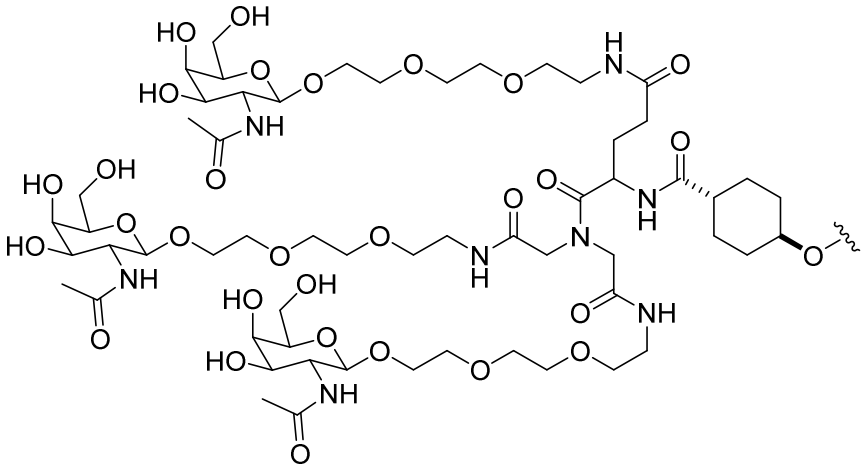
(Structure 1004);



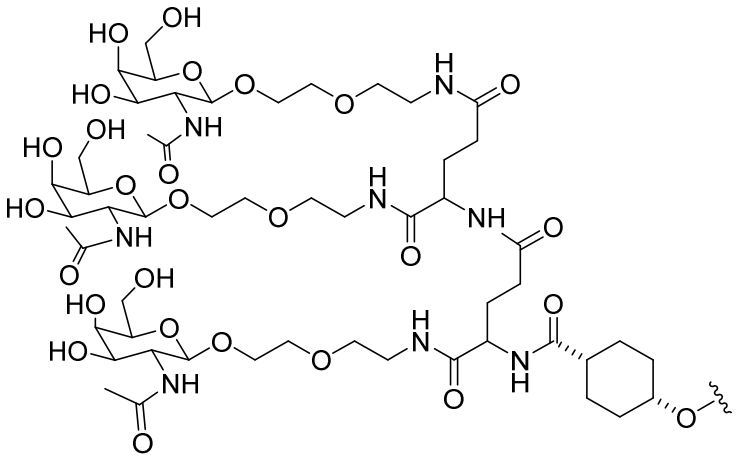
(Structure 1005);



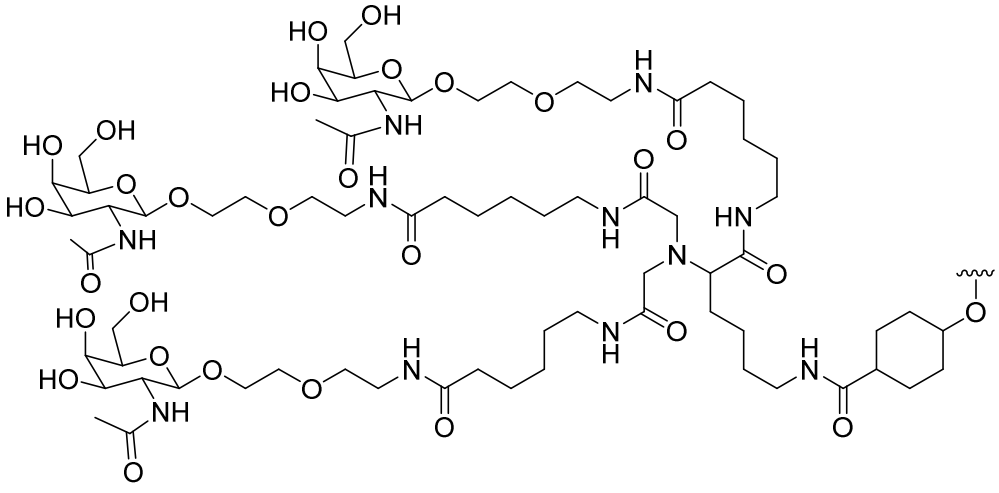
(Structure 1006);



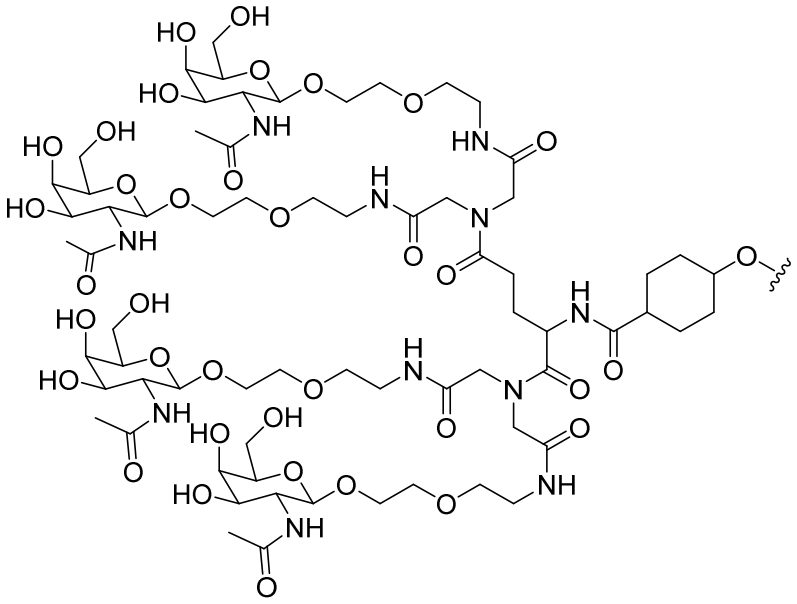
(Structure 1007);



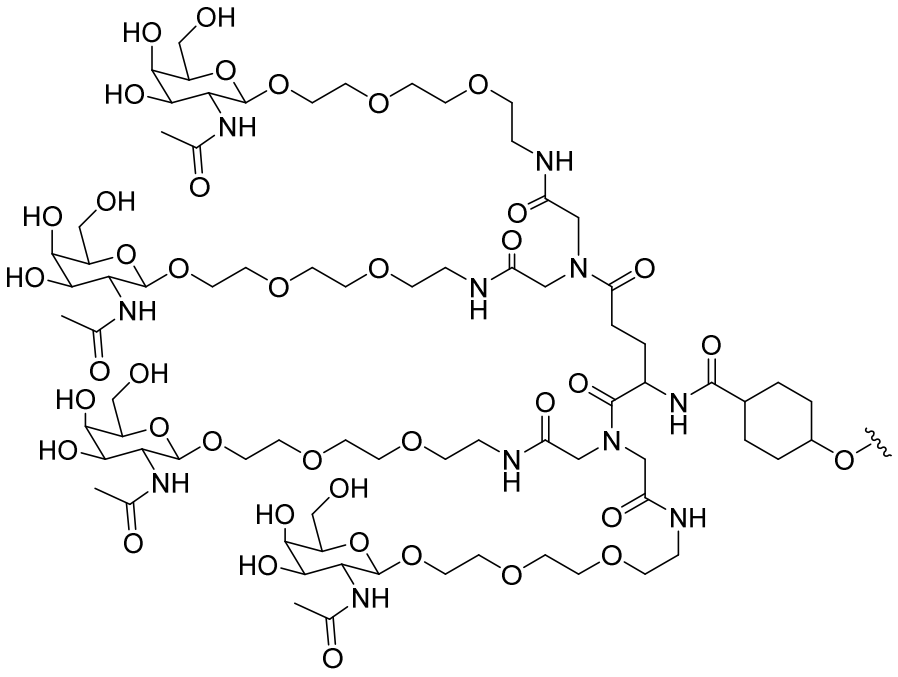
(Structure 1008);



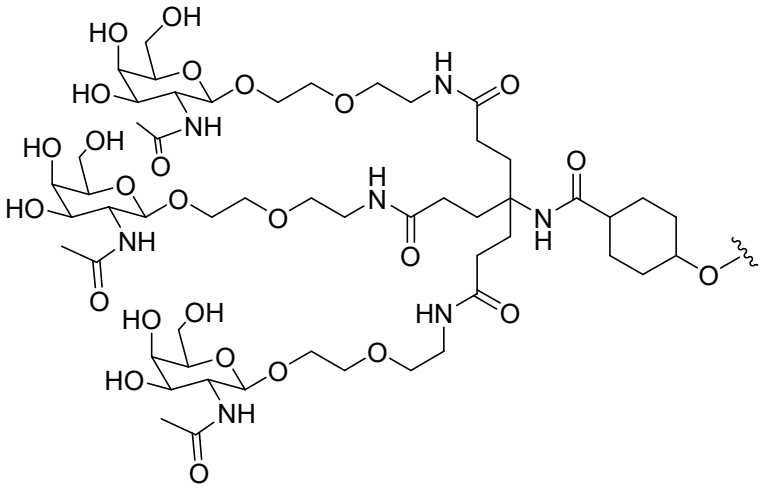
(Structure 1009);



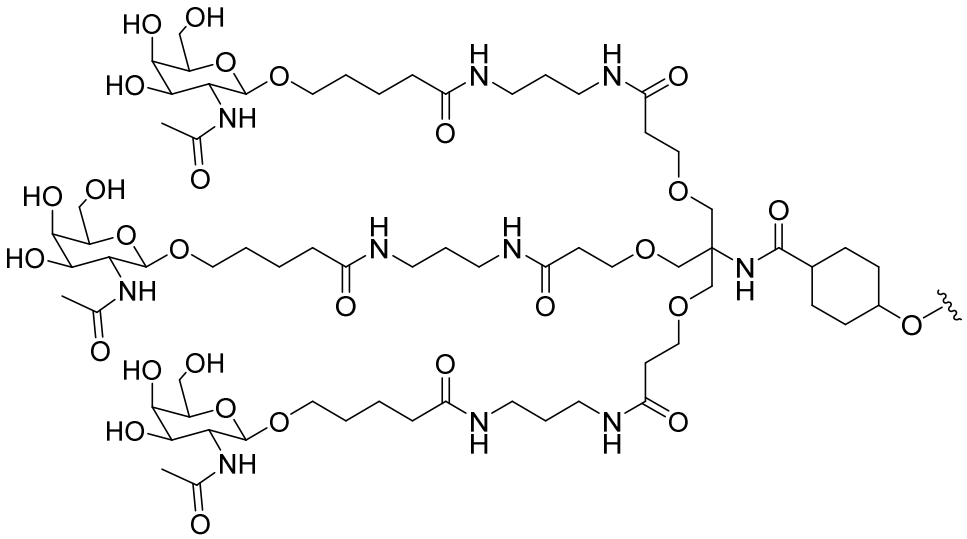
(Structure 1012);



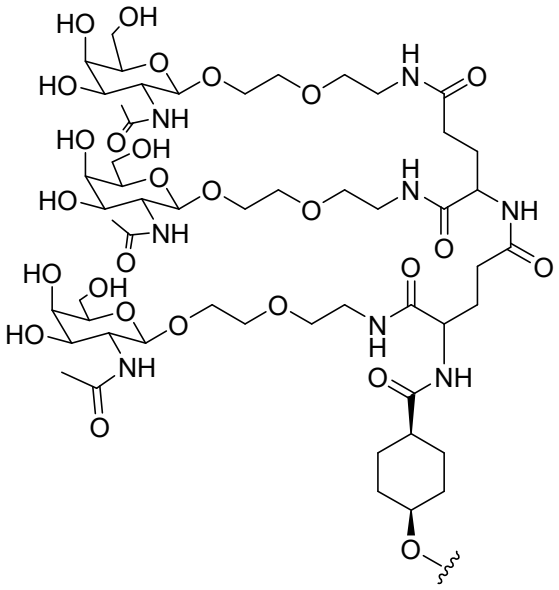
(Structure 1014);



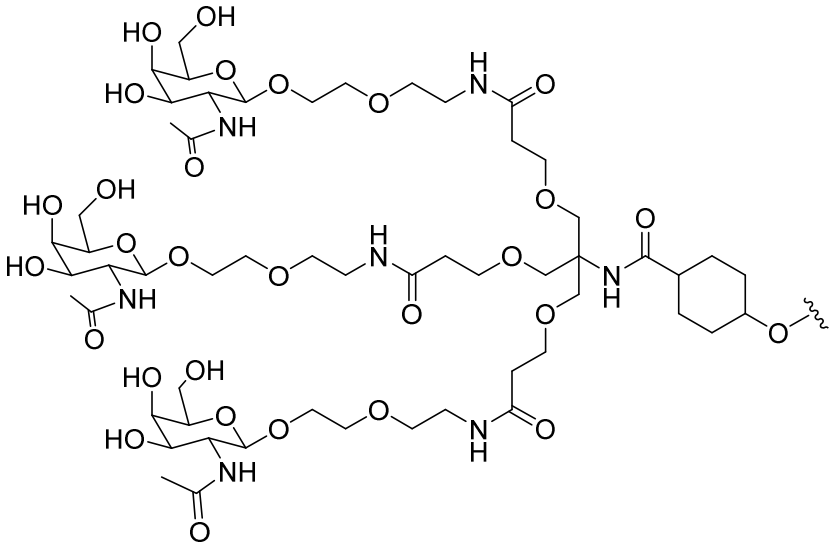
(Structure 1016);



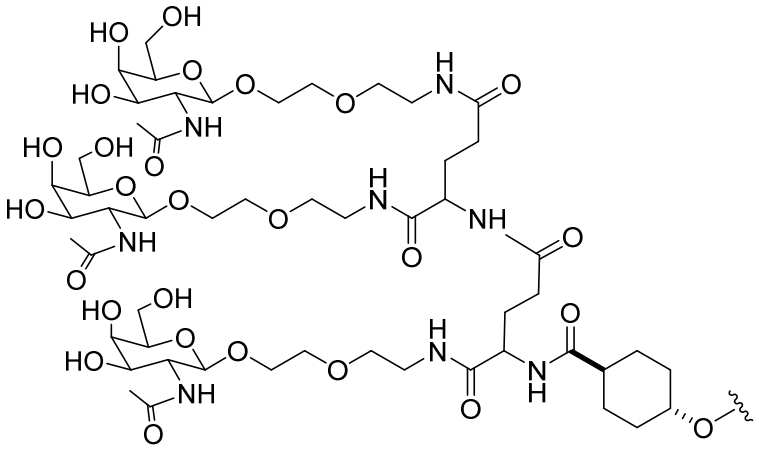
(Structure 1018);



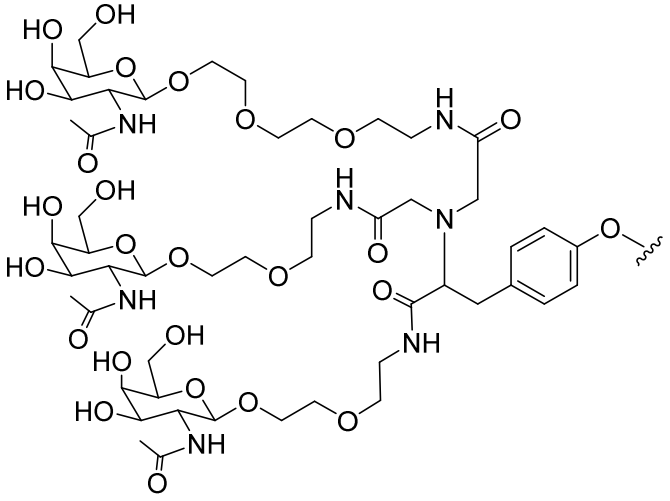
(Structure 1019);



(Structure 1021);



(Structure 1023); and



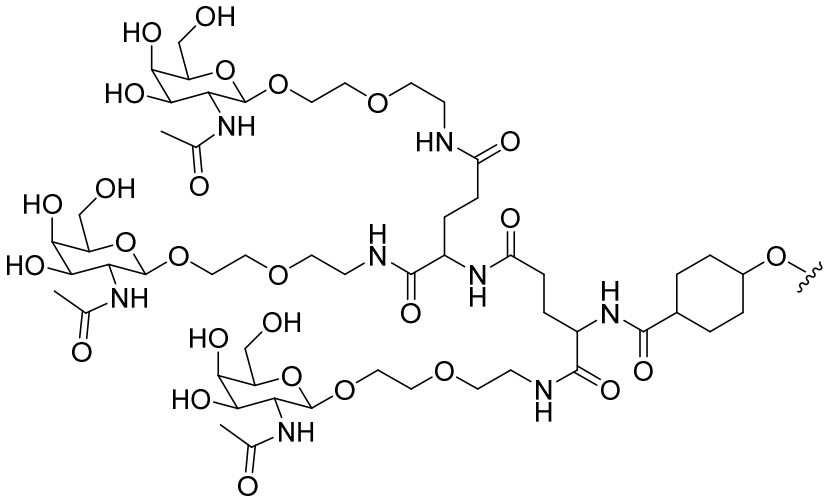
(Structure 1024),

wherein the targeting ligand is linked to an RNAi agent.

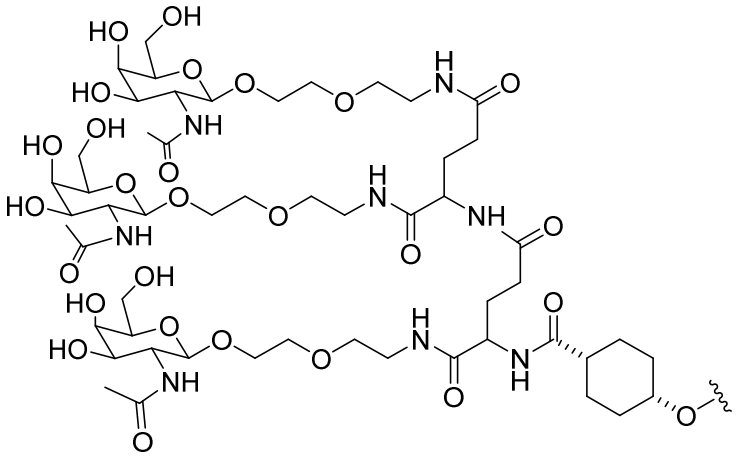
2. The targeting ligand of claim 1, wherein the RNAi agent is double-stranded.

3. The targeting ligand of claim 2, wherein the RNAi agent includes one or more modified nucleotides.

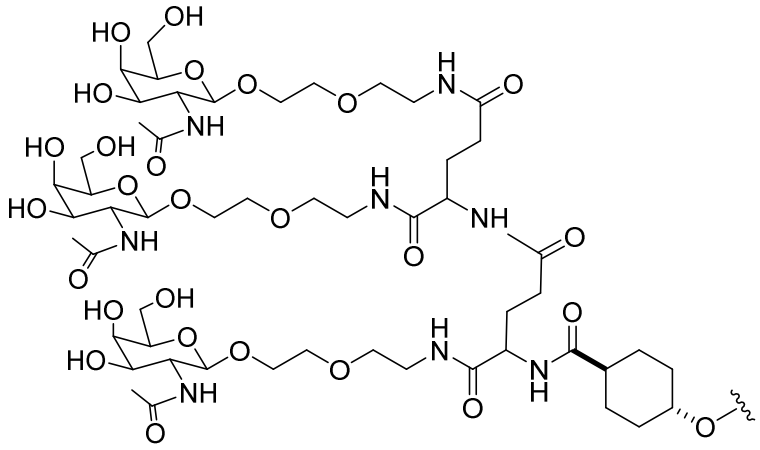
4. The targeting ligand of claim 1, wherein the structure is selected from the group consisting of:



(Structure 1003);



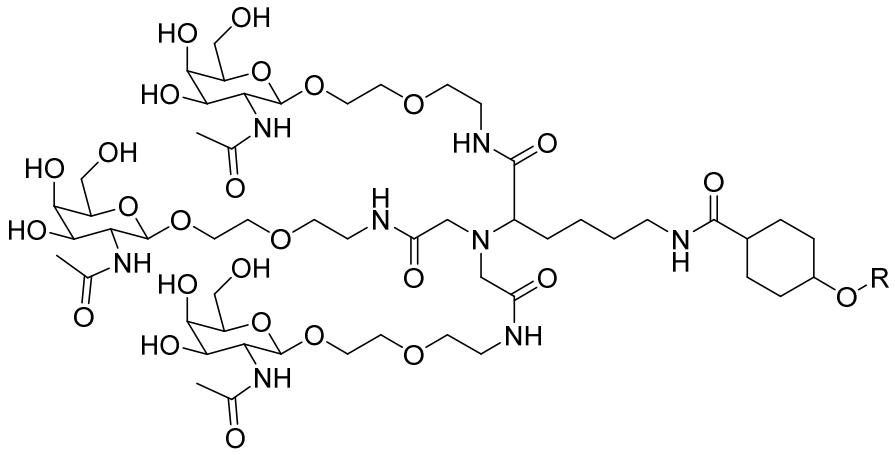
(Structure 1008); and

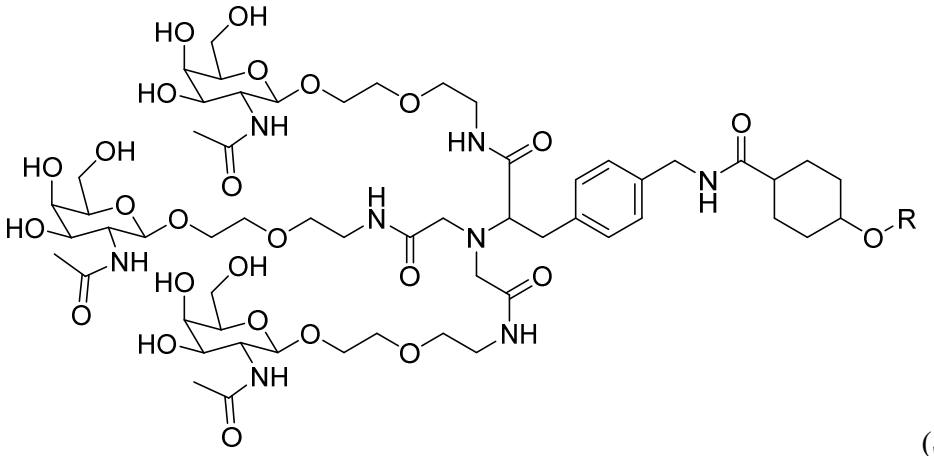

(Structure 1023).

5. The targeting ligand of claim 2, wherein the double-stranded RNAi agent is linked to the targeting ligand at the 5' terminal end of the sense strand of an RNAi agent.

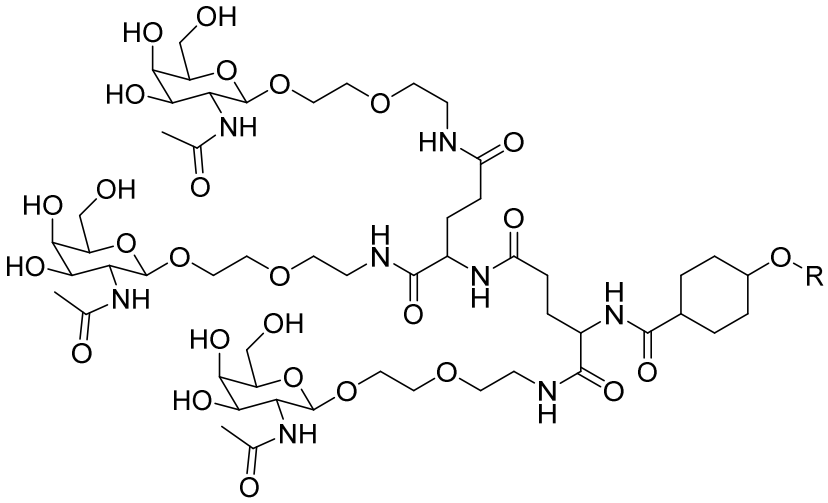
6. The targeting ligand of claim 5, wherein the RNAi agent is linked to the linker of the targeting ligand via a phosphate group, phosphorothioate group, or a phosphonate group.

7. A composition comprising a targeting ligand linked to an expression-inhibiting oligomeric compound, wherein the structure of the targeting ligand and expression-inhibiting oligomeric compound is represented by the structure selected from the group consisting of:

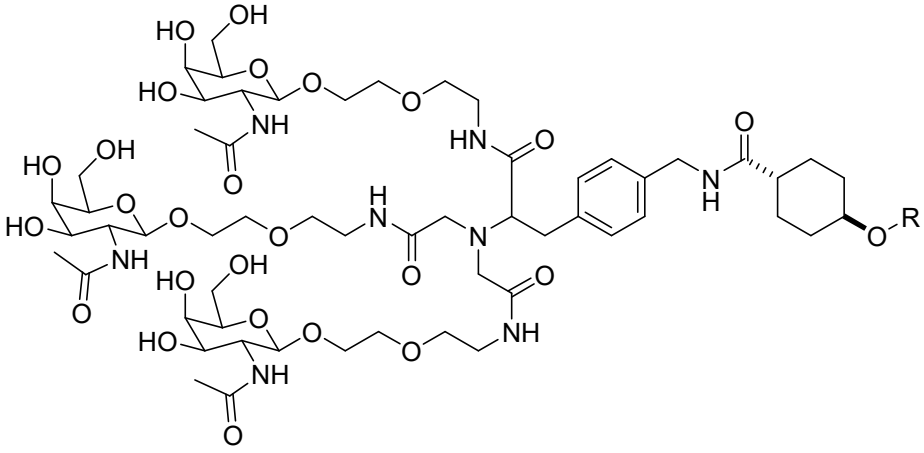

(Structure 1001a);



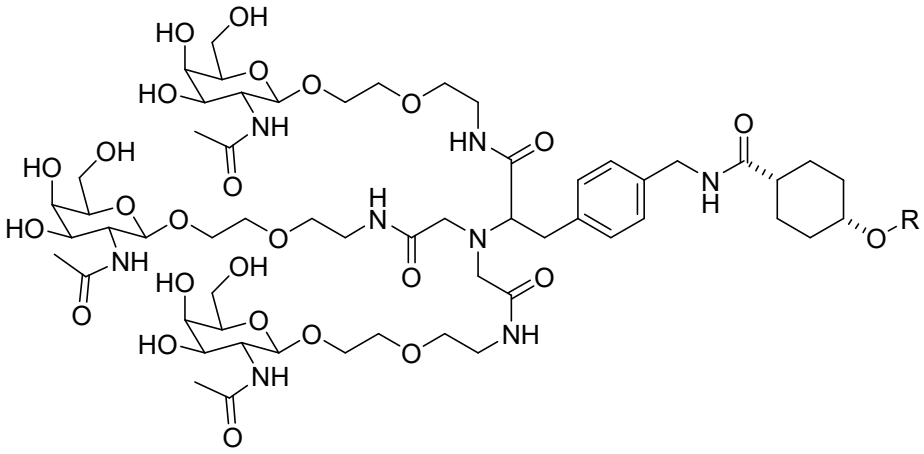
(Structure 1002a);



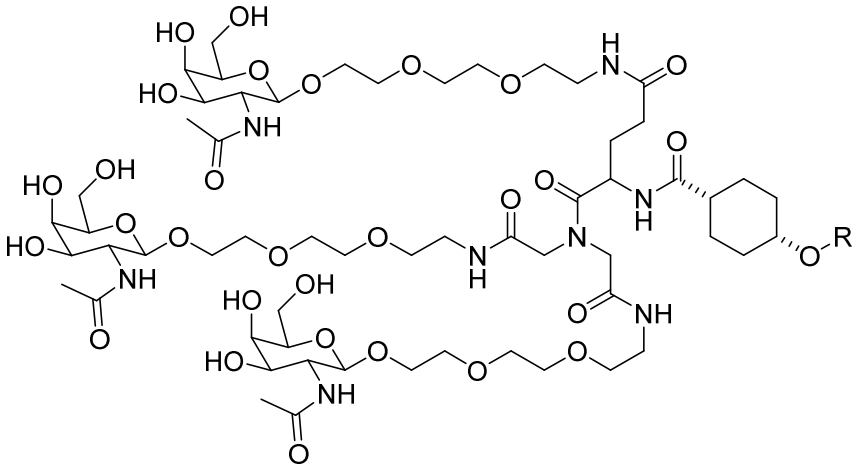
(Structure 1003a);



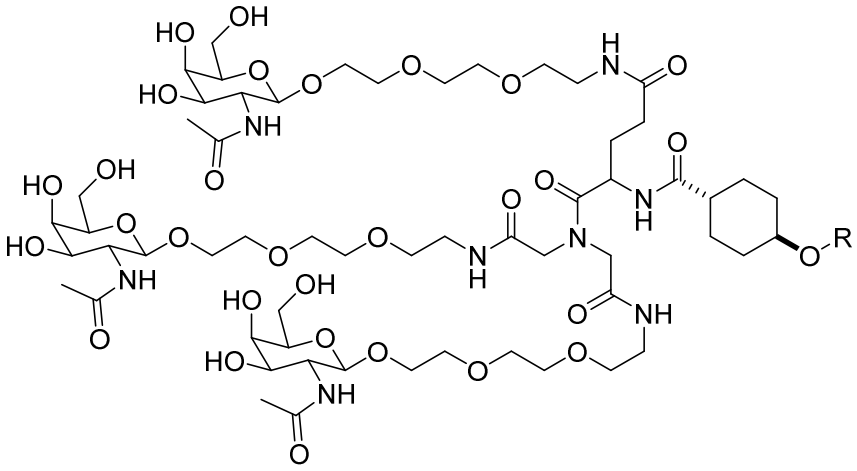
(Structure 1004a);



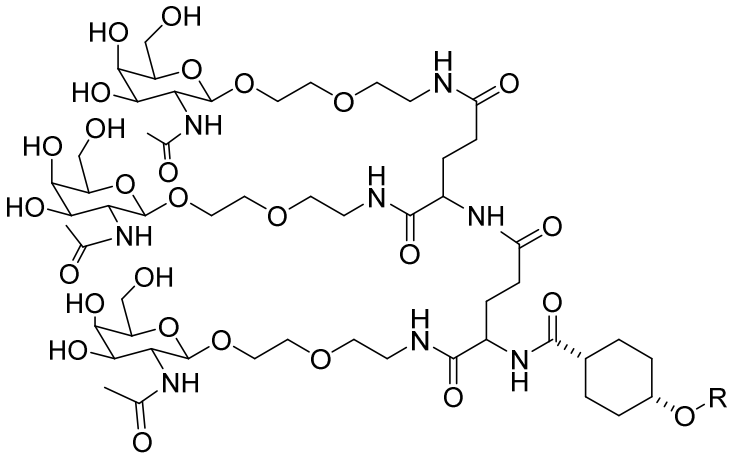
(Structure 1005a);



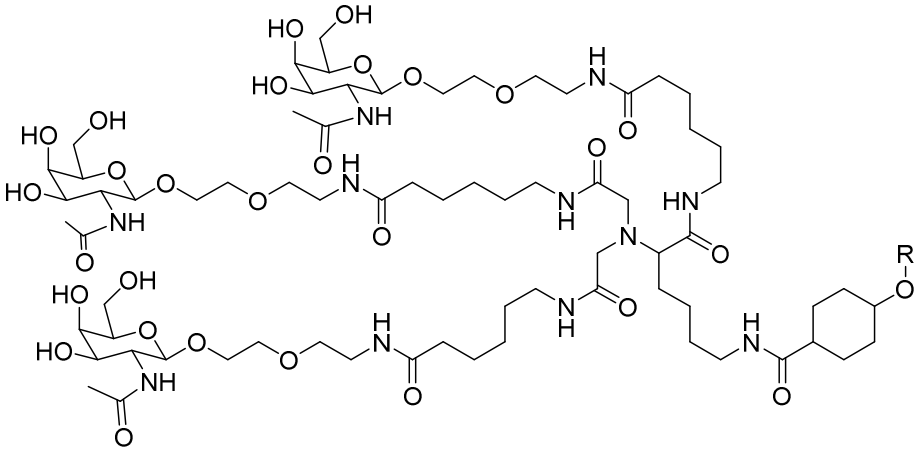
(Structure 1006a);



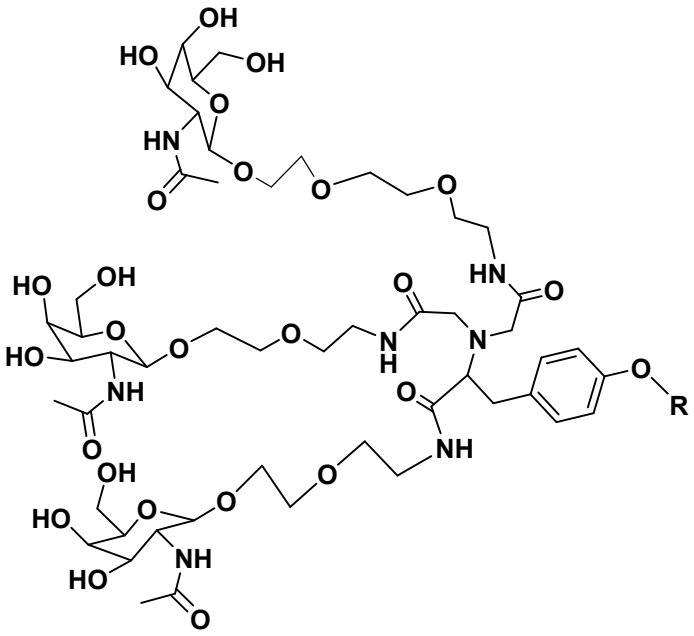
(Structure 1007a);



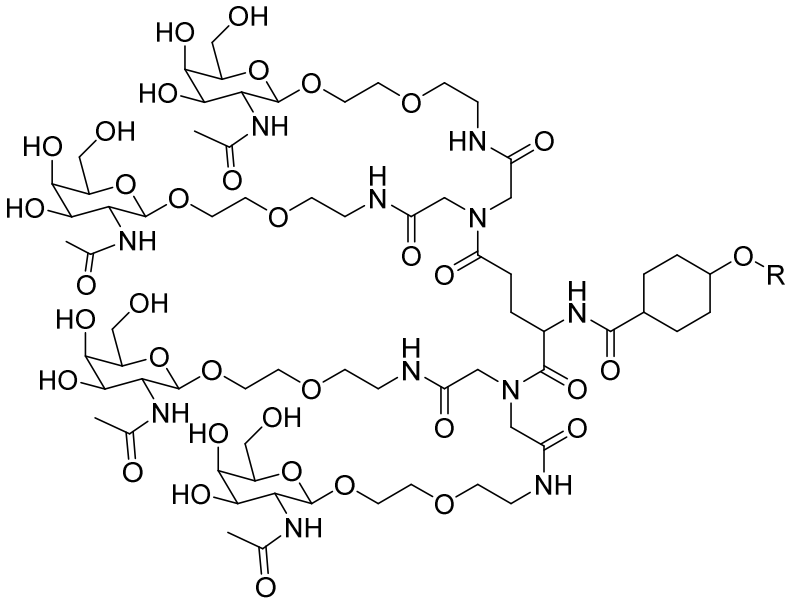
(Structure 1008a);



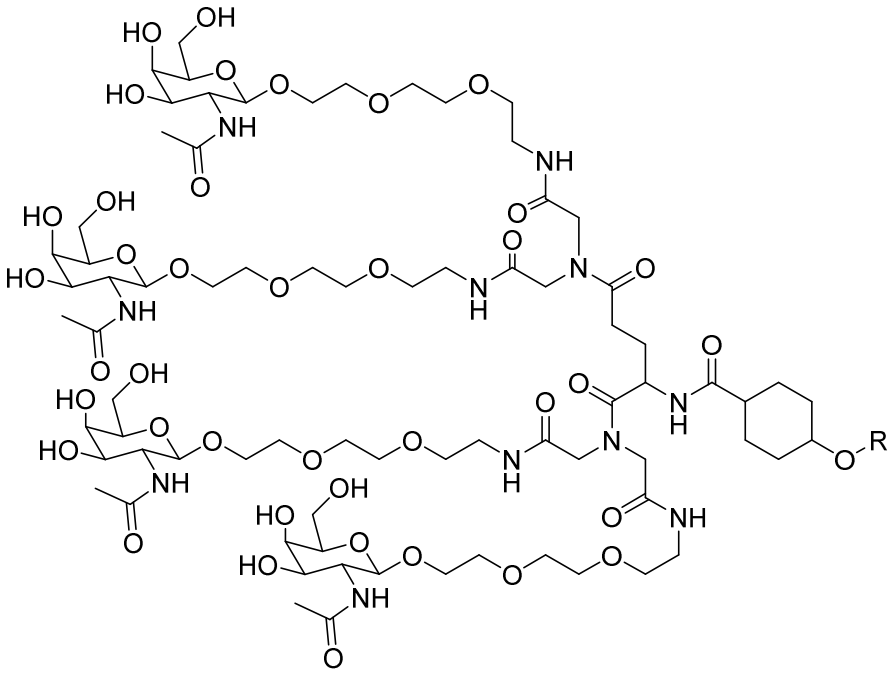
(Structure 1009a);



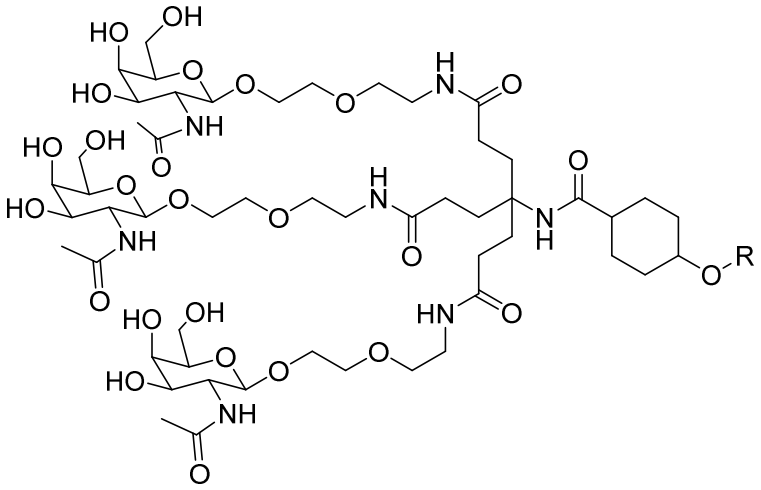
(Structure 1024a);



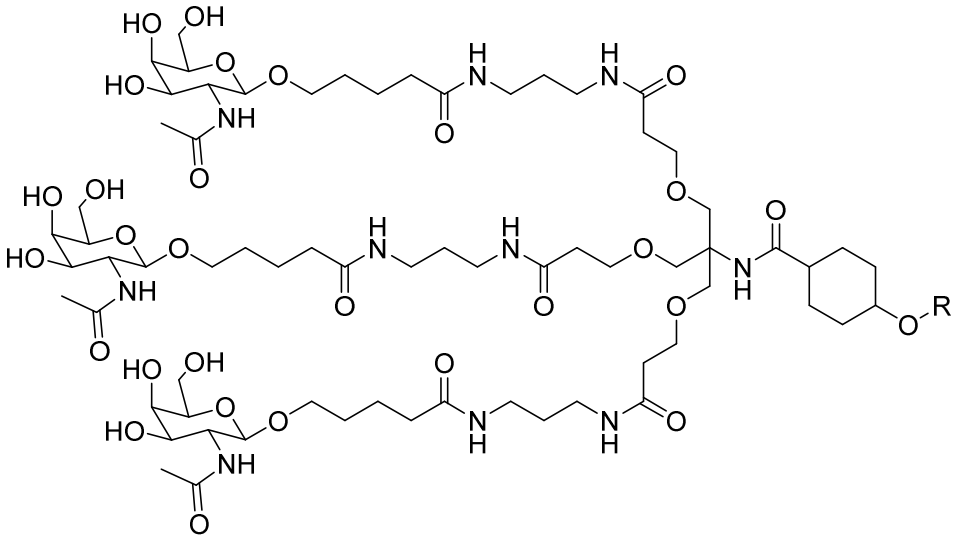
(Structure 1012a);



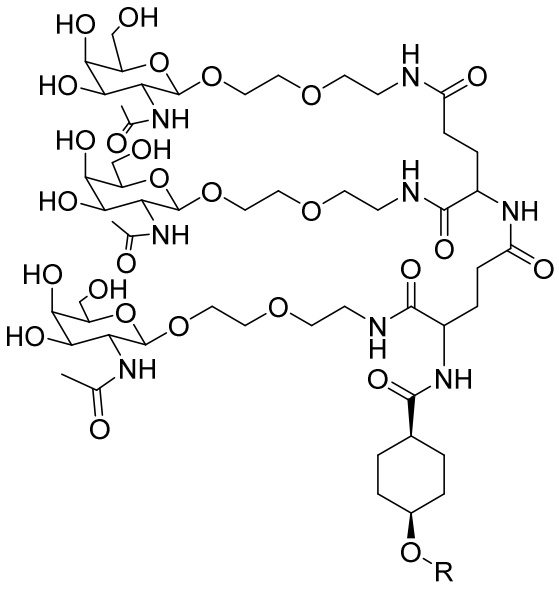
(Structure 1014a);



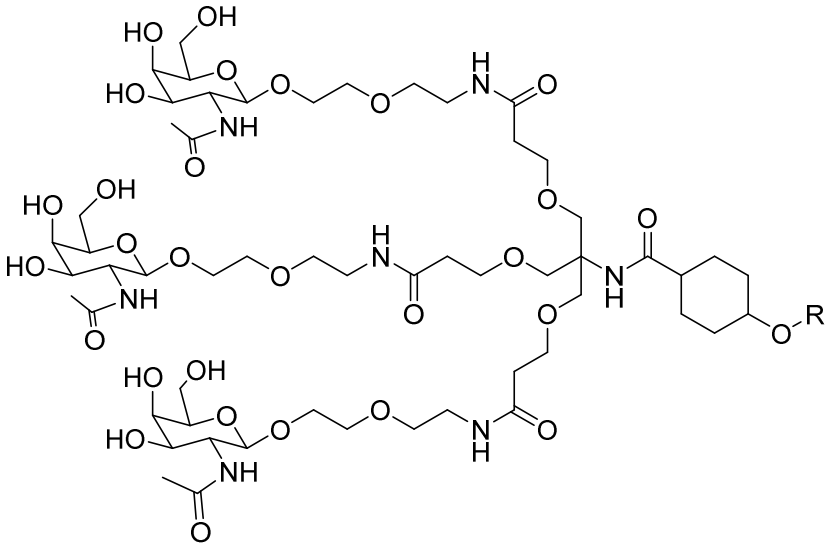
(Structure 1016a);



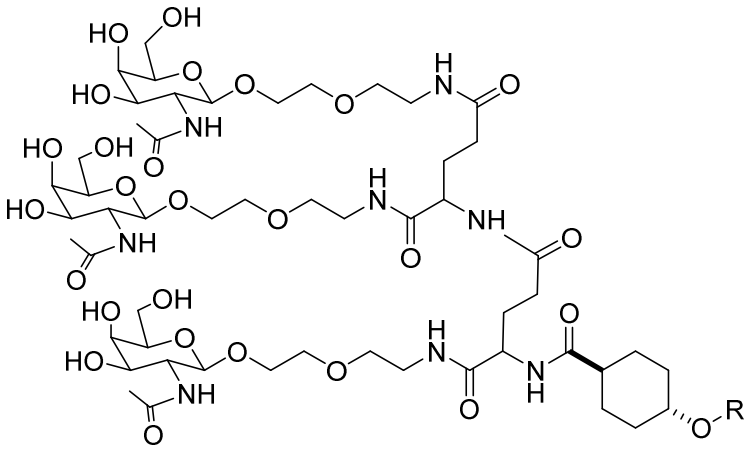
(Structure 1018a);



(Structure 1019a);



(Structure 1021a); and



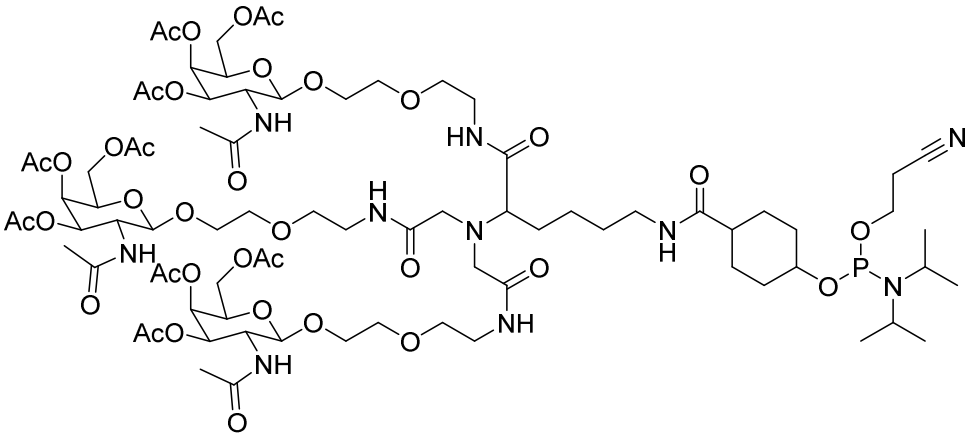
(Structure 1023a);

wherein R in each structure comprises the expression-inhibiting oligomeric compound, wherein the expression-inhibiting oligomeric compound comprises an RNAi agent, and wherein the targeting ligand is linked to the RNAi agent via a phosphate group, phosphorothioate group, or a phosphonate group.

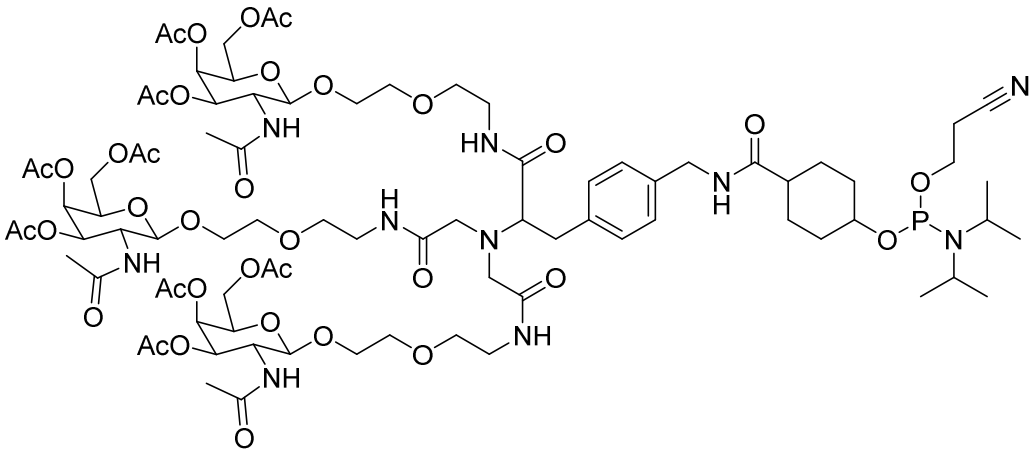
8. The composition of claim 7, wherein the RNAi agent is a double-stranded RNAi agent.

9. The composition of claim 8, wherein the targeting ligand is linked to the 5' terminal end of the sense strand of an RNAi agent.

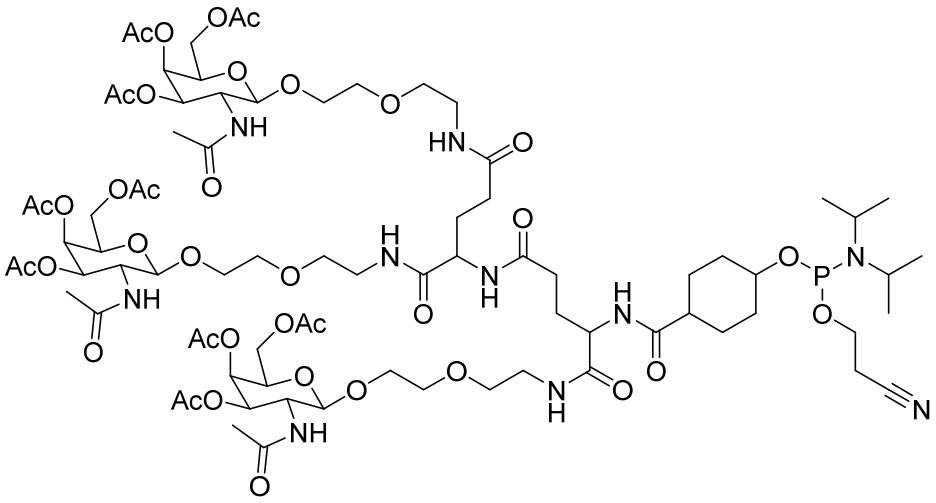
10. A compound having the structure selected from the group consisting of:



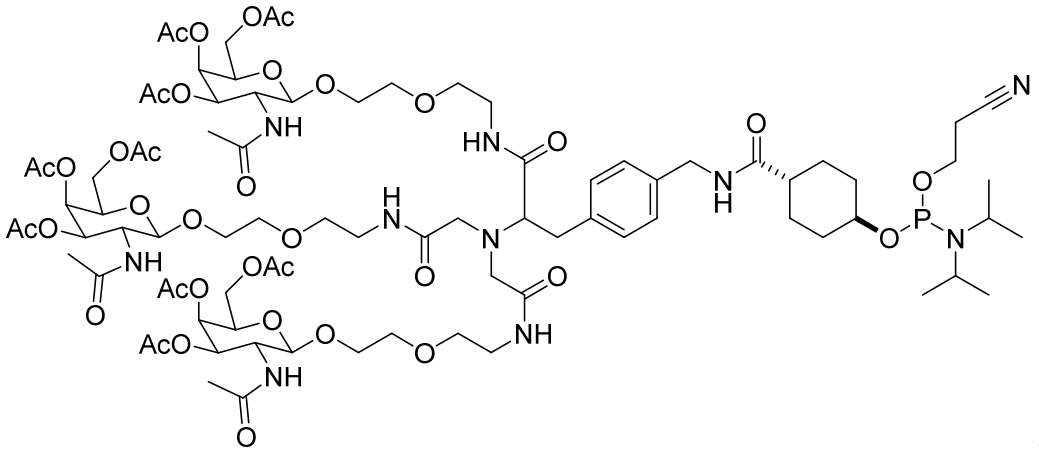
(Structure 1001b);



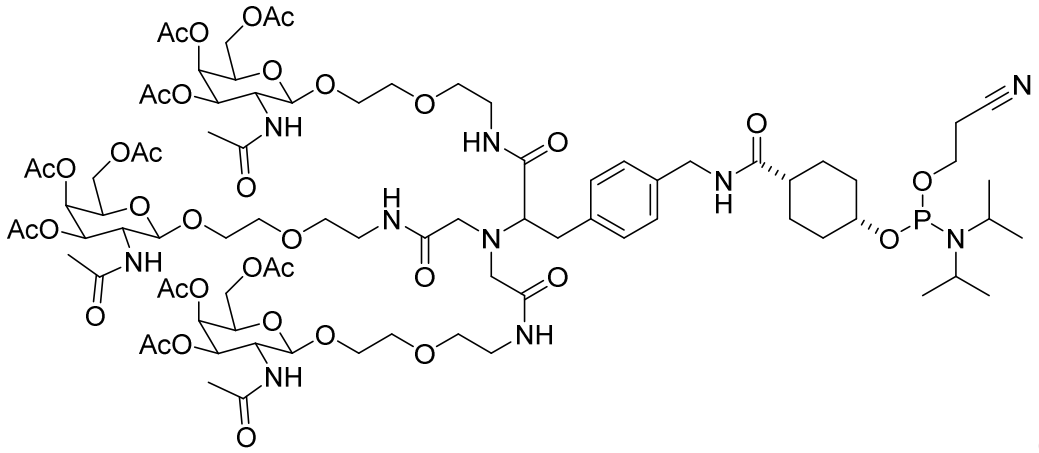
(Structure 1002b);



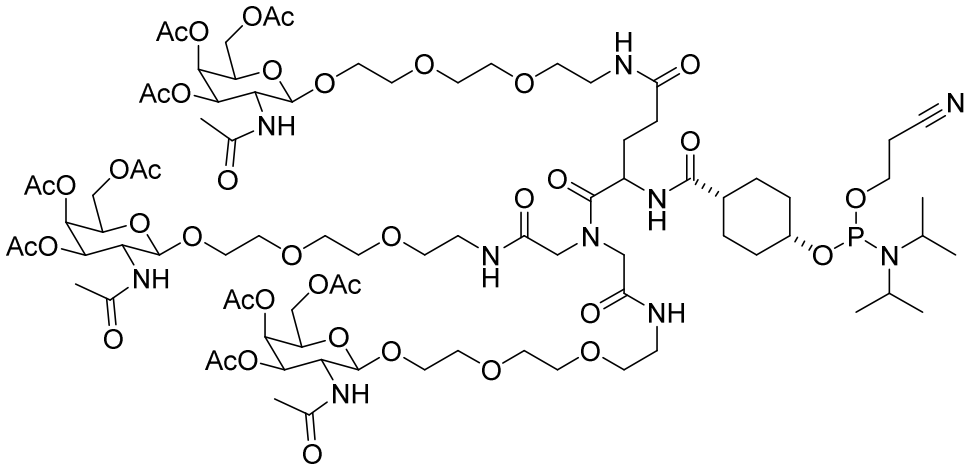
(Structure 1003b);



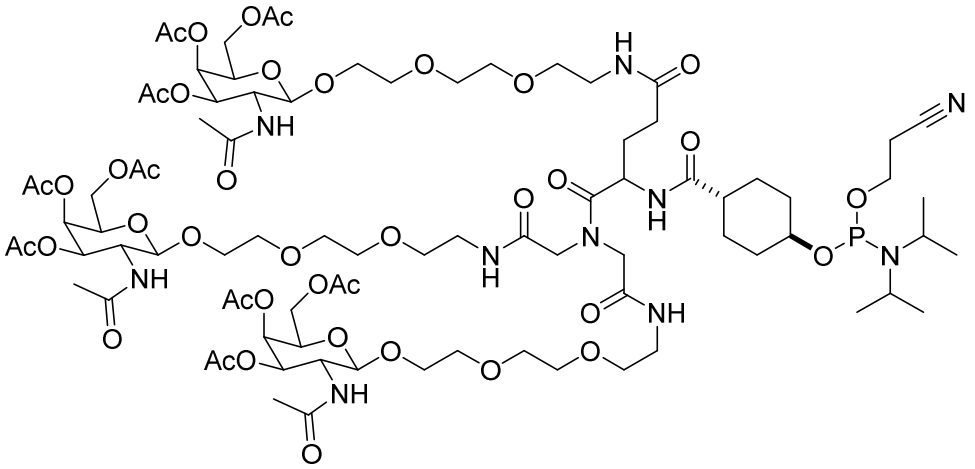
(Structure 1004b);



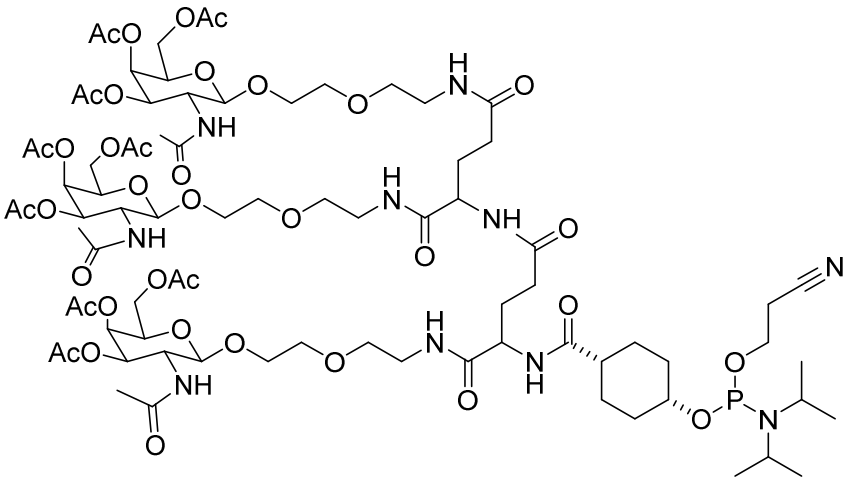
(Structure 1005b);



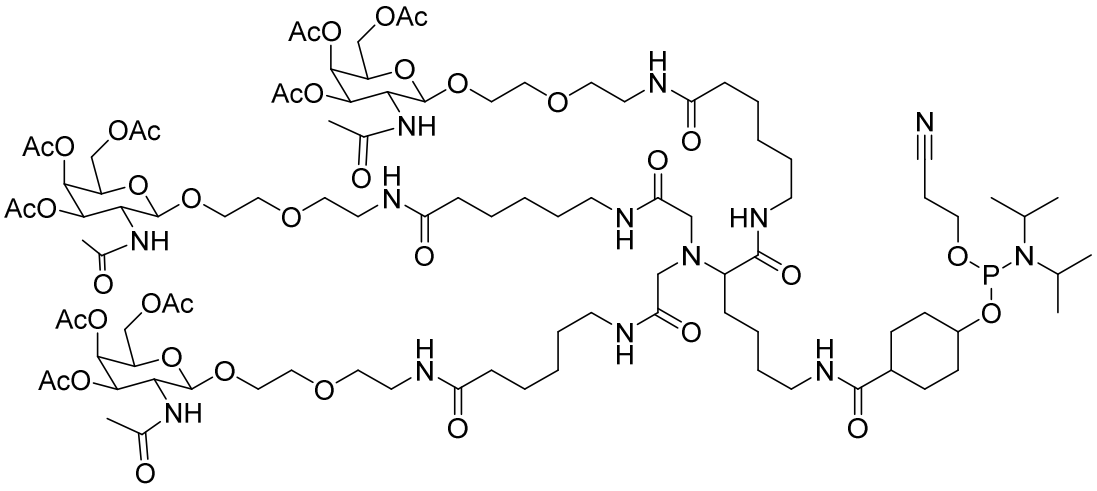
(Structure 1006b);



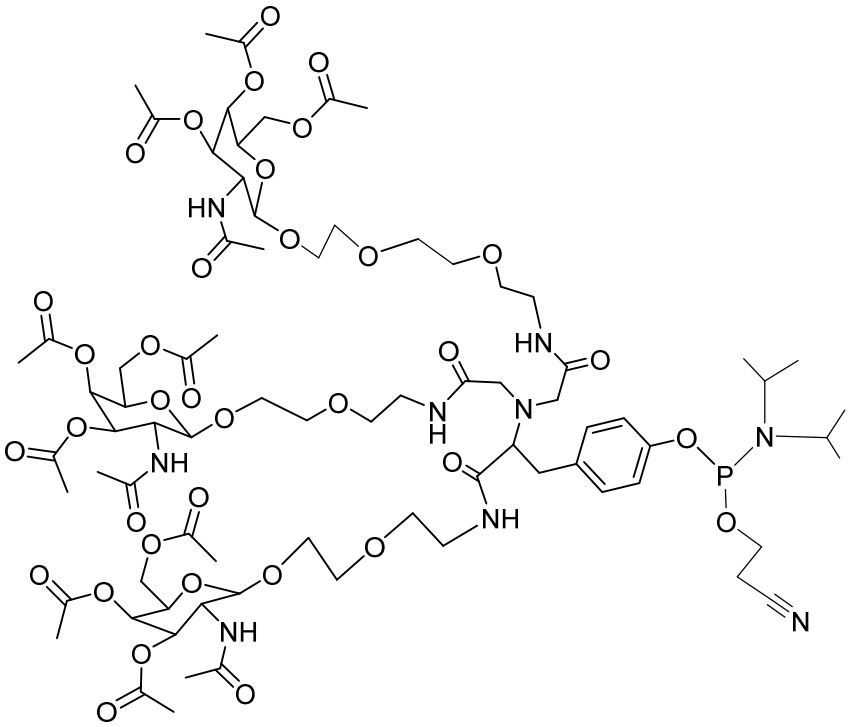
(Structure 1007b);



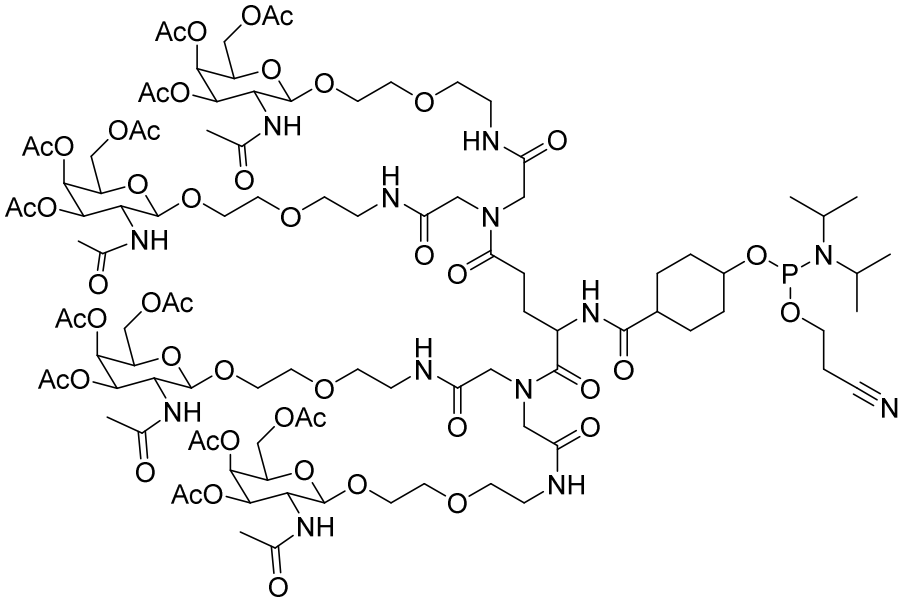
(Structure 1008b);



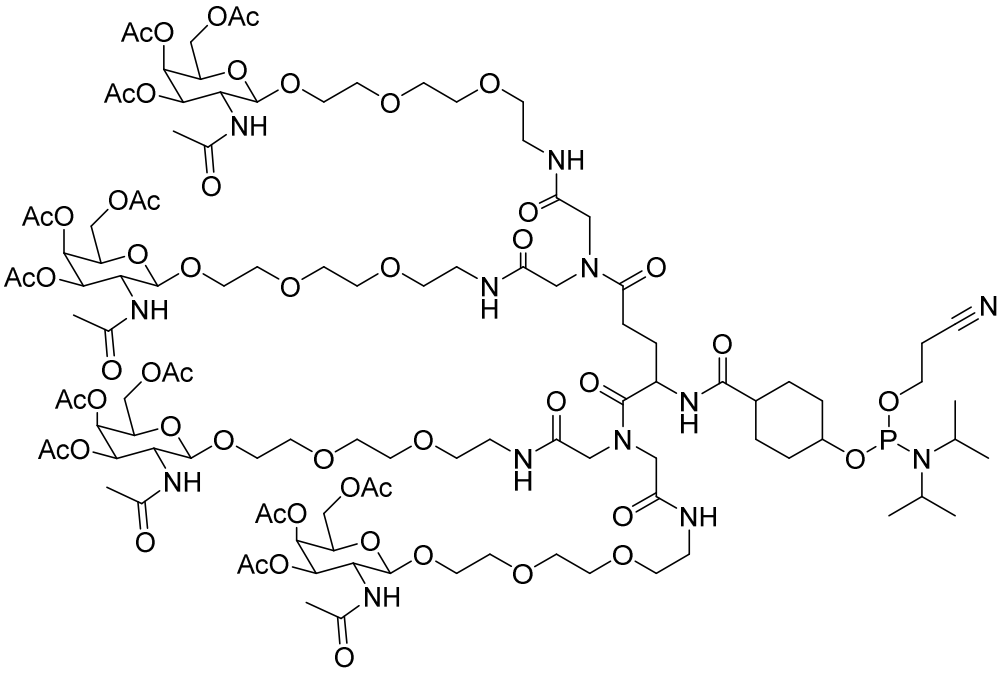
(Structure 1009b);



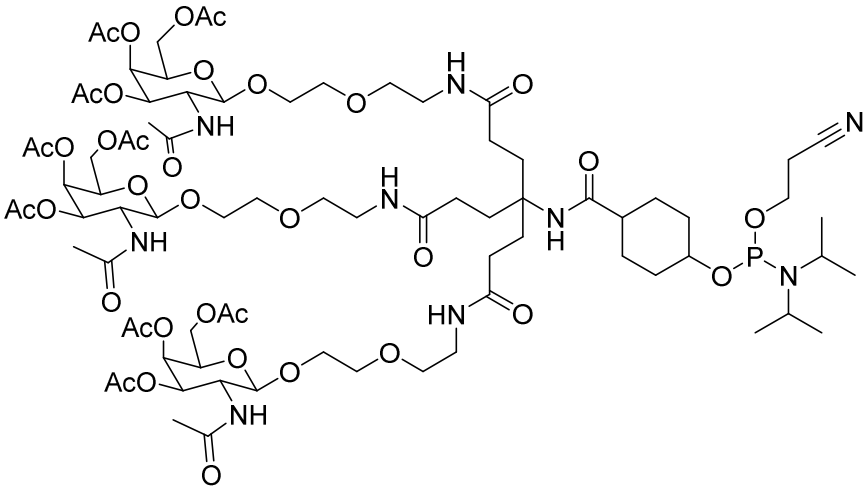
(Structure 1024b);



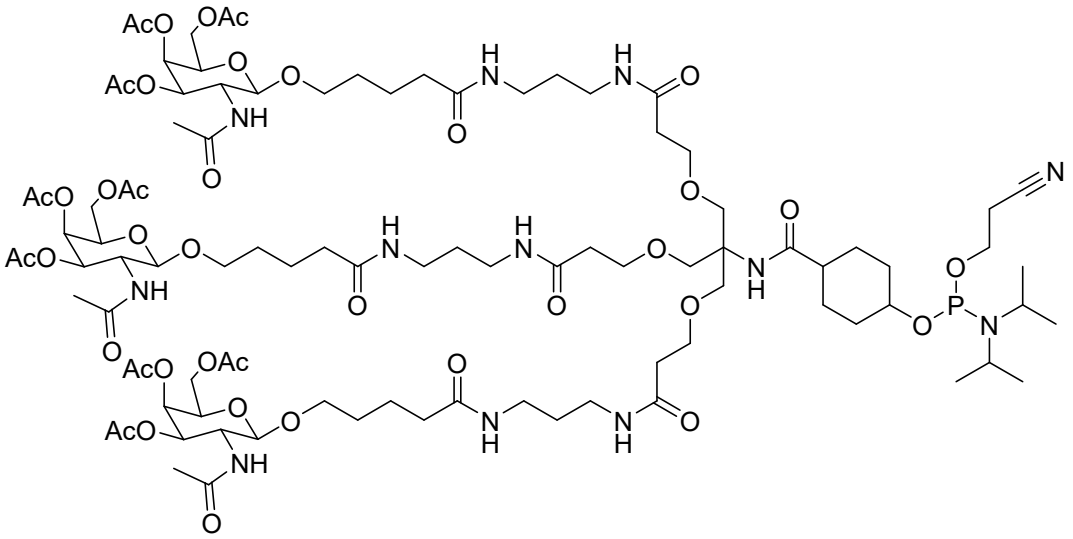
(Structure 1012b);



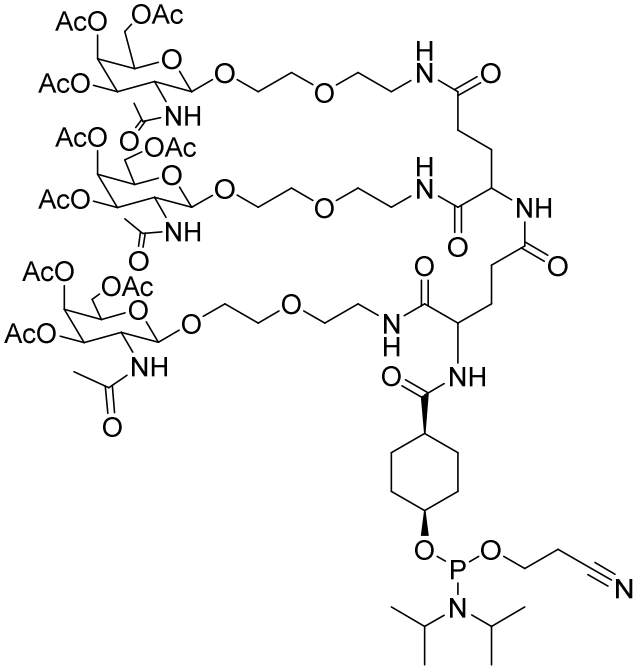
(Structure 1014b);



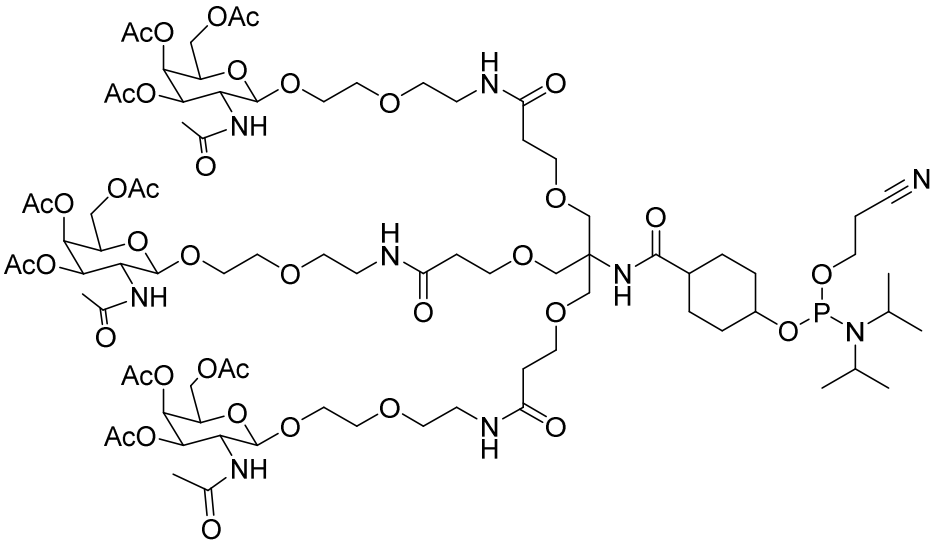
(Structure 1016b);



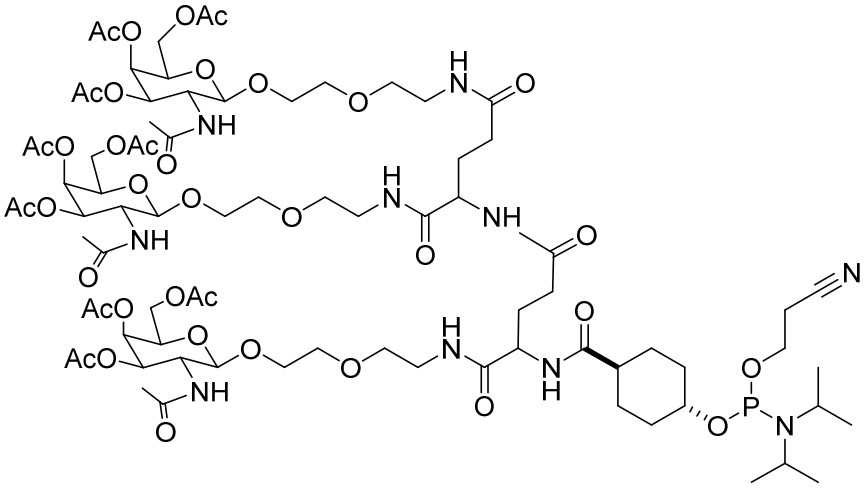
(Structure 1018b);



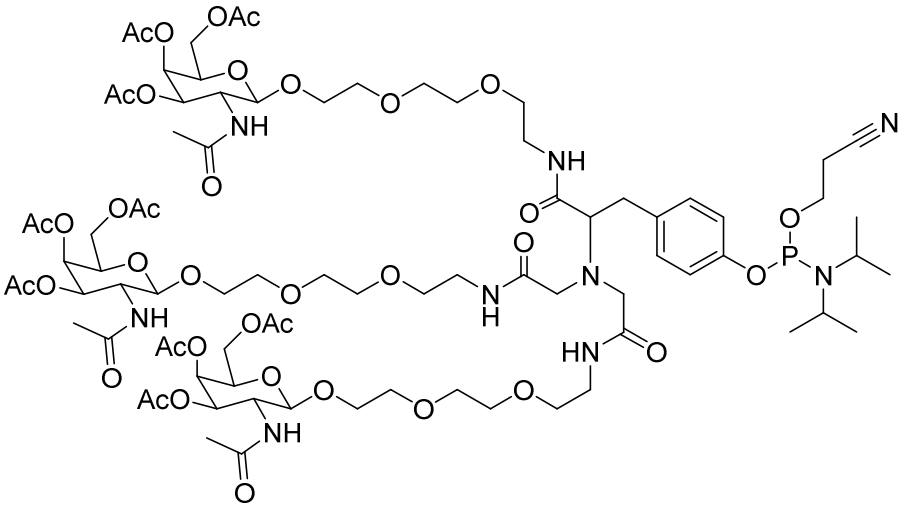
(Structure 1019b);



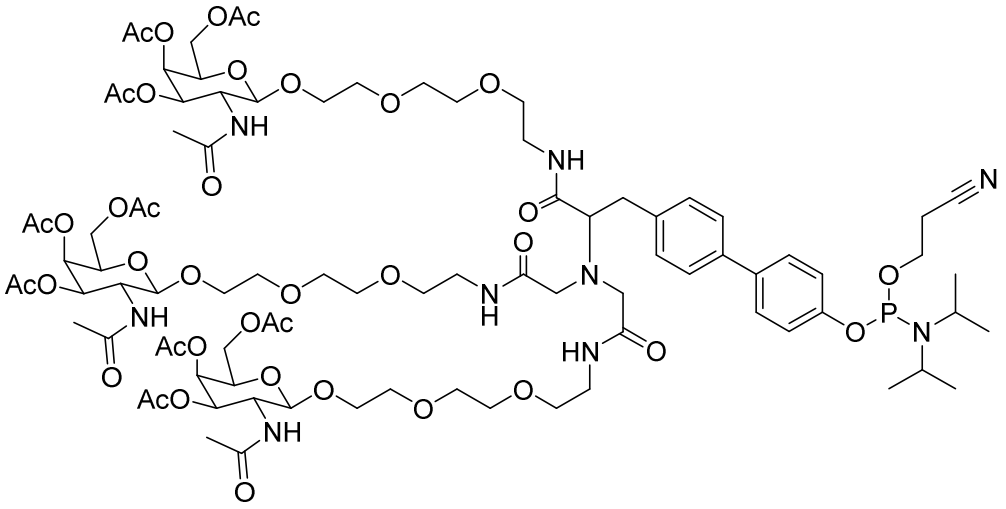
(Structure 1021b);



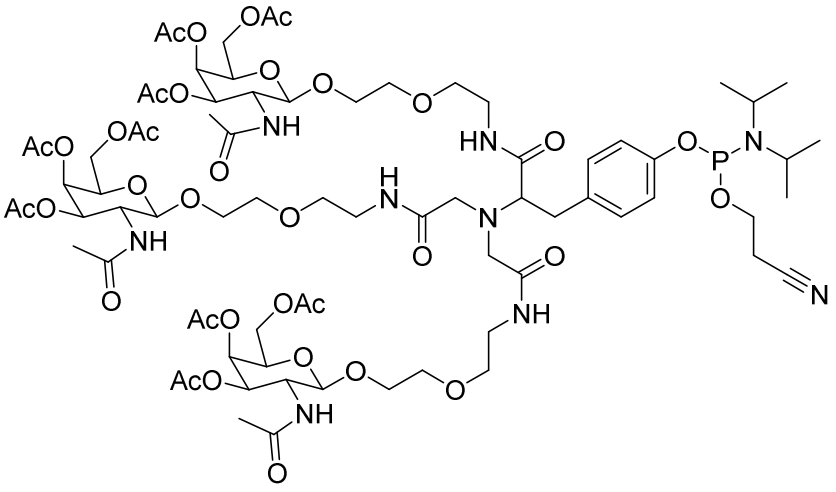
(Structure 1023b);



(Structure 1025b);

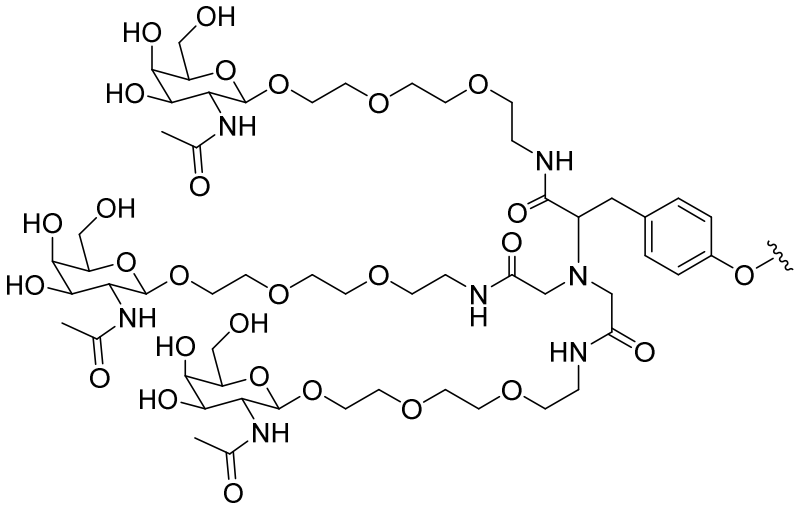


(Structure 1026b); and

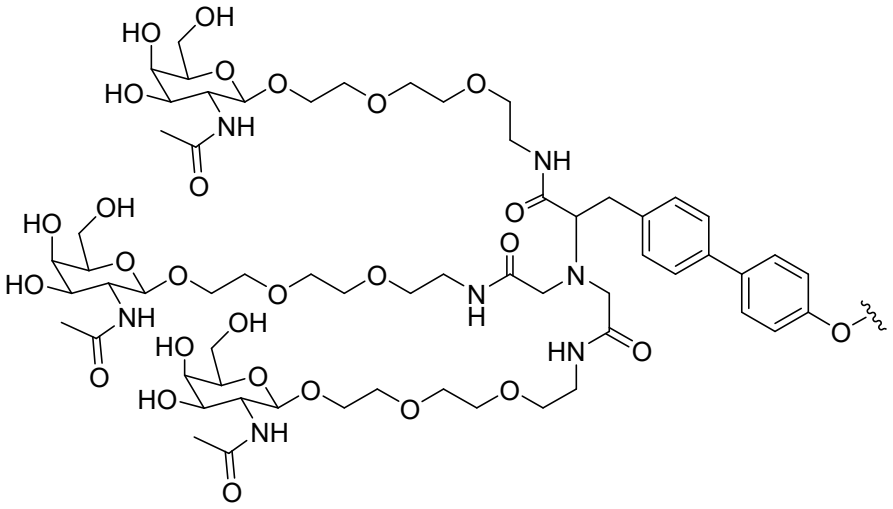


(Structure 1027b).

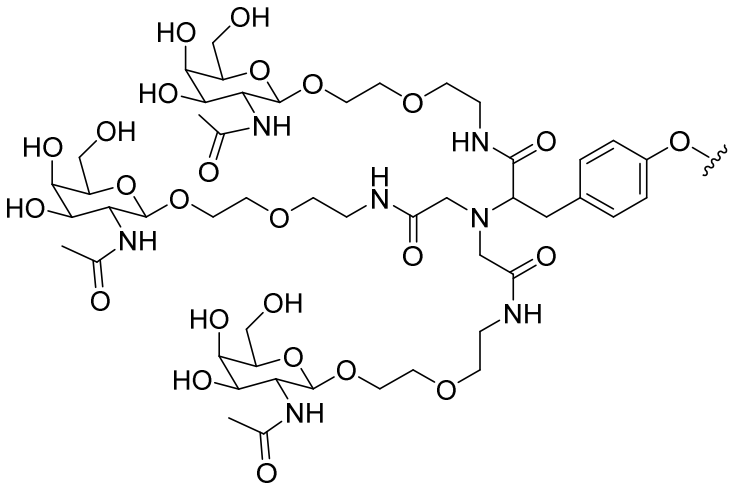
11. A targeting ligand comprising a structure selected from the group consisting of:



(Structure 1025);



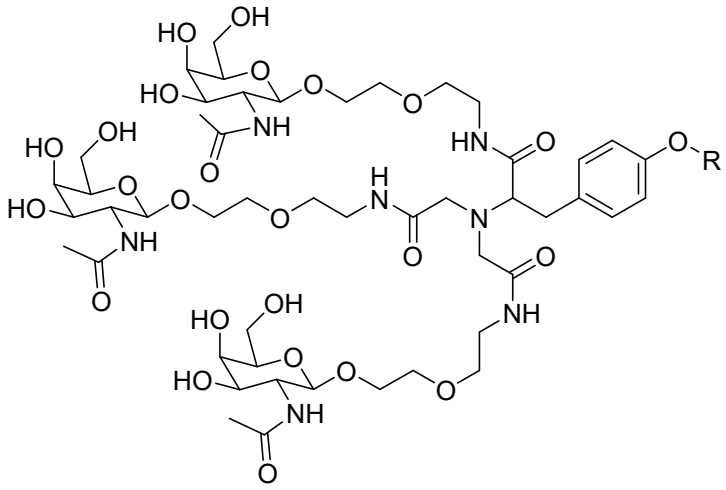
(Structure 1026); and



(Structure 1027),

wherein the targeting ligand is linked to an RNAi agent.

12. The targeting ligand of claim 11, wherein the targeting ligand linked to the RNAi agent has the following structure:



wherein R comprises the RNAi agent (Structure 1027a).

13. The targeting ligand of claim 11, wherein the RNAi agent is double stranded.

14. The targeting ligand of claim 13, wherein the RNAi agent includes one or more modified nucleotides.

15. An in vitro method of introducing a therapeutic agent into a mammalian cell, the method comprising contacting a mammalian cell with the targeting ligand of claim 1, wherein the therapeutic agent comprises the RNAi agent.

16. The method of claim 15, wherein the therapeutic agent is a double-stranded RNAi agent.

17. An in vitro method of introducing a therapeutic agent into a mammalian cell, the method comprising contacting a mammalian cell with the targeting ligand of claim 11, wherein the therapeutic agent comprises the RNAi agent.

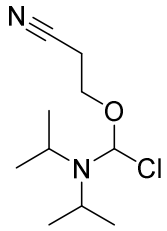
18. The method of claim 17, wherein the therapeutic agent is a double-stranded RNAi agent.

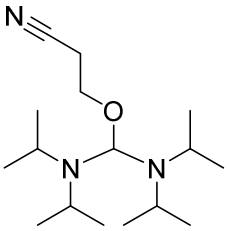
19. A method of manufacturing a phosphoramidite compound including the compound of claim 10, the method comprising:

(i) covalently linking the carboxylic acid moiety or its activated ester of the linker to a terminal amine located on the branch point group, and

(ii) linking the linker to a phosphorus atom of a phosphoramidite through a phosphitylation reaction with a phosphoramidite forming reagent; thereby forming a phosphoramidite compound that includes a targeting ligand.

20. The method of claim 19, wherein the phosphoramidite reagent is selected from the group consisting of:



and


.

21. The targeting ligand of claim 2, comprising Structure 1003.

22. The targeting ligand of claim 2, comprising Structure 1008.

23. The targeting ligand of claim 2, comprising Structure 1023.

24. The targeting ligand of claim 5, comprising Structure 1003.

25. The targeting ligand of claim 5, comprising Structure 1008.

26. The targeting ligand of claim 5, comprising Structure 1023.

27. The targeting ligand of claim 6, comprising Structure 1003.

28. The targeting ligand of claim 6, comprising Structure 1008.

29. The targeting ligand of claim 6, comprising Structure 1023.

30. The composition of claim 7, comprising Structure 1003a.

31. The composition of claim 7, comprising Structure 1008a.

32. The composition of claim 7, comprising Structure 1023a.

33. The composition of claim 8, comprising Structure 1003a.

34. The composition of claim 8, comprising Structure 1008a.

35. The composition of claim 8, comprising Structure 1023a.

36. The composition of claim 9, comprising Structure 1003a.

37. The composition of claim 9, comprising Structure 1008a.

38. The composition of claim 9, comprising Structure 1023a.

39. The compound of claim 10, comprising Structure 1003b.

40. The compound of claim 10, comprising Structure 1008b.

41. The compound of claim 10, comprising Structure 1023b.