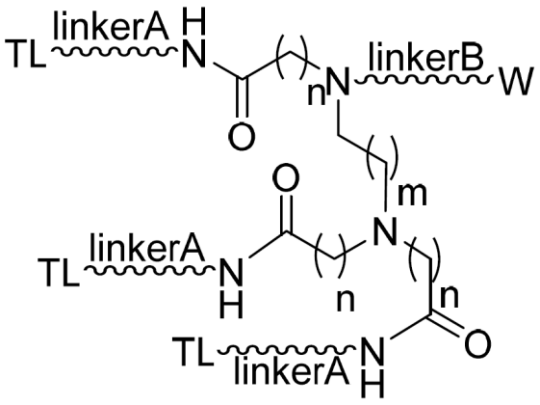
CLAIMS

What is claimed is:

1. A compound for targeted delivery of one or more pharmaceutical agents, the compound having the formula:



,

wherein:

each TL is an independently selected targeting ligand, and wherein the selected targeting ligand comprises at least one small molecule ligand, and wherein the selected targeting ligand is capable of binding to Asialoglycoprotein receptor (ASGPR), transferrin receptor, integrin receptor, folate receptor or G-protein-coupled receptor (GPCR);

m is an integral number between 1 and 10,

each n is an independently selected integral number between 1 and 10,

each linkerA is an independently selected spacer, and wherein the selected spacer comprises at least one of polyethylene glycol and alkyl group,

linkerB is a spacer, and wherein linkerB comprises one or more groups selected from the group consisting of:

a) at least one of a polyethylene glycol; an alkyl group, a cycloalkyl group, an alkenyl group, a cycloalkenyl group, an alkynyl group, an aryl group, an aralkyl group, an aralkenyl group, and an aralkynyl group;

b) at least one heteroatom;

c) at least one aliphatic heterocycle;

d) at least one heteroaryl group;

e) at least one amino acid;

f) at least one nucleotide; and/or

g) at least one saccharide; and

W is either the one or more pharmaceutical agents or a functional group capable of linking to the one or more pharmaceutical agents.

2. The compound of claim 1, wherein m is 1 or 2.

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

4. The compound of claim 1, wherein at least one of the independently selected TLs comprises:

a) at least one of N-acetylgalactosamine, galactose, galactosamine, N-formyl-galactosamine, N-propionylgalactosamine, N-butanoylgalactosamine, and N-iso-butanoylgalactosamine, a macrocycle, a folate molecule, a fatty acid, a bile acid, and a cholesterol;

b) at least one peptide;

c) at least one cyclic peptide; or

d) at least one aptamer.

5. The compound of any one of claims 1-4, wherein at least one of the independently selected linkerAs further comprises at least one of a cycloalkyl group, an alkenyl group, a cycloalkenyl group, an alkynyl group, an aryl group, an aralkyl group, an aralkenyl group, and an aralkynyl group.

6. The compound of any one of claims 1-5, wherein at least one of the independently selected linkerAs further comprises one or more groups selected from the group consisting of:

a) at least one heteroatom;

b) at least one aliphatic heterocycle;

c) at least one heteroaryl group;

d) at least one amino acid;

e) at least one nucleotide; and

f) at least one saccharide.

7. The compound of claim 6, wherein

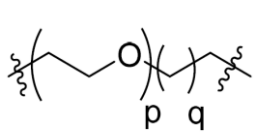
a) the at least one heteroatom comprises at least one of oxygen, nitrogen, sulfur, or phosphorous;

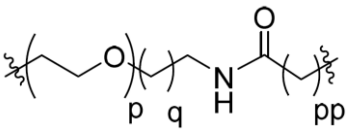
b) the at least one aliphatic heterocycle comprises at least one of tetrahydrofuran, tetrahydropyran, morpholine, piperidine, piperazine, pyrrolidine, and azetidine;

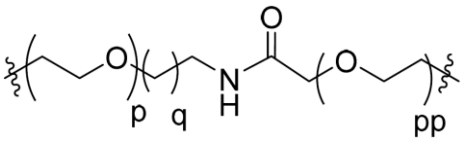
c) the at least one heteroaryl group comprises at least one of imidazole, pyrazole, pyridine, pyrimidine, triazole, and 1,2,3-triazole; or

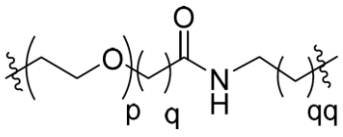
d) the at least one saccharide comprises at least one of glucose, fructose, mannose, galactose, ribose, and glucosamine.

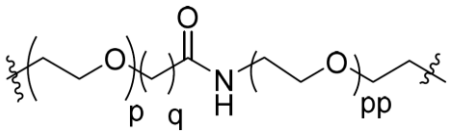
8. The compound of any one of claims 1-7, wherein at least one of the independently selected linkerAs comprises one or more of:



,


,


,


, and


,

wherein:

p is an integral number between 0 and 12,

pp is an integral number between 0 and 12,

q is an integral number between 1 and 12, and

qq is an integral number between 1 and 12.

9. The compound of claim 1, wherein:

a) the at least one heteroatom in linkerB comprises at least one of oxygen, nitrogen, sulfur, and phosphorous

b) the at least one aliphatic heterocycle in linkerB comprises at least one of tetrahydrofuran, tetrahydropyran, morpholine, piperidine, piperazine, pyrrolidine, and azetidine;

c) the at least one heteroaryl group in linkerB comprises at least one of imidazole, pyrazole, pyridine, pyrimidine, triazole, and 1,2,3-triazole;

d) the at least one nucleotide in linkerB comprises at least one of an abasic nucleotide and an inverted abasic nucleotide; or

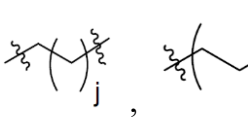
e) the at least one saccharide in linkerB comprises at least one of glucose, fructose, mannose, galactose, ribose, and glucosamine.

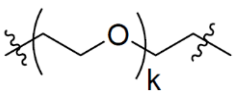
10. The compound of claim 9, wherein:

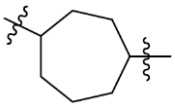
a) the abasic nucleotide is an abasic deoxyribonucleic acid or an abasic ribonucleic acid (RNA); or

b) the inverted abasic nucleotide is an inverted abasic deoxyribonucleic acid (DNA) or an inverted abasic ribonucleic acid (RNA).

11. The compound of any one of claims wherein linkerB comprises at least one of:

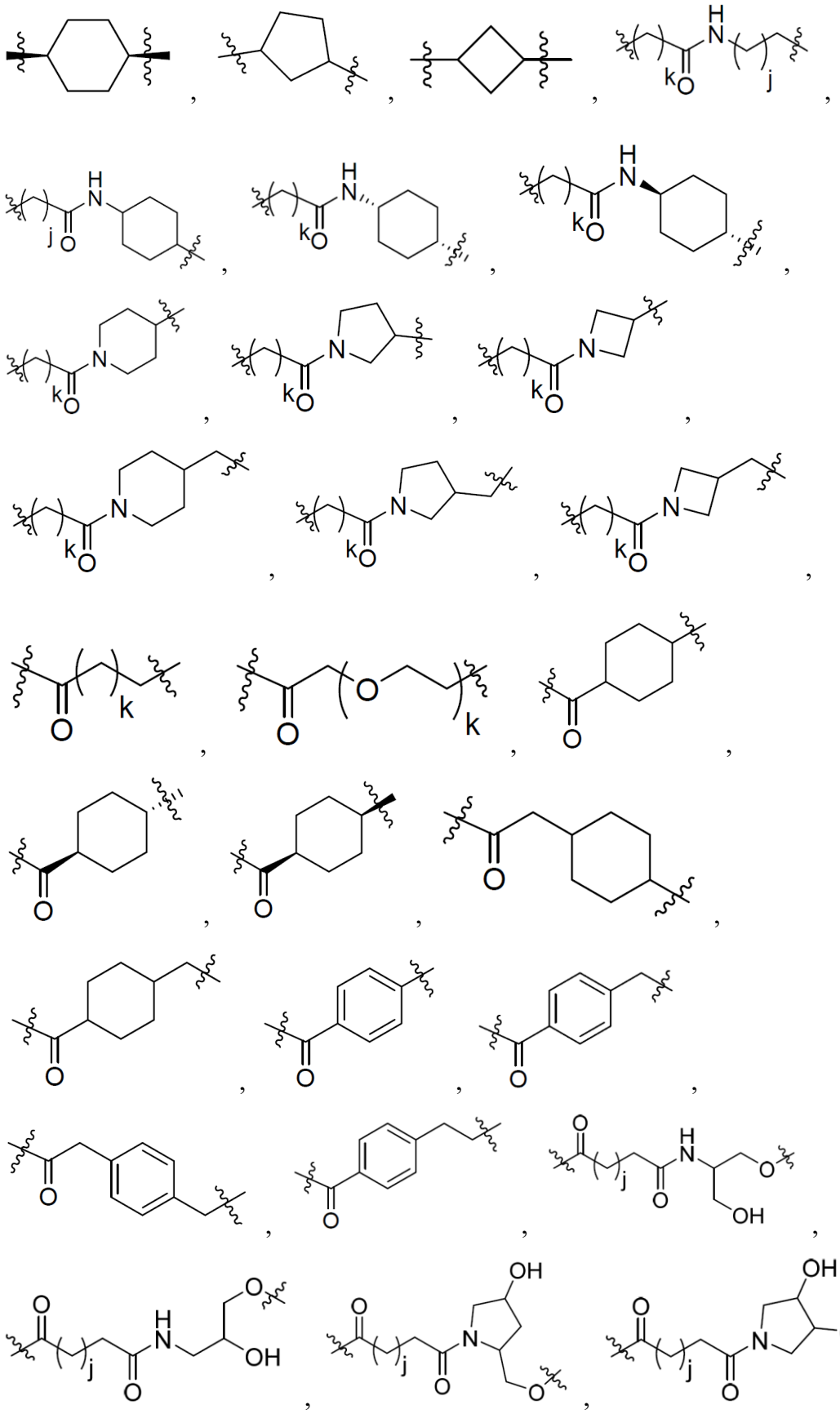


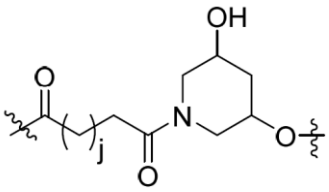
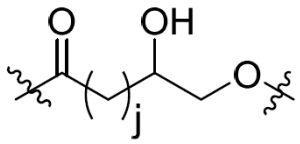
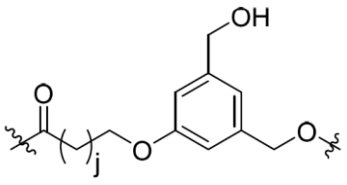
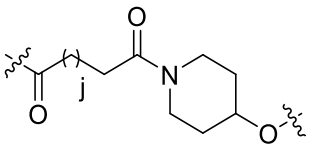
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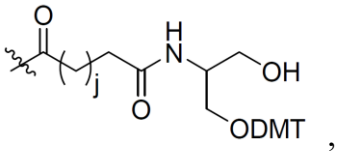
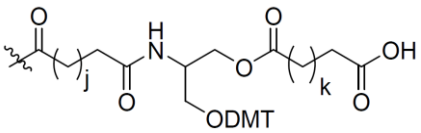
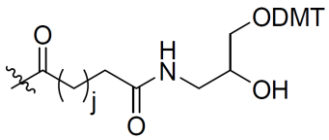
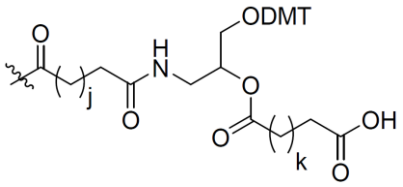
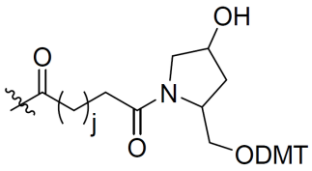
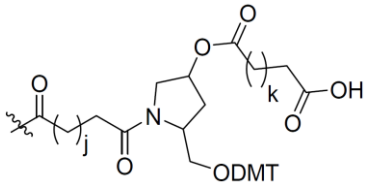
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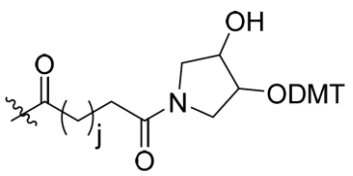
wherein:

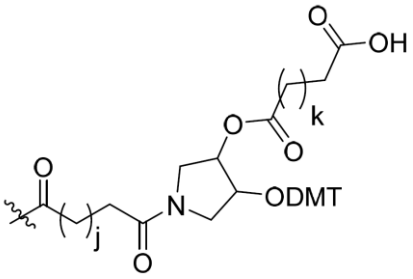
j is an integral number between 1 and 12, and

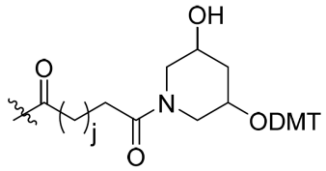
k is an integral number between 0 and 12.

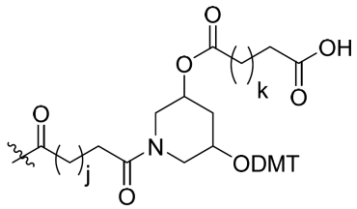
12. The compound of claim 1, wherein linkerB-W is:

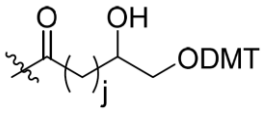







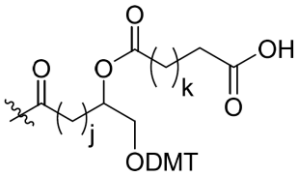


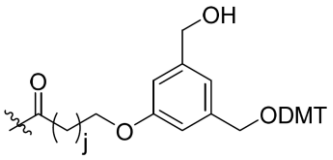
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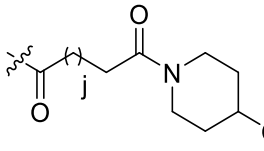
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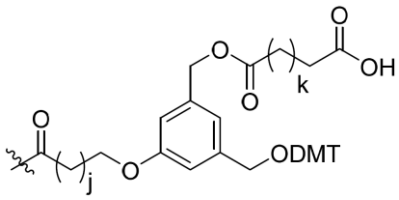
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, or


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wherein:

j is an integral number between 0 and 12, and

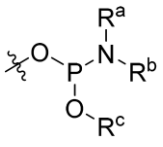
k is an integral number between 0 and 12.

13. The compound of any one of claims 1-12, wherein W is:

a) a hydroxy group,

b) a protected hydroxy group,

c) a phosphoramidite group having the formula:



,

wherein:

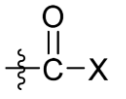
R^a is a C1 to C6 alkyl, C3 to C6 cycloalkyl, an isopropyl group, or R^a joins with R^b through a nitrogen atom to form a cycle,

R^b is a C1 to C6 alkyl, C3 to C6 cycloalkyl, an isopropyl group, or R^b joins with R^a through a nitrogen atom to form a cycle, and

R^c is a phosphite protecting group, phosphate protecting group, or a 2-cyanoethyl group;

d) a carboxyl group,

e) an activated carboxyl group having the formula:



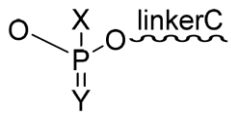
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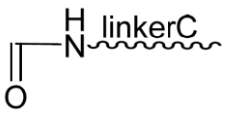
wherein X is a leaving group;

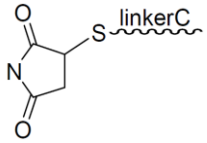
f) a Michael acceptor;

g) an oligonucleotide;

h) a formular of:



(W-1),


(W-2) or


(W-3),

wherein:

linkerC is absent or a spacer attached to a 3' or 5' end of an oligonucleotide,

X is a methyl group, oxygen, sulfur, or an amino group, and

Y is oxygen, sulfur, or an amino group; or

i) the one or more pharmaceutical agents.

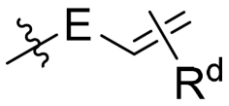
14. The compound of claim 13, wherein the protected hydroxy group is protected using at least one of 4,4'-dimethoxytrityl (DMT), monomethoxytrityl (MMT), 9-(*p*-methoxyphenyl)xanthen-9-yl (Mox), and 9-phenylxanthen-9-yl (Px).

15. The compound of claim 13, wherein the phosphite protecting group comprises at least one of methyl, allyl, 2-cyanoethyl, 4-cyano-2-butenyl, 2-cyano-1,1-dimethylethyl, 2-(trimethylsilyl)ethyl, 2-(S-acetylthio)ethyl, 2-(S-pivaloylthio)ethyl,

2-(4-nitrophenyl)ethyl, 2,2,2-trichloroethyl, 2,2,2-trichloro-1, 1-dimethylethyl, 1,1,1,3,3,3-hexafluoro-2-propyl, fluorenyl-9-methyl, 2-chlorophenyl, 4-chlorophenyl, and 2,4-dichlorophenyl; or the phosphate protecting group comprises at least one of methyl, allyl, 2-cyanoethyl, 4-cyano-2-butenyl, 2-cyano-1,1-dimethylethyl, 2-(trimethylsilyl)ethyl, 2-(S-acetylthio)ethyl, 2-(S-pivaloylthio)ethyl, 2-(4-nitrophenyl)ethyl, 2,2,2-trichloroethyl, 2,2,2-trichloro-1,1- dimethylethyl, 1,1,1,3,3,3-hexafluoro-2-propyl, fluorenyl-9-methyl, 2-chlorophenyl, 4-chlorophenyl, and 2,4-dichlorophenyl.

16. The compound of claim 13, wherein the leaving group is selected from the group consisting of carboxylate, sulfonate, chloride, phosphate, imidazole, hydroxybenzotriazole (HOBt), N-hydroxysuccinimide (NHS), tetrafluorophenol, pentafluorophenol, and *para*-nitrophenol.

17. The compound of claim 13, wherein the Michael acceptor has the formula:



,

wherein:

E is an electron withdrawing group; and

R^d is hydrogen or a C1-C6 alkyl substitution group on olefin.

18. The compound of claim 17, wherein the electron withdrawing group is carboxamide or an ester, or E and the carbon-carbon double bond are part of maleimide.

19. The compound of claim 13, wherein:

a) the oligonucleotide is a single-stranded oligonucleotide;

b) the oligonucleotide is a double-stranded oligonucleotide;

c) the oligonucleotide comprises at least 3 independently selected nucleotides;

d) the oligonucleotide comprises between 16 and 23 independently selected nucleotides;

e) the oligonucleotide comprises about 100 independently selected nucleotides; or

f) the oligonucleotide comprises up to fourteen thousand independently selected nucleotides.

20. The compound of claim 13, wherein linkerC comprises one or more groups selected from the group consisting of:

a) at least one of polyethylene glycol (PEG), an alkyl group, and a cycloalkyl group;

b) at least one heteroatom

c)at least one aliphatic heterocycle;

d) at least one heteroaryl group;

e) at least one amino acid;

f) at least one nucleotide; and

g) at least one saccharide.

21. The compound of claim 20, wherein

a) the at least one heteroatom comprises at least one of oxygen, nitrogen, sulfur, and phosphorous;

b) the at least one aliphatic heterocycle comprises at least one of tetrahydrofuran, tetrahydropyran, morpholine, piperidine, piperazine, pyrrolidine, and azetidine;

c) the at least one heteroaryl group comprises at least one of imidazole, pyrazole, pyridine, pyrimidine, triazole, and 1,2,3-triazole;

d) the at least one nucleotide comprises at least one of an abasic nucleotide and an inverted abasic nucleotide; or

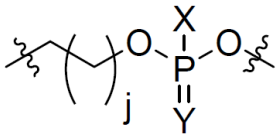
e) the at least one saccharide comprises at least one of glucose, fructose, mannose, galactose, ribose, and glucosamine.

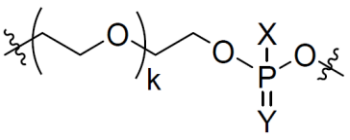
22. The compound of claim 21, wherein:

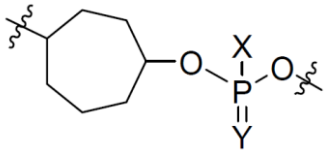
a) the abasic nucleotide is an abasic deoxyribonucleic acid (DNA) or an abasic ribonucleic acid (RNA); or

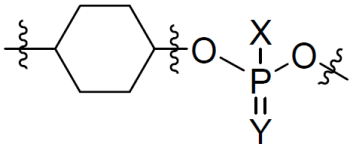
b) the inverted abasic nucleotide is an inverted abasic deoxyribonucleic acid (DNA) or an inverted abasic ribonucleic acid (RNA).

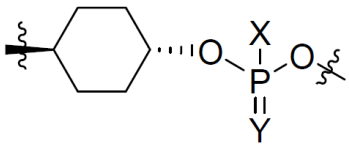
23. The compound of any one of claims 16-22, wherein linkerC comprises one or more of:

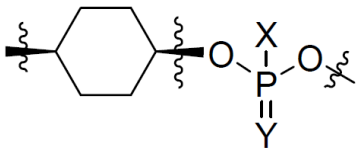


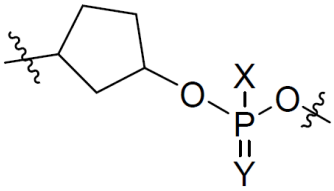
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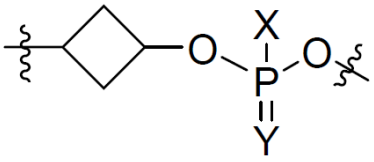
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, and


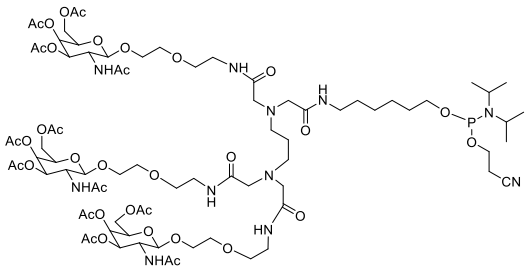
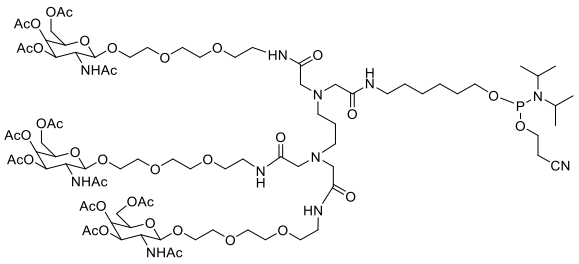
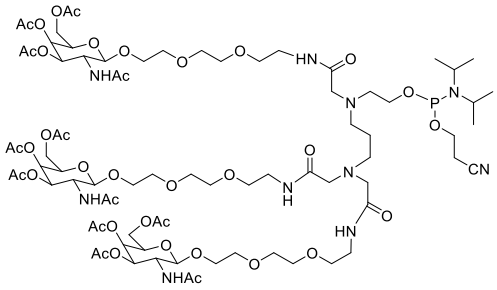
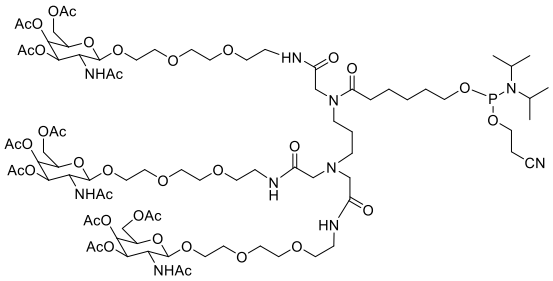
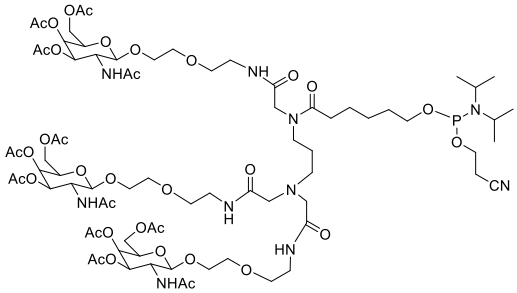
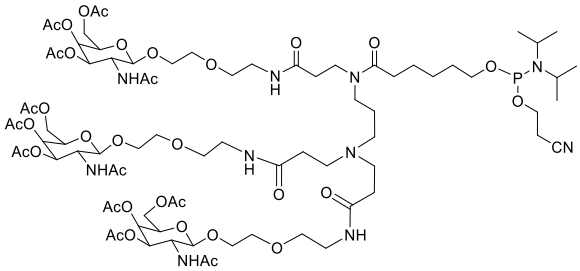
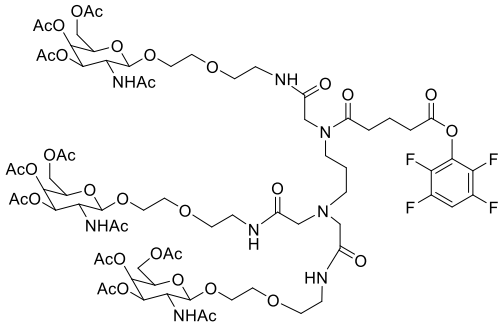
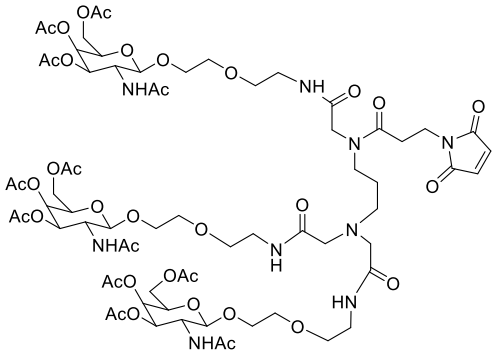
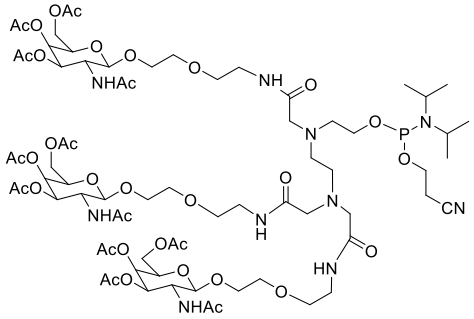
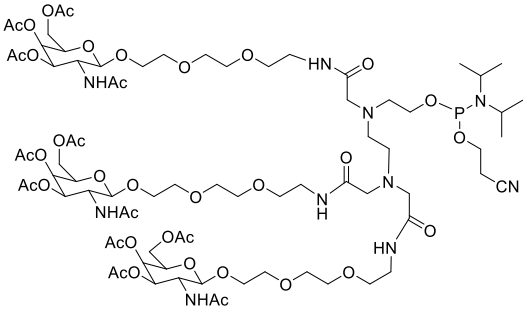
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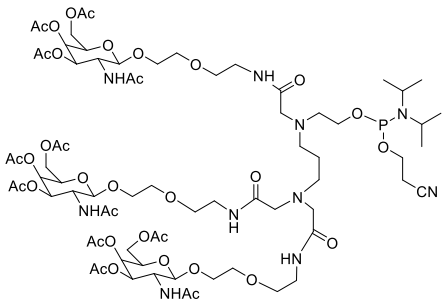
wherein:

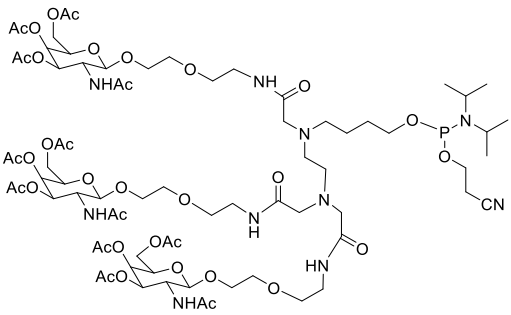
j is an integral number between 1 and 12, and

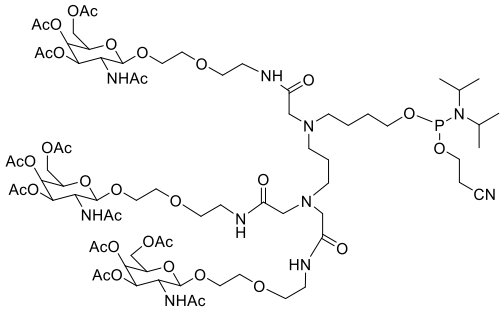
k is an integral number between 0 and 12.

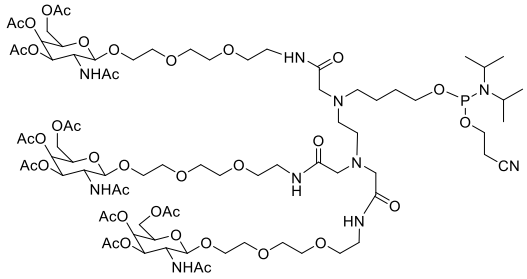
24. The compound of any one of claims 1-23, wherein the compound is selected from the group consisting of:

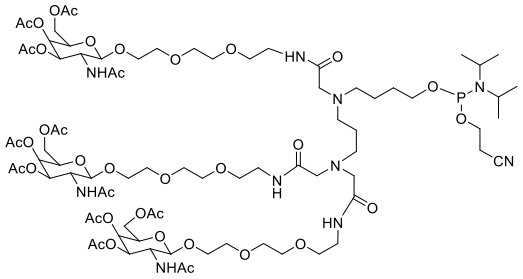
 Compound 1	 Compound 2
 Compound 3	 Compound 4
 Compound 5	 Compound 6
 Compound 7	 Compound 8
 Compound 9	 Compound 10

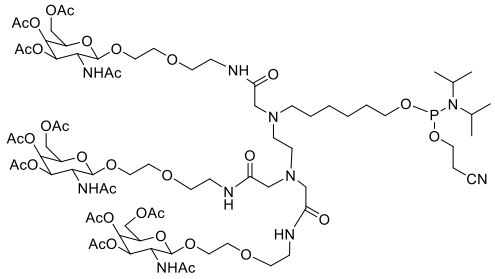

Compound 11

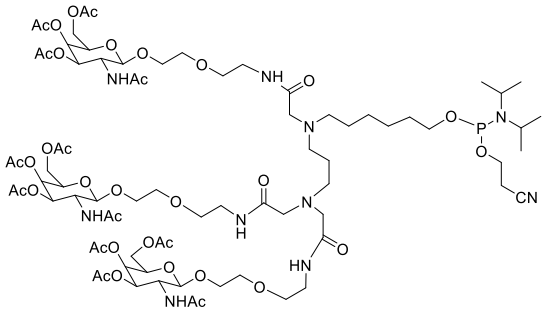

Compound 12

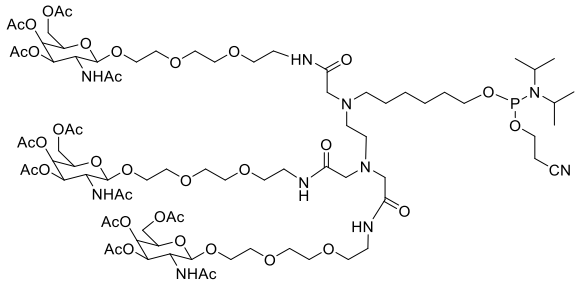

Compound 13

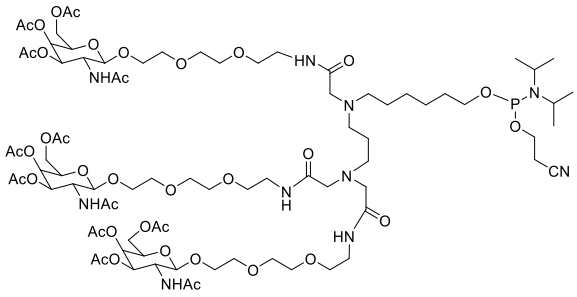

Compound 14

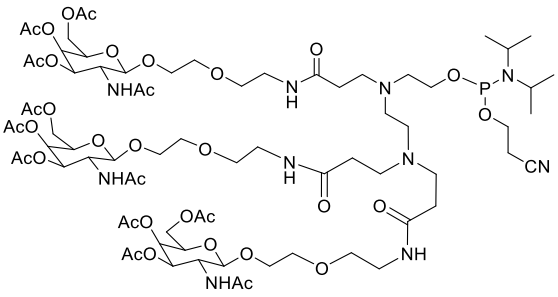

Compound 15

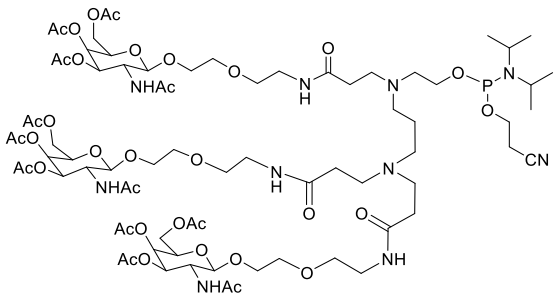

Compound 16


Compound 17

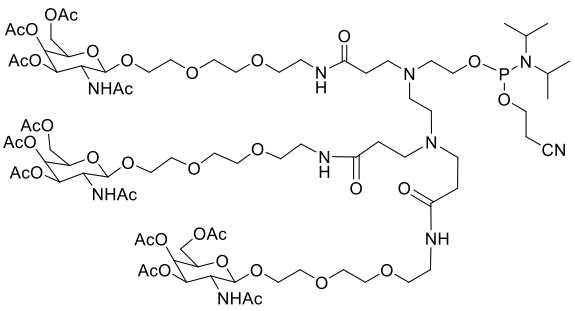

Compound 18


Compound 19

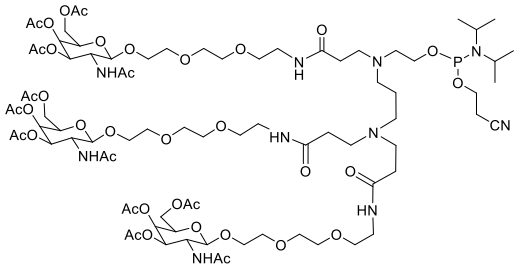

Compound 20



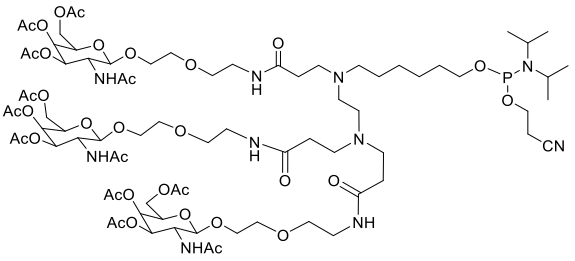
Compound 21



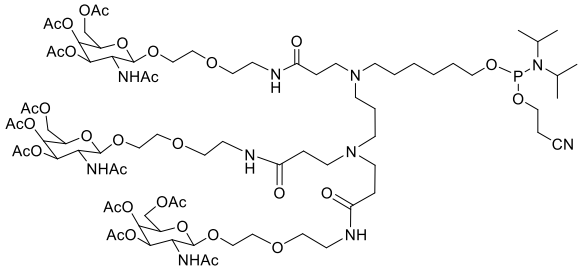
Compound 22



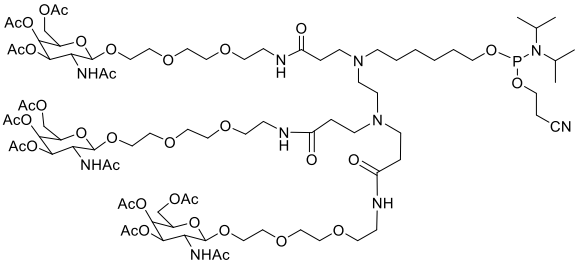
Compound 23



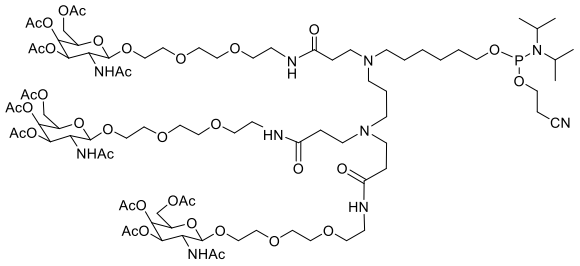
Compound 24



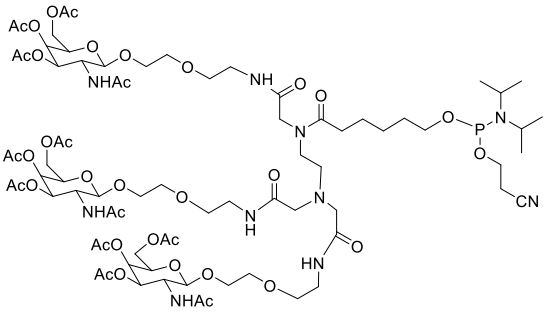
Compound 25



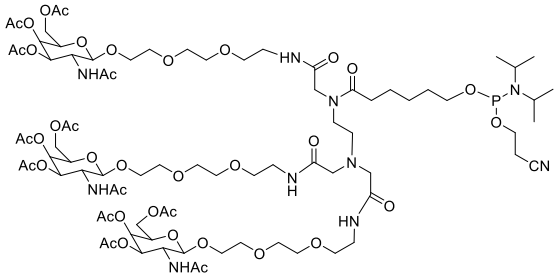
Compound 26



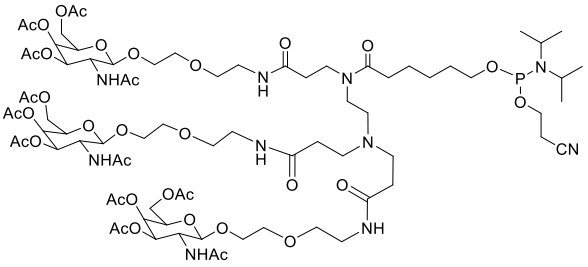
Compound 27



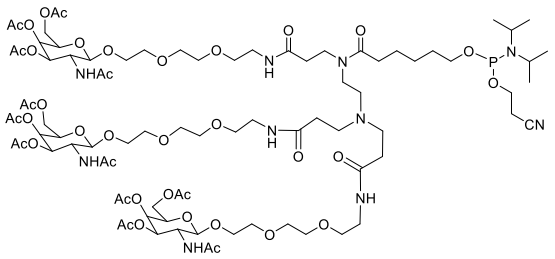
Compound 28

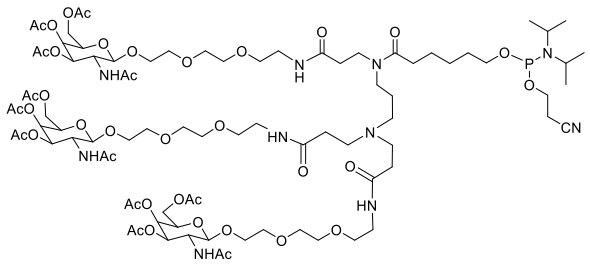


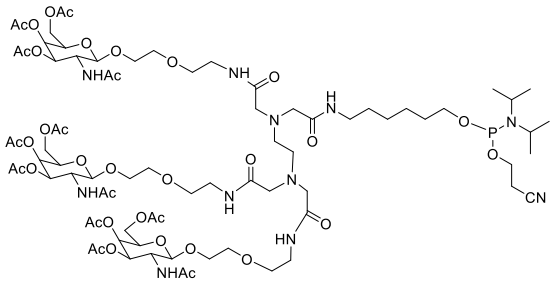
Compound 29

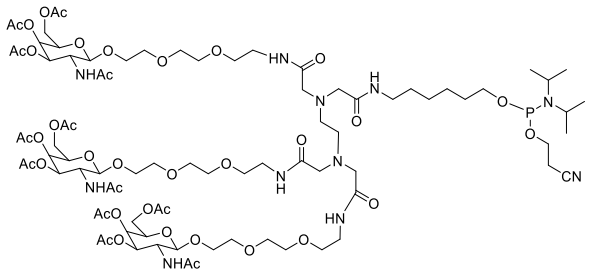


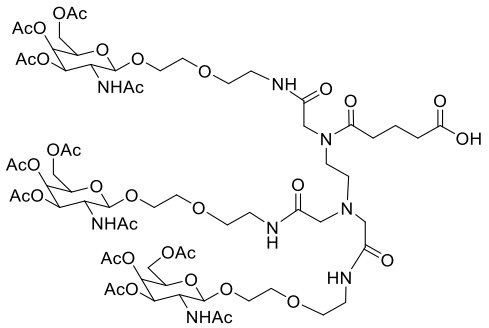
Compound 30

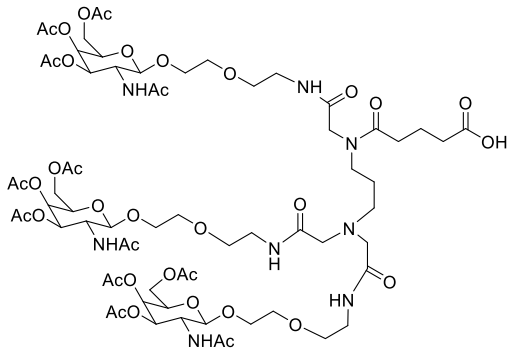

Compound 31

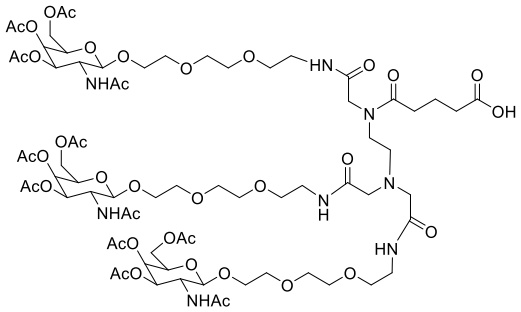

Compound 32

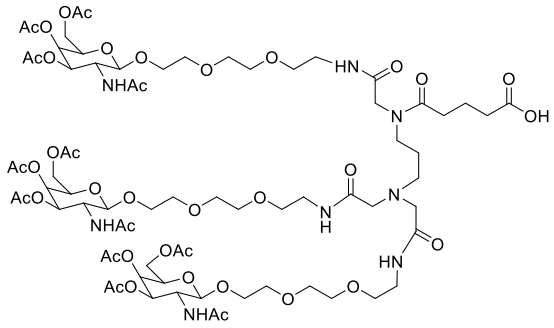

Compound 33

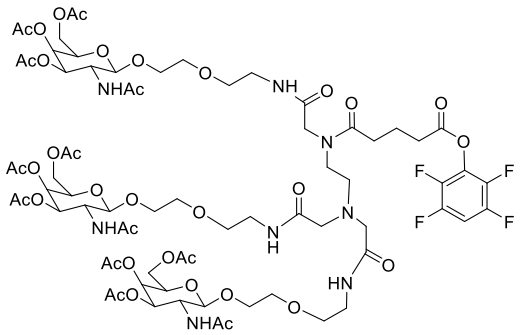

Compound 34

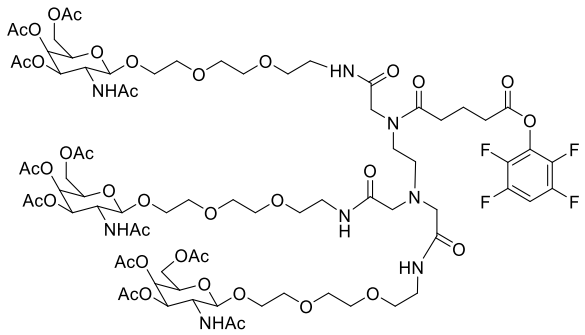

Compound 35

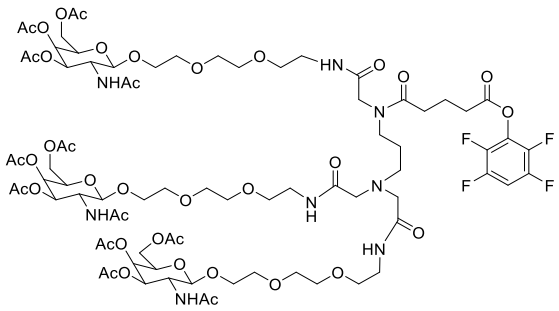

Compound 36


Compound 37

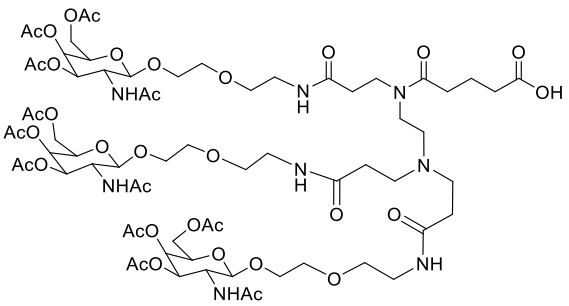

Compound 38


Compound 39

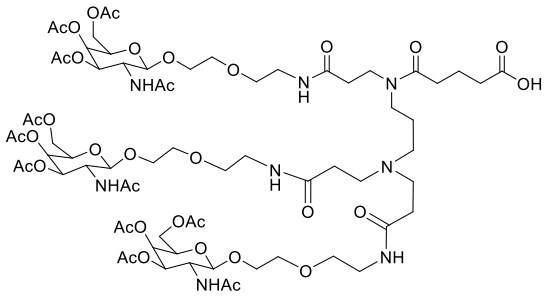

Compound 40



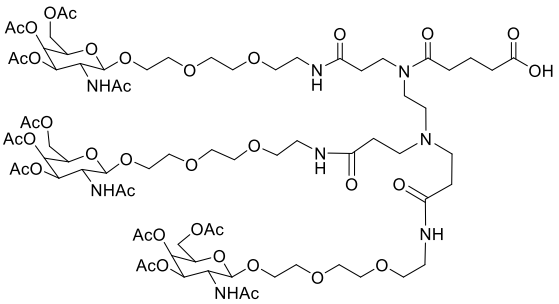
Compound 41



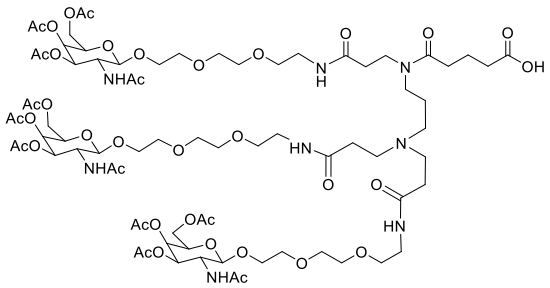
Compound 42



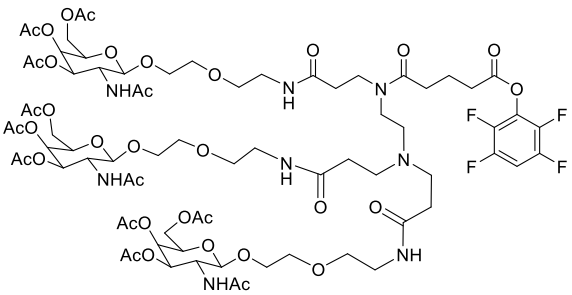
Compound 43



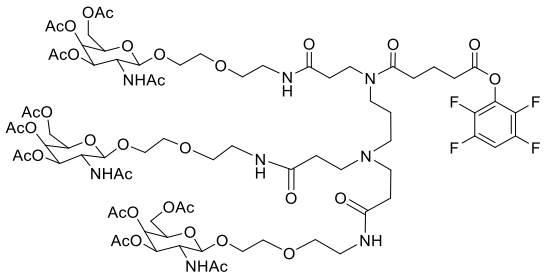
Compound 44



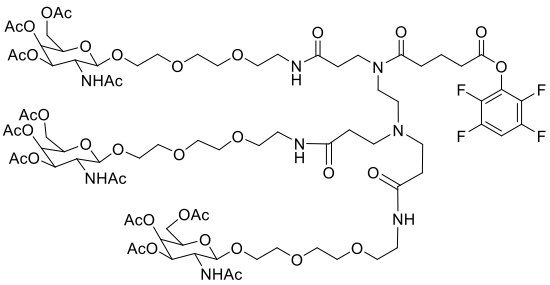
Compound 45



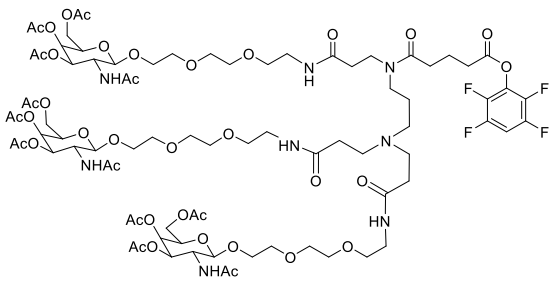
Compound 46



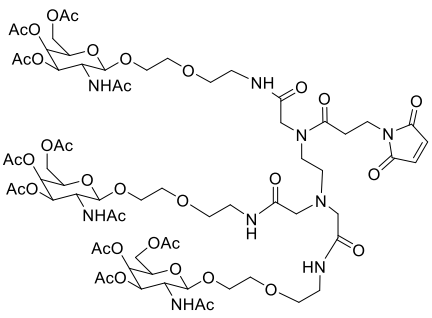
Compound 47



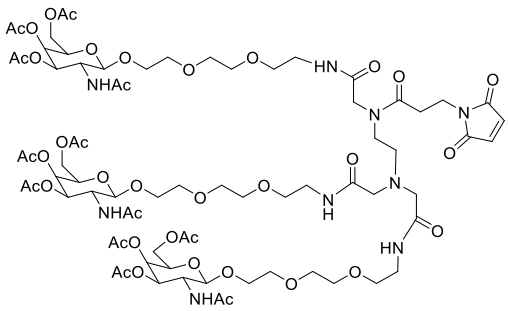
Compound 48

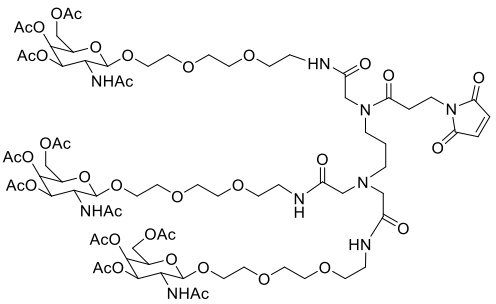


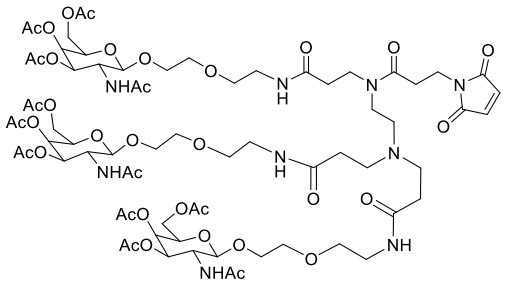
Compound 49

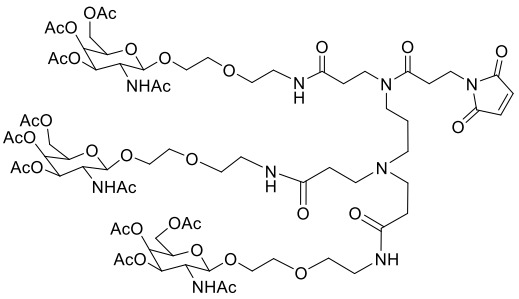


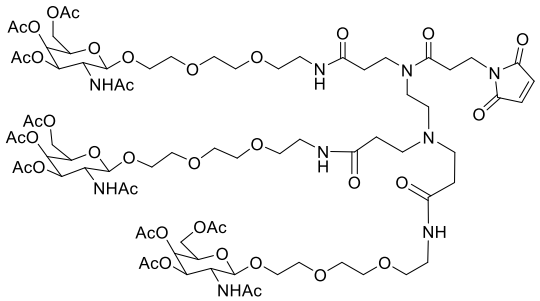
Compound 50

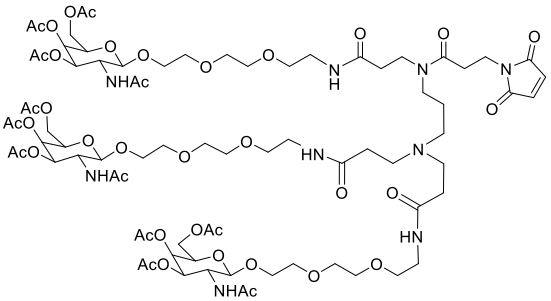

Compound 51

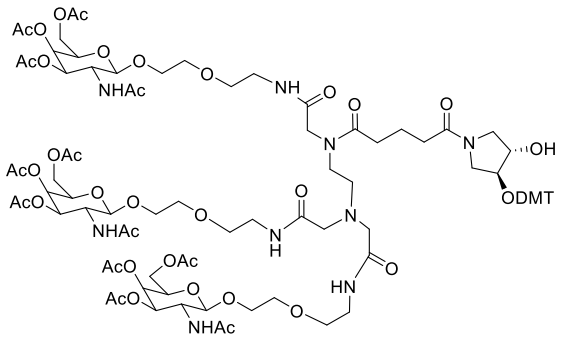

Compound 52

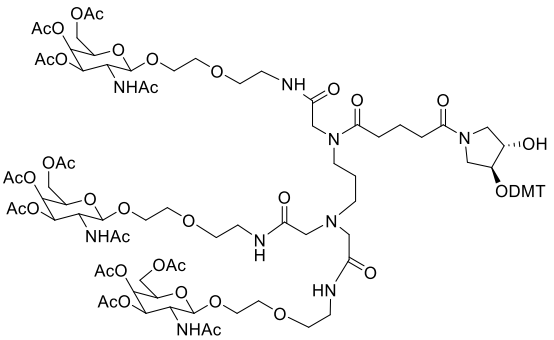

Compound 53

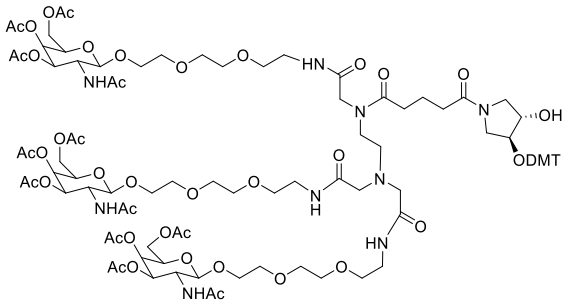

Compound 54

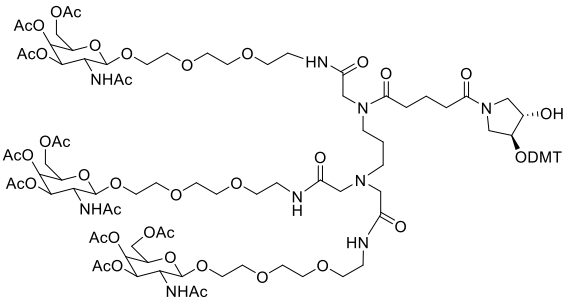

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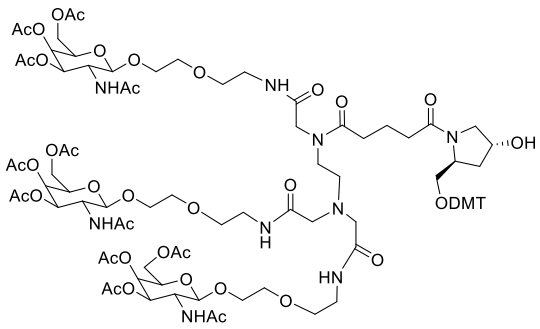

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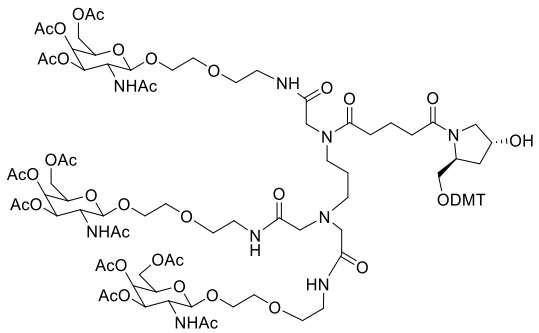

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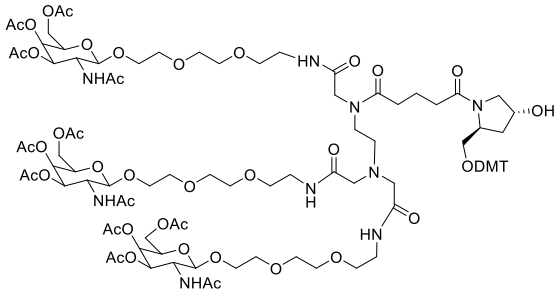

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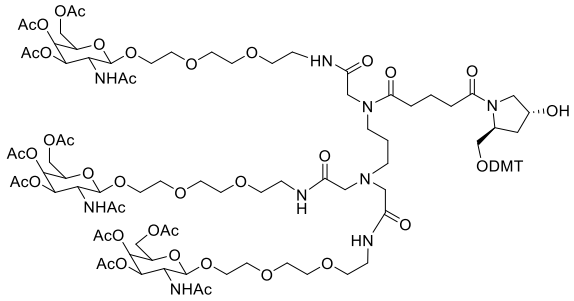

Compound 59

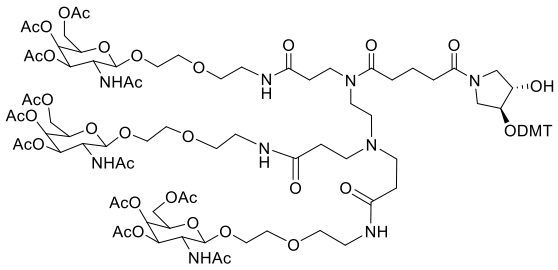

Compound 60

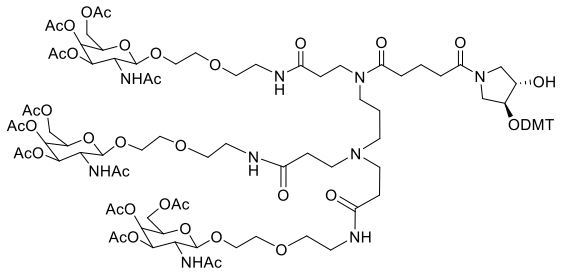

Compound 61

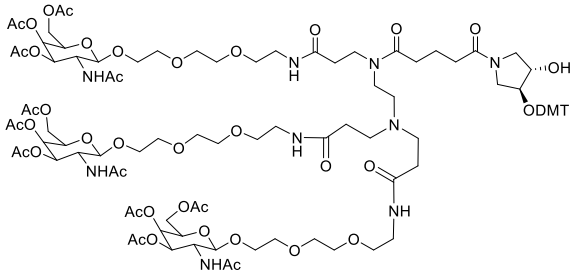

Compound 62

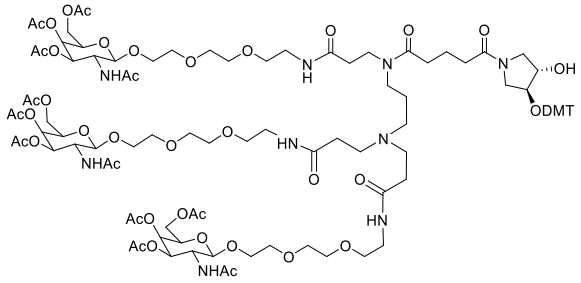

Compound 63

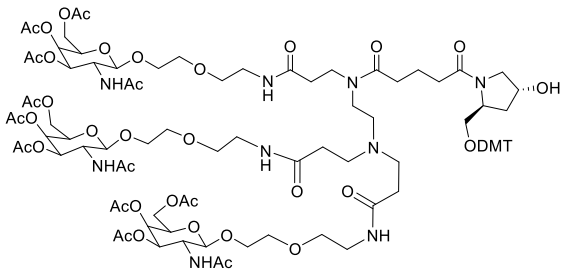

Compound 64

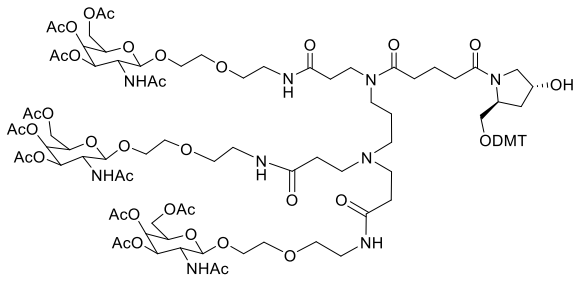

Compound 65

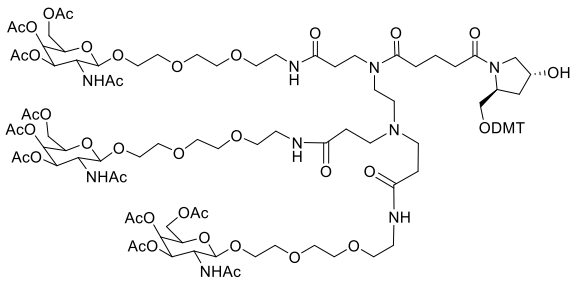
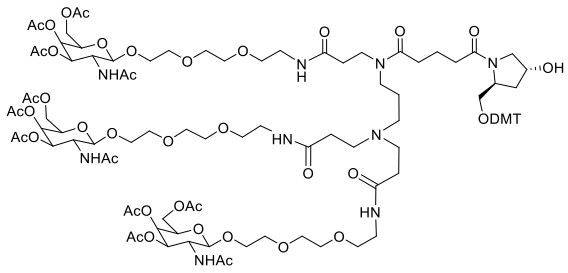
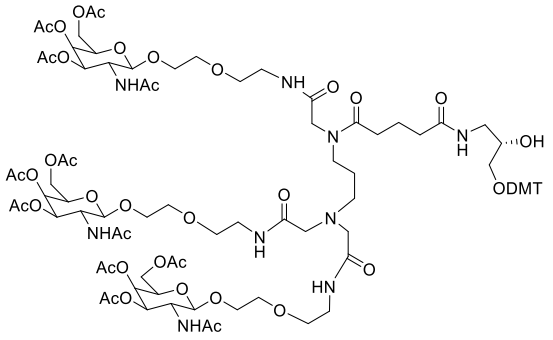
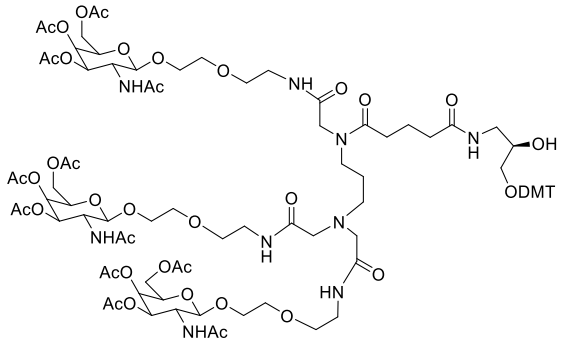
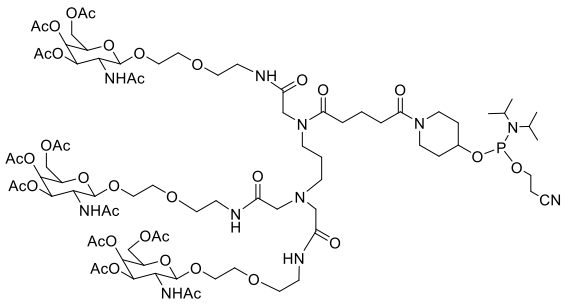

Compound 66


Compound 67


Compound 68


Compound 69


Compound 70

 Compound 71	 Compound 72
 Compound 73	 Compound 74
 Compound 75.	

25. The compound of claim 1, wherein the compound is a stereoisomer of one of Compound 1-75 of claim 24.

26. The compound of claim 13, wherein the one or more pharmaceutical agents comprises at least one of a small interfering RNA (siRNA), a single strand siRNA, a double stranded siRNA, a small activating RNA, an RNAi, a microRNA (miRNA), an antisense oligonucleotide, a short guide RNA (gRNA), a single guide RNA (sgRNA), a messenger RNA (mRNA), a ribozyme, a plasmid, an immune-stimulating nucleic acid, an antagomir, and an aptamer.

27. The compound of claim 26, wherein the double stranded siRNA comprises one or more features selected from the group consisting of:

a) the double stranded siRNA comprises at least one modified ribonucleotide;

b) substantially all ribonucleotides of the double stranded siRNA are modified;

c) all ribonucleotides of the double stranded siRNA are modified;

d) at least one strand of the double-stranded siRNA comprises at least one phosphorothioate linkage;

e) at least one strand of the double-stranded siRNA comprises up to 6 phosphorothioate linkages;

f) the double-stranded siRNA comprises at least one locked nucleic acid;

g) the double-stranded siRNA comprises at least one unlocked nucleic acid; and

h) he double-stranded siRNA comprises at least one glycerol nucleic acid.

28. The compound of claim 27, wherein the modified ribonucleotide comprises a 2'-O-methyl nucleotide,2'-Fluoro nucleotide, 2'-deoxy nucleotide, 2'3'-seco nucleotide mimic, locked nucleotide, 2'-F-Arabino nucleotide, 2'-methoyxyethyl nucleotide, abasic nucleotide, ribitol, inverted nucleotide, inverted abasic nucleotide, inverted 2'-OMe nucleotide, inverted 2'deoxy nucleotide, 2'-amino-modified nucleotide, 2'-alkyl-modified nucleotide, mopholino nucleotide, and 3'-OMe nucleotide, a nucleotide comprising a 5'-phosphorothioate group, or a 5'-(E)-vinyl phosphonate nucleotide (antisense strand only), or a terminal nucleotide linked to a cholesteryl derivative or dodecanoic acid bisdecylamide group, a 2'-amino-modified nucleotide, 2'-alkyl-modified nucleotide, a phosphoramidate, or a non-natural base comprising nucleotide.

29. A pharmaceutical composition comprising the compound of any one of claims 1-28.

30. A method for making the compound for targeted delivery of one or more pharmaceutical agents of any one of claims 1-28, the method comprising:

receiving a first compound comprising a diamine, the diamine comprises a first nitrogen and a second nitrogen, the first nitrogen being a primary amine, the second nitrogen being a secondary amine comprising a protecting group;

producing a second compound by coupling a plurality of protected carboxylic acids to the first compound, the first nitrogen in the second compound being a tertiary amine comprising a first protected carboxylic acid and a second protected carboxylic acid, the second nitrogen of the second compound being a tertiary amine comprising the protecting group and a third protected carboxylic acid;

producing a third compound by deprotecting the second nitrogen of the second compound, resulting in the second nitrogen becoming a secondary amine comprising the third protected carboxylic acid;

producing a fourth compound by attached a moiety comprising a hydroxy group to the second nitrogen of the third compound, resulting in the second nitrogen becoming a tertiary amine or an amide comprising the third protected carboxylic acid and the moiety comprising the hydroxy group;

producing a fifth compound by converting the protected carboxylic acids of the fourth compound into carboxylic acids; and

producing a sixth compound by performing an amide coupling reaction using the fifth compound, the first nitrogen in the sixth compound being a tertiary amine comprising a first amide and a second amide, the second nitrogen in the sixth compound being a tertiary amine comprising the moiety comprising the hydroxy group and a third amide, wherein the first amide, the second amide, and the third amide are each coupled to an independently selected targeting ligand.

31. A method for making the compound for targeted delivery of one or more pharmaceutical agents of any one of claims 1-28, the method comprising:

receiving a first compound comprising a diamine, the diamine comprising a first nitrogen and a second nitrogen, the first nitrogen being a secondary amine comprising a first protecting group, the second nitrogen being an amine comprising a second protecting group;

producing a second compound by coupling a first protected carboxylic acid to the first nitrogen of the first compound, resulting in the first nitrogen becoming a tertiary amine;

removing the first protecting group from the first nitrogen of the second compound to produce a third compound comprising the first nitrogen and the second nitrogen, the first nitrogen being a secondary amine comprising the first protected carboxylic acid, the second nitrogen being an amine comprising the second protecting group;

producing a fourth compound by coupling a second protected carboxylic acid to the first nitrogen of the third compound, resulting in the first nitrogen becoming a tertiary amine;

removing the second protecting group from the fourth compound to produce a fifth compound comprising the first nitrogen and the second nitrogen, the first nitrogen being a tertiary amine comprising the first protected carboxylic acid and the second protected carboxylic acid, the second nitrogen being a primary amine;

producing a sixth compound by coupling a third protected carboxylic acid to the second nitrogen of the fifth compound, resulting in the second nitrogen becoming a secondary amine;

producing a seventh compound by attaching a moiety comprising a hydroxy group to the second nitrogen of sixth compound, resulting in the second nitrogen becoming a tertiary amine;

producing an eighth compound by converting the third protected carboxylic acid of the seventh compound into a first carboxylic acid;

producing a ninth compound by performing an amide coupling reaction using the eighth compound, the first nitrogen of the ninth compound comprising the first protected carboxylic acid and the second protected carboxylic acid, the second nitrogen of the ninth compound comprising the a first amide having a first targeting ligand coupled thereto and the moiety comprising the hydroxy group;

producing a tenth compound by converting the second protected carboxylic acid of the ninth compound into a second carboxylic acid;

producing an eleventh compound by performing an amide coupling reaction using the tenth compound, the first nitrogen of the eleventh compound comprising the first protected carboxylic acid and a second amide having a second targeting ligand coupled thereto, the second nitrogen of the eleventh compound comprising the first amide having the first targeting ligand coupled thereto and the moiety comprising the hydroxy group;

producing a twelfth compound by converting the first protected carboxylic acid of the eleventh compound into a third carboxylic acid; and

producing a thirteenth compound by performing an amide coupling reaction using the twelfth compound, the first nitrogen of the thirteenth compound comprising the second amide having the second targeting ligand coupled thereto and a third amide having a third targeting ligand coupled thereto, the second nitrogen of the thirteenth compound comprising the first amide having the first targeting ligand coupled thereto and the moiety comprising the hydroxy group.

32. The compound of any one of claims 1-28 or the composition of claim 29 for use in delivering a pharmaceutical agent to a subject, wherein W is the one or more pharmaceutical agents.