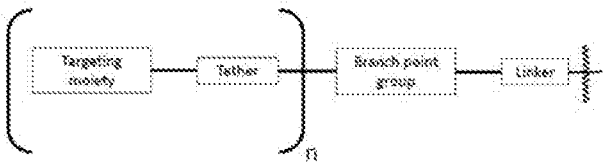
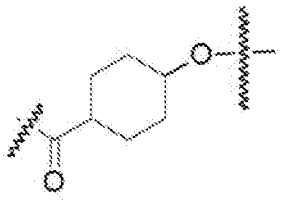
Claims:

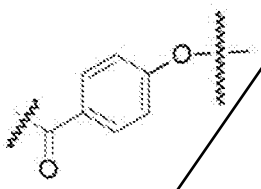
1. A targeting ligand comprising a structure of Formula I:



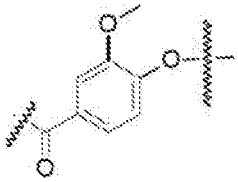
, comprising a linker, a branch point group, one or more tethers, and one or more targeting moieties, wherein n is an integer from 1 to 4, and wherein the linker is a structure selected from the group consisting of:



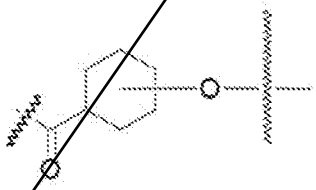
(Structure 1);



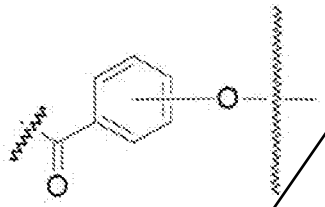
(Structure 2);



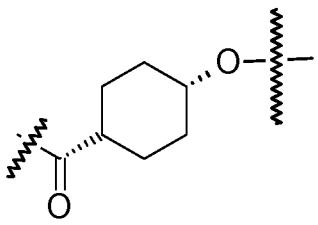
(Structure 3);



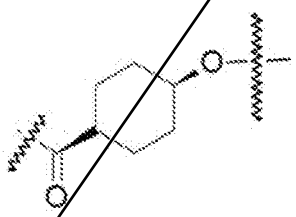
(Structure 4);



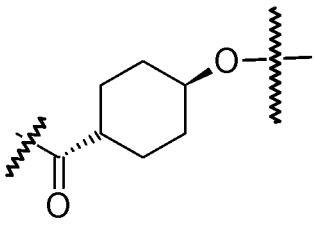
(Structure 5);



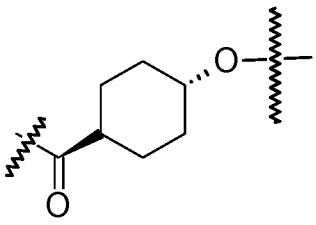
(Structure 6a);

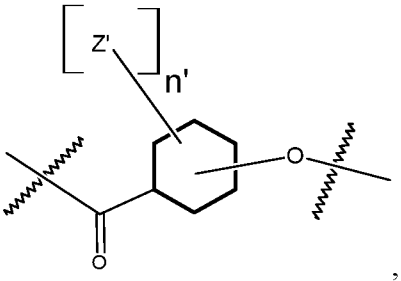


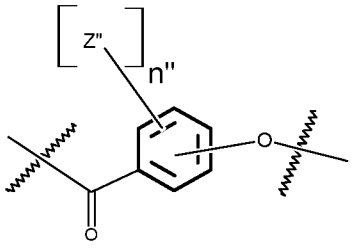
(Structure 6b);

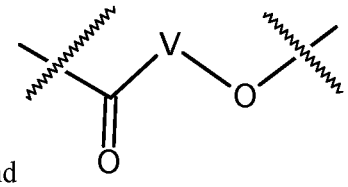


(Structure 6c);



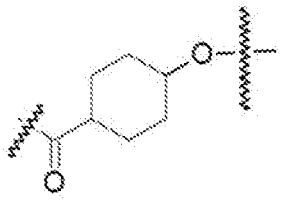
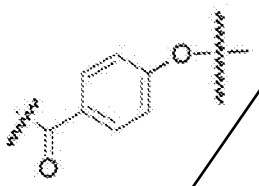
(Structure 6d); , wherein n′ is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, and when present, each Z′ is independently selected from the group consisting of: C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, substituted or unsubstited amino, carboxyl, C1-C6 alkoxy, substituted C1-C6 alkyl, C1-C6 aminoalkyl, substituted C2-C6 alkenyl, substituted C2-C6 alkynyl, substituted C1-C6 alkoxy, substituted C1-C6 aminoalkyl, halogen (e.g., F), hydroxyl, amido, substituted amide, cyano, substituted or unsubstituted keto, substituted or unsubstituted alkoxycarbonyl, substituted or unsubstituted aryloxycarbonyl, substituted or unsubstituted heteroaryloxycarbonyl, and sulfhydryl (Structure 7);

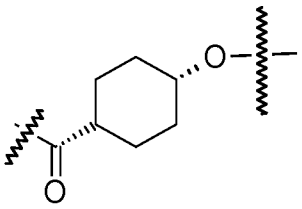
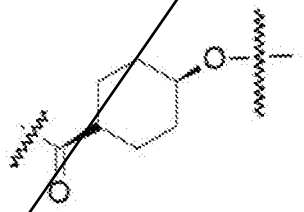


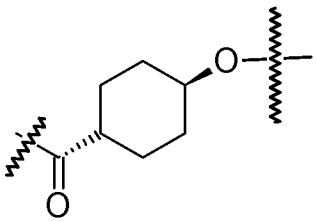
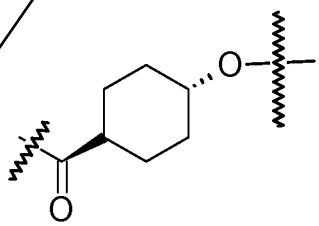
, wherein n″ is 0, 1, 2, 3, 4, and when present, each Z″ is independently selected from the group consisting of: C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, C1-C6 alkoxy, substituted C1-C6 alkyl, C1-C6 aminoalkyl, substituted C2-C6 alkenyl, substituted C2-C6 alkynyl, substituted or unsubstituted amino, carboxyl, substituted C1-C6 alkoxy, substituted C1-C6 aminoalkyl, halogen (e.g., F), hydroxyl, amido, substituted amide, cyano, substituted or unsubstituted keto, substituted or unsubstituted alkoxycarbonyl, substituted or unsubstituted aryloxycarbonyl, substituted or unsubstituted heteroaryloxycarbonyl, and sulfhydryl (Structure 8); and , wherein V comprises one or more substituted or unsubstituted cycloalkyl (e.g., cyclohexyl, cyclopropyl, cyclobutyl, cyclopentyl, cycloheptyl, cycloocty, etc.), substituted or unsubstituted cycloalkenyl (e.g., cyclohexenyl, cyclobutenyl, cyclopentenyl, cycloheptenyl, cyclooctenyl, cyclohexadienyl, cyclopentadienyl, cycloheptadienyl, cyclooctadienyl, etc.), substituted or unsubstituted aryl (e.g., phenyl, naphthyl, binapthyl, anthracenyl, etc.), substituted or unsubstituted heteroaryl (e.g., pyridyl, pyrimidinyl, pyrrole, imidazole, furan, benzofuran,

indole, etc.), or substituted or unsubstituted heterocyclyl (e.g., tetrahydrofuran, tetrahydropyran, piperidine, pyrrolidine, etc.), or any covalently linked combination thereof. (Structure 9).

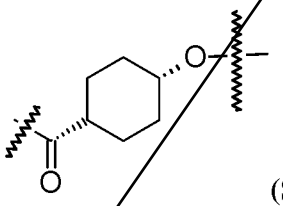
2. The targeting ligand of claim 1, wherein the linker is a structure selected from the group consisting of:

 (Structure 1),  (Structure 2),

 (Structure 6a),  (Structure 6b),

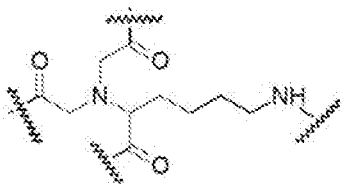
 (Structure 6c); and  (Structure 6d).

3. The targeting ligand of claim 1 or 2, wherein the linker is:

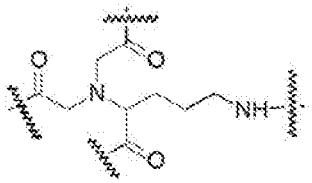


(Structure 6a).

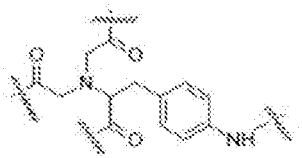
4. The targeting ligand of any of claims 1 to 3, wherein the branch point group is a structure selected from the group consisting of:



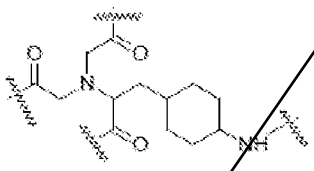
(Structure 201);



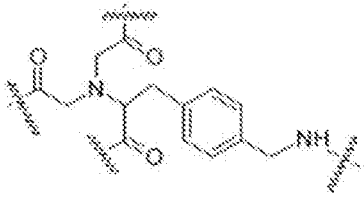
(Structure 202);



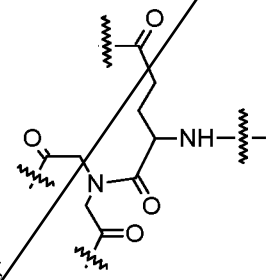
(Structure 203);



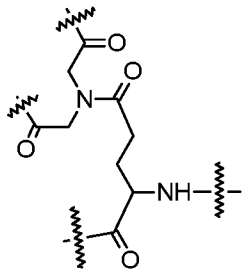
(Structure 204);



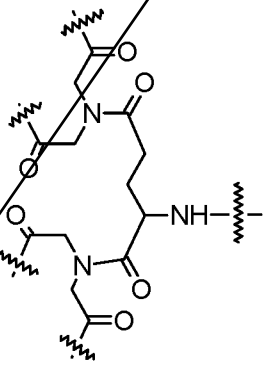
(Structure 205);



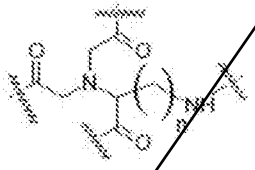
(Structure 206);



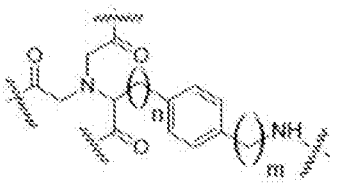
(Structure 207);



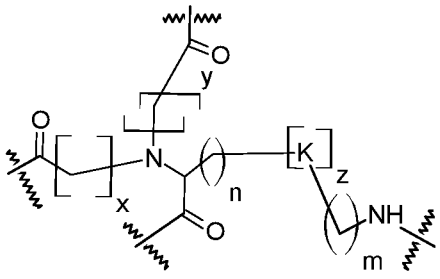
(Structure 208);



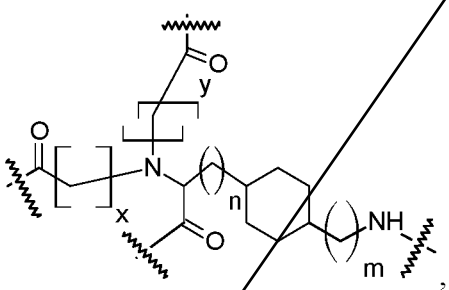
, wherein n is an integer from 1 to 20 (Structure 209);



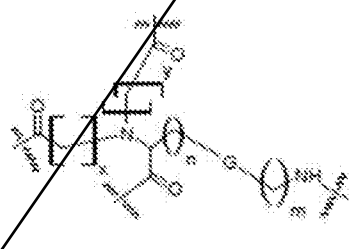
, wherein m is an integer from 0 to 20, and n is an integer from 0 to 20 (Structure 210);



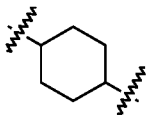
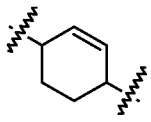
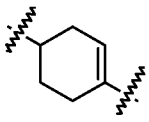
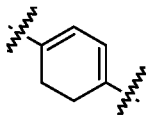
, wherein m is an integer from 0 to 20; n is an integer from 0 to 20; x is an integer from to 1 to 10; y is an integer from 1 to 10; z is an integer from 1 to 4; and K is selected from the group consisting of substituted or unsubstituted cycloalkyl (e.g., cyclohexyl, cyclopropyl, cyclobutyl, cyclopentyl, cycloheptyl, cycloocty, etc.), substituted or unsubstituted cycloalkenyl (e.g., cyclohexenyl, cyclobutenyl, cyclopentenyl, cycloheptenyl, cyclooctenyl, cyclohexadienyl, cyclopentadienyl, cycloheptadienyl, cyclooctadienyl, etc.), substituted or unsubstituted aryl (e.g., phenyl, naphthyl, binapthyl, anthracenyl, etc.), substituted or unsubstituted heteroaryl (e.g., pyridyl, pyrimidinyl, pyrrole, imidazole, furan, benzofuran, indole, etc.), and substituted or unsubstituted heterocyclyl (e.g., tetrahydrofuran, tetrahydropyran, piperidine, pyrrolidine, etc.), or any combination thereof (Structure 211);

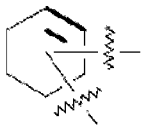
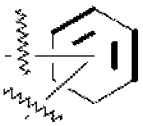


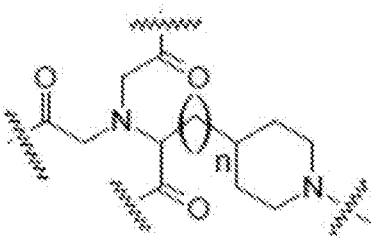
, wherein m is an integer from 0 to 20; n is an integer from 0 to 20; x is an integer from to 1 to 10; and y is an integer from 1 to 10 (Structure 212);



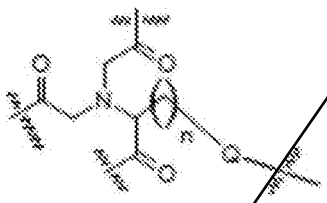
, wherein m is an integer from 0 to 20; n is an integer from 0 to 20; x is an integer from to 1 to 10; y is an integer from 1 to 10; G is selected from the group

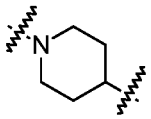
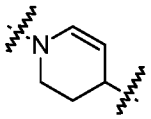
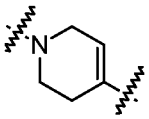
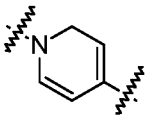
consisting of:  ;  ;  ;  ;  ;

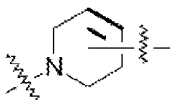
 ;  ; or any substituted or unsubstituted cyclic or heterocyclic structure having a ring size of 5, 6, 7, 8, or 9 atoms, for example, substituted or unsubstituted cycloalkyl (e.g., cyclohexyl, cyclopropyl, cyclobutyl, cyclopentyl, cycloheptyl, cycloocty, etc.), cycloalkenyl (e.g., cyclohexenyl, cyclobutenyl, cyclopentenyl, cycloheptenyl, cyclooctenyl, cyclohexadienyl, cyclopentadienyl, cycloheptadienyl, cyclooctadienyl, etc.), aryl (e.g., phenyl, naphthyl, binapthyl, anthracenyl, etc.), heteroaryl (e.g., pyridyl, pyrimidinyl, pyrrole, imidazole, furan, benzofuran, indole, etc.), or heterocyclyl (e.g., tetrahydrofuran, tetrahydropyran, piperidine, pyrrolidine, etc.) (Structure 213);

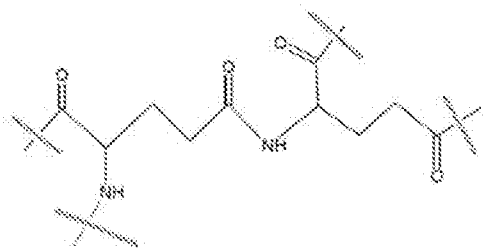


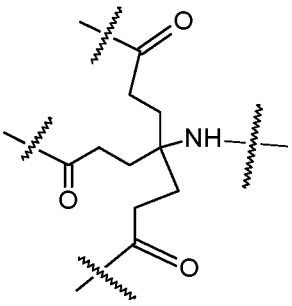
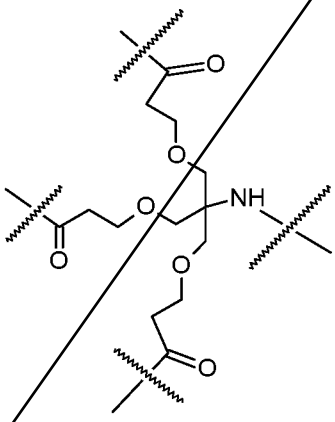
, wherein n is an integer from 0 to 20 (Structure 214);

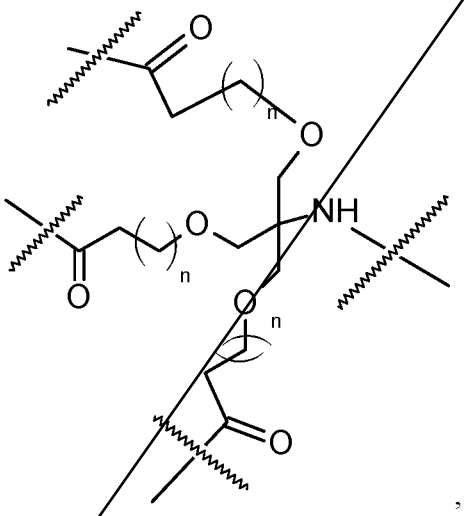


, wherein n is an integer from 0 to 20, and Q is selected from the group consisting of:  ;  ;  ;  ;

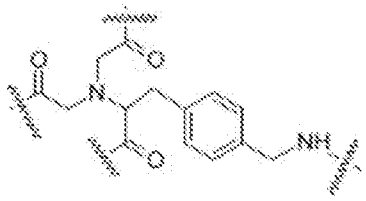

; 
; 
; or  (Structure 215);


(Structure 216);

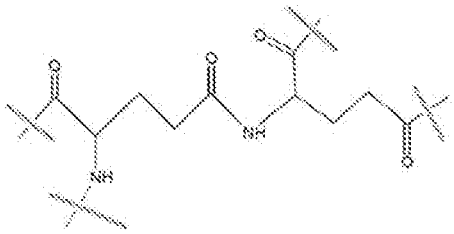

(Structure 217); 
(Structure 218);


, wherein n is an integer selected from 1 to 7 (Structure 219).

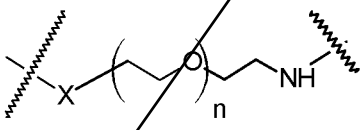
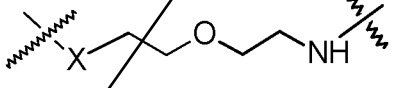
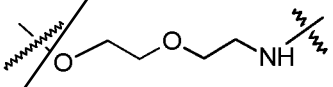
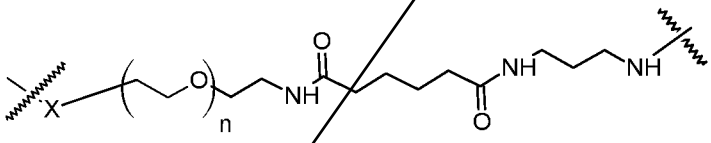
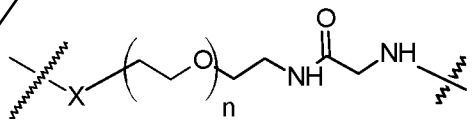
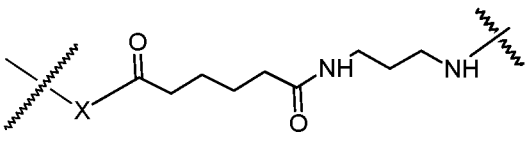
5. The targeting ligand of any of claims 1 to 4, wherein the branch point group is:

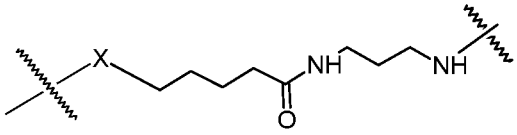


(Structure 205) or



(Structure 216).

6. The targeting ligand of any of claims 1 to 5, wherein the tether is independently selected from the group consisting of:  , wherein n is an integer from 1 to 20 (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20), and X is O, S, or NH (Structure 301);  , wherein X is O, S, or NH (Structure 302);  (Structure 302a);  , wherein n is an integer from 1 to 20 (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20), and X is O, S, or NH (Structure 303);  , wherein n is an integer from 1 to 20 (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20), and X is O, S, or NH. (Structure 304);  , wherein X is O, S, or NH

(Structure 305); and 

, wherein X is O, S, or NH (Structure 306).

7. The targeting ligand of any of claims 1 to 6, wherein the targeting moiety is independently selected from the group consisting of: N-acetyl-galactosamine, galactose, galactosamine, N-formyl-galactosamine, N-propionyl-galactosamine, N-n-butanoylgalactosamine, and N-iso-butanoylgalactosamine.

8. The targeting ligand of claim 7, wherein the targeting moiety is N-acetyl-galactosamine.

9. The targeting ligand of claim 7, wherein the targeting moiety is independently selected from glycans, haptens, vitamins, folate, biotin, aptamers, and peptides, such as RGD-containing peptides, insulin, EGF, and transferrin.

10. The targeting ligand of any of claims 1-9, wherein n of Formula I is 3.

11. The targeting ligand of any of claims 1-9, wherein n of Formula I is 4.

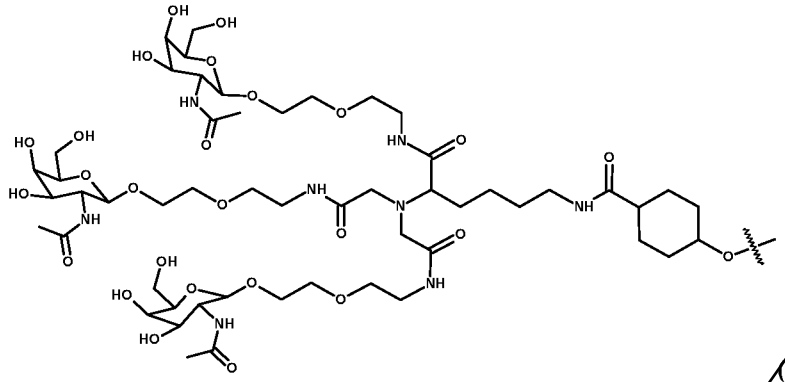
12. The targeting ligand of any of claims 1-11, wherein the targeting ligand is linked to an expression-inhibiting oligomeric compound.

13. The targeting ligand of claim 12, wherein the expression-inhibiting oligomeric compound is an RNAi agent.

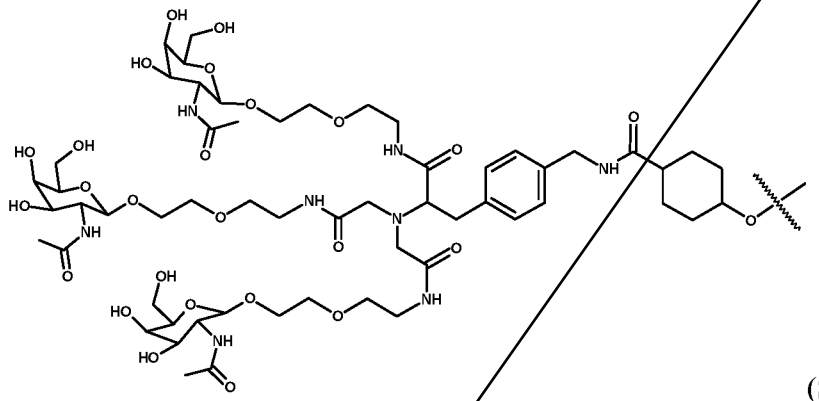
14. The targeting ligand of claim 13, wherein the RNAi agent is double-stranded.

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

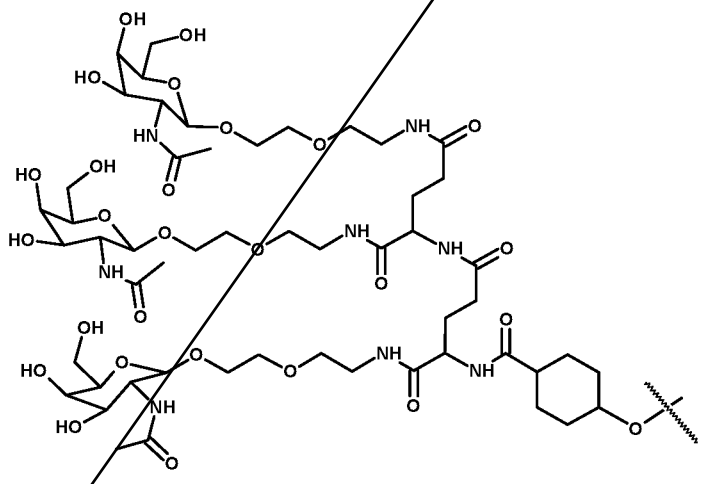
16. The targeting ligand of claim 1, wherein the targeting ligand comprises the structure selected from the following:



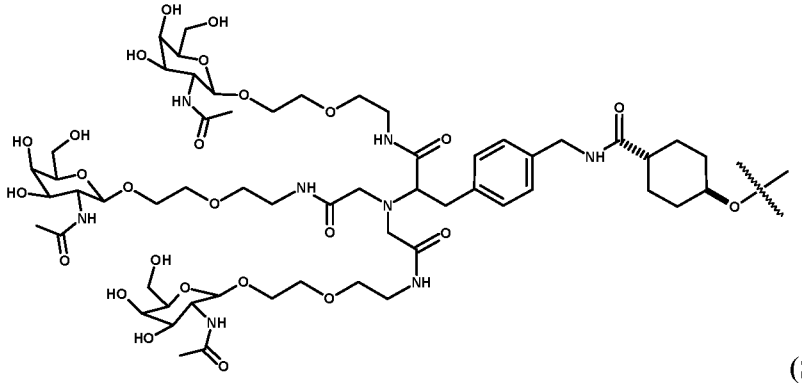
(Structure 1001);



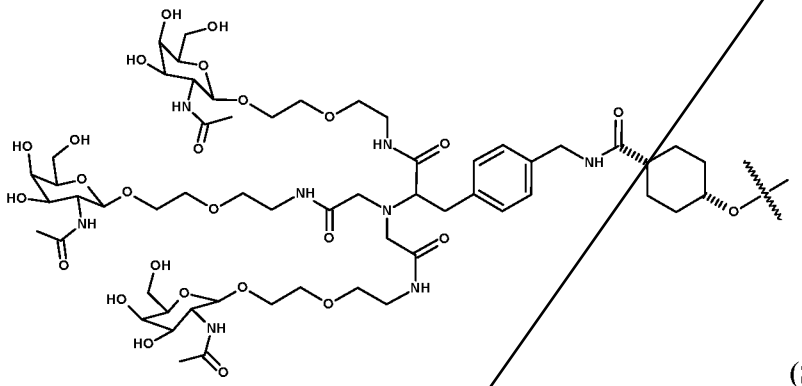
(Structure 1002);



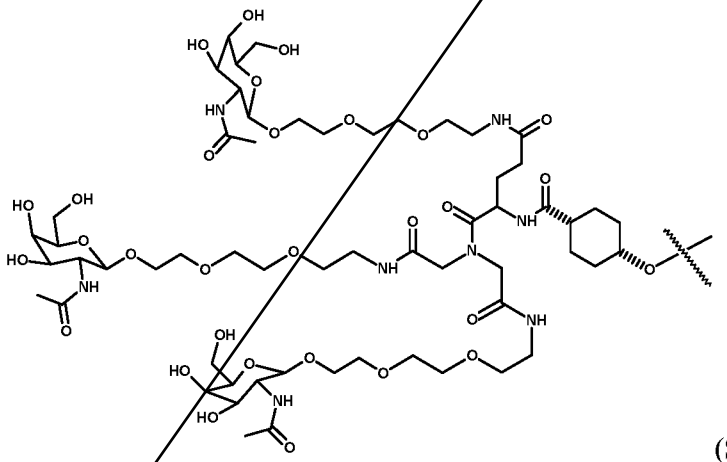
(Structure 1003);



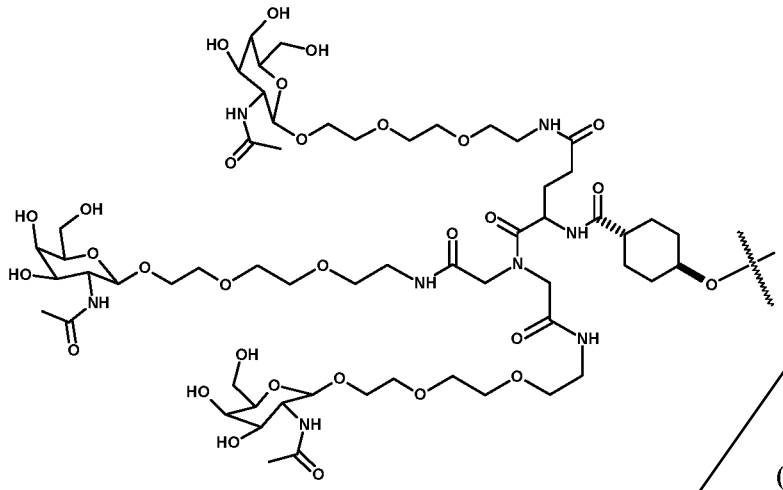
(Structure 1004);



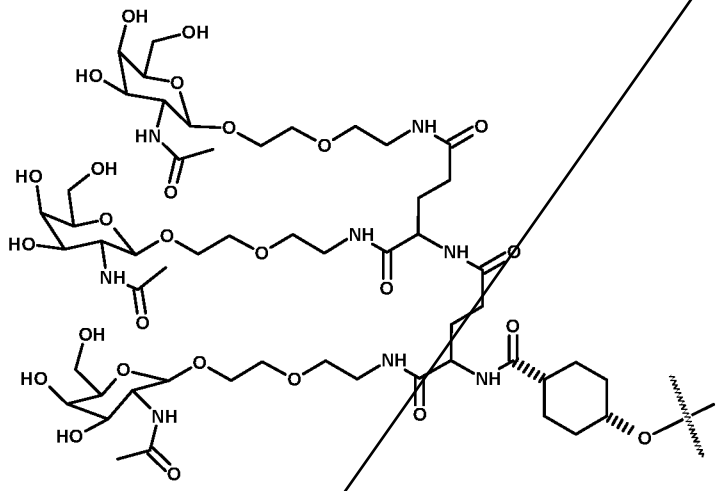
(Structure 1005);



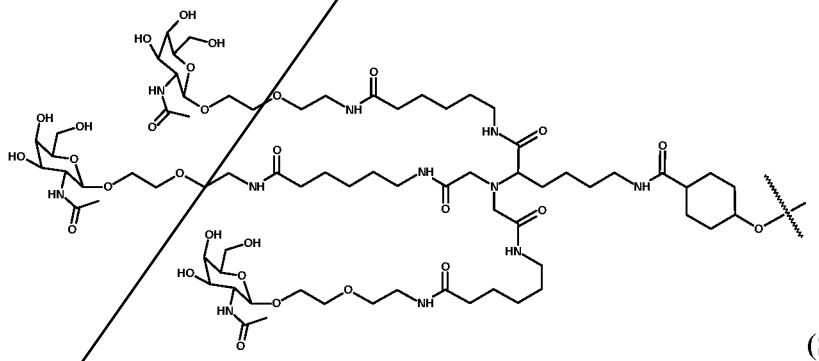
(Structure 1006);



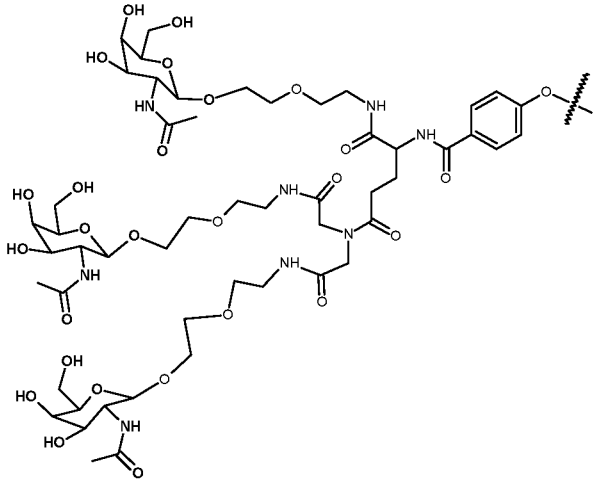
(Structure 1007);



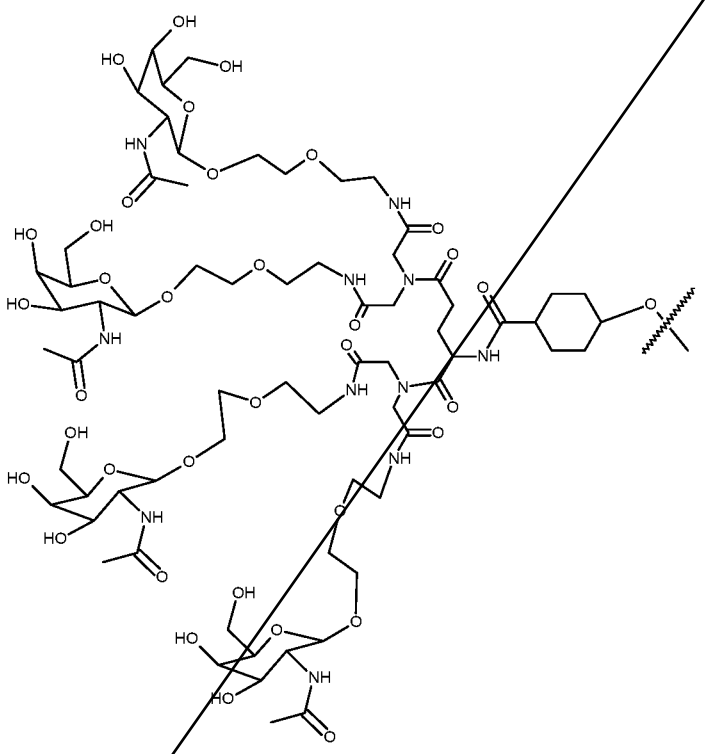
(Structure 1008);



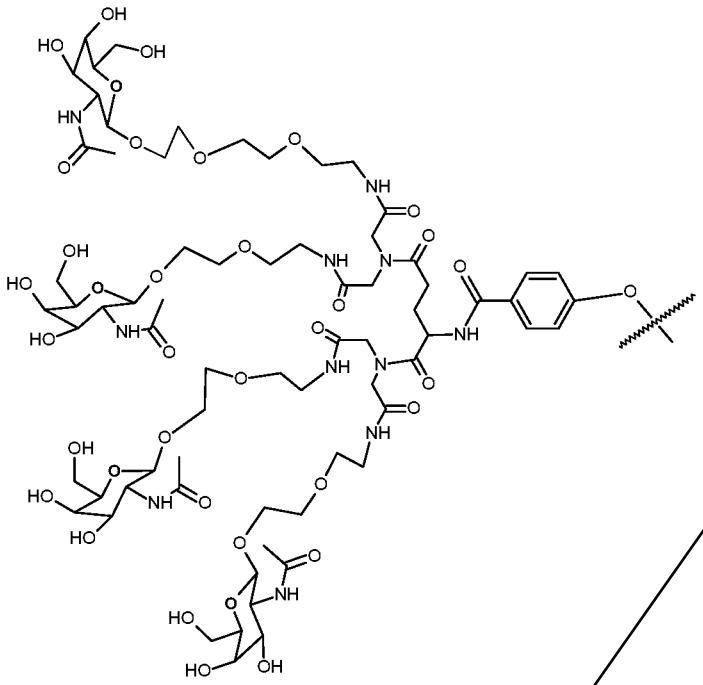
(Structure 1009);



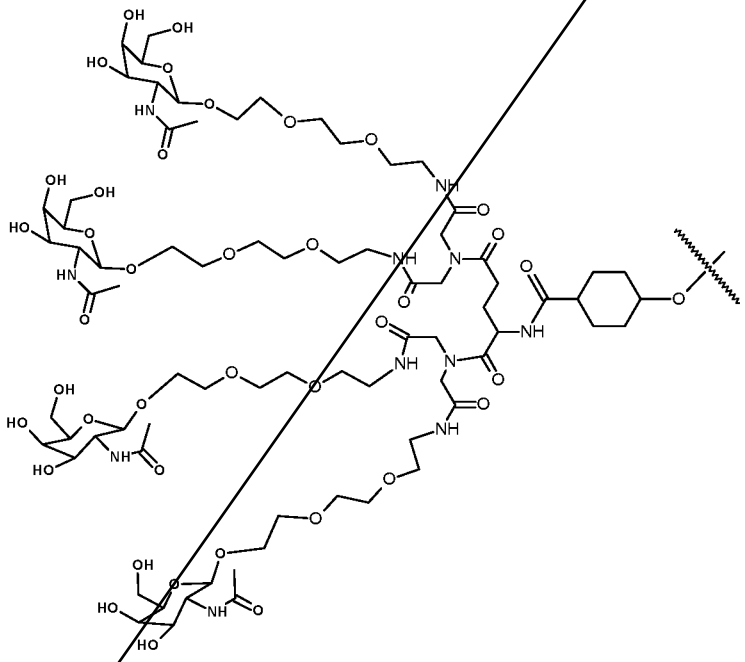
(Structure 1010);



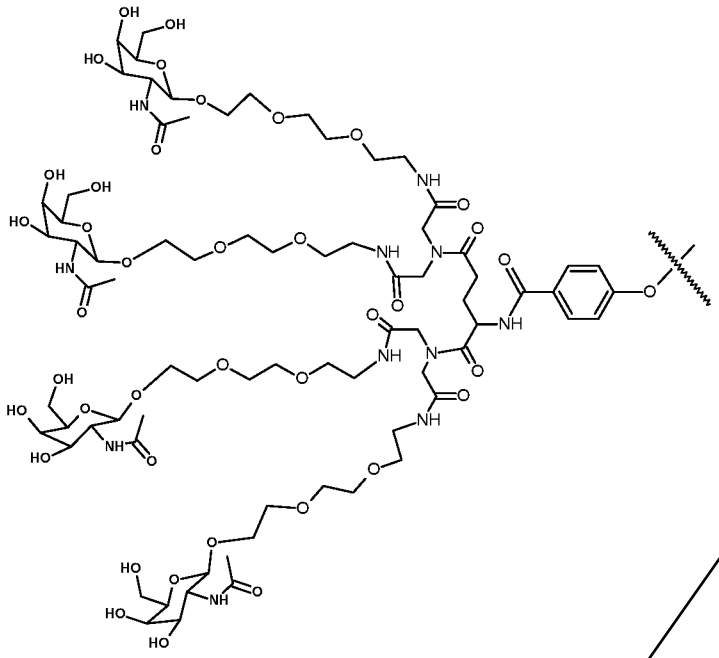
(Structure 1012);



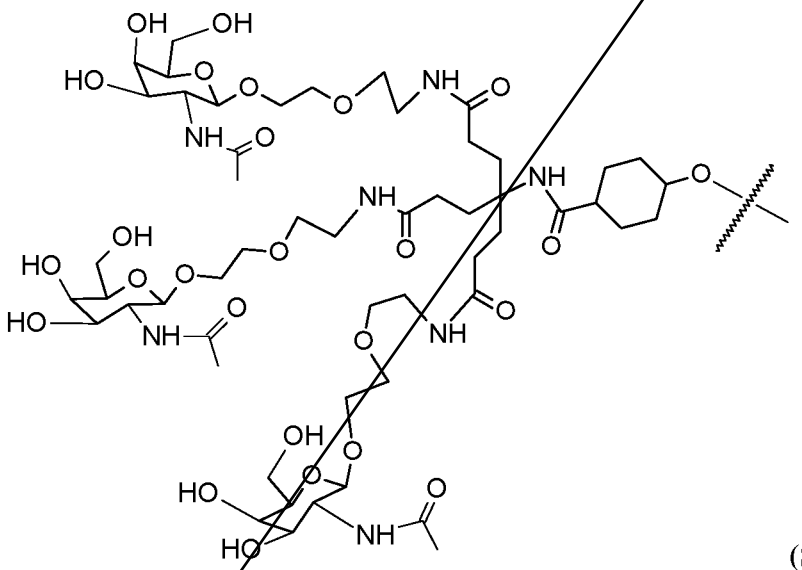
(Structure 1013);



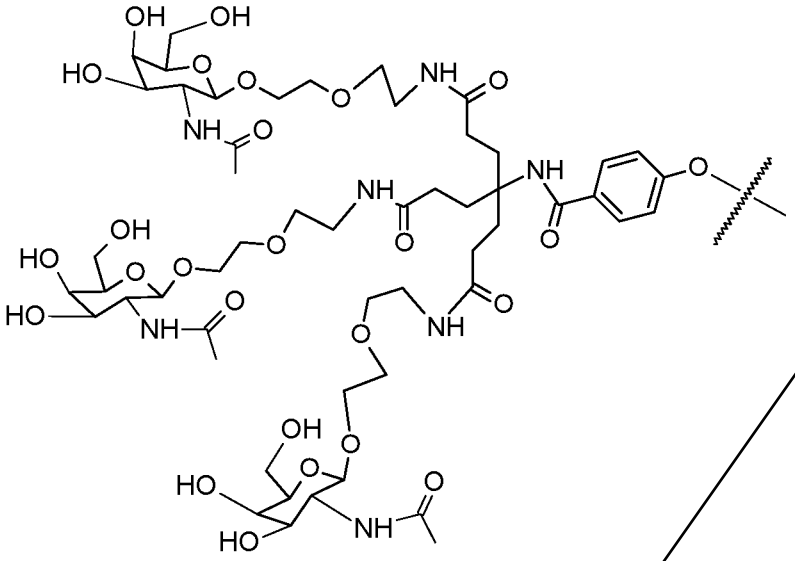
(Structure 1014);



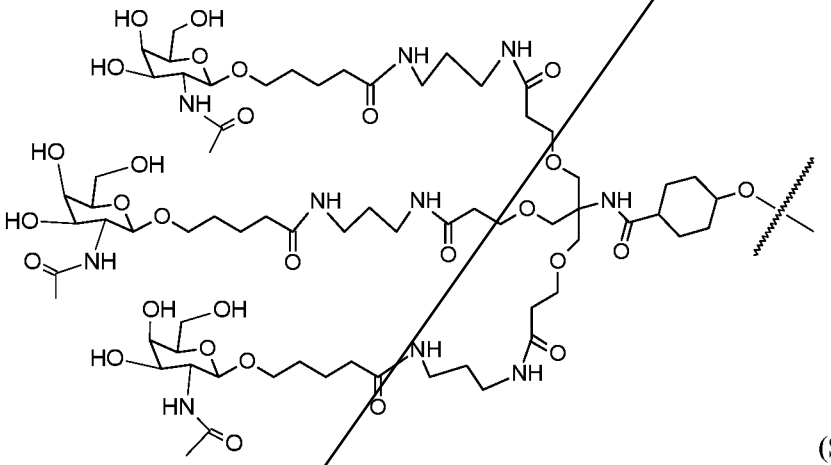
(Structure 1015);



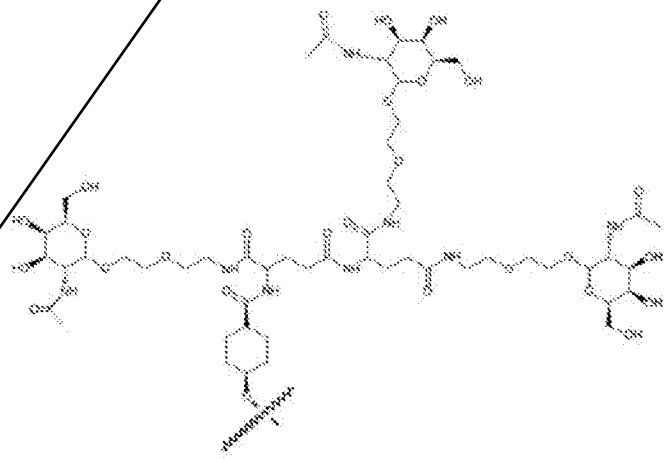
(Structure 1016);



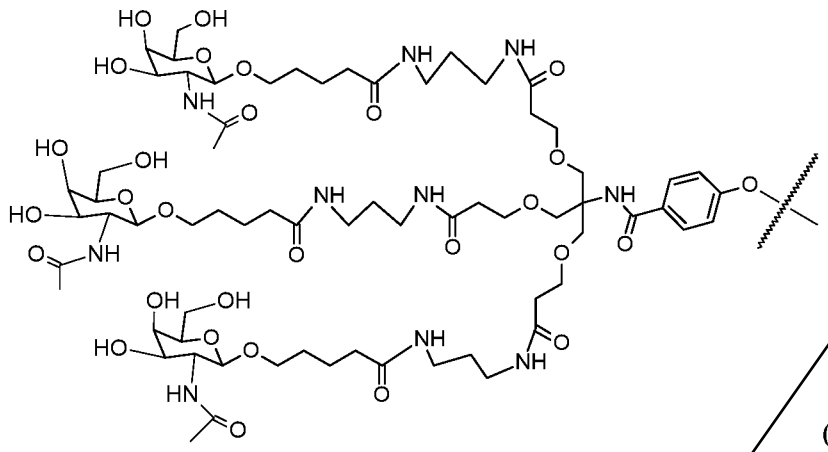
(Structure 1017);



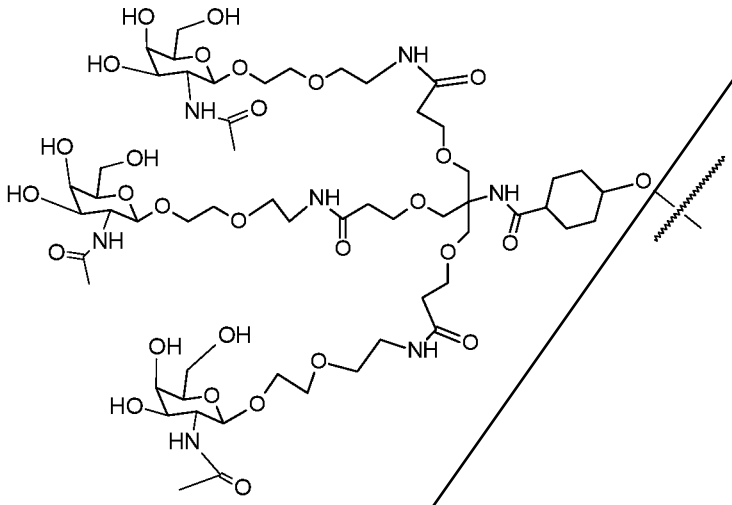
(Structure 1018);



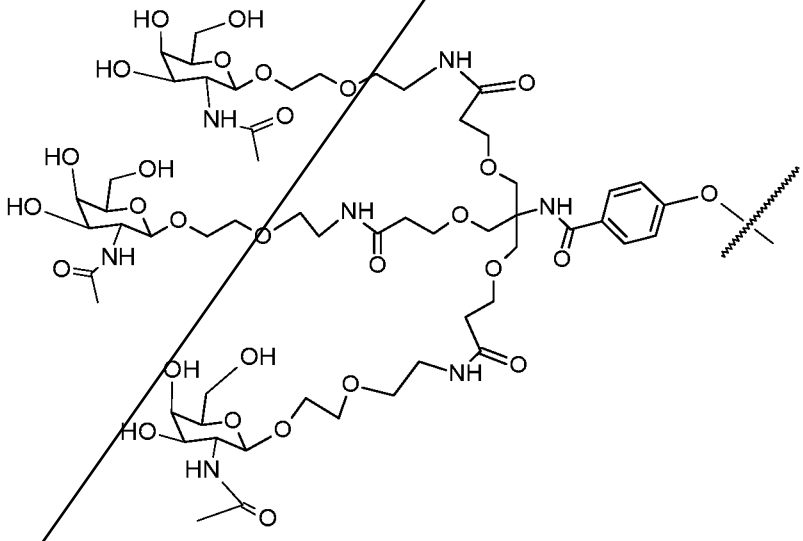
(Structure 1019);



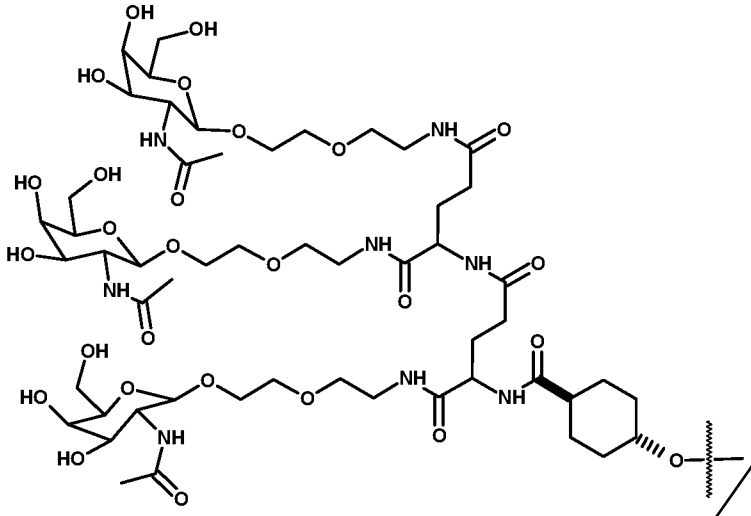
(Structure 1020);



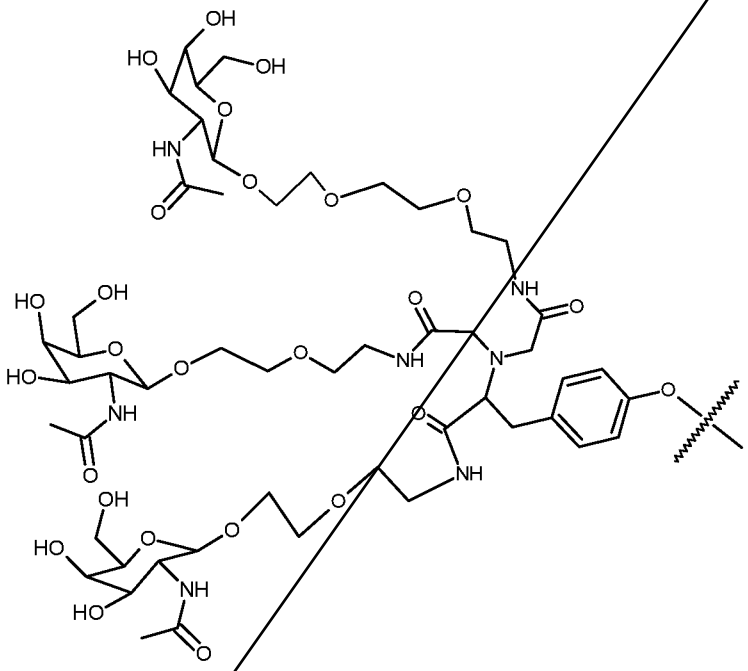
(Structure 1021);



(Structure 1022);

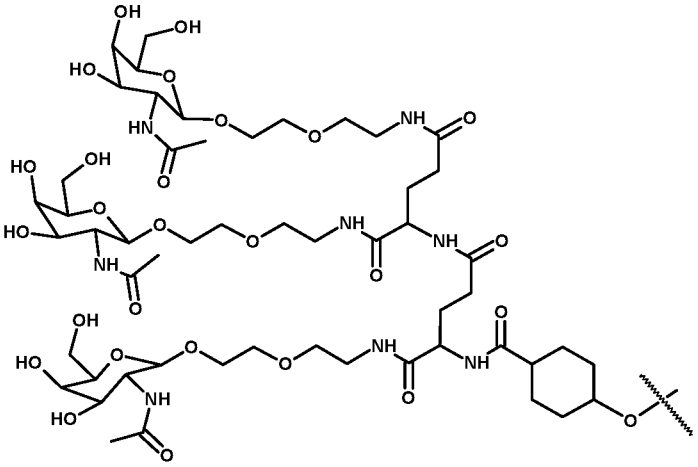


(Structure 1023); and

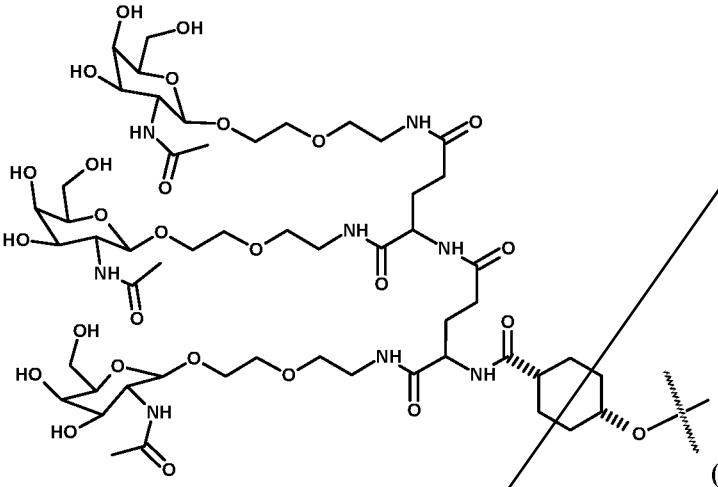


(Structure 1024).

17. The targeting ligand of claim 1, wherein the structure is selected from:



(Structure 1003); and



(Structure 1008).

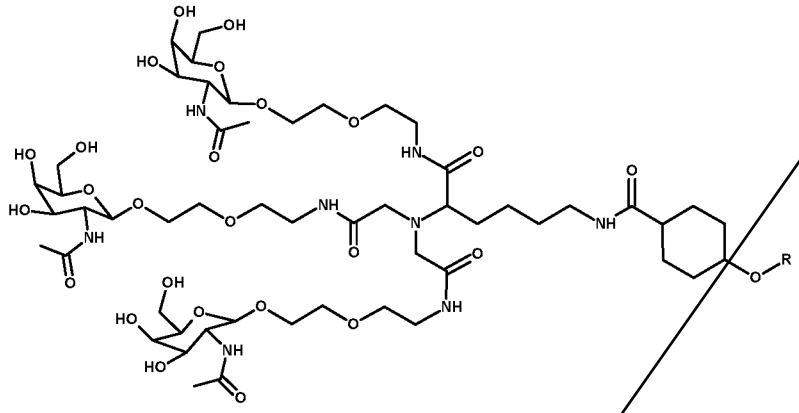
18. The targeting ligand of any of claims 1-17, wherein the targeting ligand is linked to an RNAi agent.

19. The targeting ligand of claim 18, wherein the RNAi agent is double-stranded.

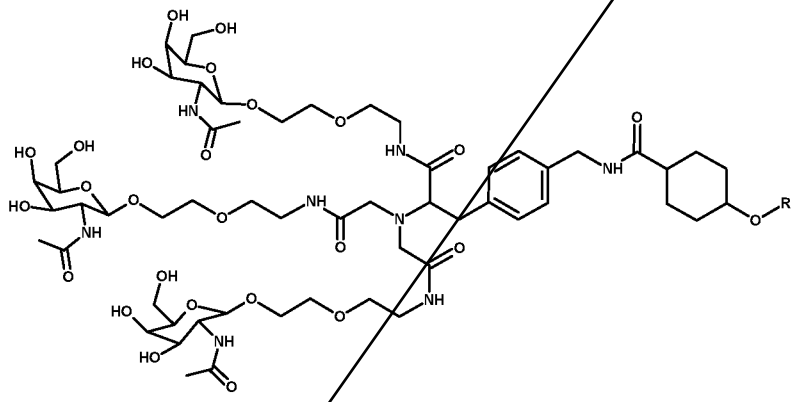
20. The targeting ligand of claim 19, wherein the double-stranded RNAi agent is linked to the targeting ligand at the 5' terminal end of the sense strand of an RNAi agent.

21. The targeting ligand of any of claims 18-20, wherein the RNAi agent is linked to the linker of the targeting ligand via a phosphate group, phosphorothioate group, or a phosphonate group.

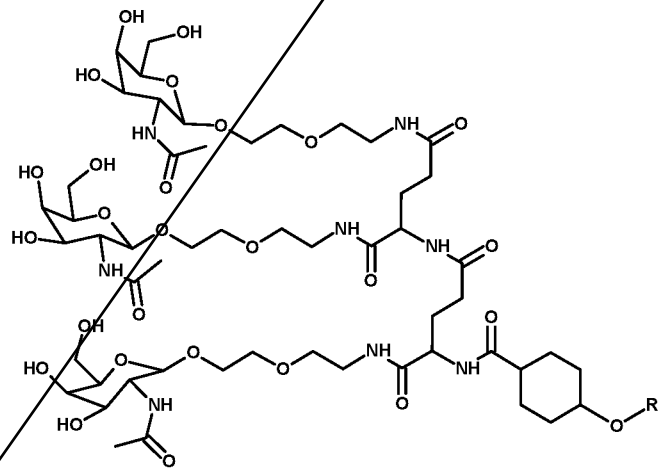
22. A composition comprising a targeting ligand of claim 1, wherein the targeting ligand is linked to an expression-inhibiting oligomeric compound, wherein the structure of the targeting ligand and expression-inhibiting oligomeric compound is represented by the structure selected from the group consisting of:



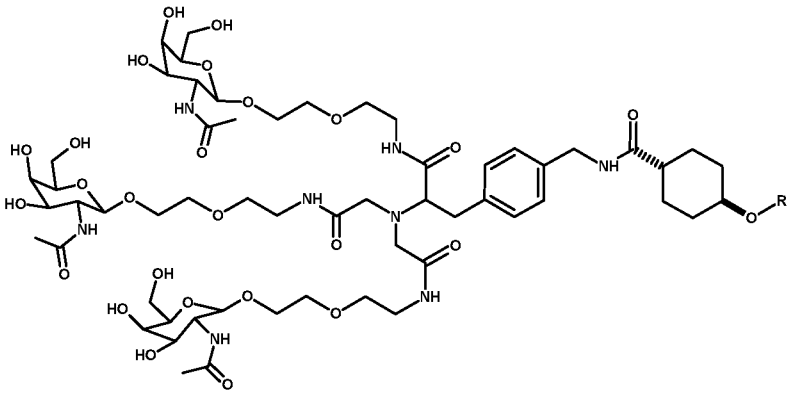
(Structure 1001a);



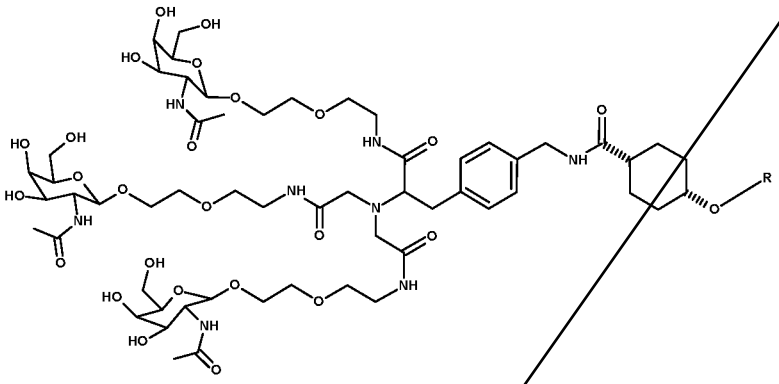
(Structure 1002a);



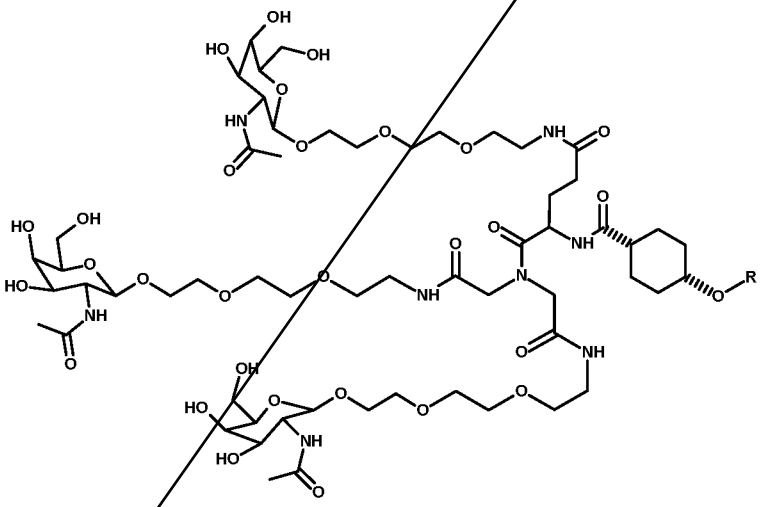
(Structure 1003a);



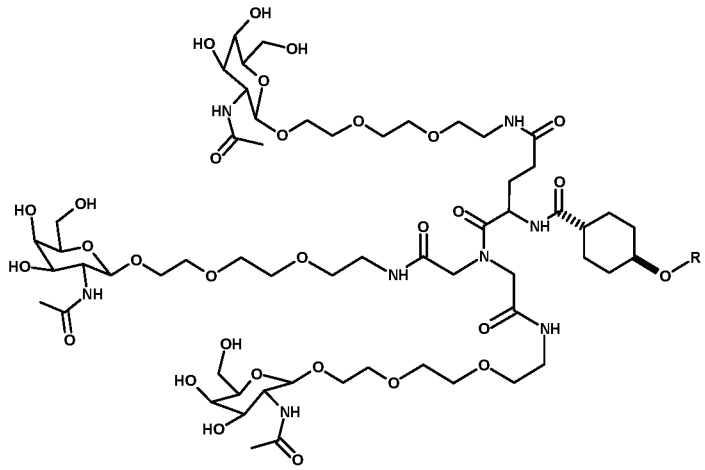
(Structure 1004a);



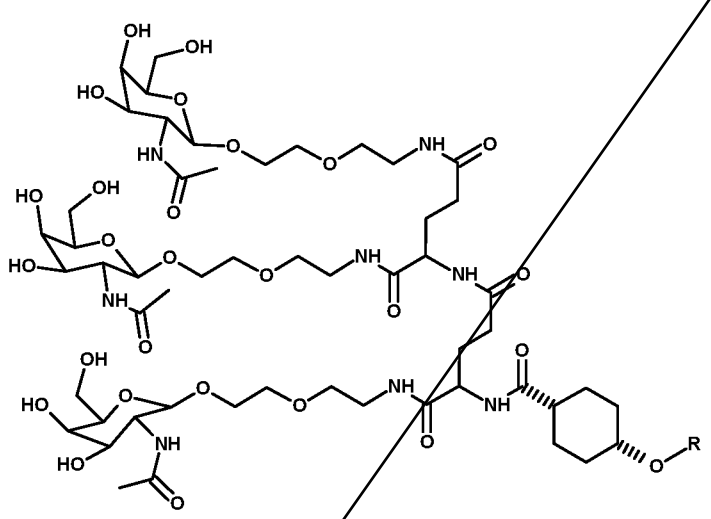
(Structure 1005a);



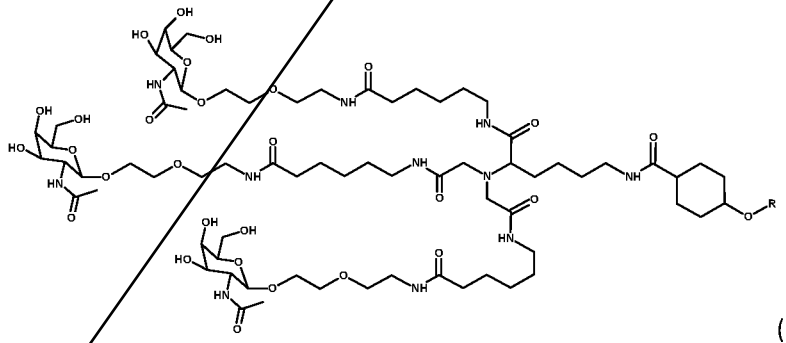
(Structure 1006a);



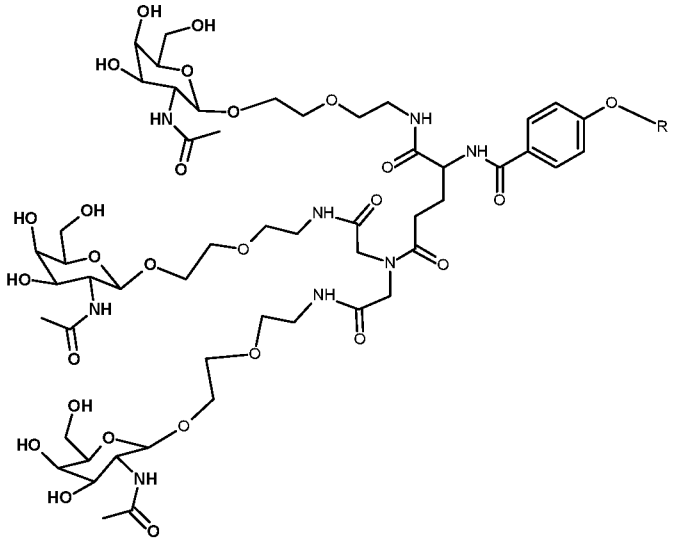
(Structure 1007a);



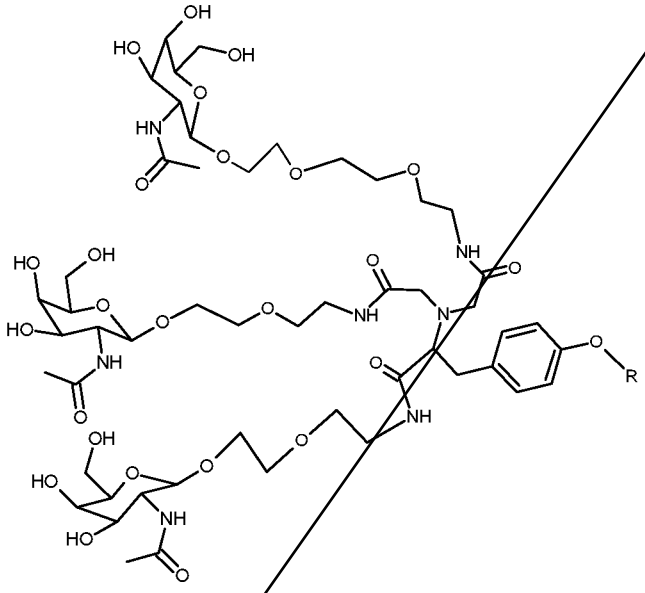
(Structure 1008a);



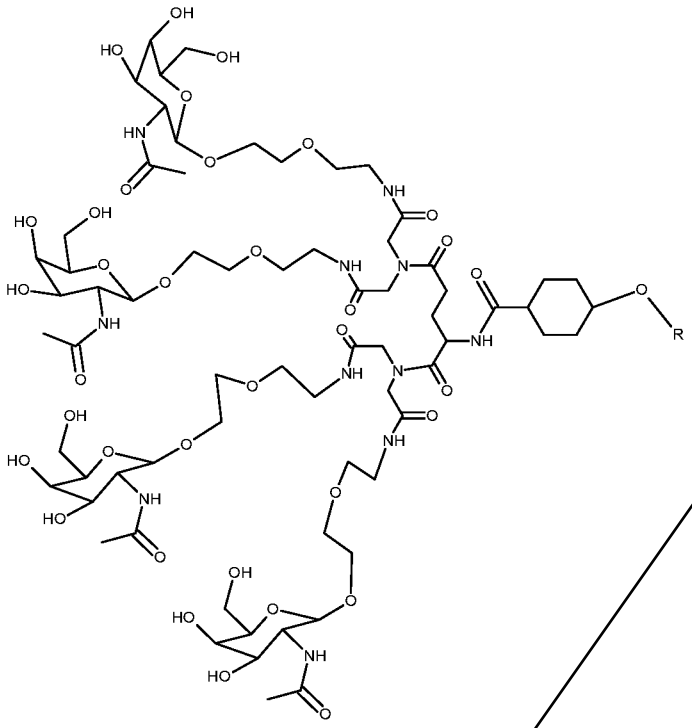
(Structure 1009a);



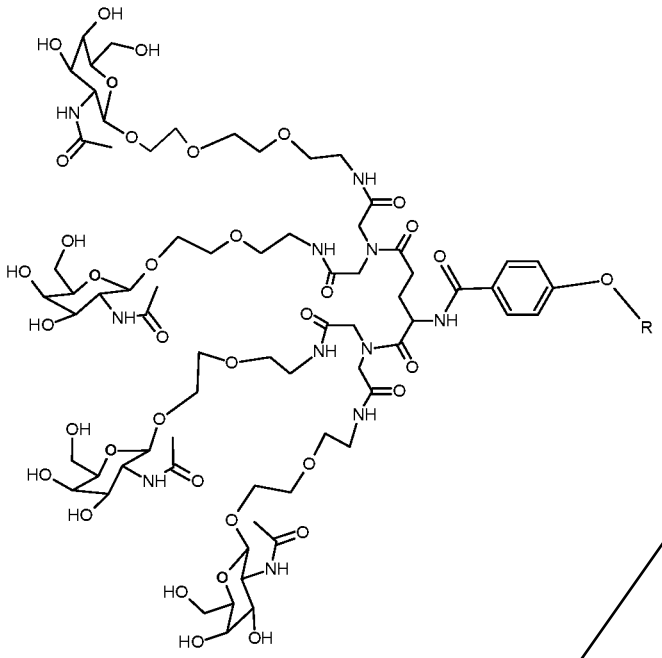
(Structure 1010a);



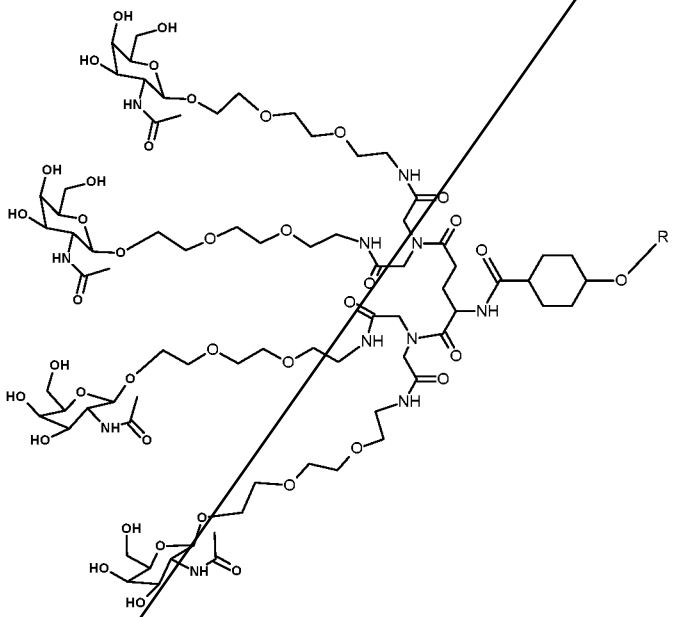
(Structure 1024a);



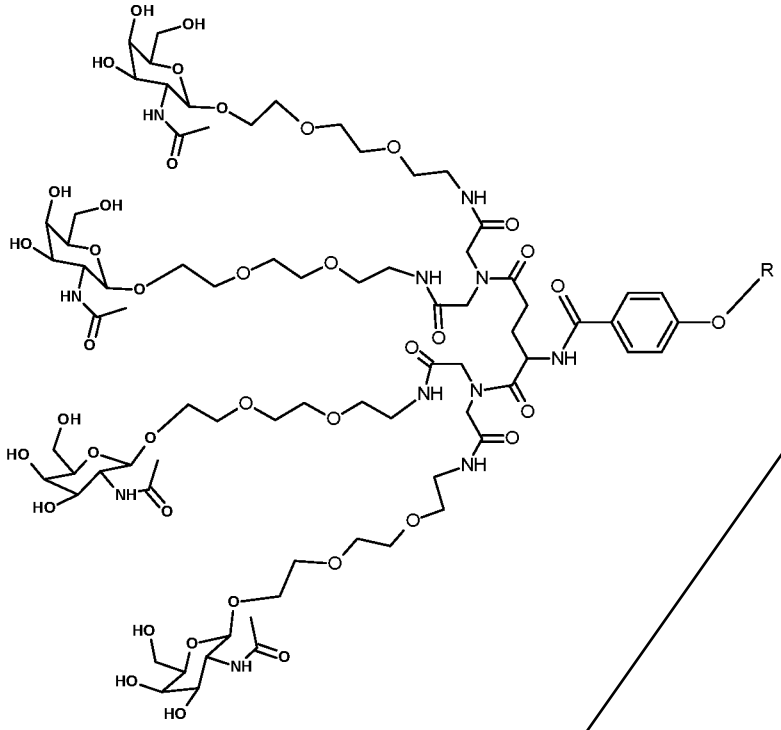
(Structure 1012a);



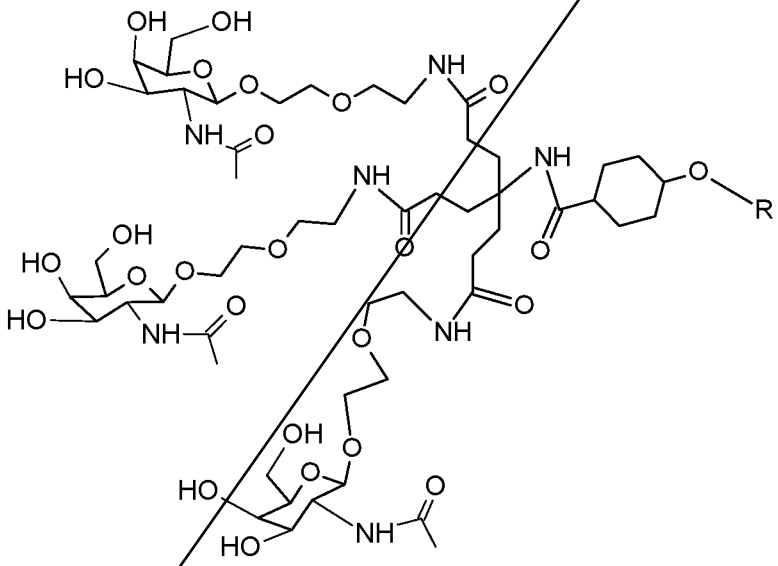
(Structure 1013a);



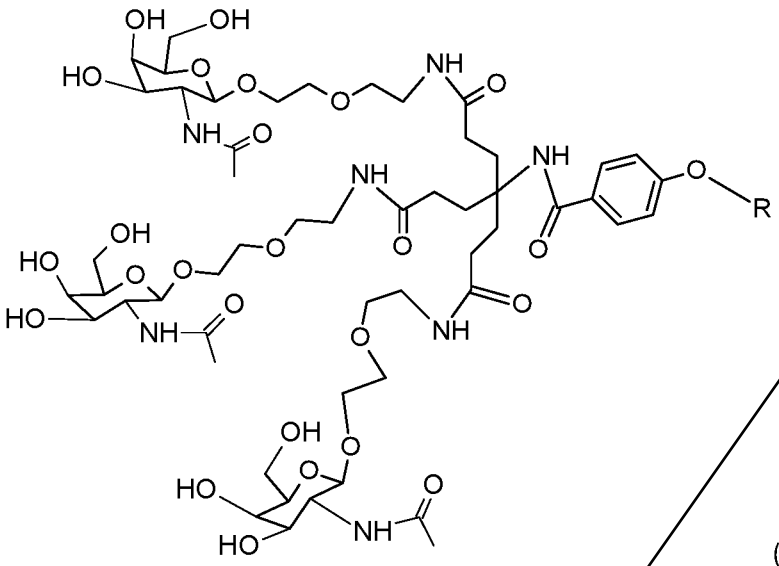
(Structure 1014a);



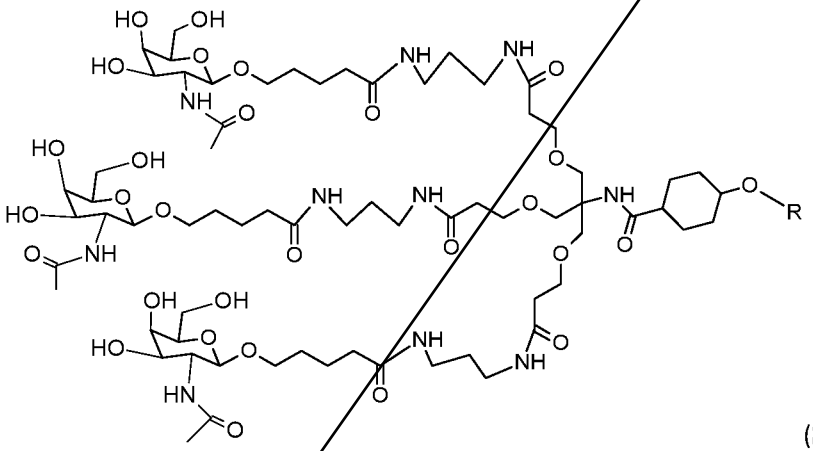
(Structure 1015a);



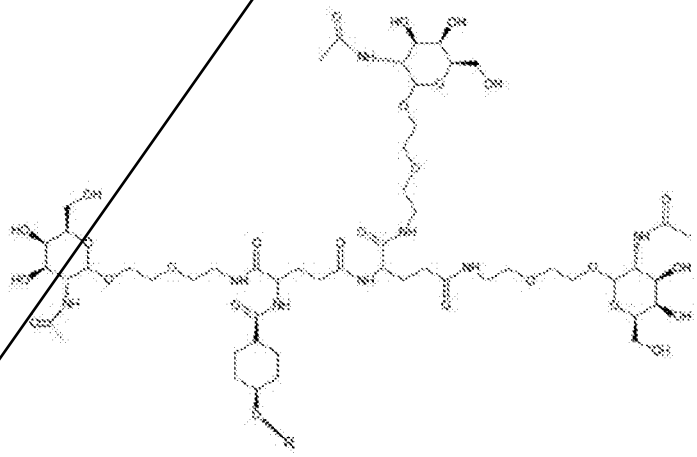
(Structure 1016a);



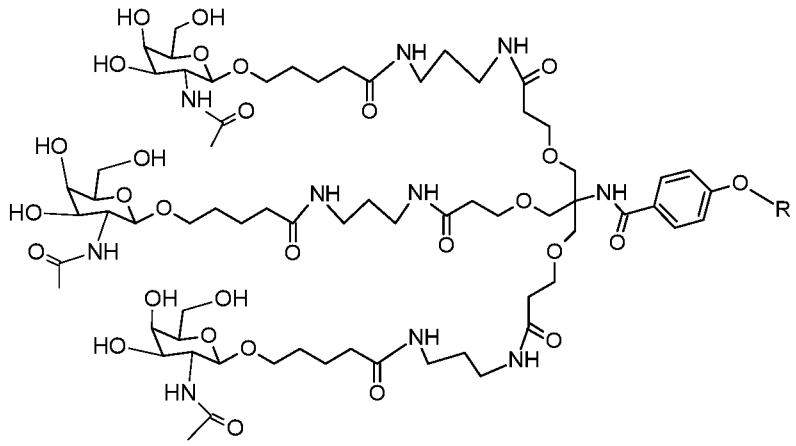
(Structure 1017a);



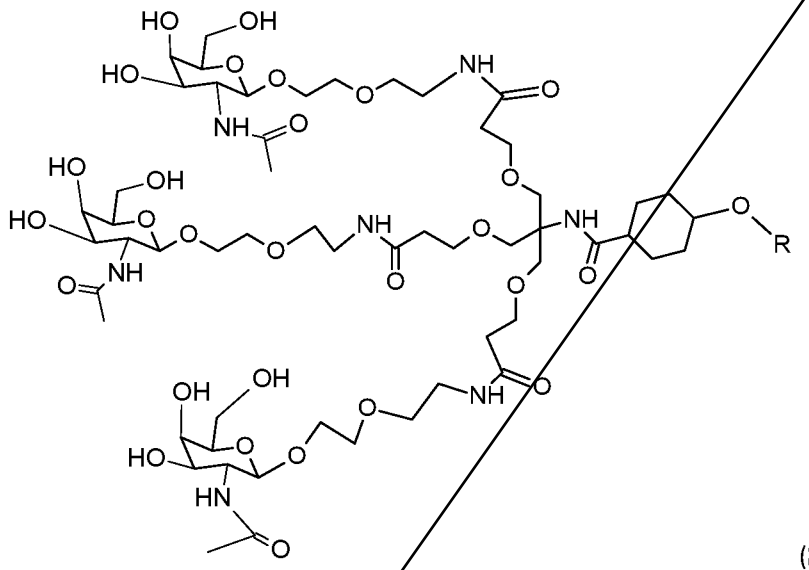
(Structure 1018a);



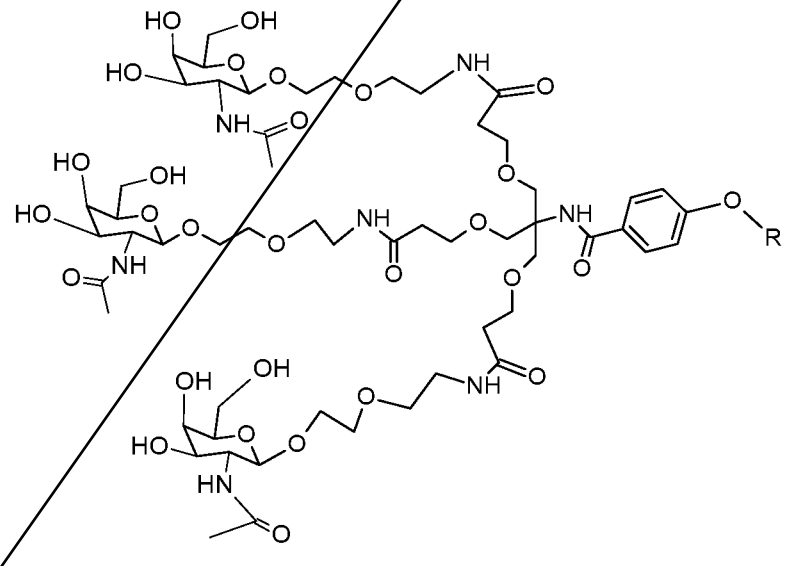
(Structure 1019a);



(Structure 1020a);

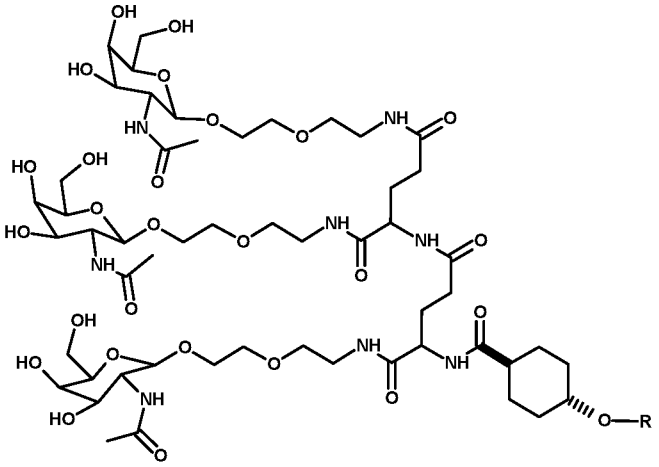


(Structure 1021a);



(Structure 1022a);

and



(1023a); wherein R in each structure includes an expression-inhibiting oligomeric compound.

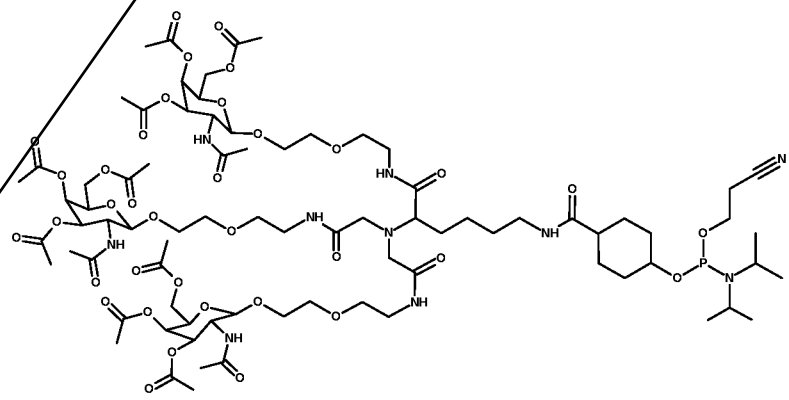
23. The composition of claim 22, wherein the targeting ligand is linked to the expression-inhibiting oligomeric compound via a phosphate group, phosphorothioate group, or a phosphonate group.

24. The composition of claim 22 or 23, wherein the expression-inhibiting oligomeric compound is an RNAi agent.

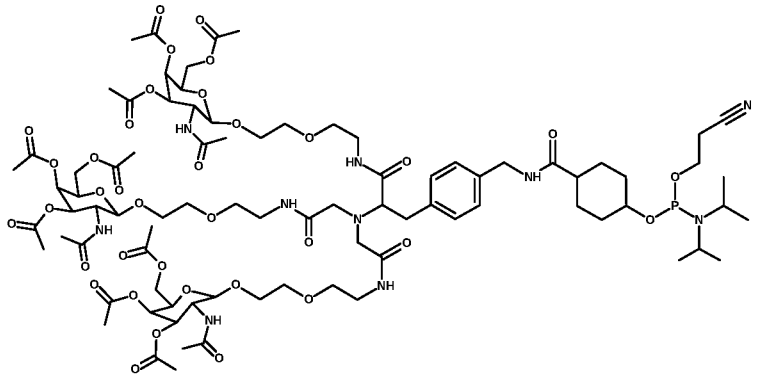
25. The composition of claim 24, wherein the RNAi agent is a double-stranded RNAi agent.

26. The composition of claim 25, wherein the targeting ligand is linked to the 5' terminal end of the sense strand of an RNAi agent.

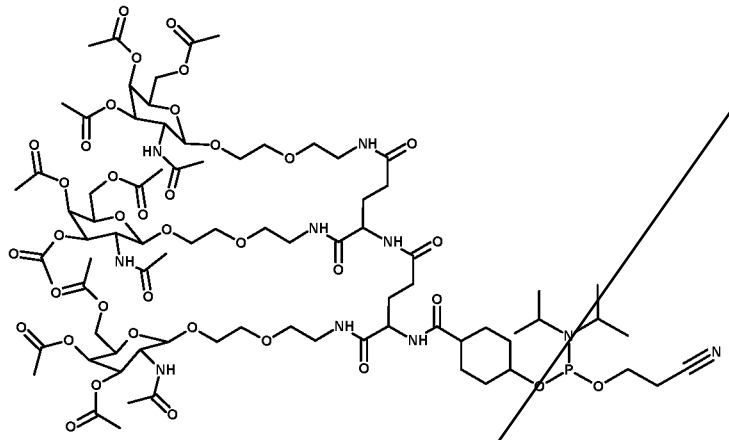
27. A compound having the structure selected from the group consisting of:



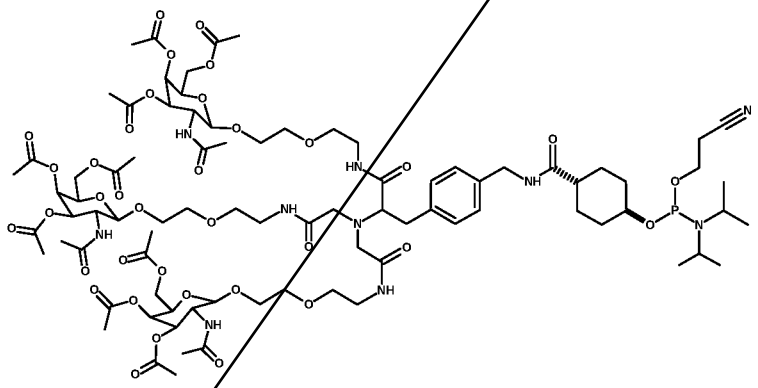
(Structure 1001b);



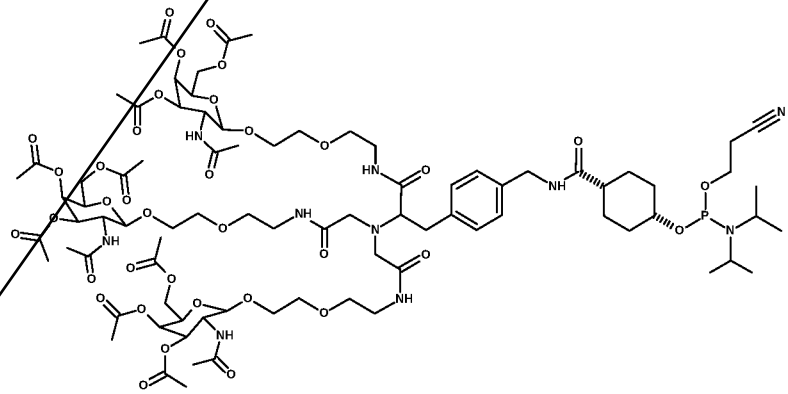
(Structure 1002b);



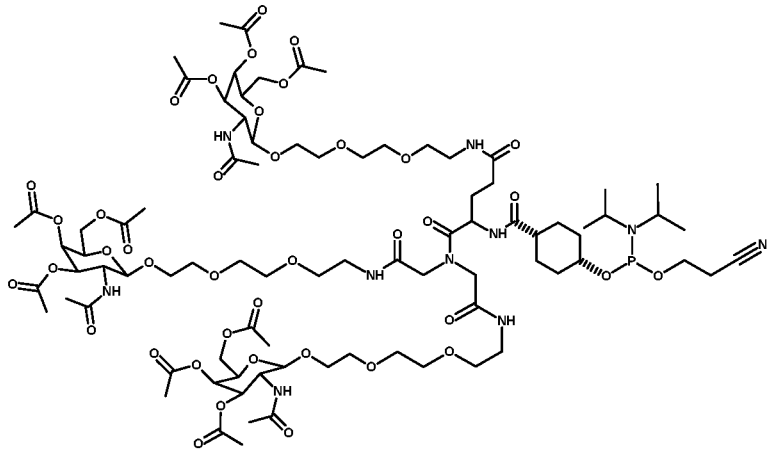
(Structure 1003b);



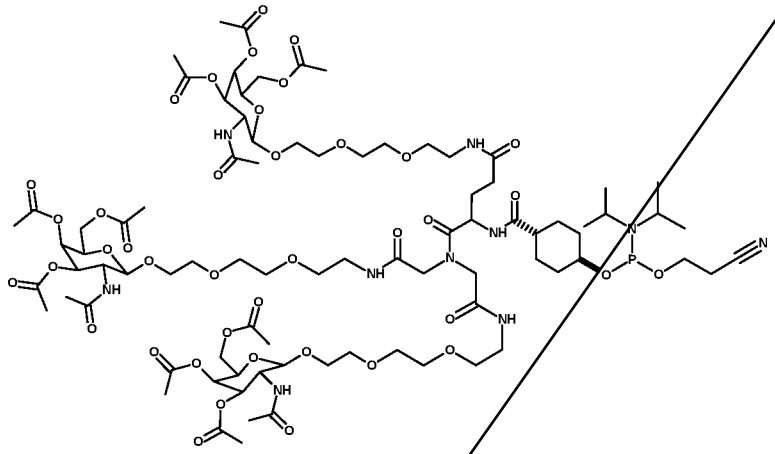
(Structure 1004b);



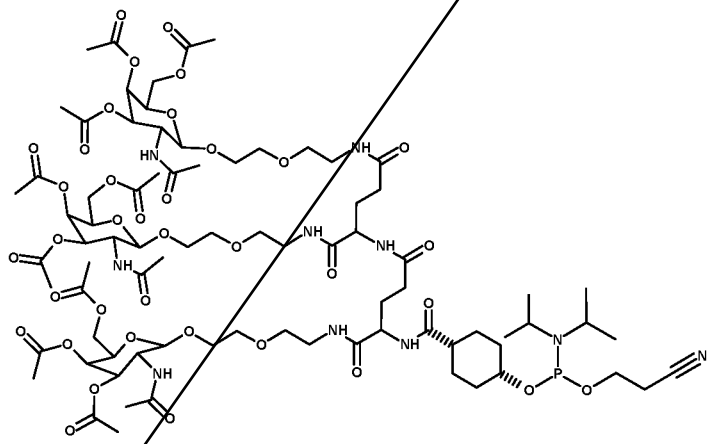
(Structure 1005b);



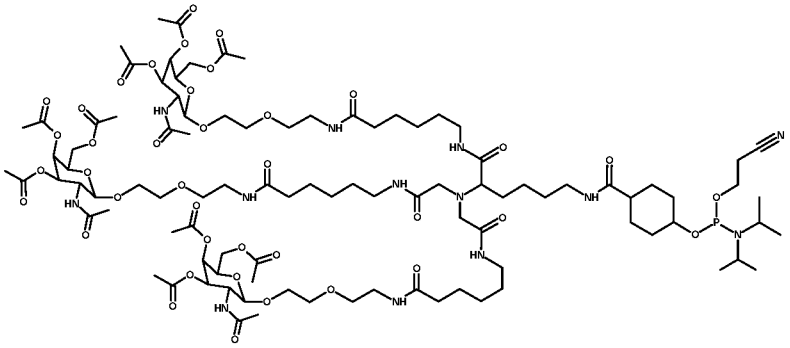
(Structure 1006b);



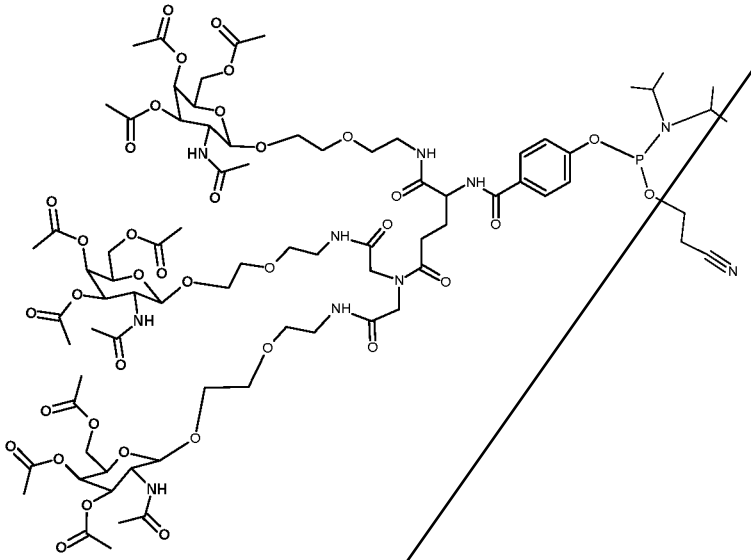
(Structure 1007b);



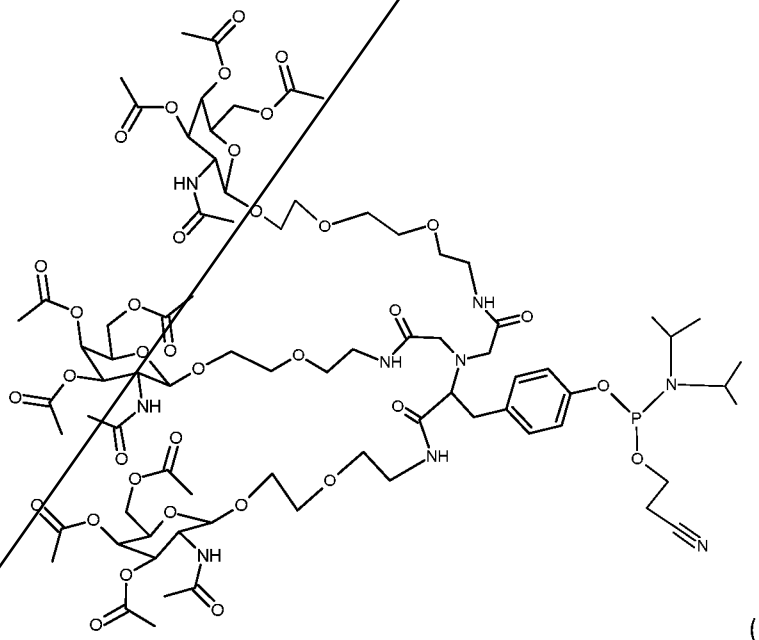
(Structure 1008b);



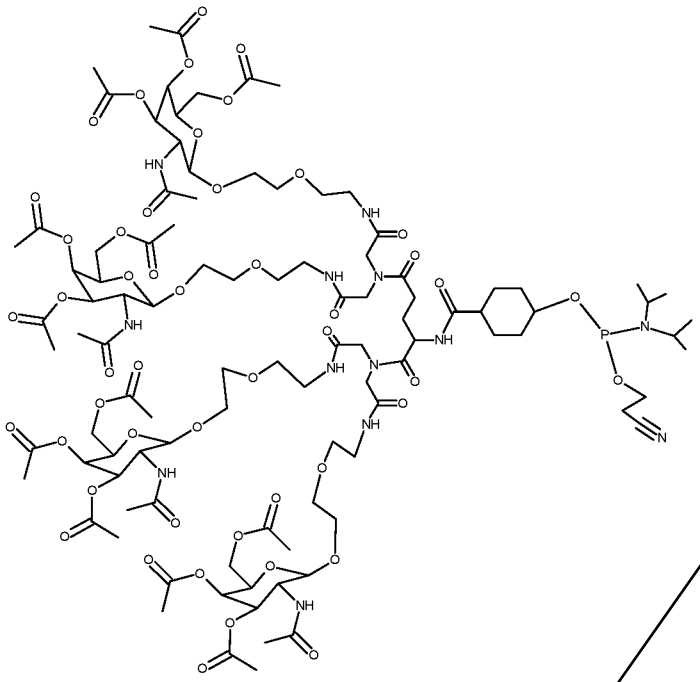
(Structure 1009b);



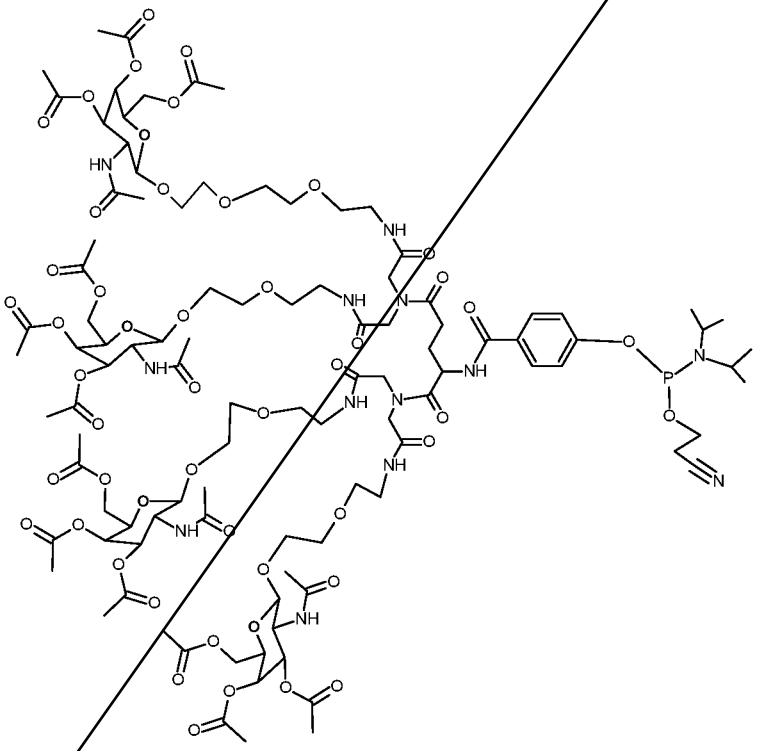
(Structure 1010b);



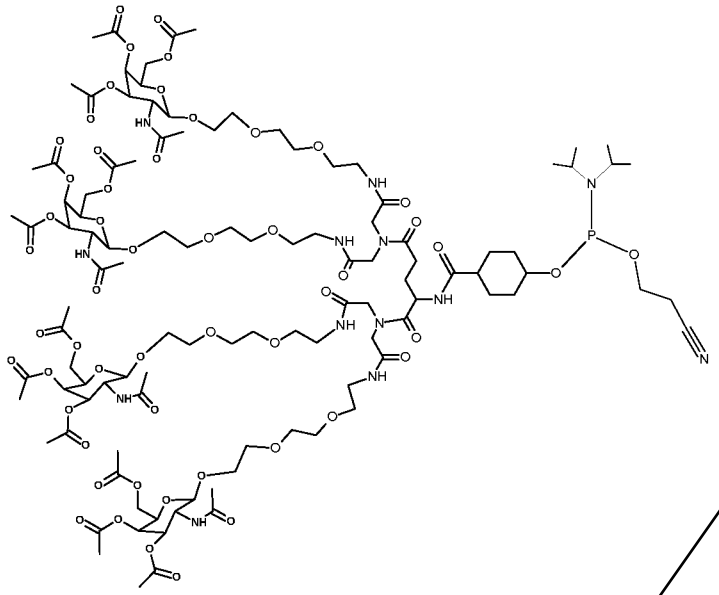
(Structure 1024b);



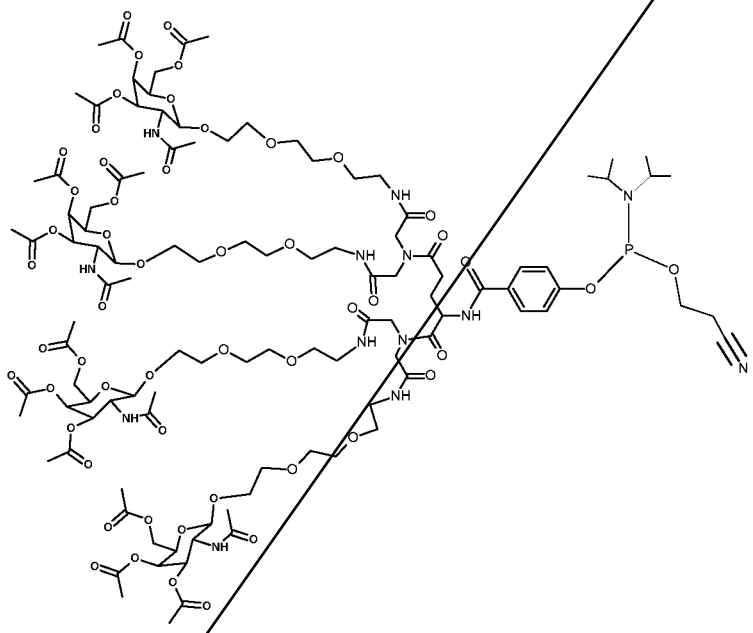
(Structure 1012b);



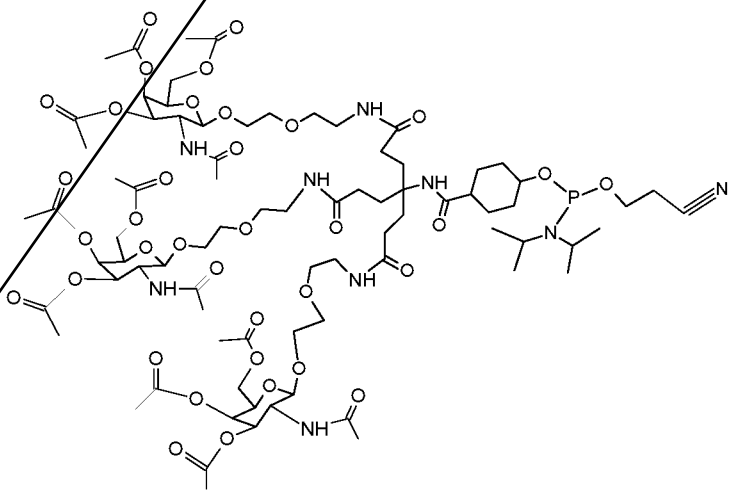
(Structure 1013b);



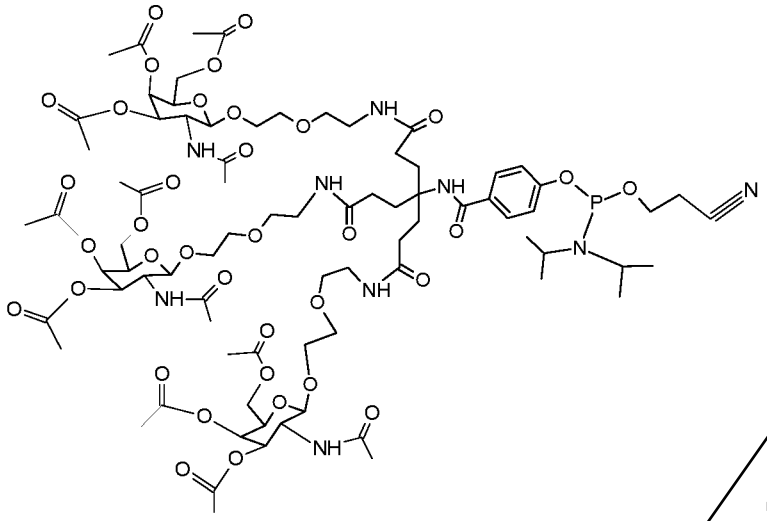
(Structure 1014b);



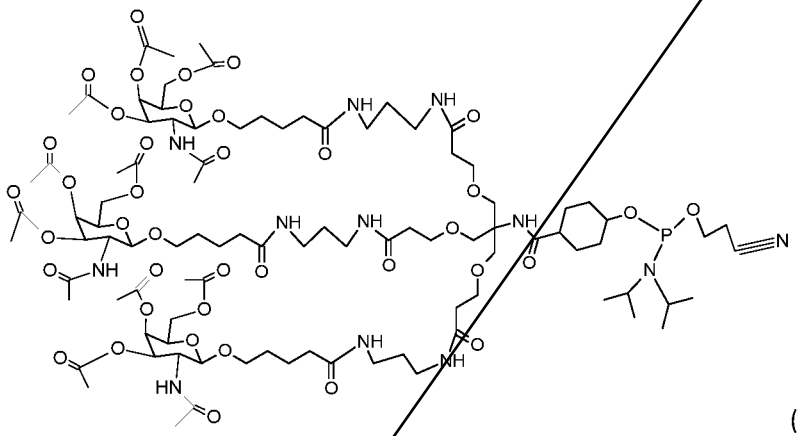
(Structure 1015b);



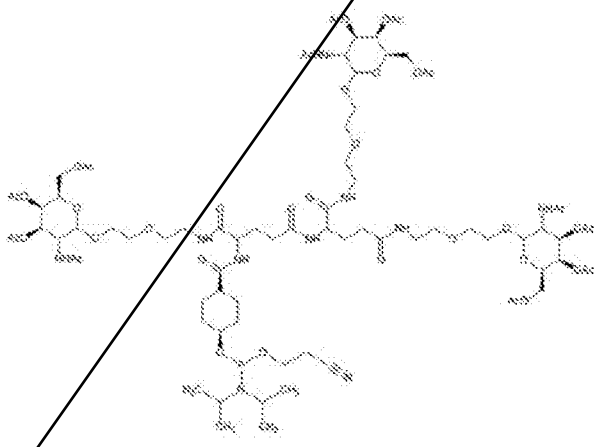
(Structure 1016b);



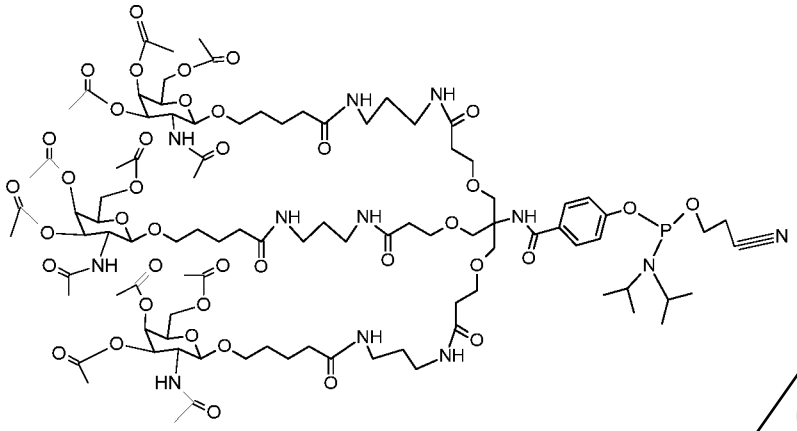
(Structure 1017b);



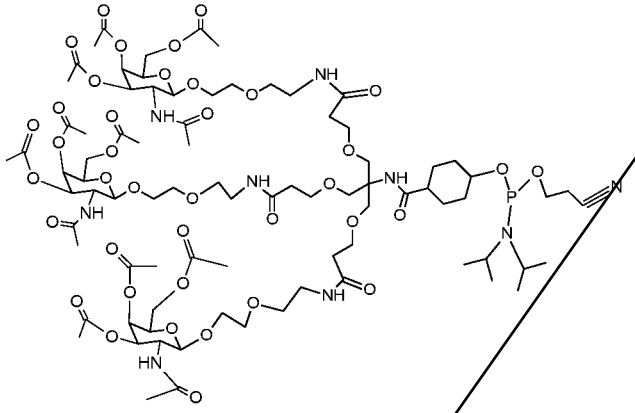
(Structure 1018b);



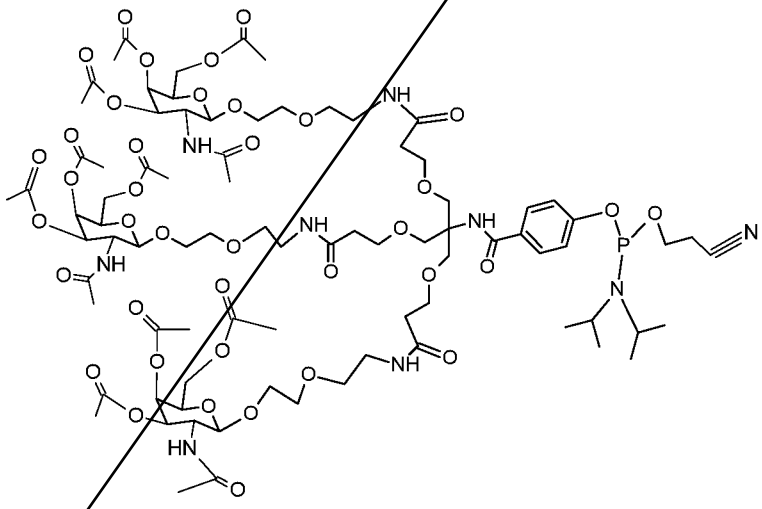
(Structure 1019b);



(Structure 1020b);

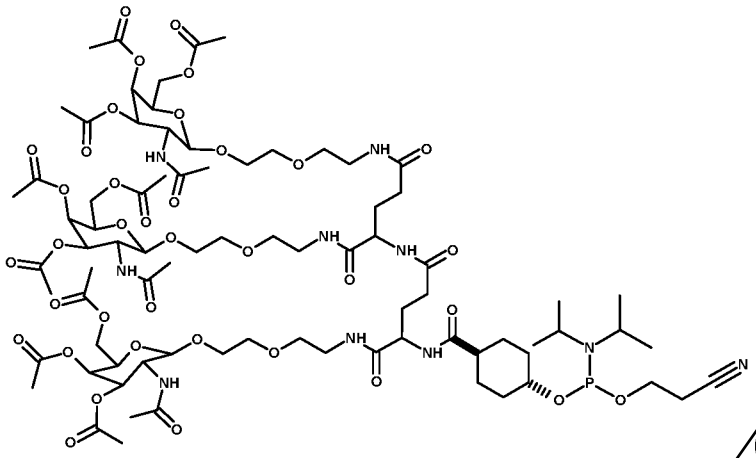


(Structure 1021b);

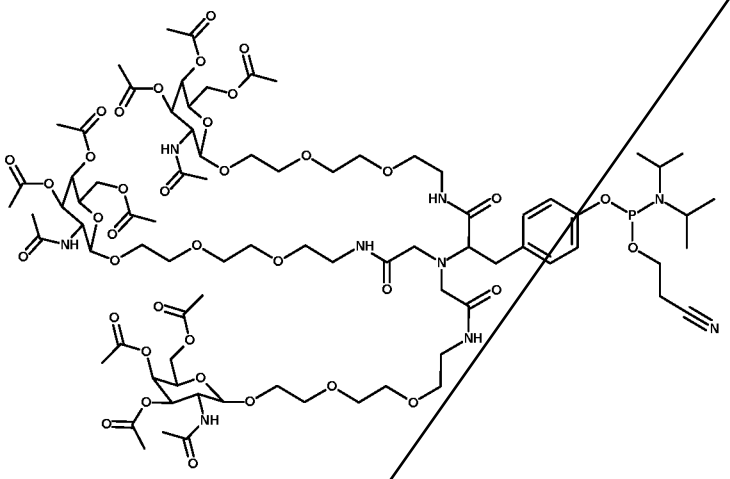


(Structure 1022b);

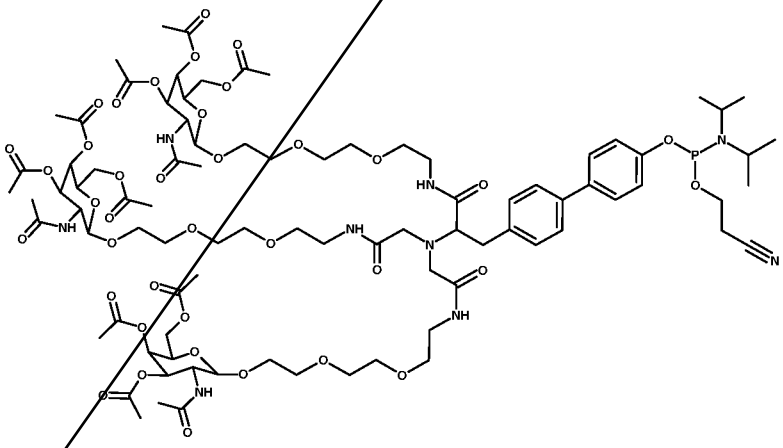
and



(Structure 1023b).

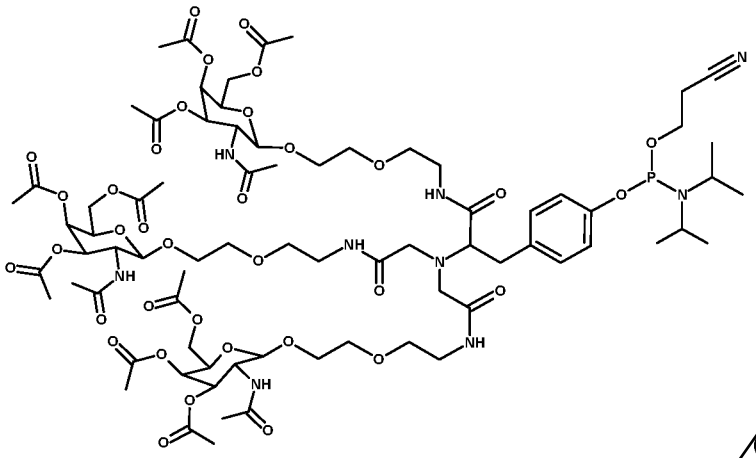


(Structure 1025b);



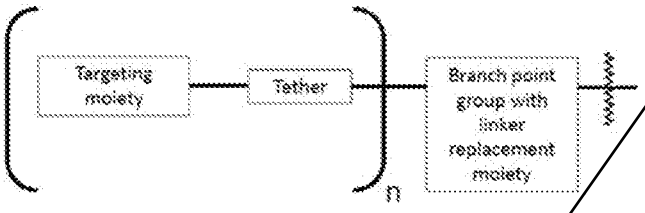
(Structure 1026b);

and



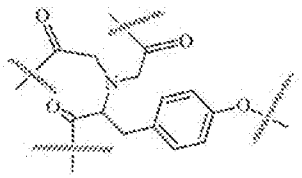
(Structure 1027b).

28. A targeting ligand comprising a structure of Formula II:

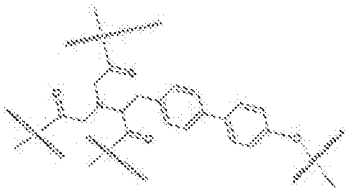


, comprising a branch point group with linker replacement moiety, one or more tethers, and one or more targeting moieties, wherein n is an integer between 1 and 4, and wherein the linker replacement moiety includes one or more substituted or unsubstituted cycloalkyl (e.g., cyclohexyl, cyclopropyl, cyclobutyl, cyclopentyl, cycloheptyl, cycloocty, etc.), substituted or unsubstituted cycloalkenyl (e.g., cyclohexenyl, cyclobutenyl, cyclopentenyl, cycloheptenyl, cyclooctenyl, cyclohexadienyl, cyclopentadienyl, cycloheptadienyl, cyclooctadienyl, etc.), substituted or unsubstituted aryl (e.g., phenyl, naphthyl, binapthyl, anthracenyl, etc.), substituted or unsubstituted heteroaryl (e.g., pyridyl, pyrimidinyl, pyrrole, imidazole, furan, benzofuran, indole, etc.), or substituted or unsubstituted heterocyclyl (e.g., tetrahydrofuran, tetrahydropyran, piperidine, pyrrolidine, etc.), or any combination thereof, is located within the branch point group.

29. The targeting ligand of claim 28, wherein the branch point group with linker replacement moiety is selected from:

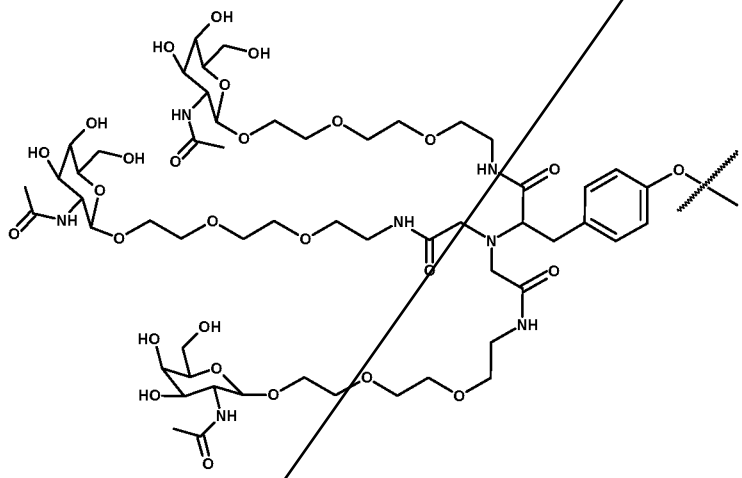


(Structure 220), and

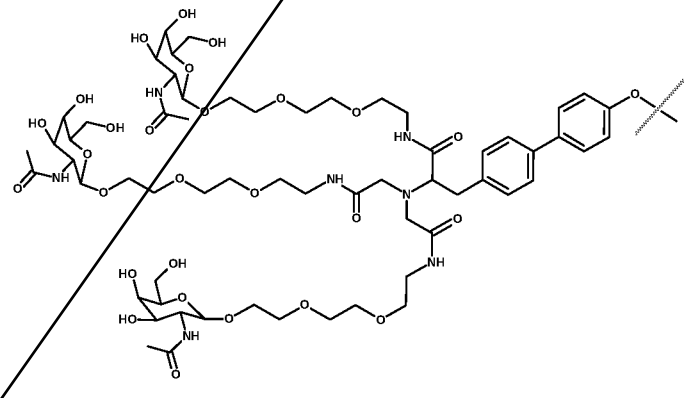


(Structure 221).

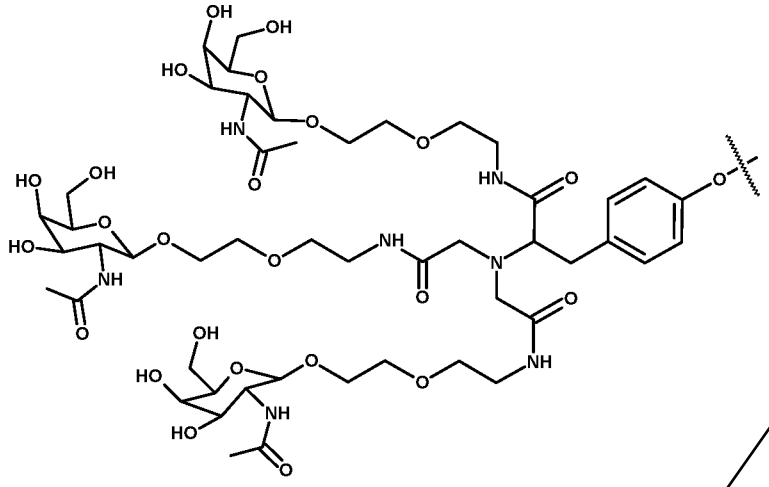
30. The targeting ligand of claim 29, comprising the structure selected from:



(Structure 1025),



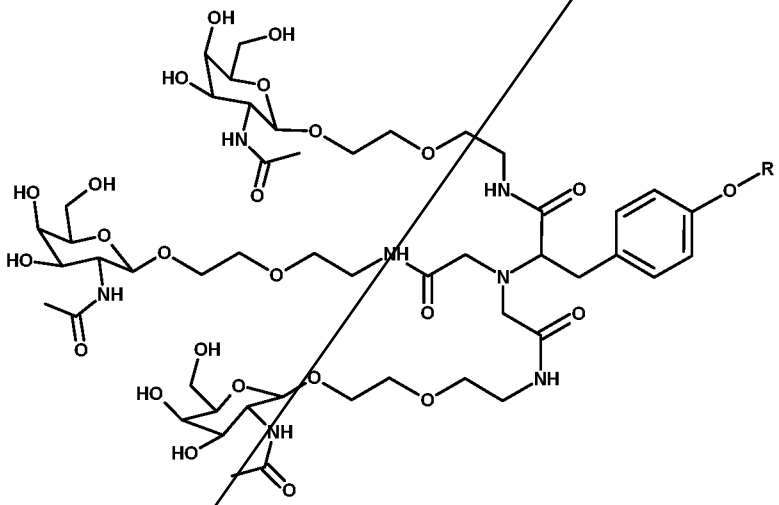
(Structure 1026), and



(Structure 1027).

31. The targeting ligand of any of claims 28-30, wherein the targeting ligand is linked to an expression-inhibiting oligomeric compound.

32. The targeting ligand of claim 31, wherein the targeting ligand linked to an expression-inhibiting oligomeric compound has the following structure:



, wherein R includes an expression-inhibiting oligomeric compound (Structure 1027a).

33. The targeting ligand of any of claims 28-32, wherein the expression-inhibiting oligomeric compound is an RNAi agent.

34. The targeting ligand of claim 33, wherein the RNAi agent is double stranded.

35. The targeting ligand of claim 34, wherein the RNAi agent includes one or more modified nucleotides.

36. A method of inhibiting expression of a target nucleic acid in a subject, the method comprising administering to the subject a therapeutic amount of an expression-inhibiting oligomeric compound linked to any of the targeting ligands of claims 1 to 21 or 28 to 35.

37. A method of introducing a therapeutic agent into a mammalian cell, the method comprising contacting a mammalian cell with the targeting ligand of any one of claims 1 to 21 or 28 to 35, linked to the therapeutic agent.

38. The method of claim 37, wherein the cell is present in a subject.

39. The method of claim 38, wherein the subject is a human.

40. The method of any of claims 37-39, wherein the therapeutic agent is an expression-inhibiting oligomeric compound.

41. The method of claim 40, wherein the expression-inhibiting oligomeric compound is a double-stranded RNAi agent.

42. A method of treating a disease or disorder that would benefit from administration of a therapeutic compound, the method comprising administering a therapeutic amount of the targeting ligand of any one of claims 1 to 21 or 28 to 35 linked to a therapeutic compound to a subject in need of treatment thereof.

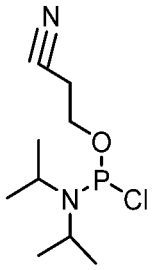
43. A method of treating a disease or disorder that would benefit from administration of a therapeutic compound, the method comprising administering a therapeutic amount of the composition of any one of claims 22 to 26 to a subject in need of treatment thereof.

44. A method of manufacturing a phosphoramidite compound including a targeting ligand of any of claims 1-21, the method comprising:

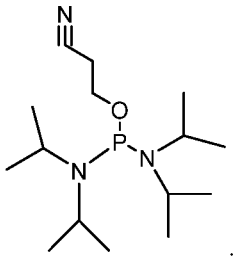
(i) covalently linking the carboxylic acid moiety (or its activated ester) of the linker to a terminal amine located on the branch point group, and

(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.

45. The method of claim 44, wherein the phosphoramidite reagent is selected from:



and



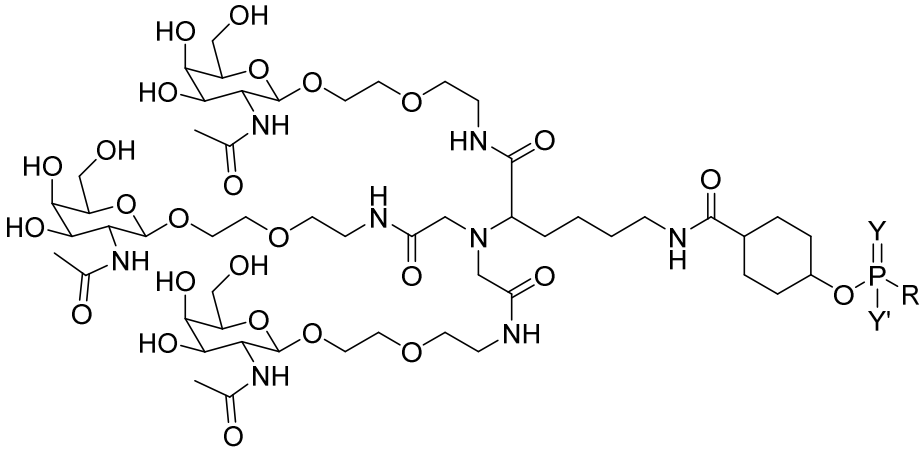
.

46. A targeting ligand of any one of claims 1 to 21 or 29 to 36, linked to a therapeutic agent, for use as a medicament.

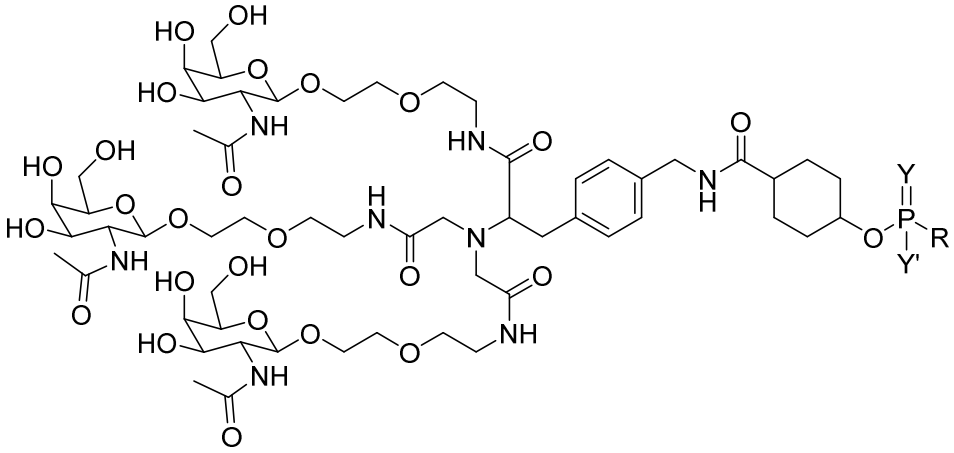
47. A targeting ligand of any one of claims 1 to 21 or 29 to 36, linked to a therapeutic agent, for use in introducing a therapeutic agent into a mammalian cell, for inhibiting expression of a target nucleic acid in a subject, or for treating a disease or disorder that would benefit from administration of a therapeutic agent.

Claims:

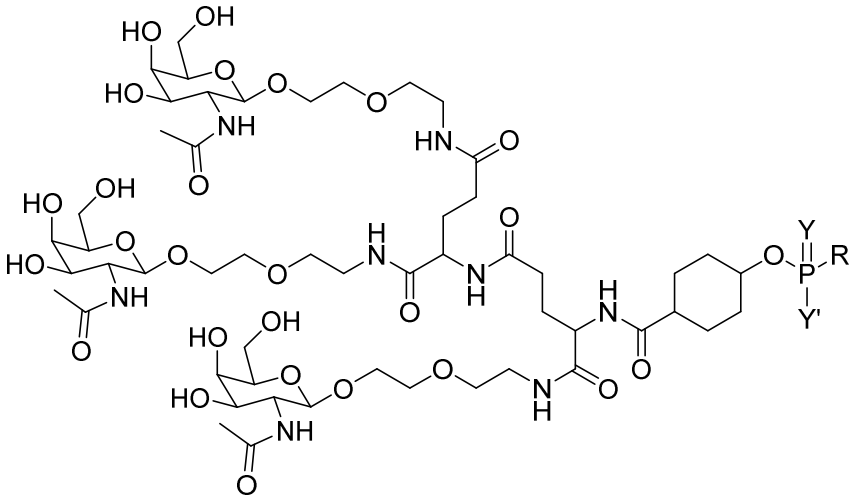
1. A compound having a structure selected from the group consisting of:



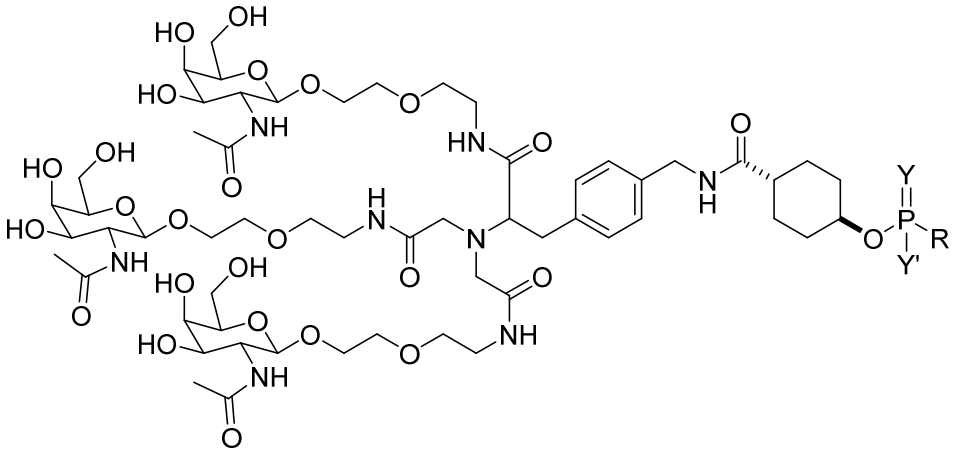
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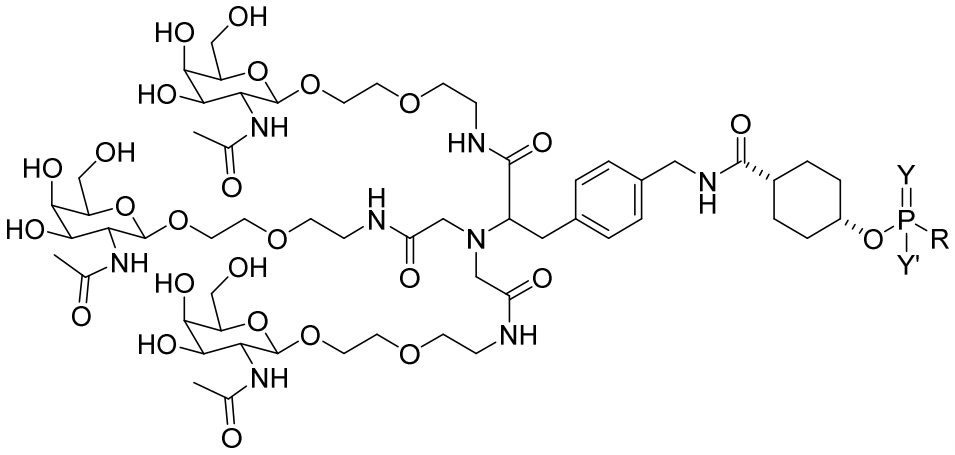
(Structure 1002a(i));



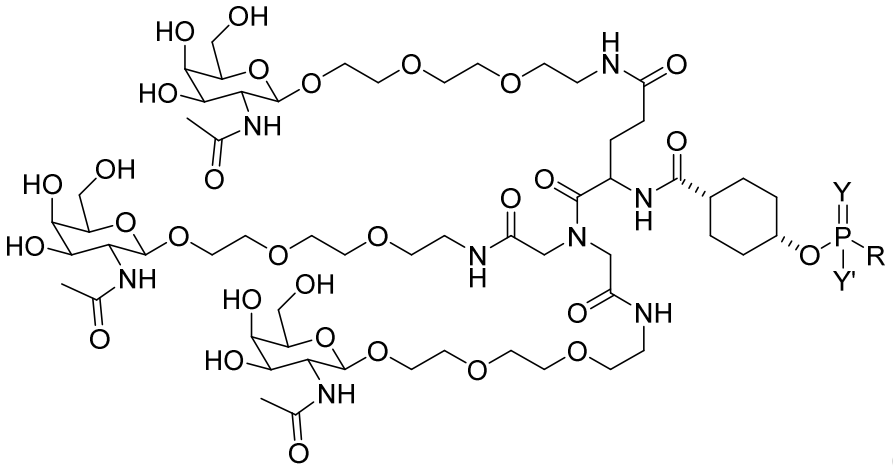
(Structure 1003a(i));



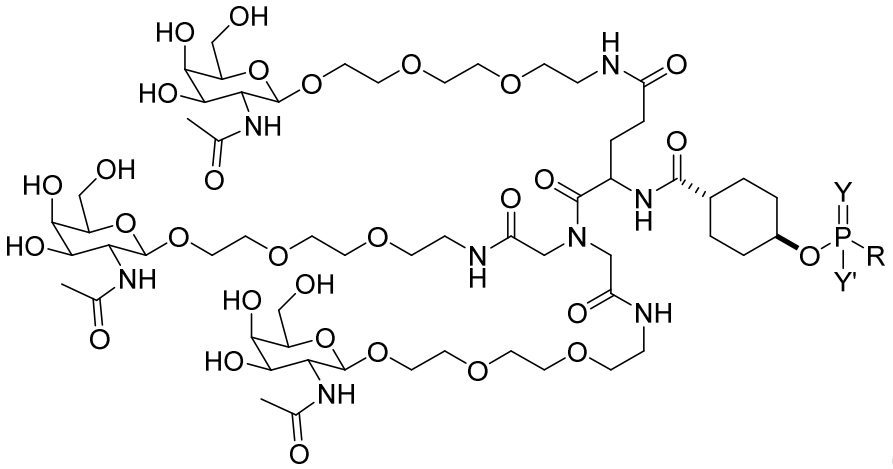
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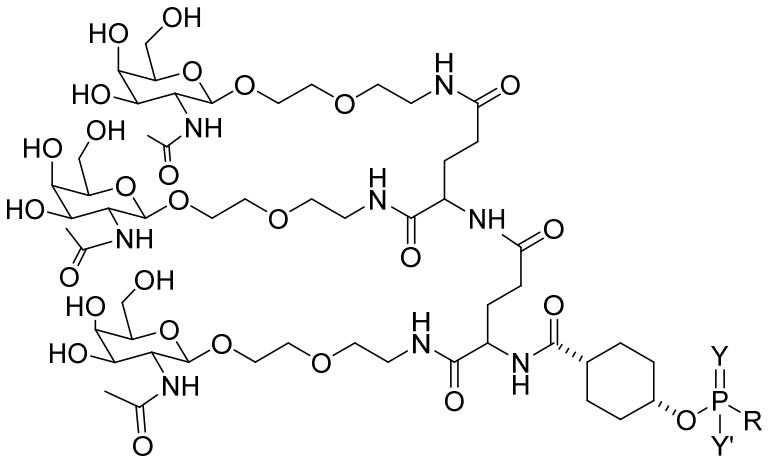
(Structure 1005a(i));



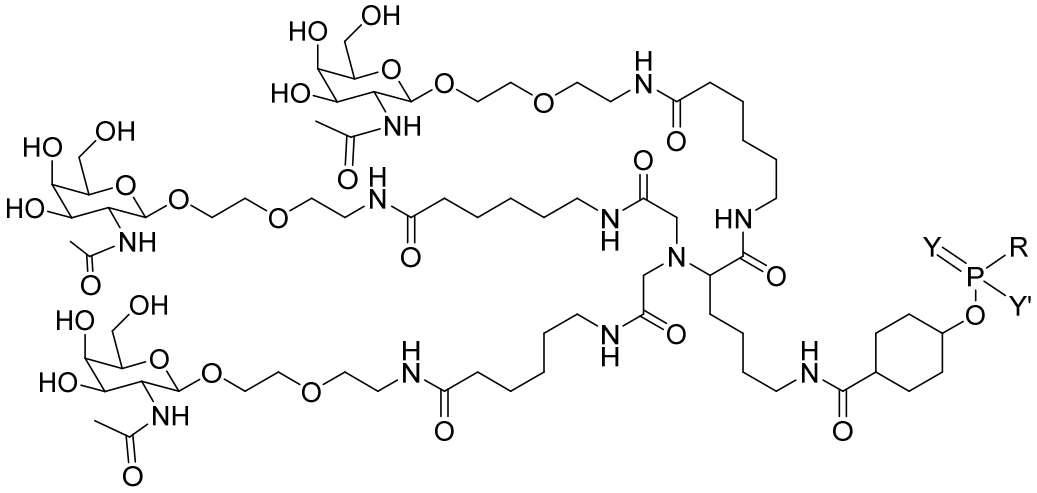
(Structure 1006a(i));



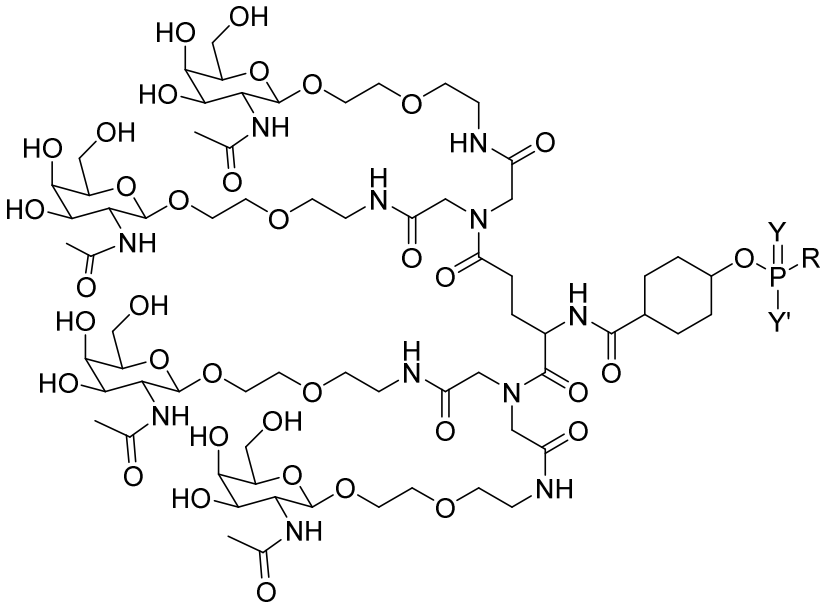
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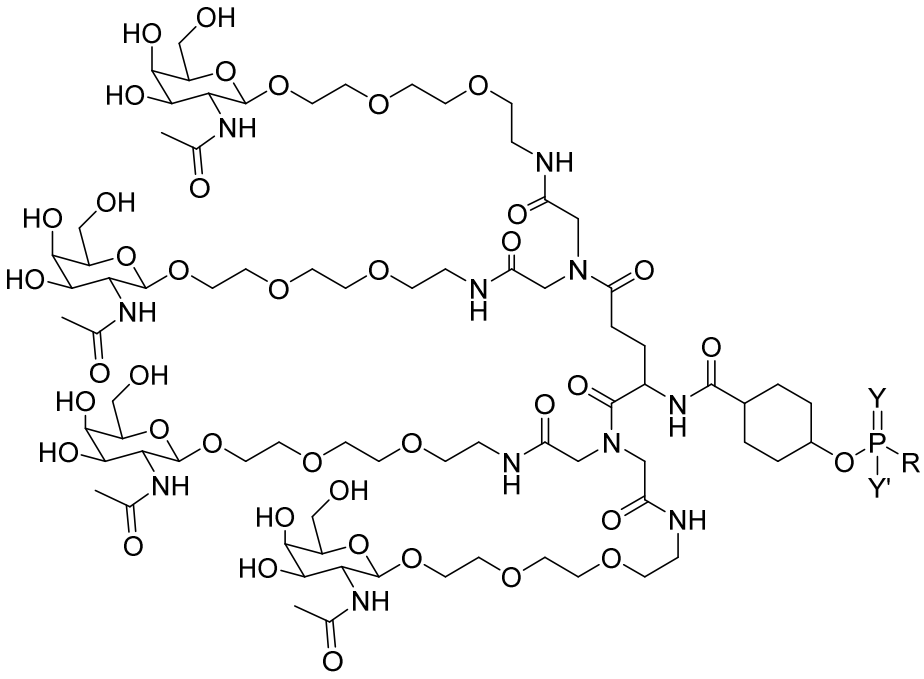
(Structure 1008a(i));



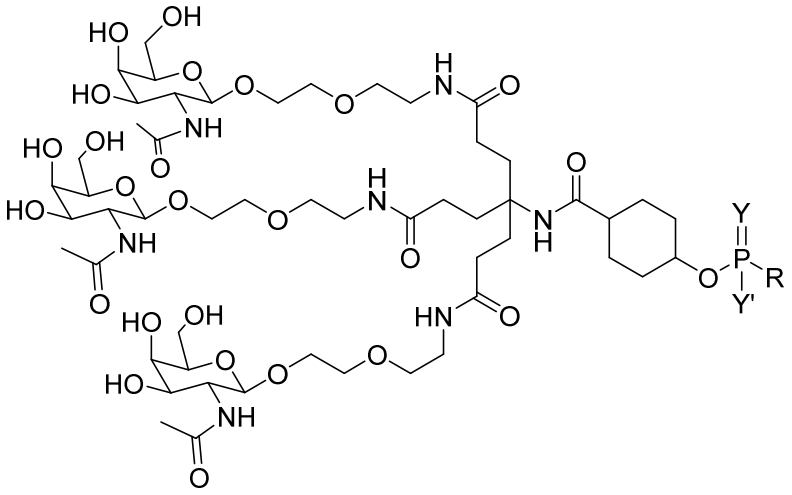
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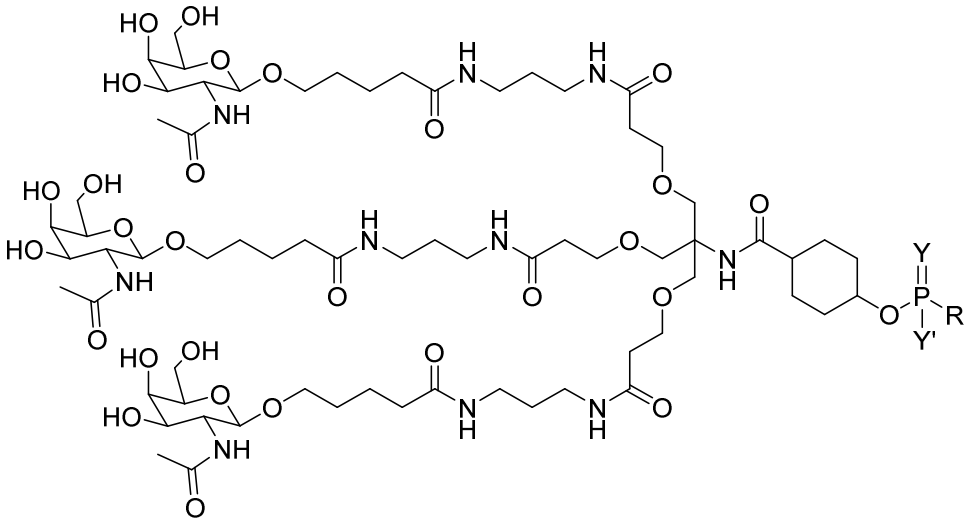
(Structure 1012a(i));



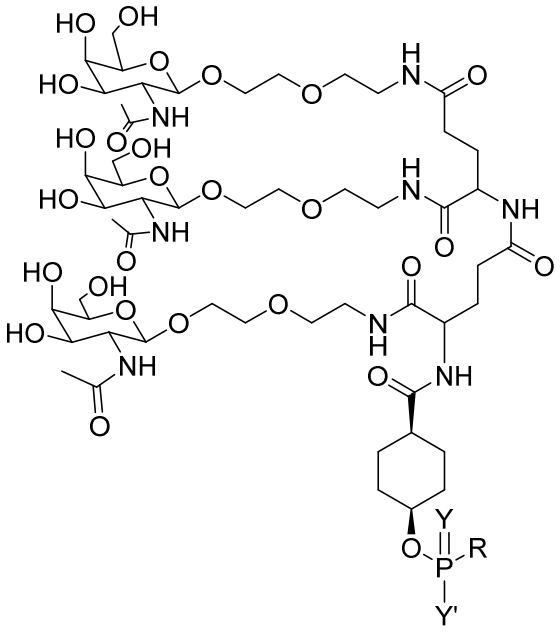
(Structure 1014a(i));



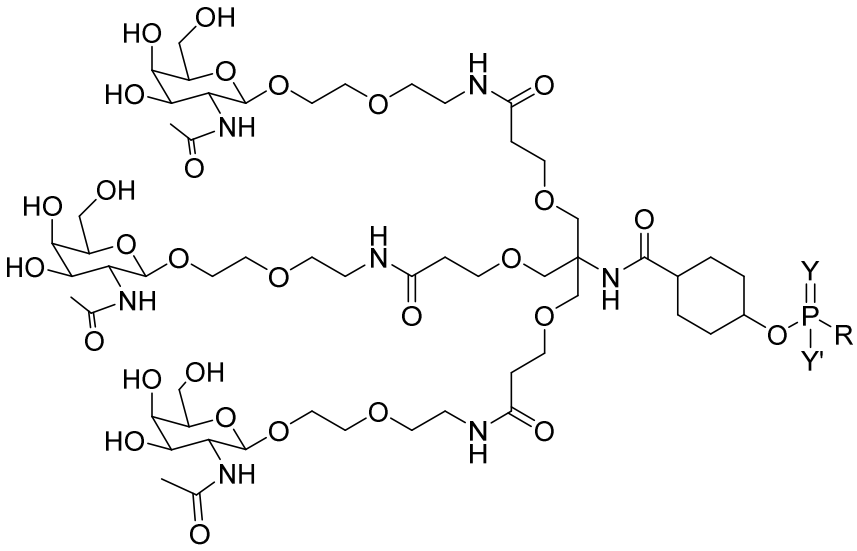
(Structure 1016a(i));



(Structure 1018a(i));



(Structure 1019a(i)); and



(Structure 1021a(i));

or a pharmaceutically acceptable salt thereof, wherein R is an RNAi agent, Y is O or S, and Y' is O^-, S^-, or NH^-.

2. The compound of claim 1, wherein Y is S.

3. The compound of claim 1, wherein Y is O.

4. The compound of claim 1, wherein Y' is O^-.