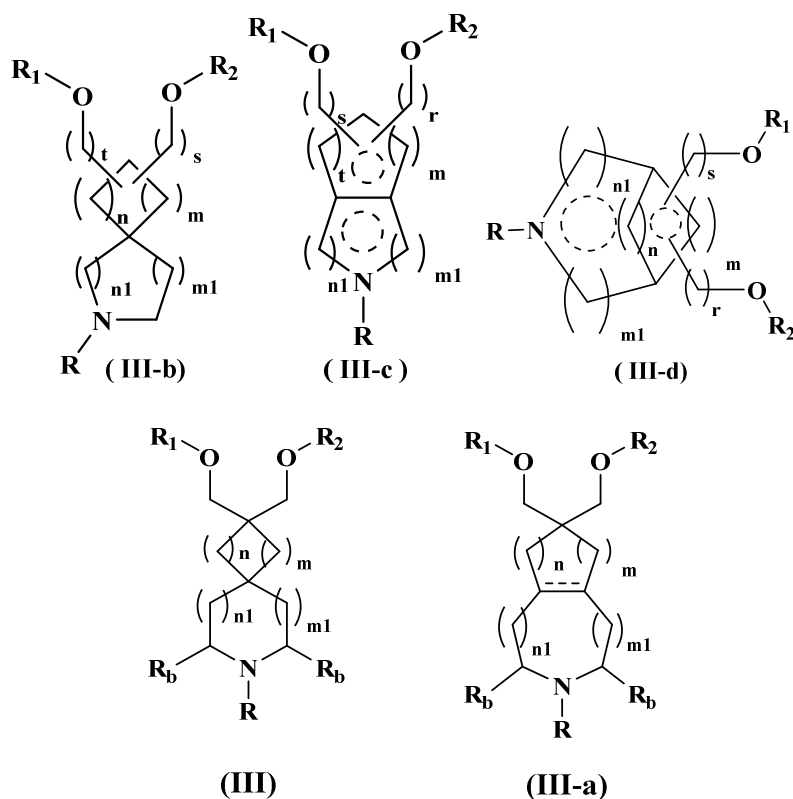


Claims

1. A targeting ligand having the structure shown in formula (III-b), (III-c) or (III-d) or (III) or (III-a):



(i) in formula (III-b), (III-c) or (III-d):

R₁ is hydrogen or a protecting group;

R₂ is hydrogen or a solid support, optionally linked via a linker group, or a phosphoramidite;

R is a carbohydrate or a derivative thereof having hydroxyl protecting group, linked via a linker group;

m is independently selected from 0, 1, 2, 3; 4 and 5;

n is independently selected from 1, 2, 3; 4 and 5;

each of r, s and t is independently selected from 0, 1 and 2;

each of m₁ and n₁ is each independently selected from 0, 1, 2, 3 and 4;

(ii) in formula (III) or (III-a):

 is a single or double bond;

R₁ is hydrogen or a protecting group;

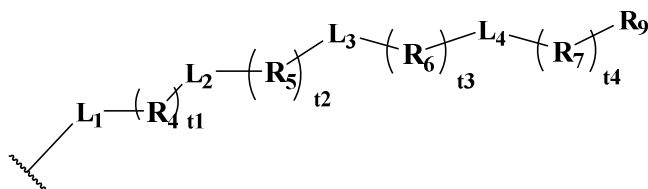
R₂ is hydrogen or a solid support, optionally linked via a linker group, or a phosphoramidite;

R is a carbohydrate or a derivative thereof having hydroxyl protecting group, linked via a linker group;

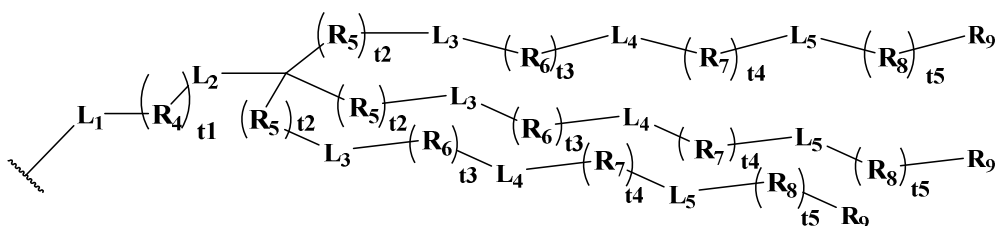
R_b is independently selected from the group of hydrogen and oxo;

each of m and n is independently selected from 1, 2, 3; 4 and 5;
each of m₁ and n₁ is independently selected from 0, 1, 2, 3 and 4.

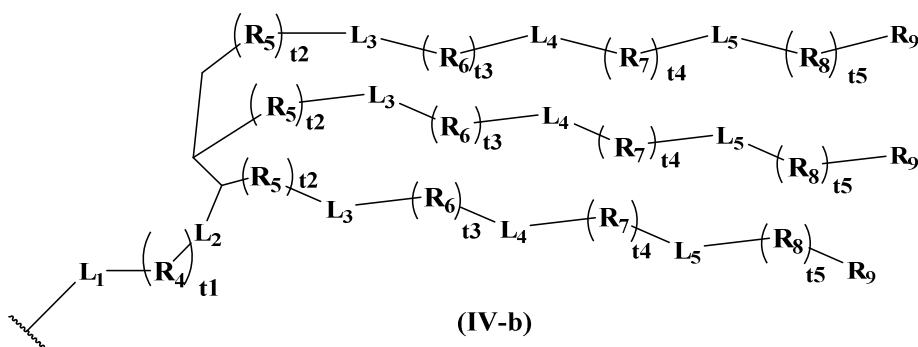
2. The targeting ligand of claim 1, wherein the R having the structure shown in formula (IV), (IV-a), (IV-b) or (IV-c):



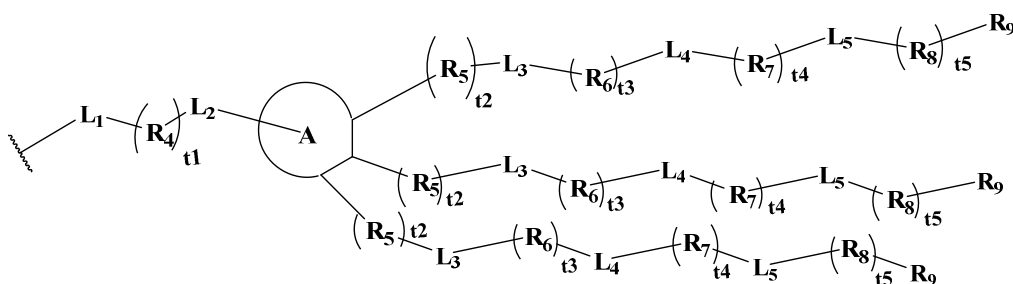
(IV)



(IV-a)



(IV-b)



(IV-c)

A is C₃₋₁₀ cycloalkyl or 4-12 membered heterocyclyl;

each of L₁, L₂, L₃, L₄ and L₅ is independently selected from the group of substituents consisting of absent, O, S, S-S, NH, CO, CONH, NHCO and 4-10 membered heterocyclyl;

each of R₄, R₆, R₇ and R₈ is independently selected from the group of substituents consisting of CH₂, OCH₂CH₂ and CH₂CH₂O;

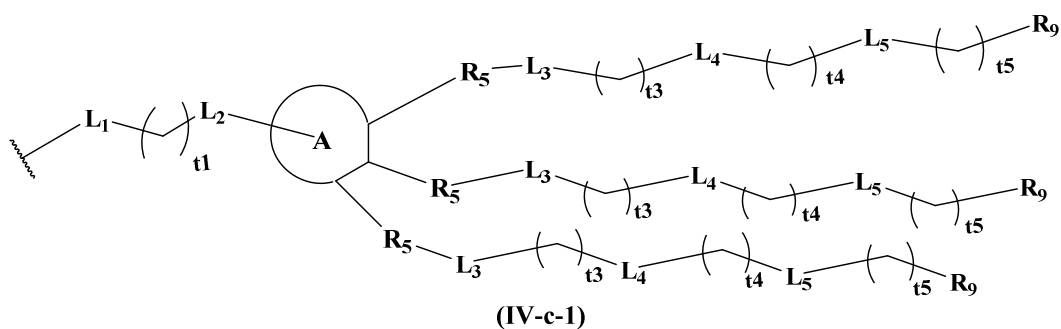
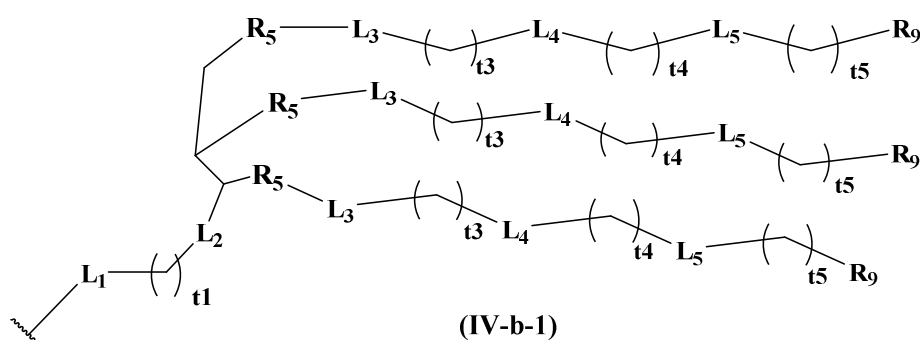
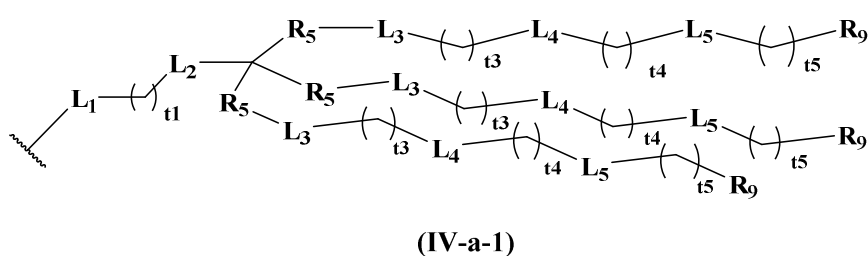
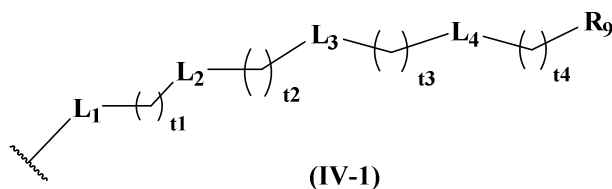
R₅ is independently selected from the group of substituents consisting of absent, CH₂,

OCH₂, CH₂O, OCH₂CH₂, CH₂CH₂O, NHCH₂, CH₂NH, NHCH₂CH₂, CH₂CH₂NH, C₀₋₆ alkyl (C₃₋₈ cycloalkyl) and C₀₋₆ alkyl (4-10 membered heterocyclyl);

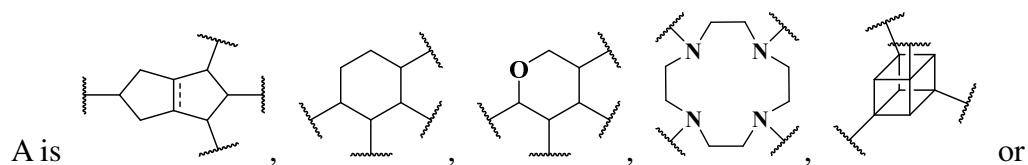
R₉ is a carbohydrate;

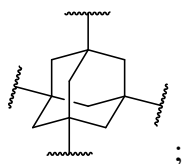
each of t₁, t₂, t₃, t₄ and t₅ is independently selected from 0, 1, 2, 3, 4, 5 and 6.

3. The targeting ligand of claim 2, wherein the R having the structure shown in formula (IV-1), (IV-a-1), (IV-b-1) or (IV-c-1):

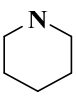


wherein,



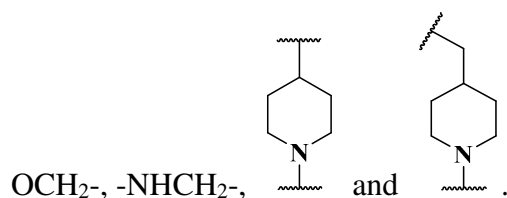


each of L₁, L₃, L₄ and L₅ is independently selected from the group of substituents consisting of absent, O, S, S-S, NH, CO, CONH and NHCO;

L₂ is absent, O, S, S-S, NH, CO, CONH, NHCO and  ;

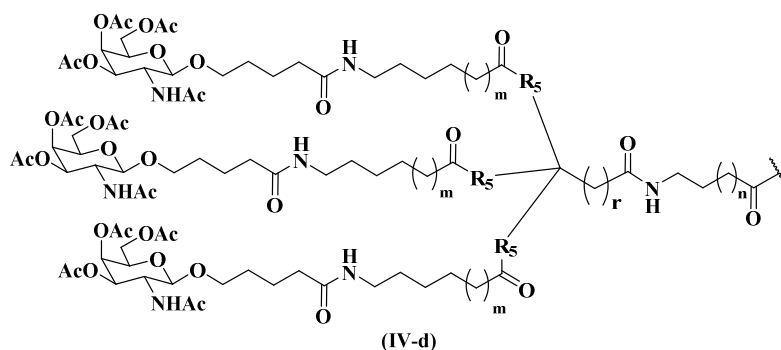
R₅ is independently selected from the group of substituents consisting of absent, CH₂, CH₂O, CH₂NH, C₃₋₆ cycloalkyl, C₃₋₆ CycloalkylC₁₋₃ alkyl, 4-8 membered heterocyclyl containing 1, 2 or 3 of heteroatoms selected from N or O and 4-8 membered heterocyclylC₁₋₃ alkyl containing 1, 2 or 3 of ring heteroatoms selected from N or O.

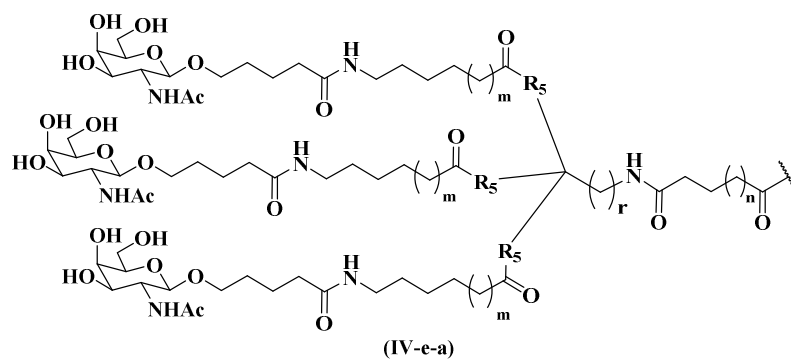
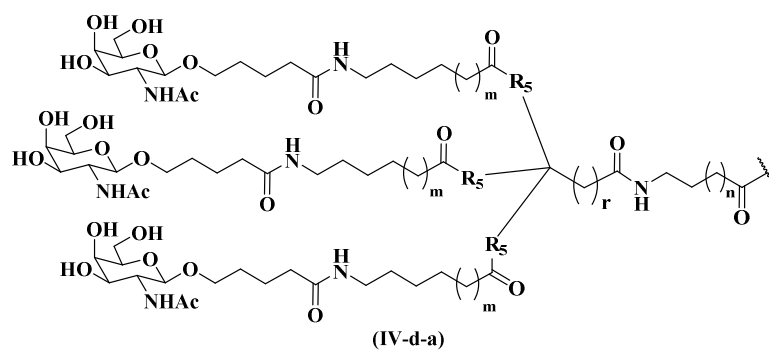
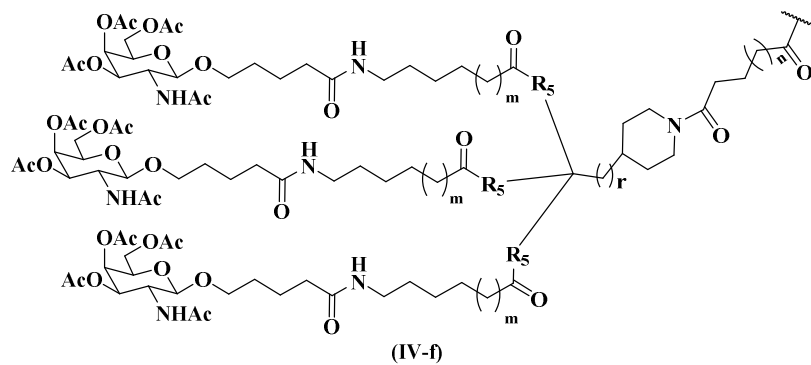
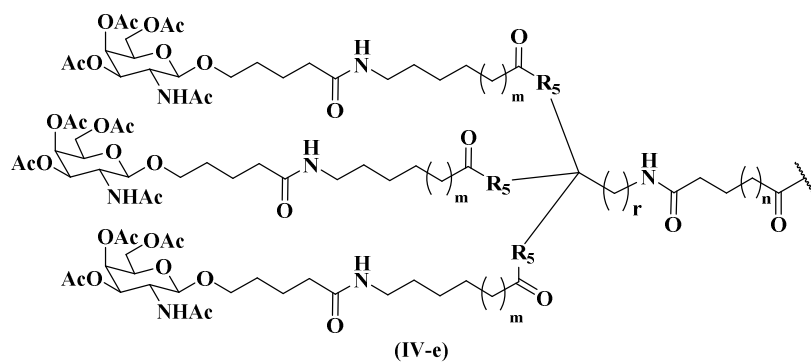
4. The targeting ligand of claim 2, wherein the R₅ is independently selected from -

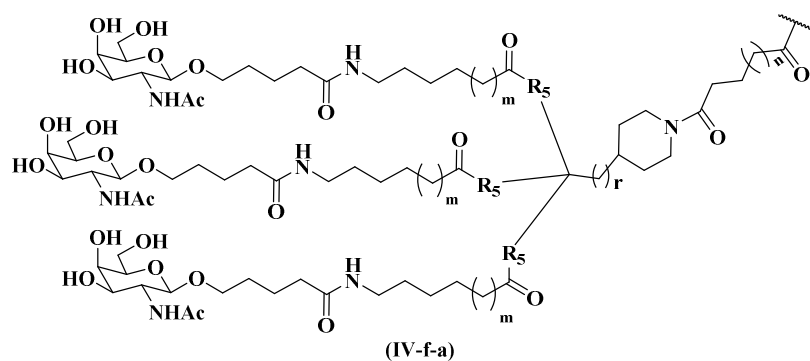


5. The targeting ligand of claim 2, wherein R₉ is selected from the group consisting of galactose, galactosamine, N-acetylgalactosamine (GalNAc), D-galactosaminitol, mannose, mannosamine, mannose-6-phosphate, glucose, glucosamine, N-acetylglucosamine (GluNAc), glucose-6-phosphate, glucosaminitol, glucose glyceraldehyde, fucose, fucosamine, fucose, lactose, allose, altrose, arabinose, cladinose, erythrose, erythrulose, fructose, D-fucitol, L-fucitol, L-glycero-D-mannose-heptose, glycerol, glycerone, gulose, idose, lyxose, psicose, quinovose, quinovosamine, rhamnose, rhamnitol, rhamnosamine, ribose, ribulose, sedoheptulose, sorbose, tagatose, talose, tartaric acid, threose, xylose, and xylulose; preferably, R₉ is N-acetylgalactosamine.

6. The targeting ligand of claim 2, wherein the R having the structure shown in formula (IV-d), (IV-e), (IV-f), (IV-d-a), (IV-e-a) or (IV-f-a):







wherein,

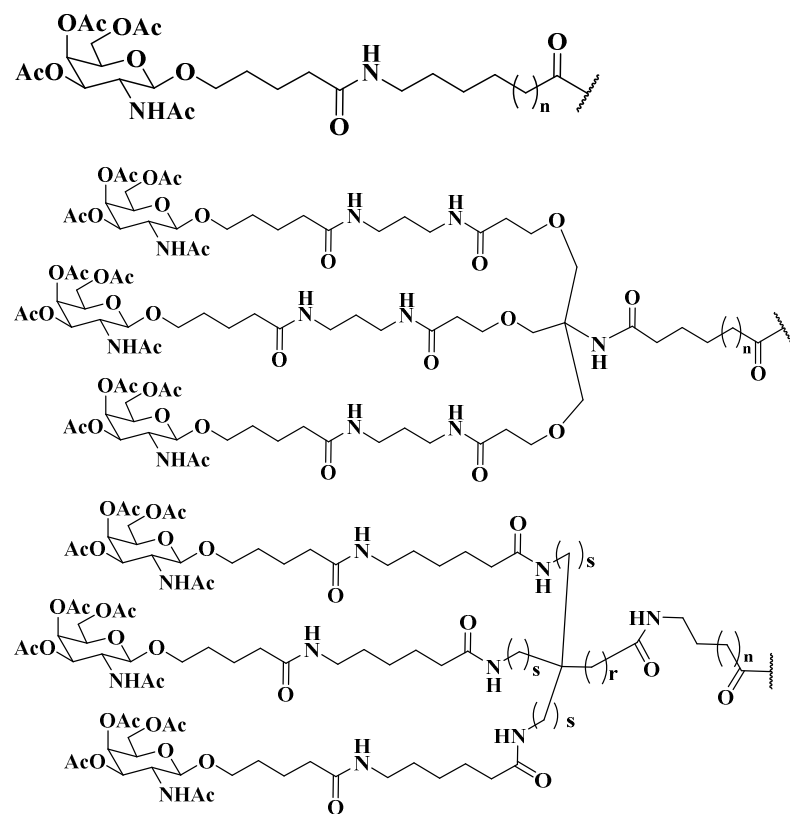
R_5 is independently selected from the group of substituents consisting of OCH_2 , $NHCH_2$ and 4-6 membered heterocyclyl containing 1 or 2 of heteroatoms selected from N or O;

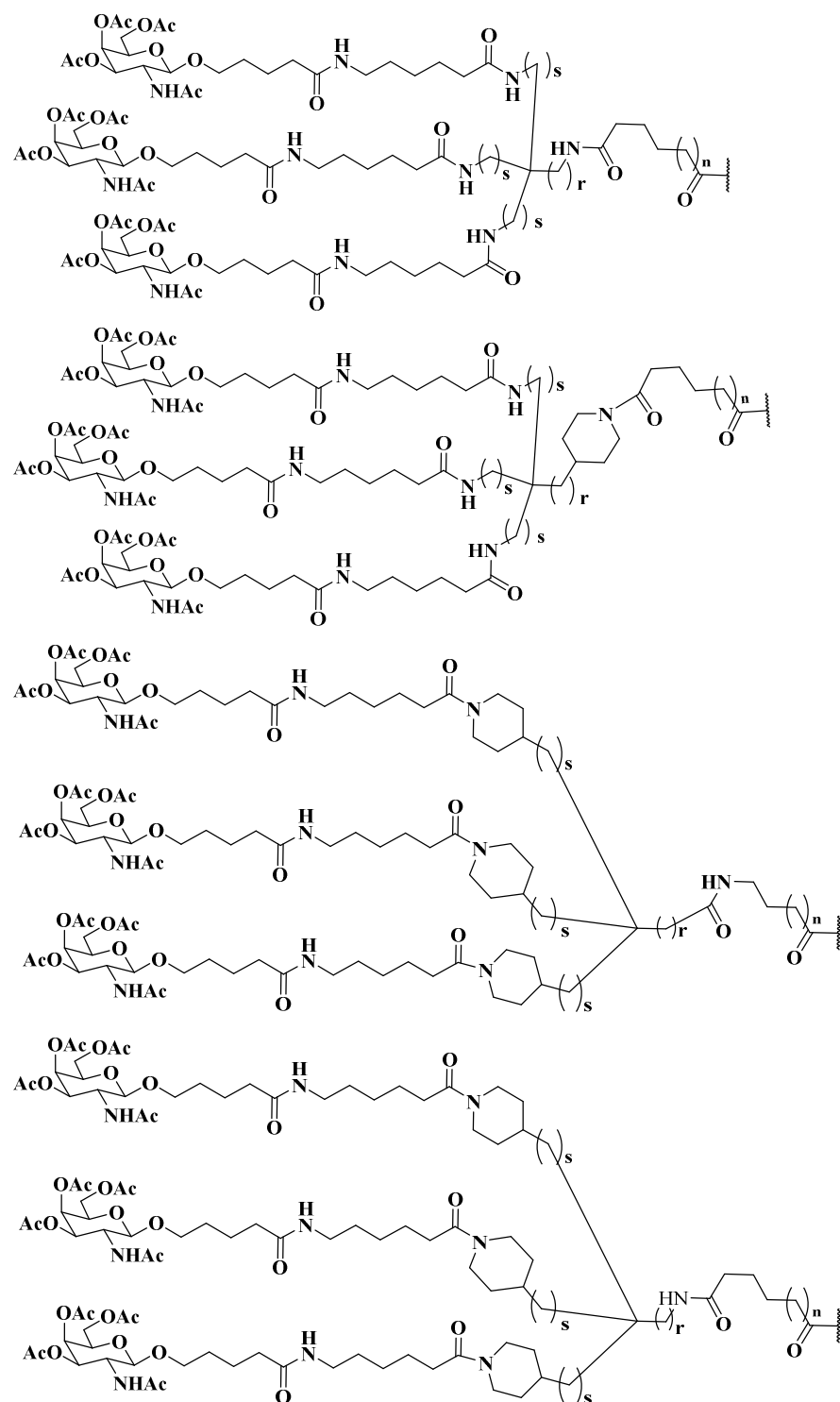
m is independently selected from 0, 1, 2, 3, 4, 5 and 6;

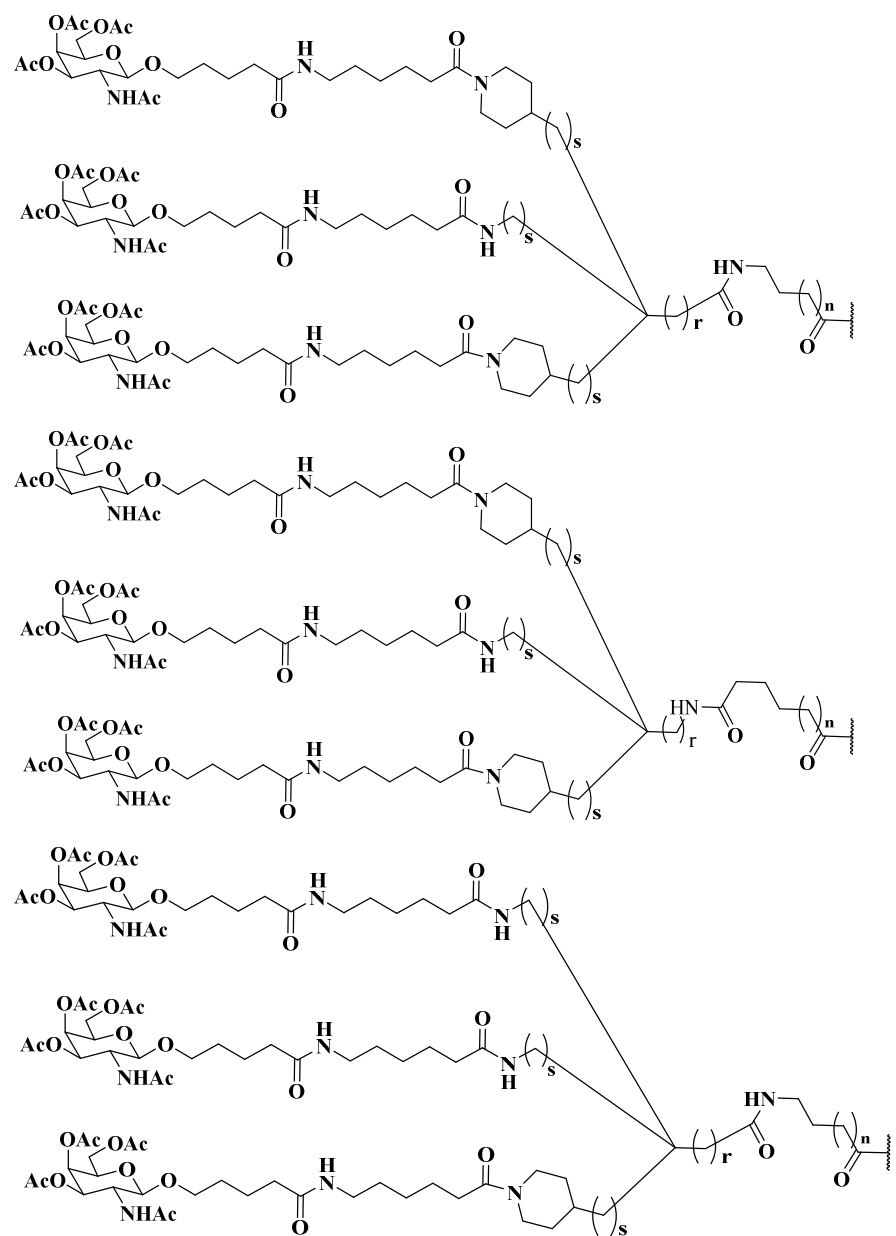
n is independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10; and

r is independently selected from 0, 1, 2, 3, 4 and 5.

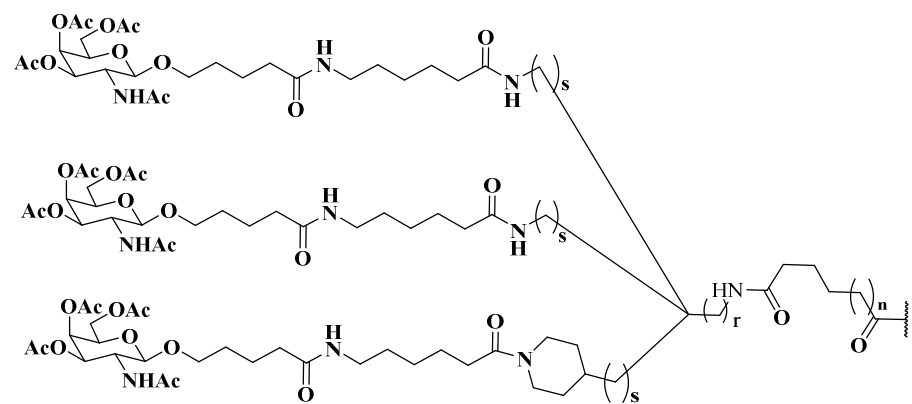
7. The targeting ligand of claim 2, wherein the R is:







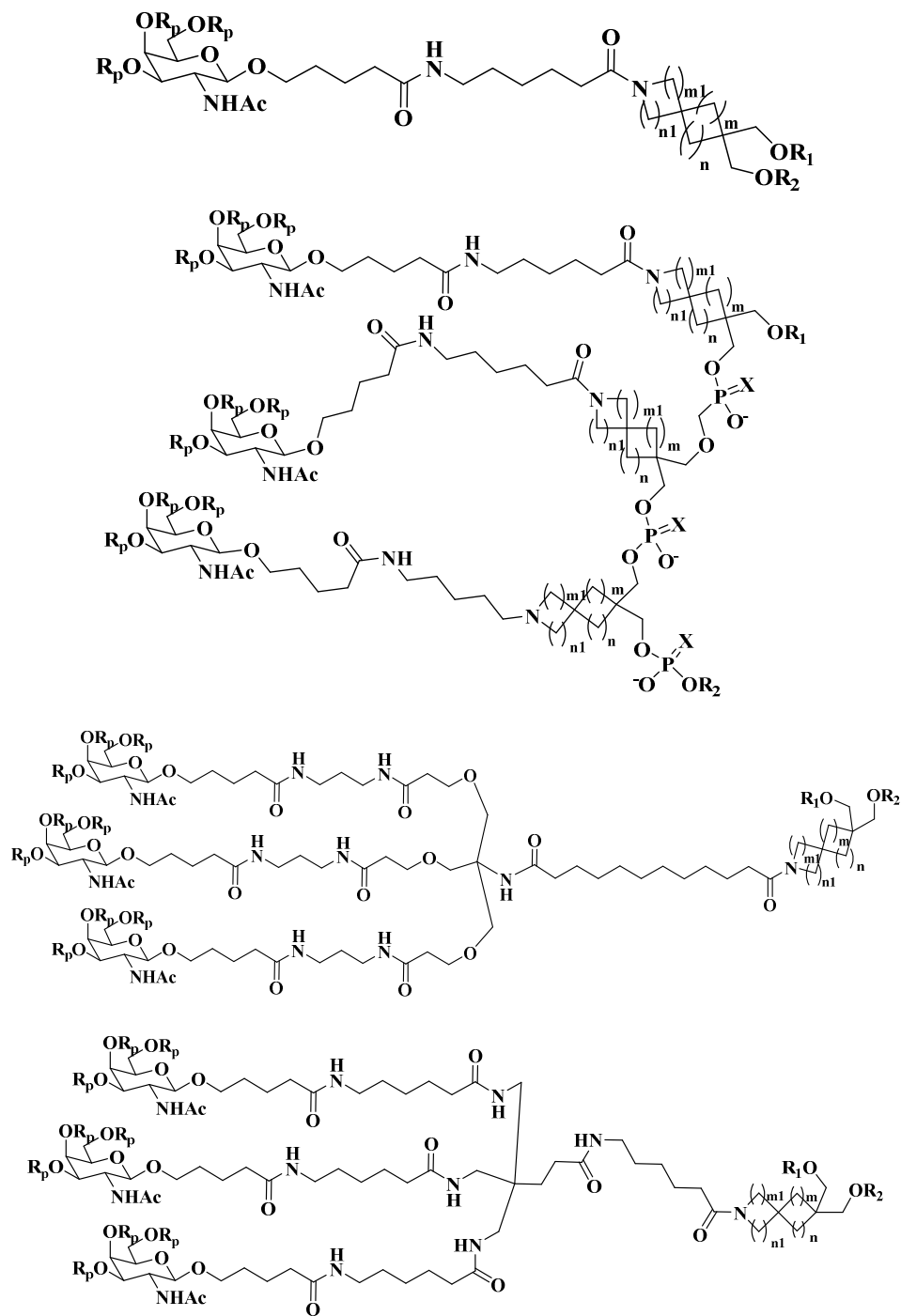
and

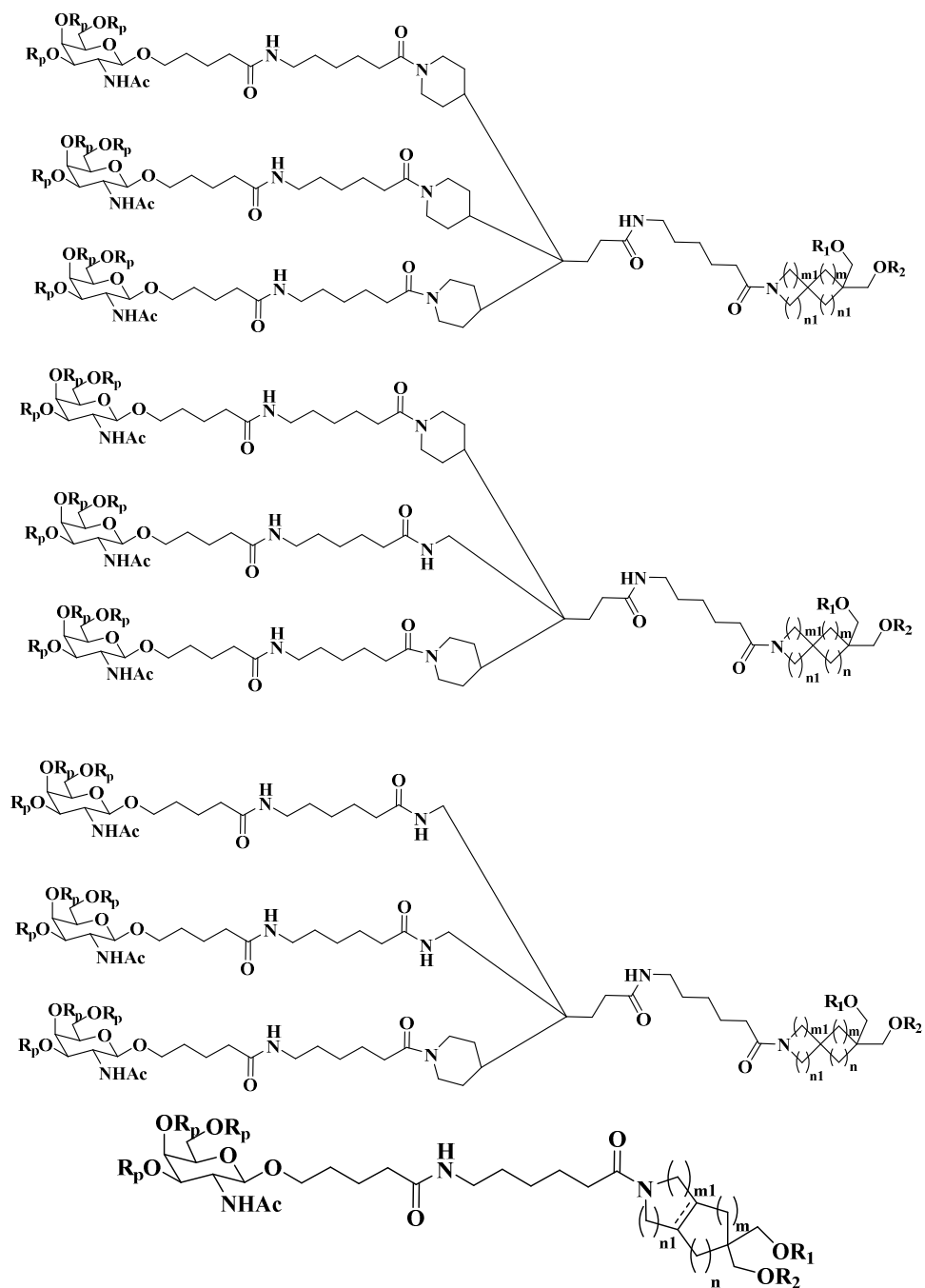


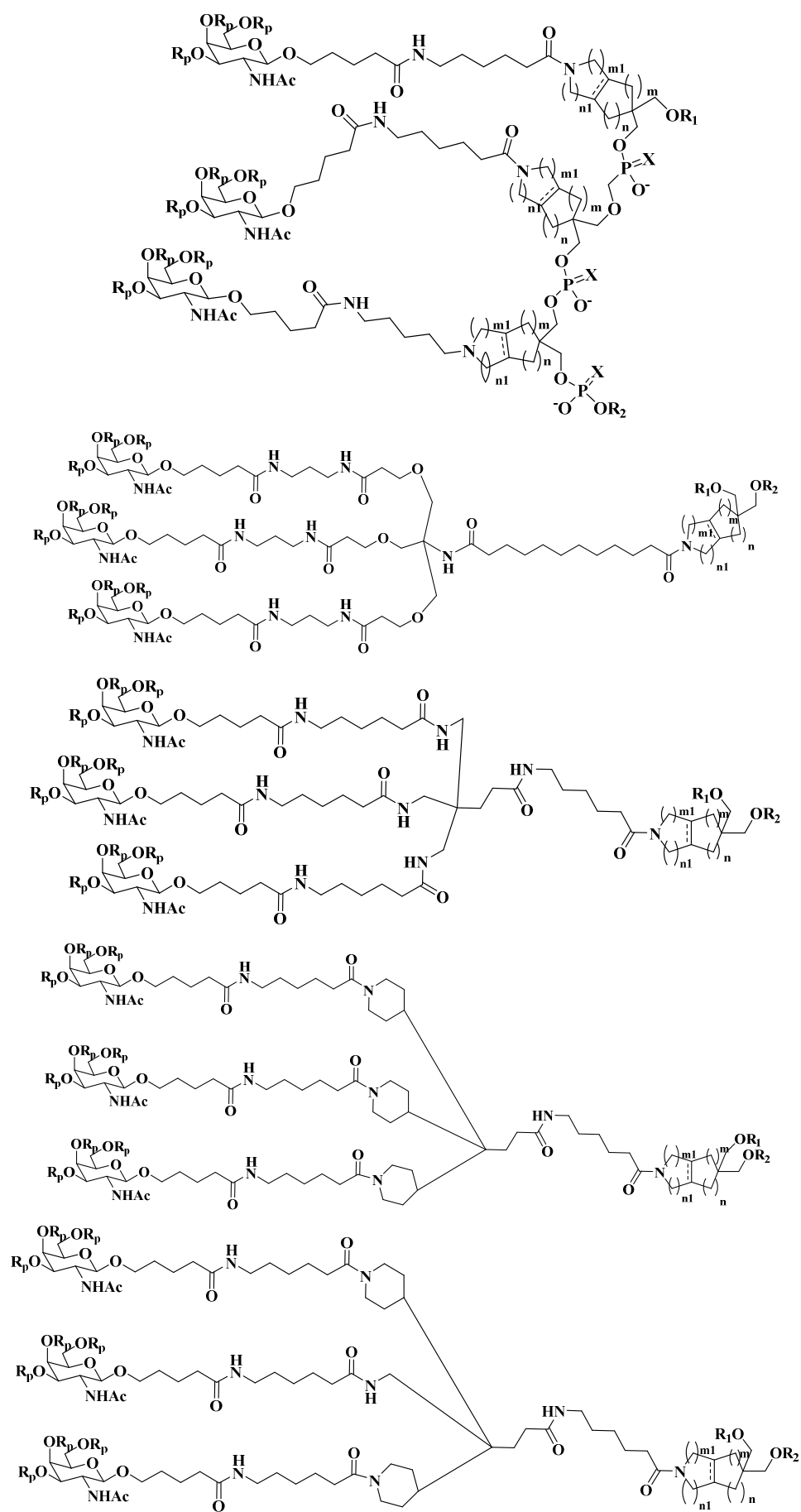
s is independently selected from 0, 1, 2 and 3;
 r is independently selected from 0, 1, 2, 3, 4 and 5;

n is independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10.

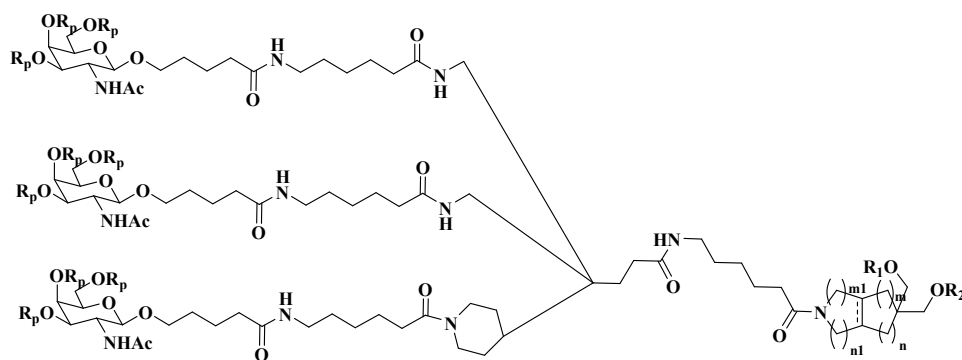
8. The targeting ligand of claim 2, wherein the targeting ligand is:







and



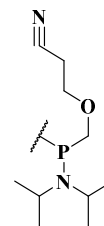
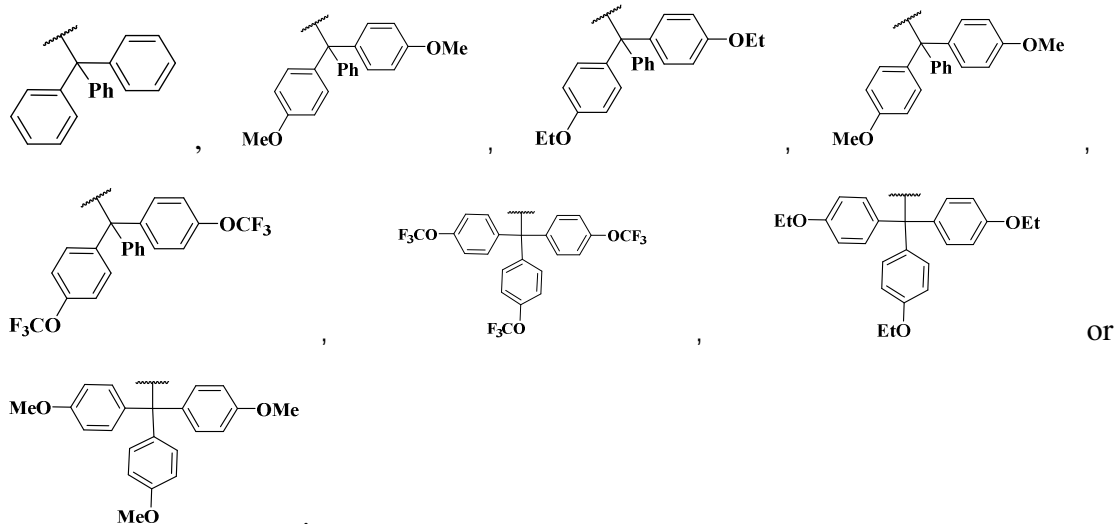
R_p is H or hydroxyl protecting group, preferably, hydroxyl protecting group is acetyl;

X is O or S;

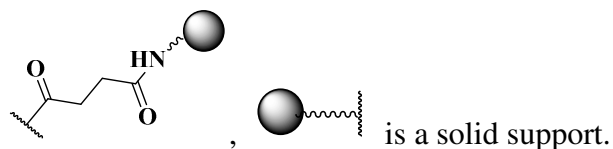
each of m and n is independently selected from 1 or 2;

each of m_1 and n_1 is independently selected from 1, 2 or 3.

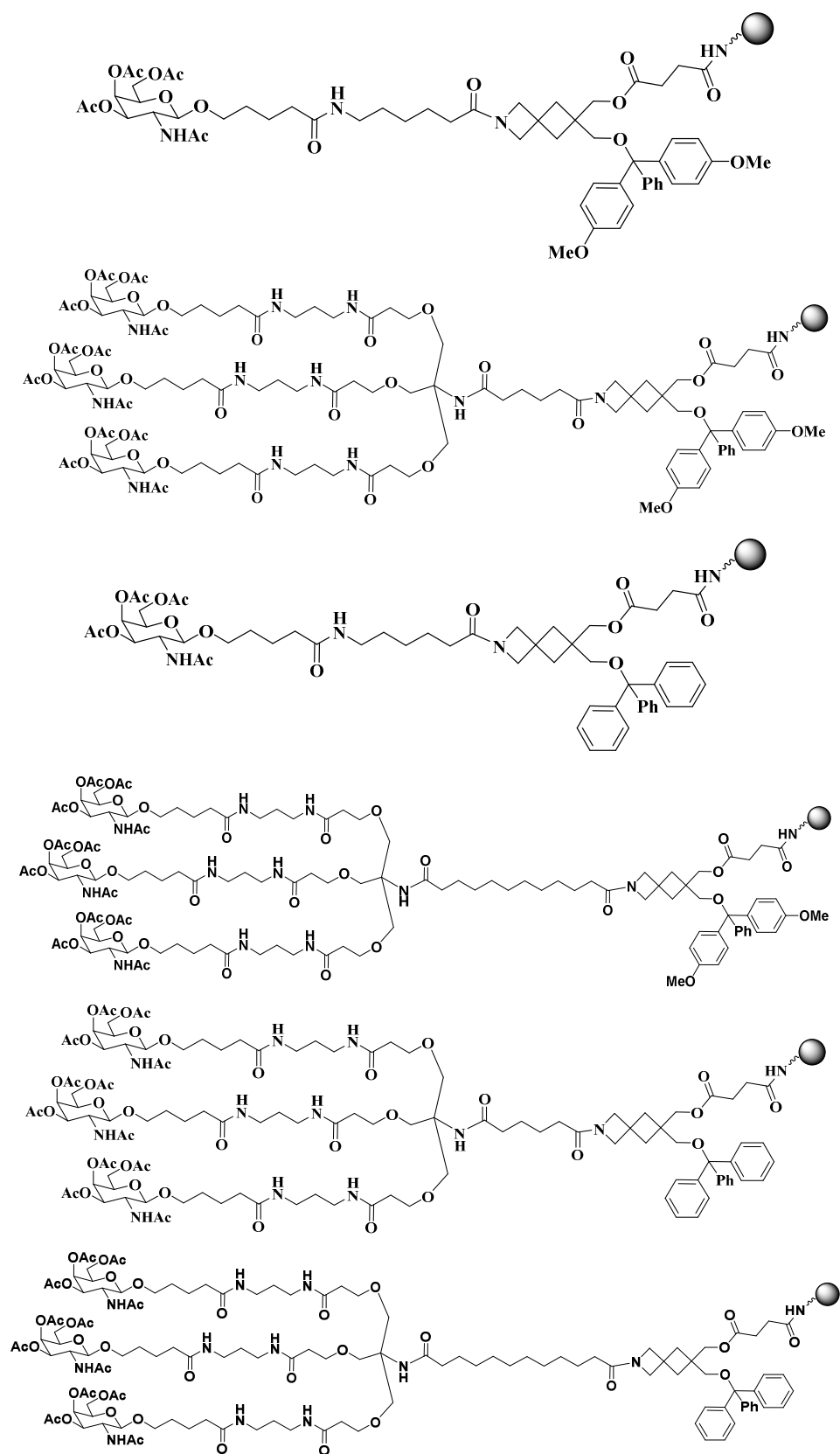
9. The targeting ligand of claim 2 or 8, wherein R₁ is hydrogen or substituted or unsubstituted triphenylmethyl hydroxyl protecting group; preferably, R₁ is

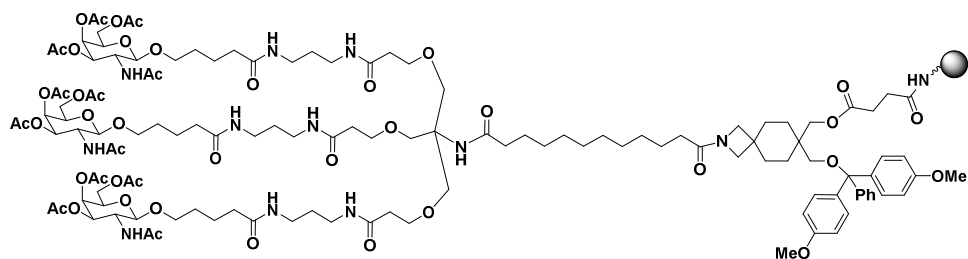
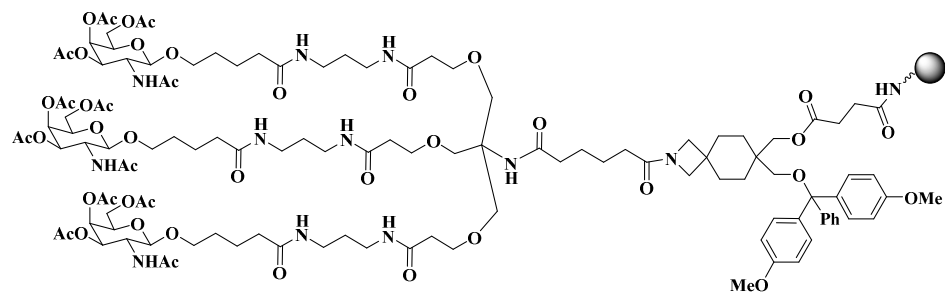
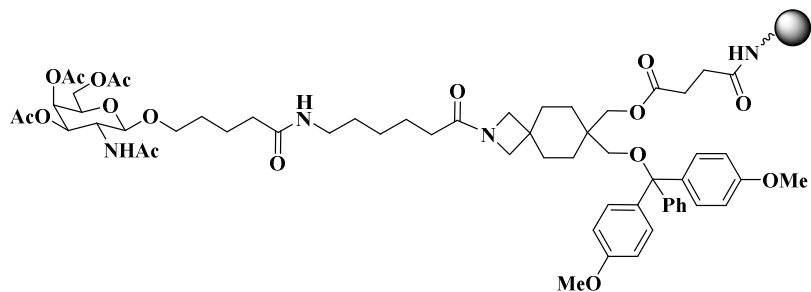
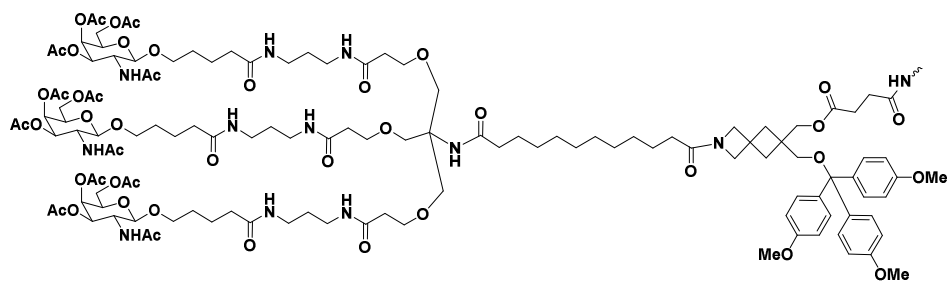
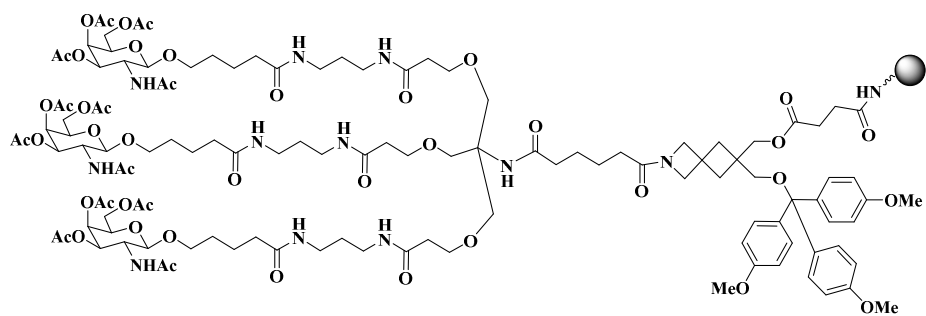
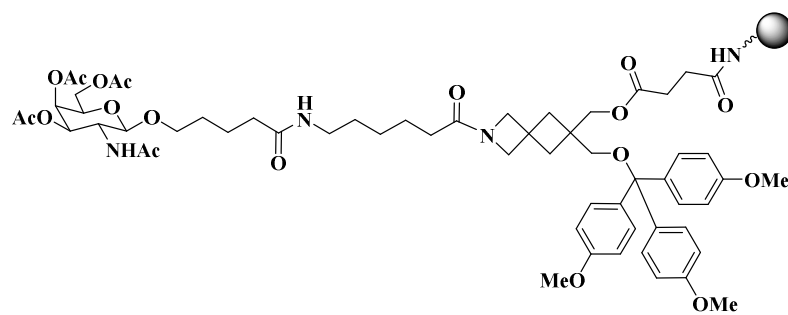


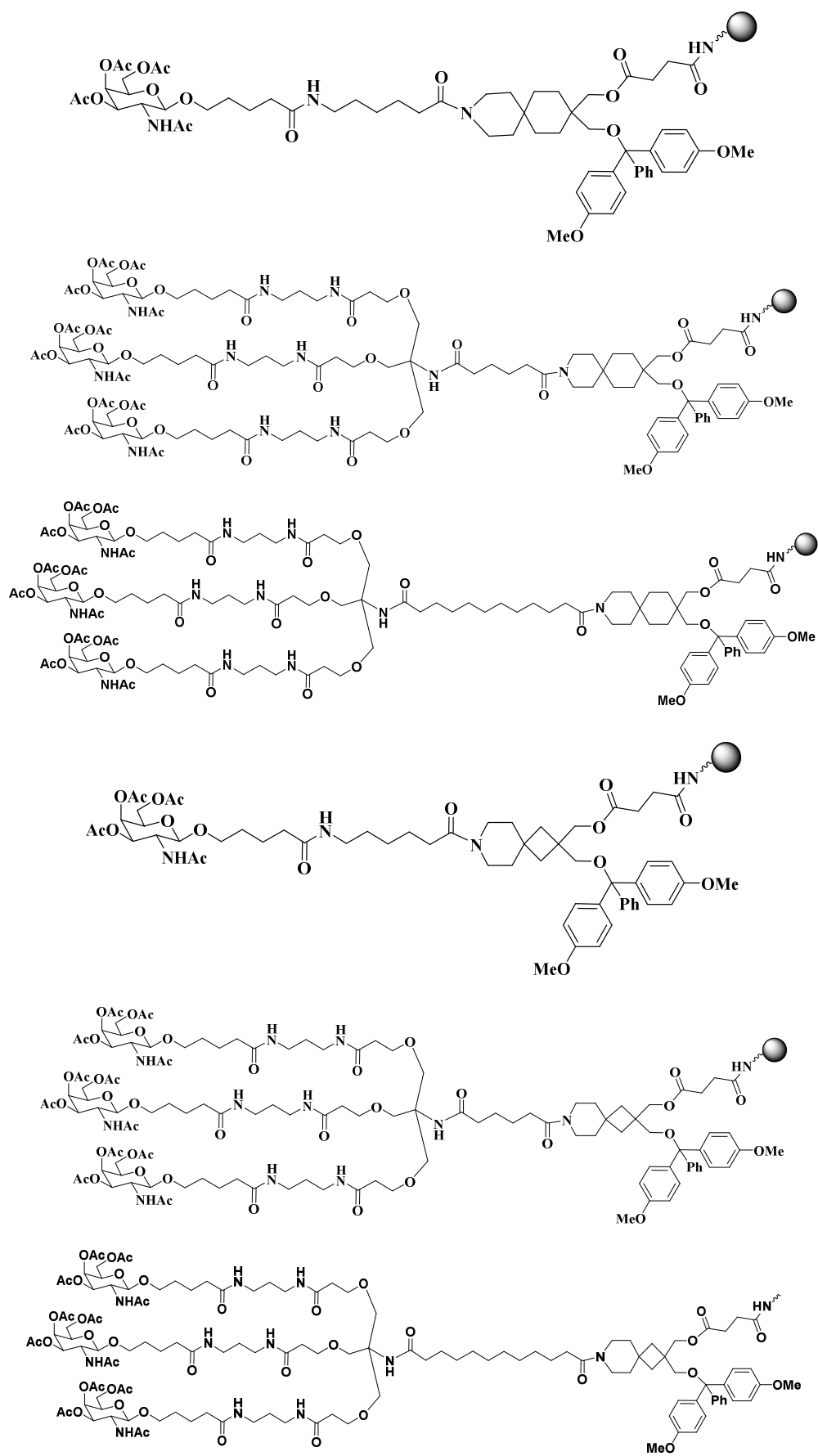
10. The targeting ligand of claim 2 or 8, wherein R₂ is hydrogen,

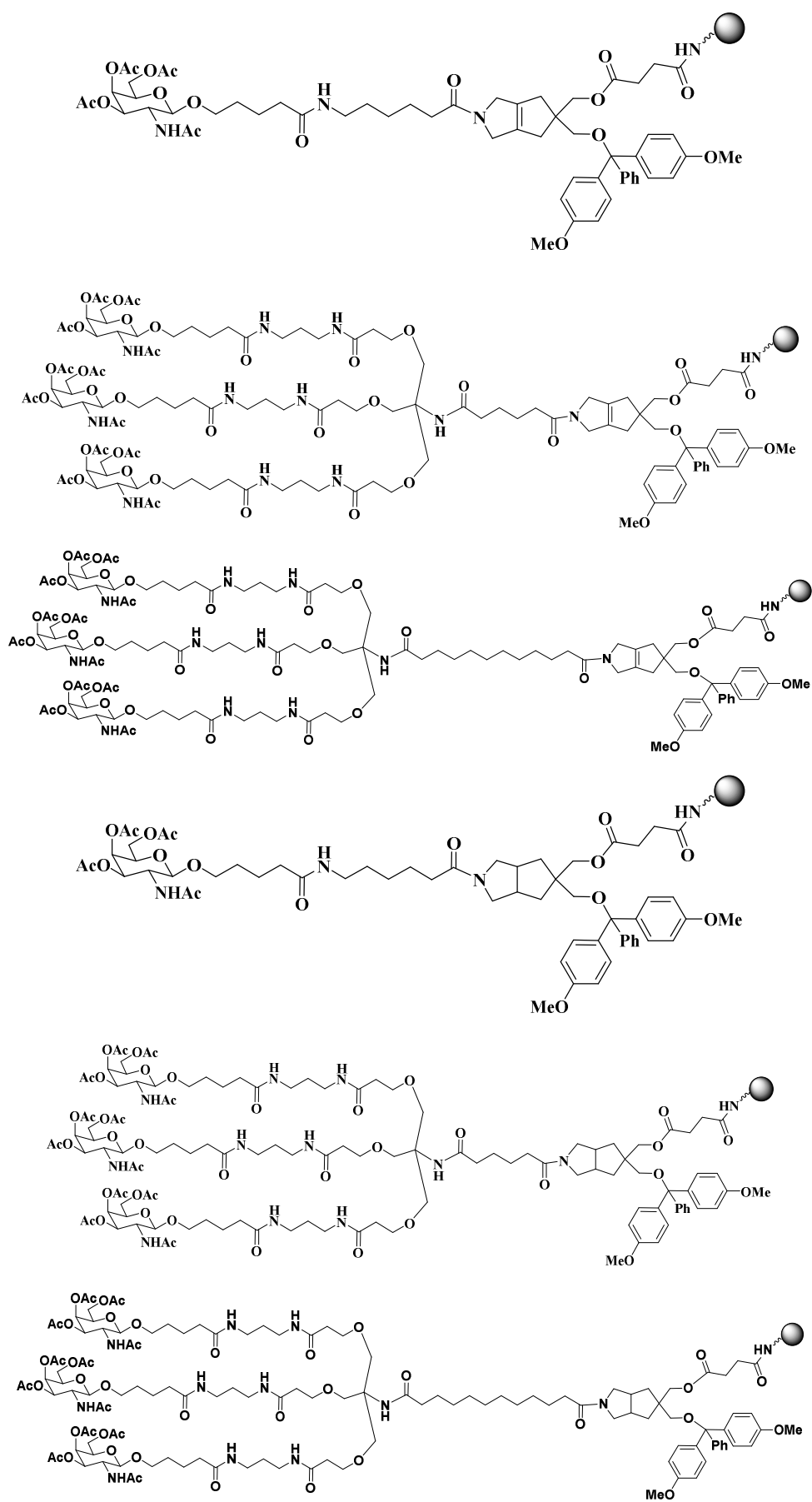


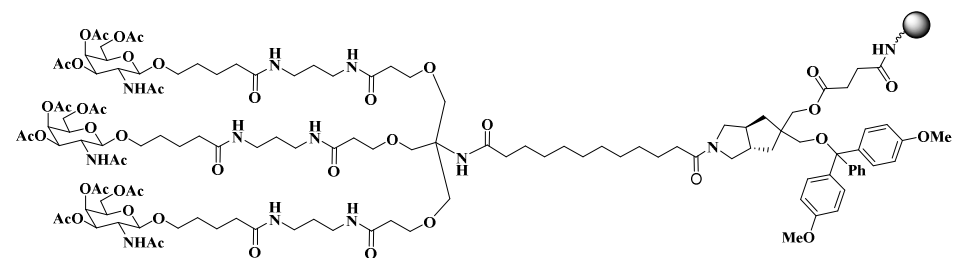
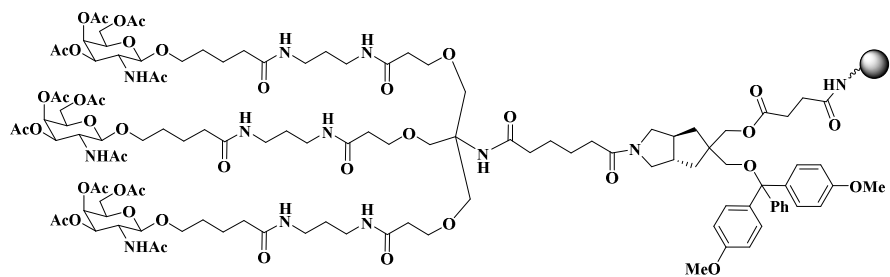
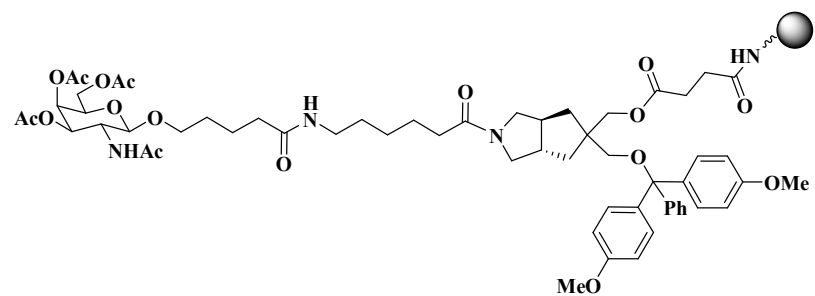
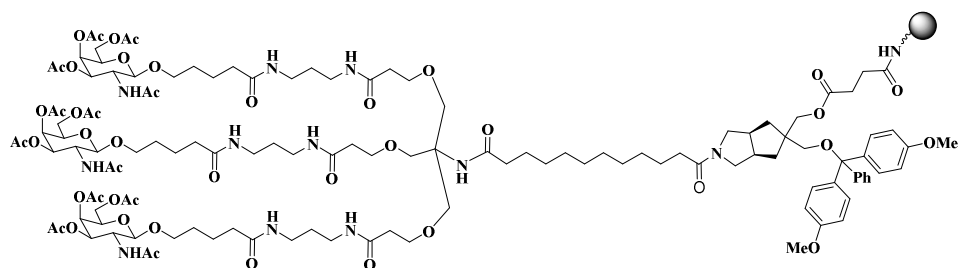
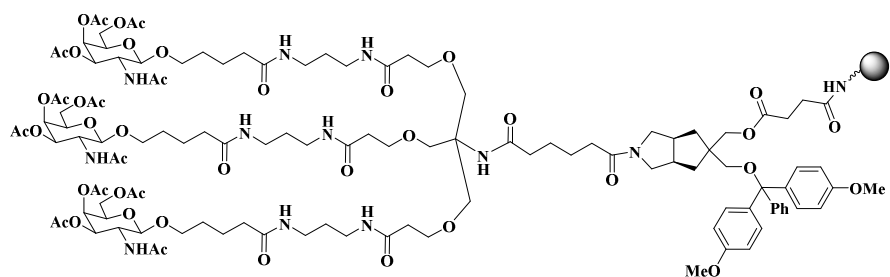
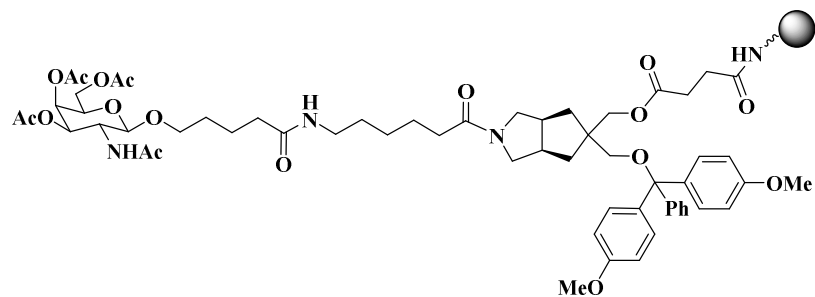
11. The targeting ligand of claim 2, wherein the targeting ligand is:



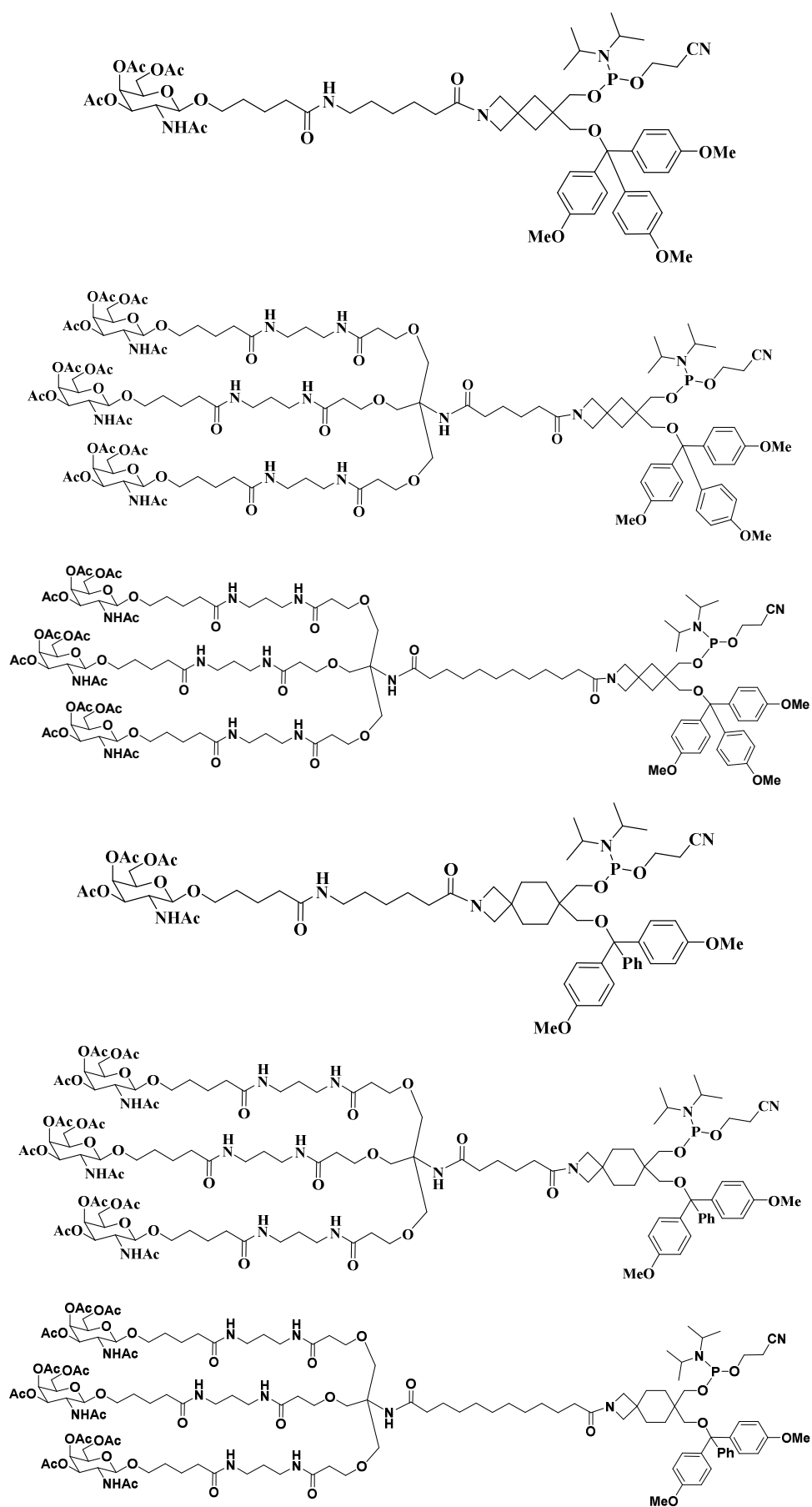


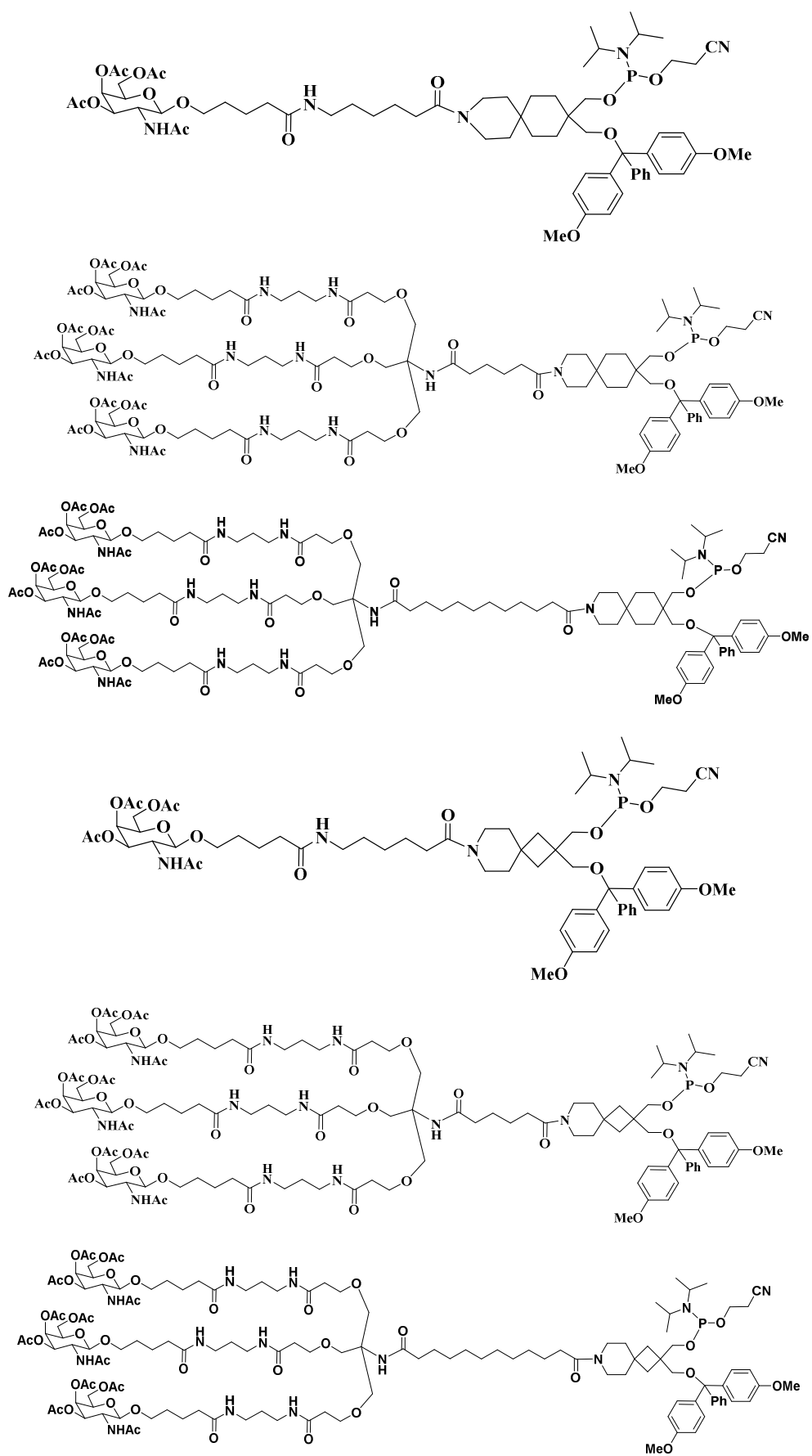


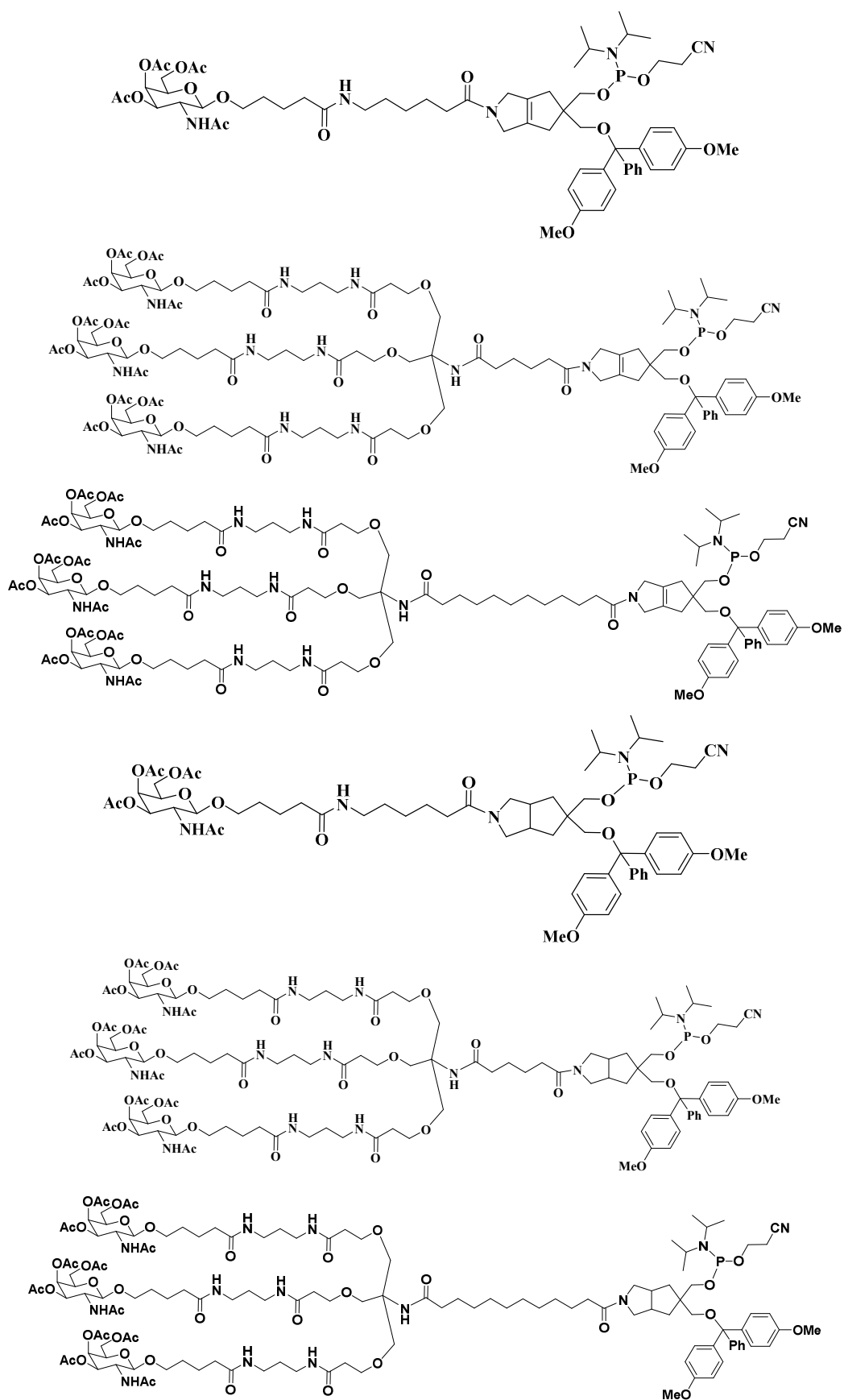


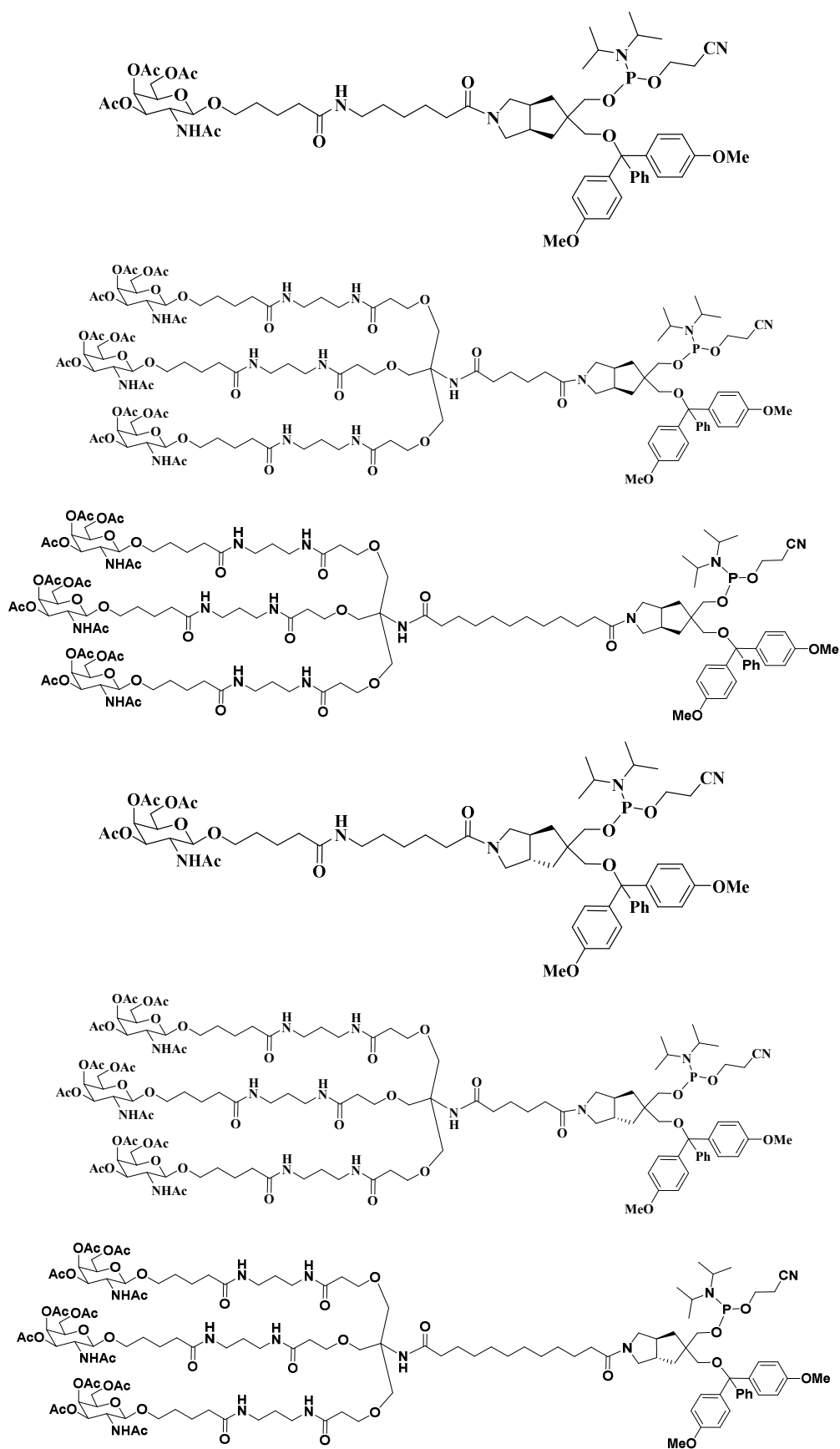


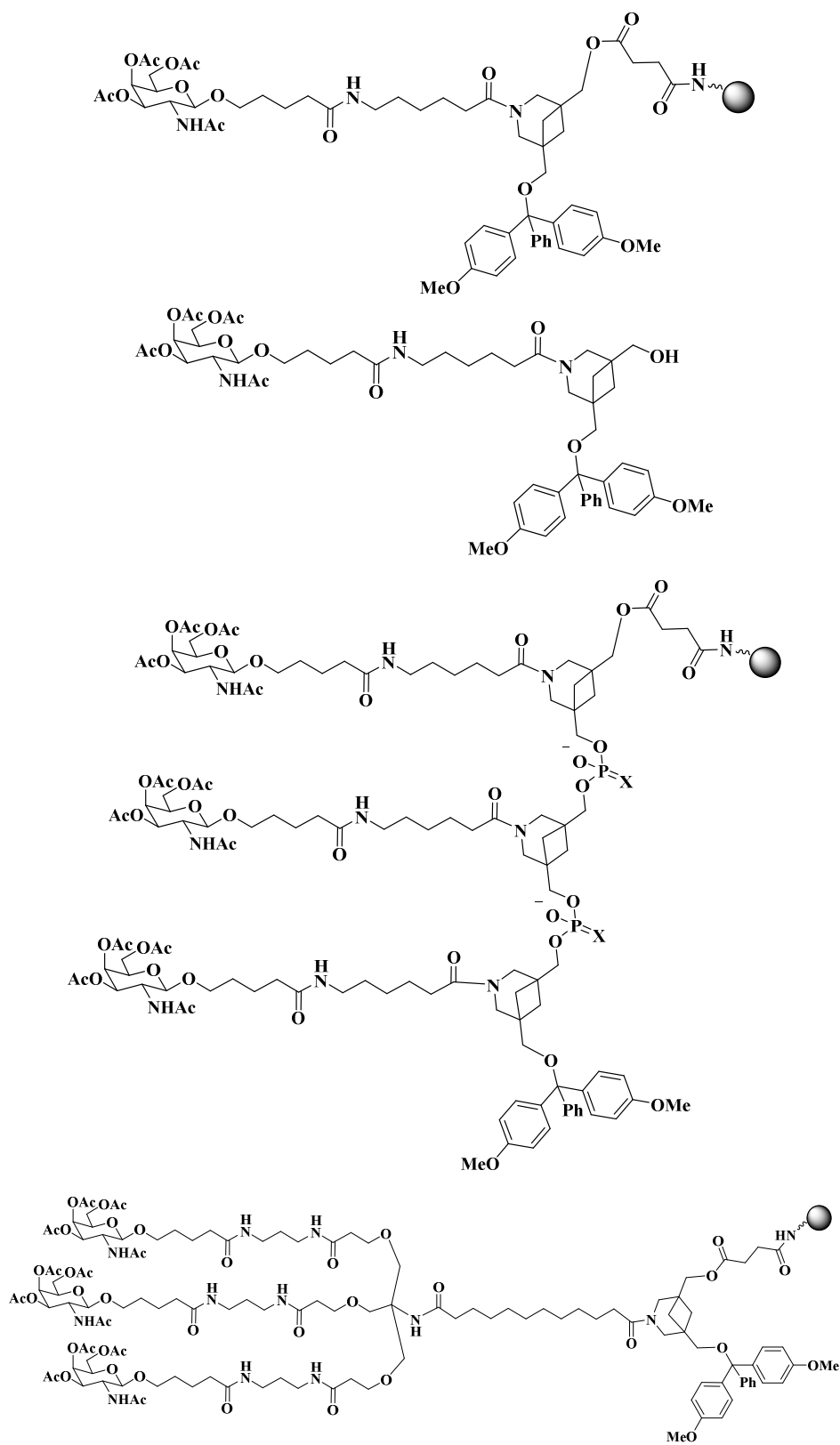


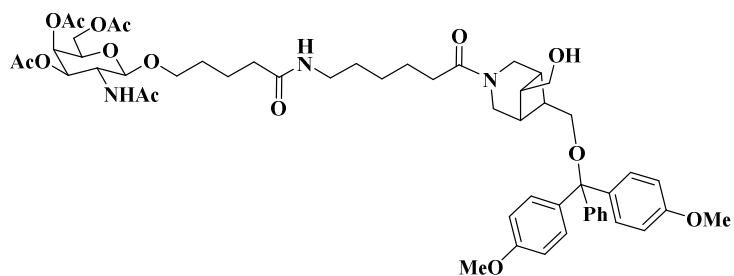
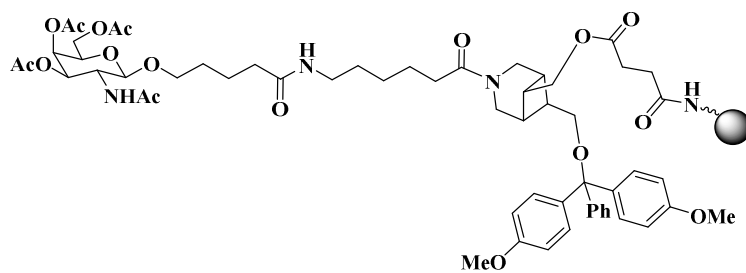
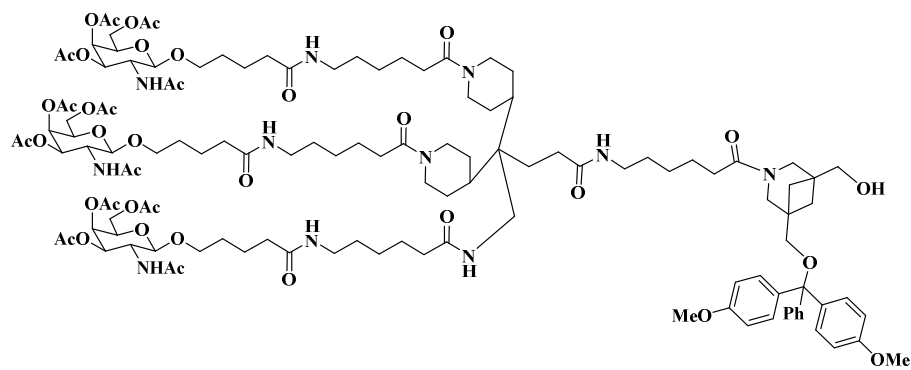
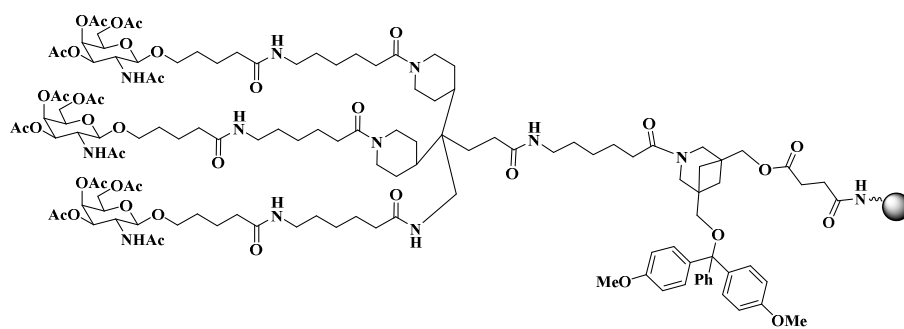
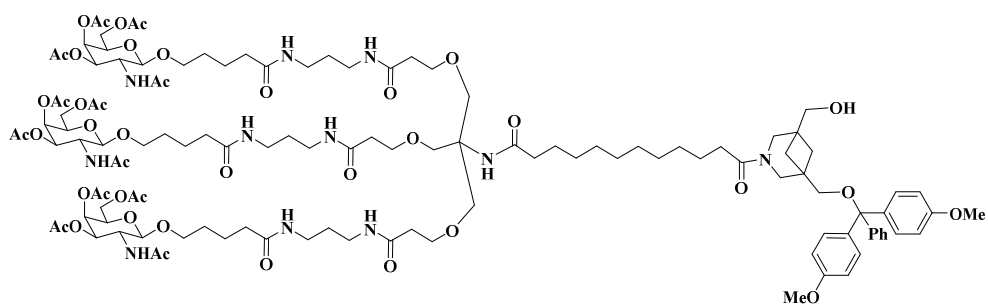


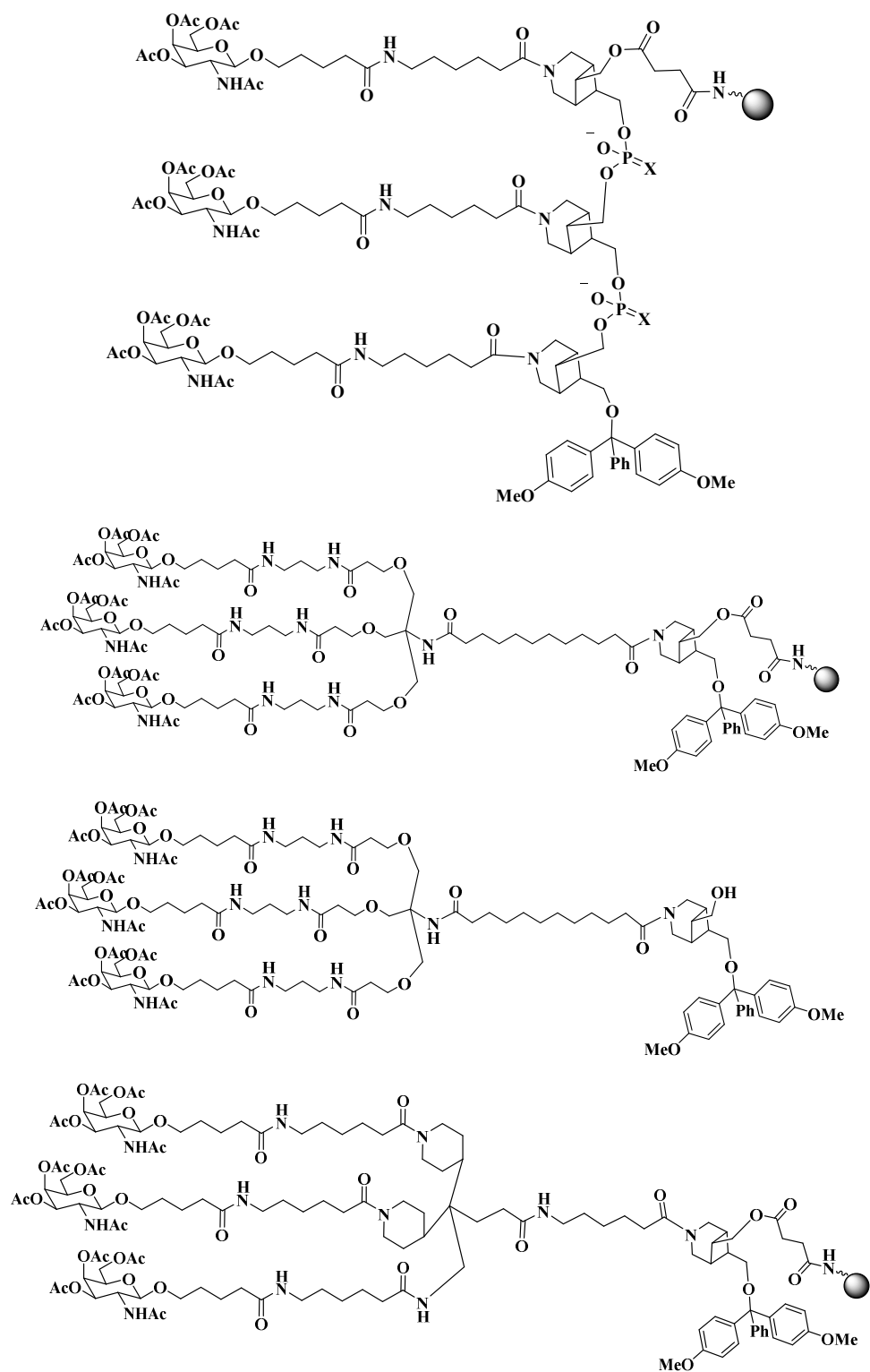




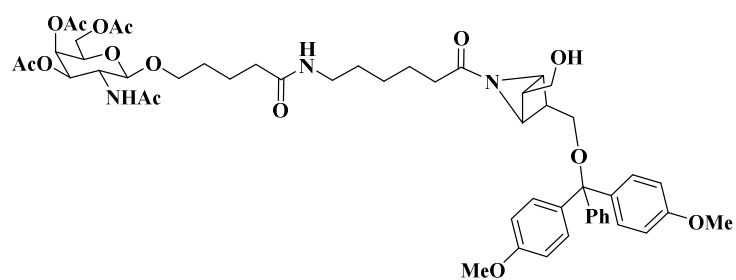
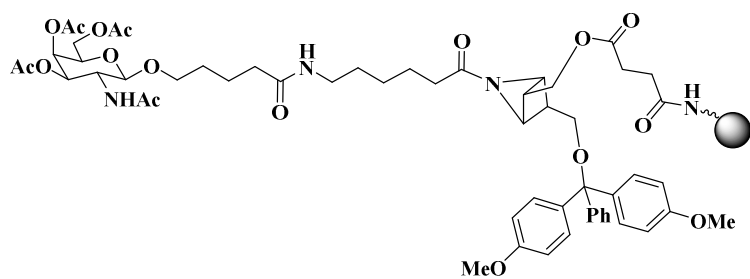
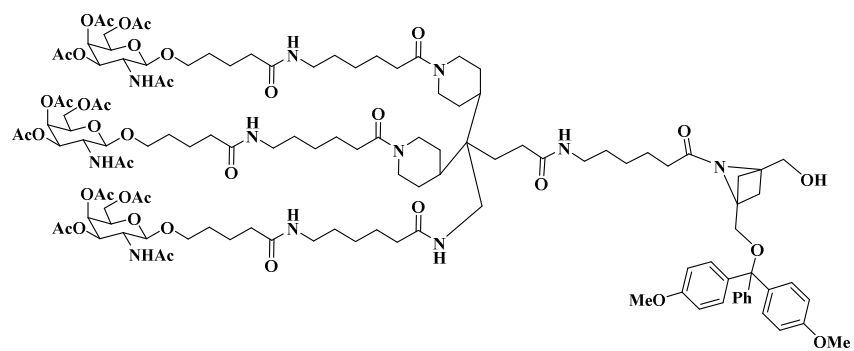
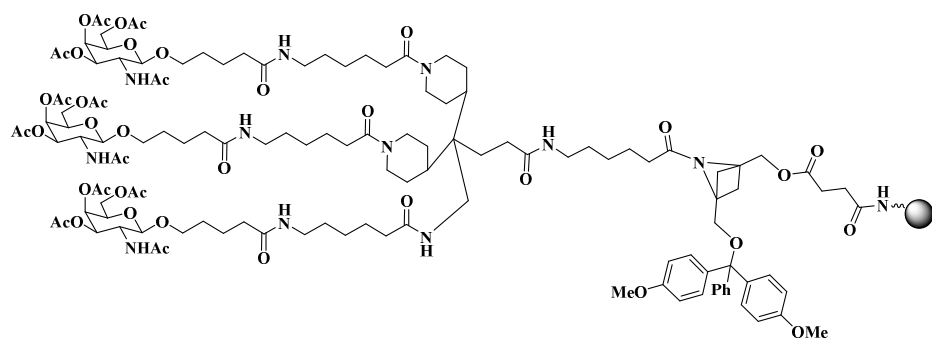
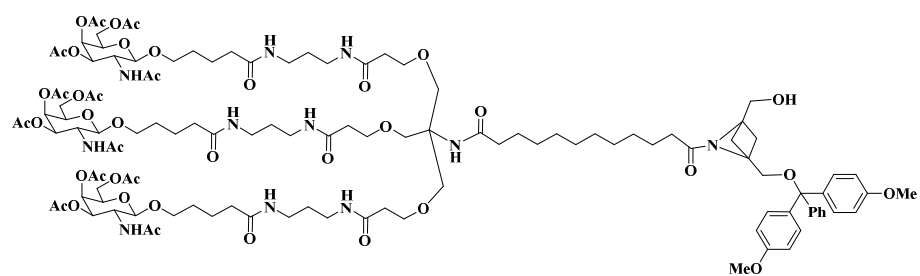


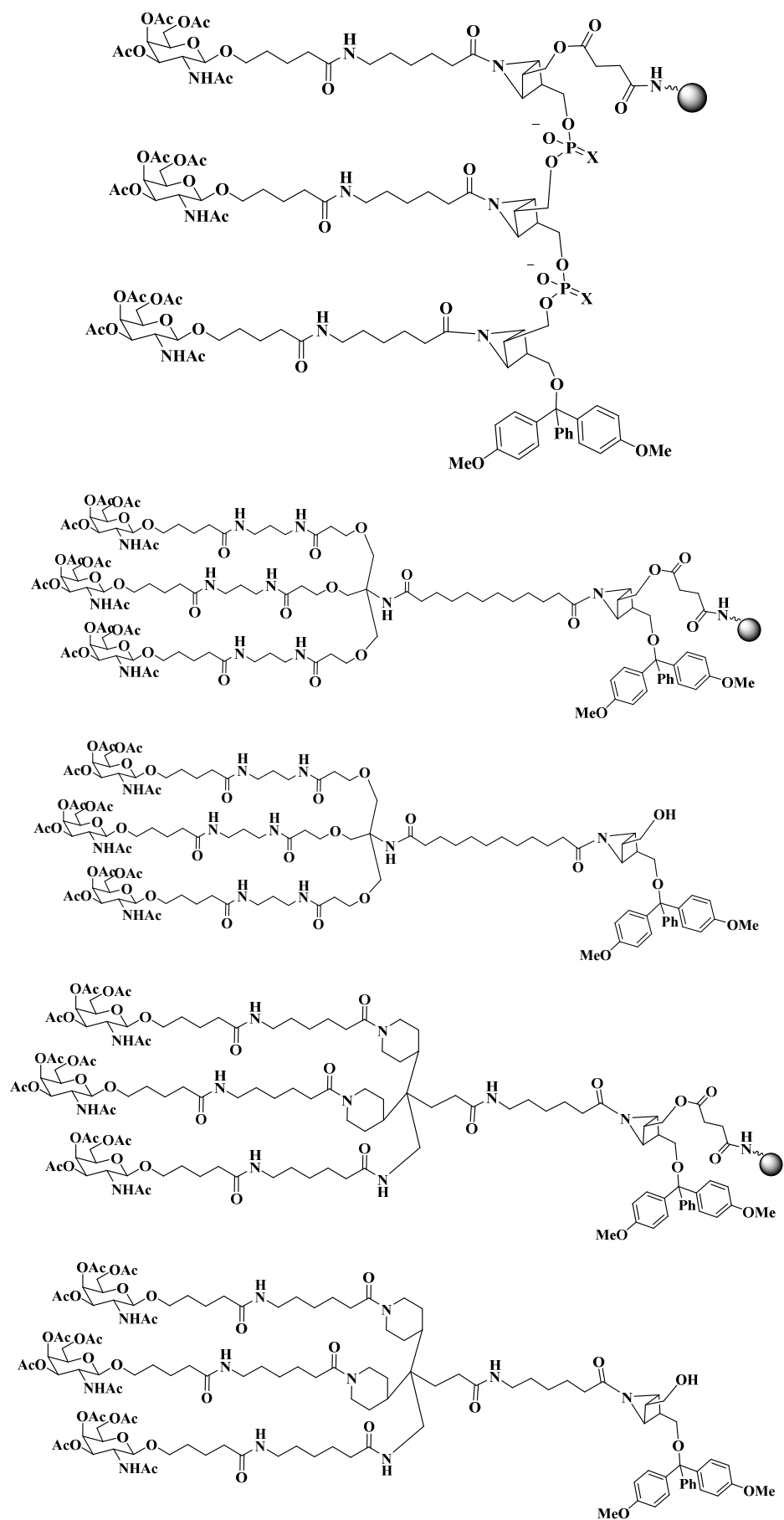


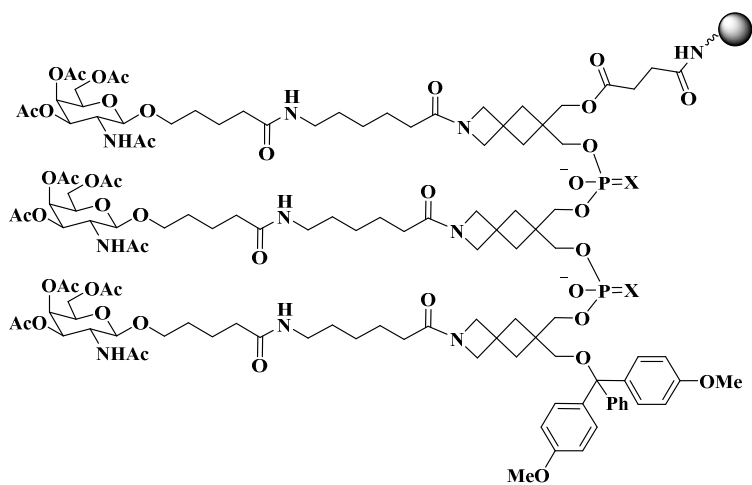
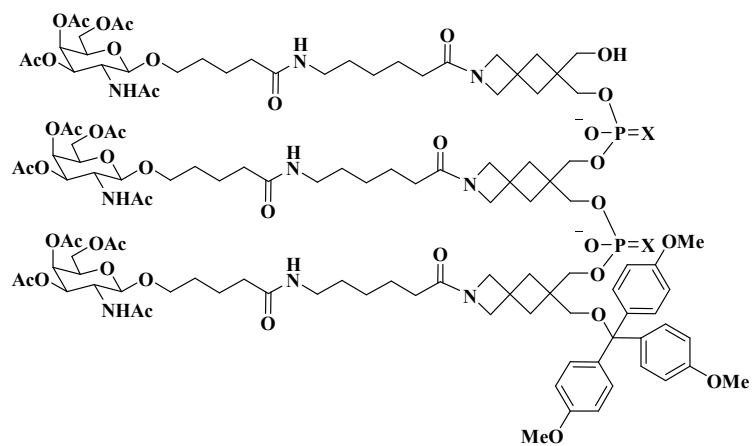
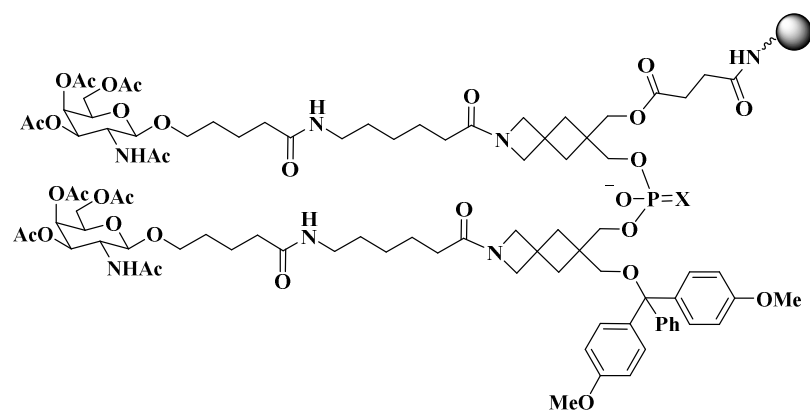


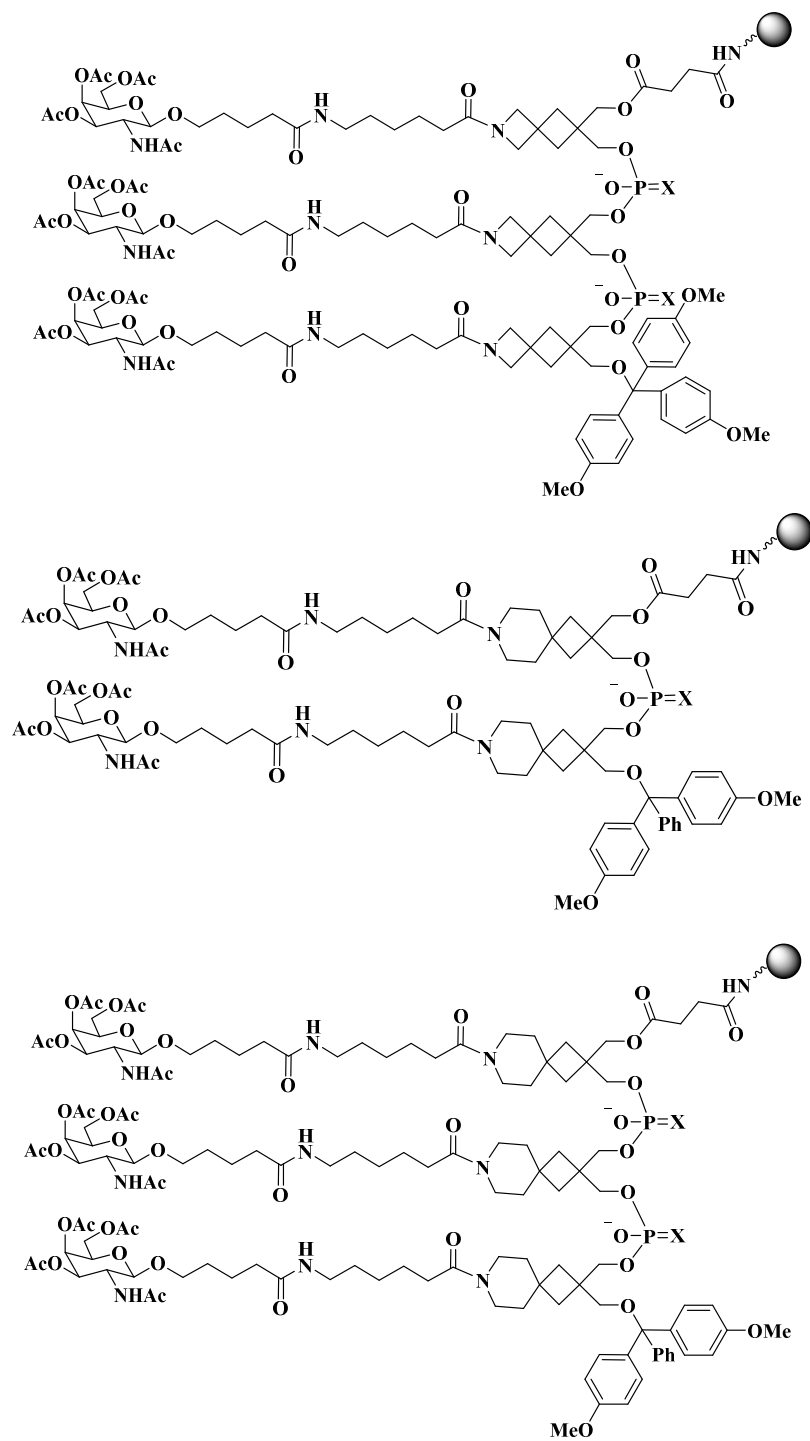


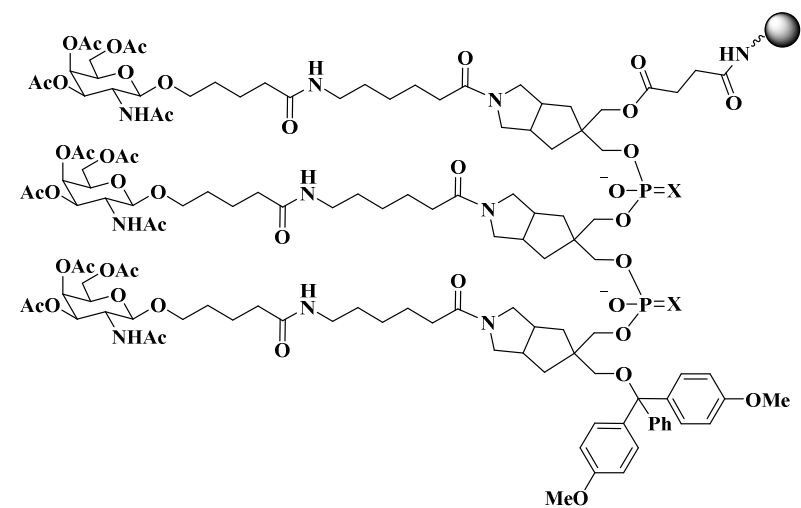
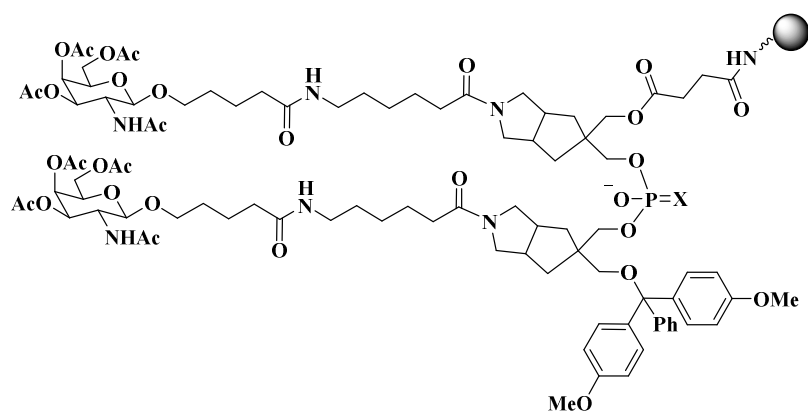
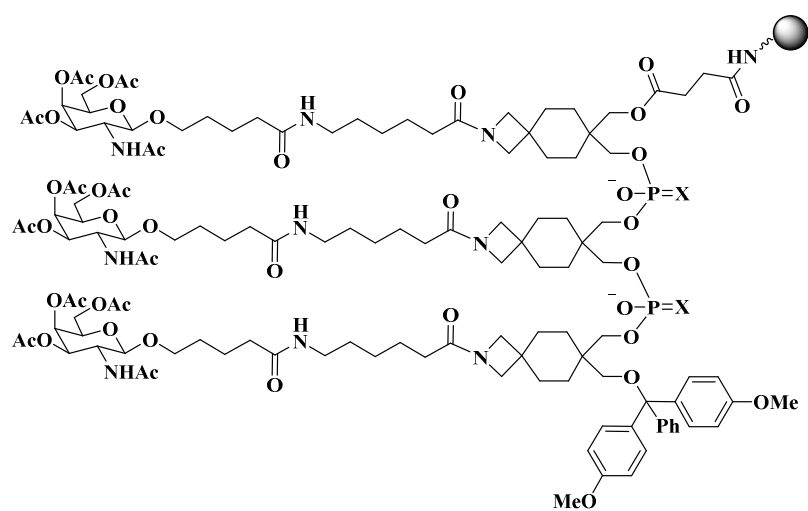


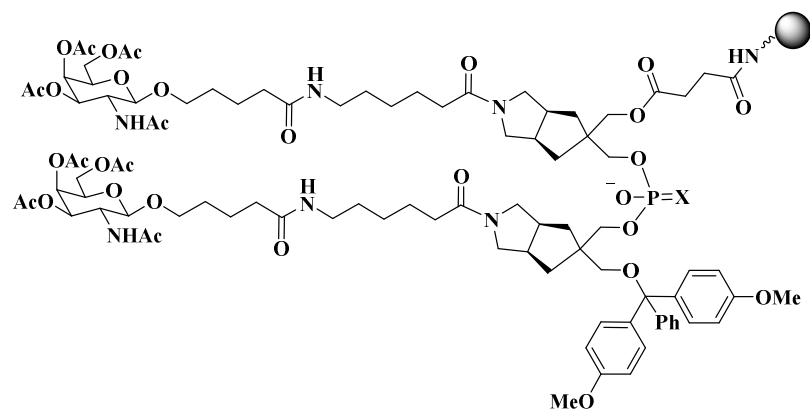
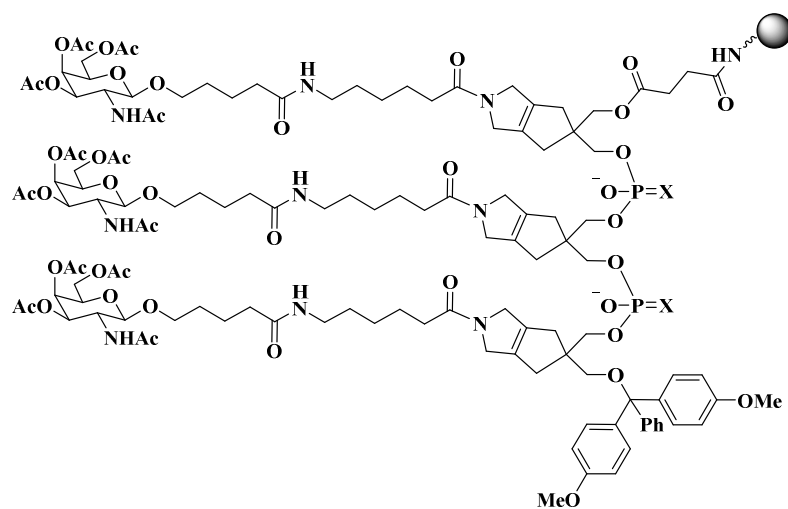
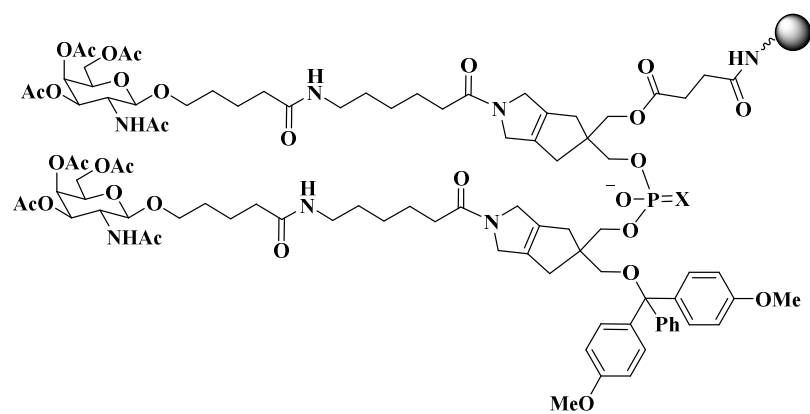


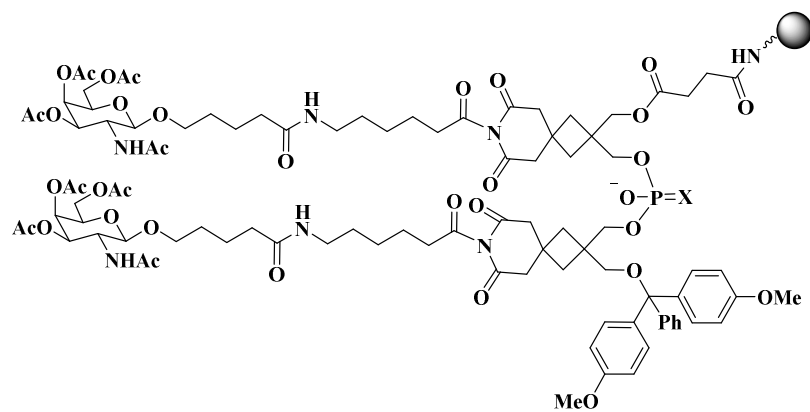
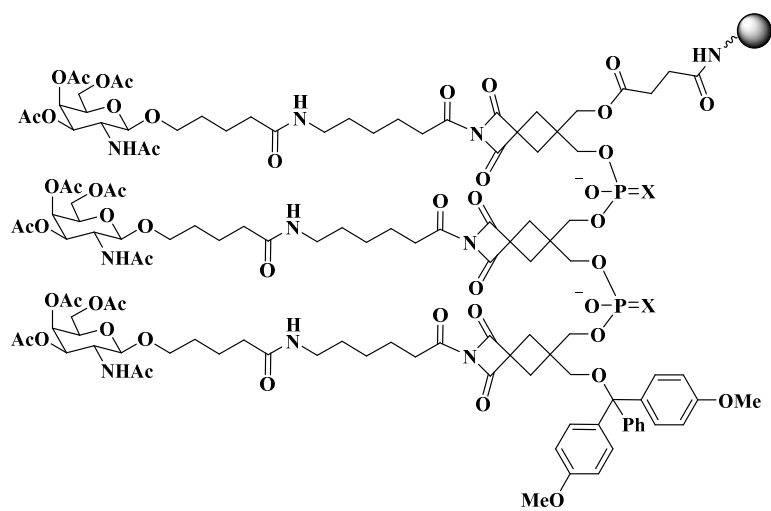
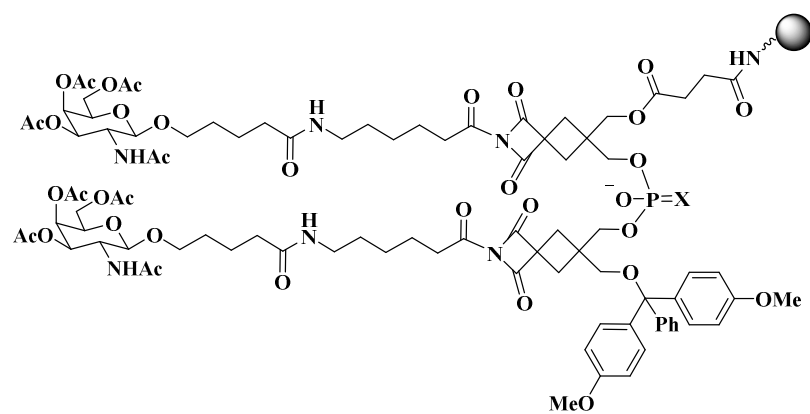


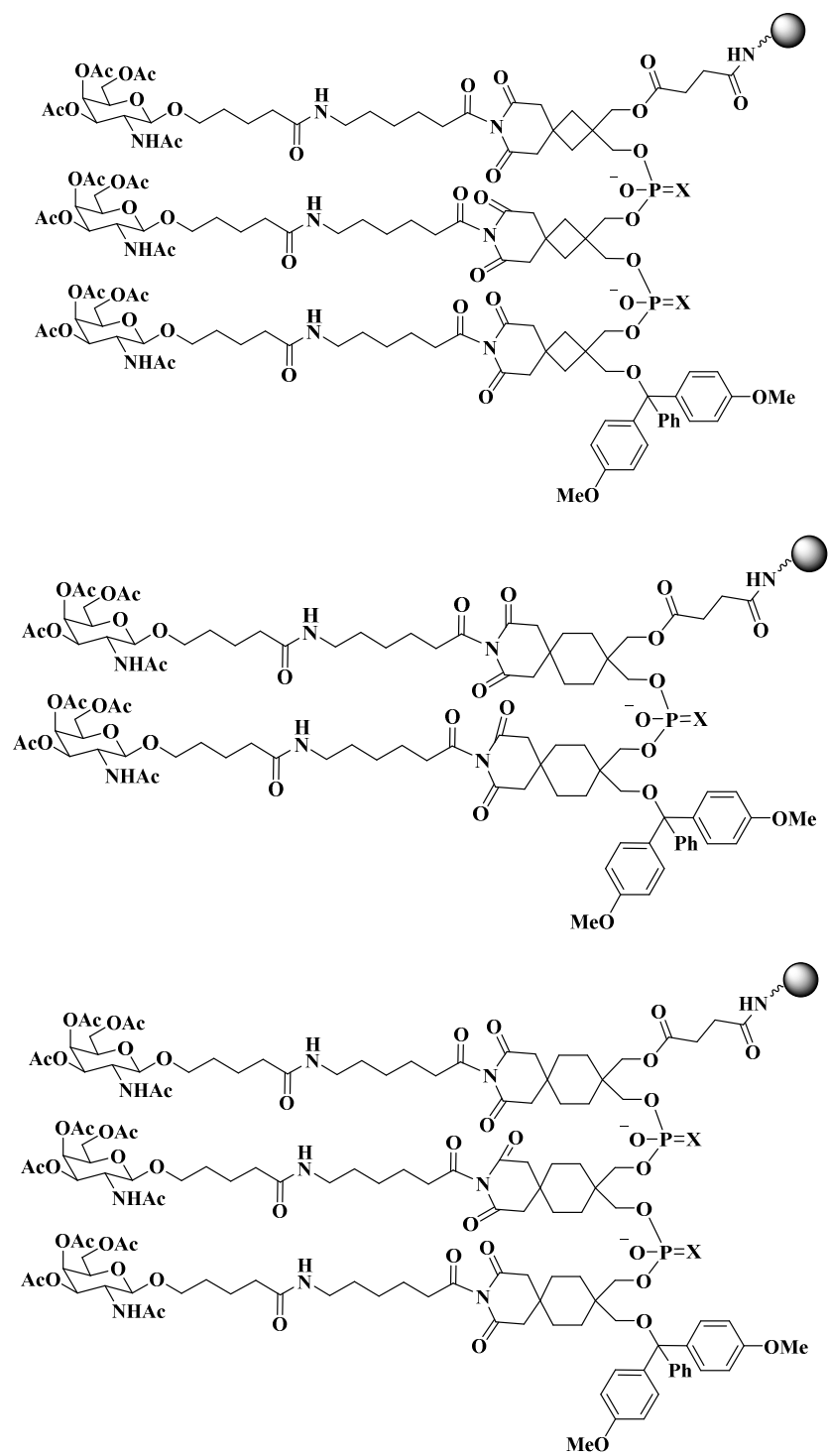


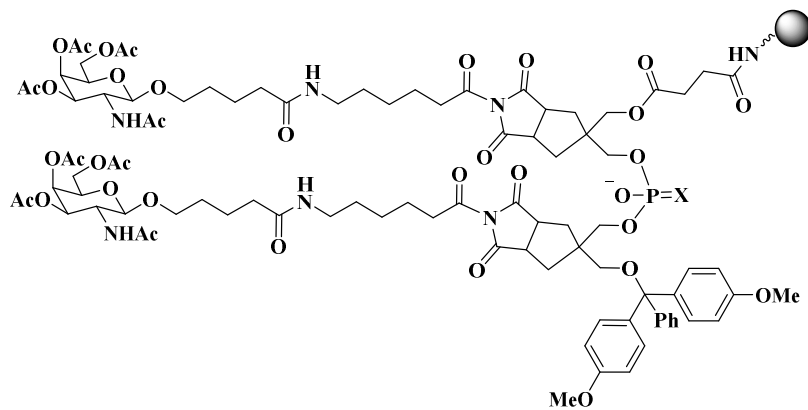
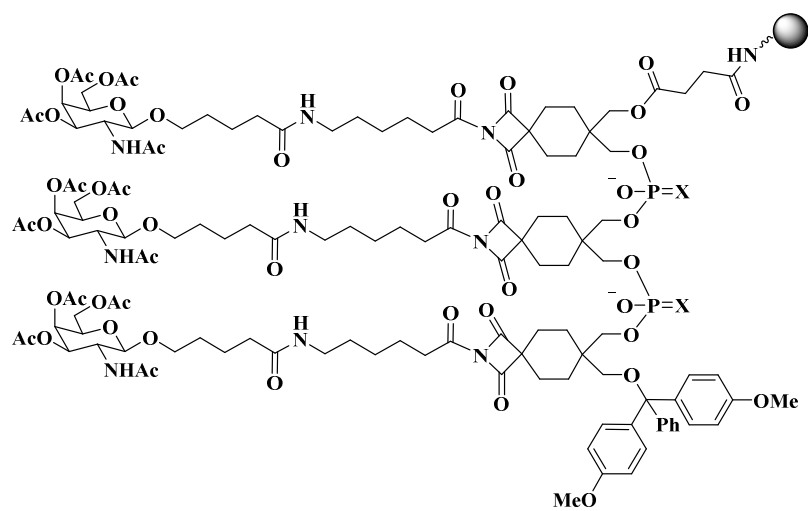
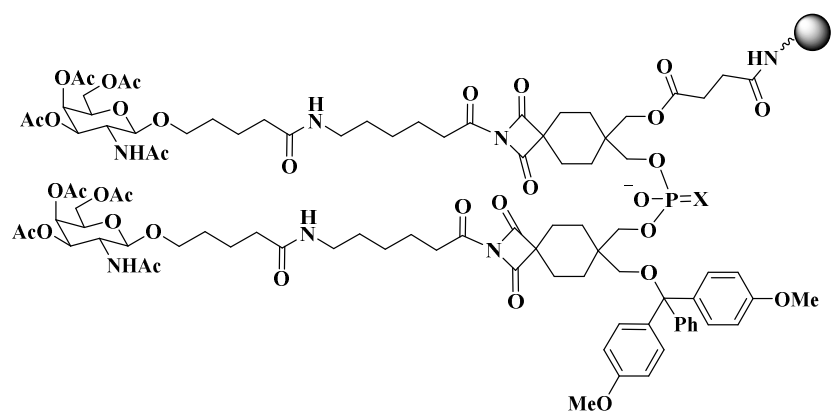


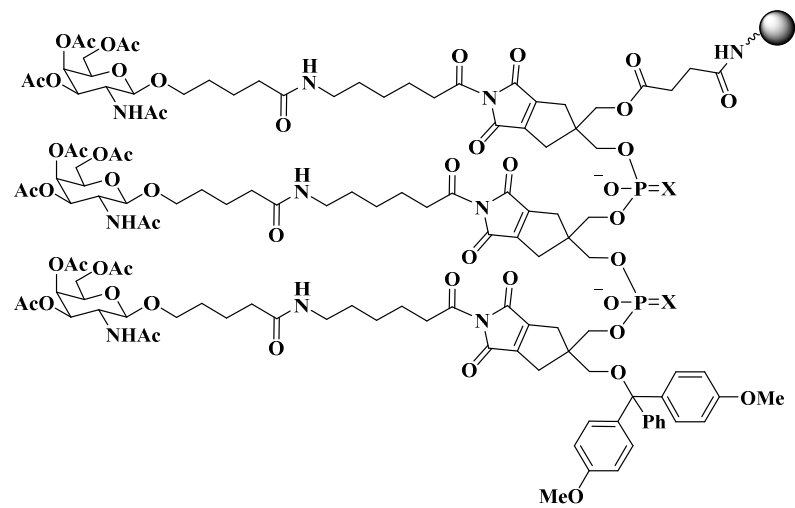
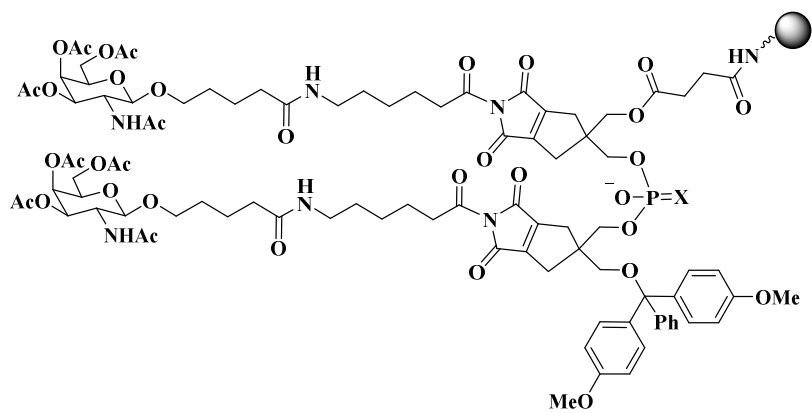
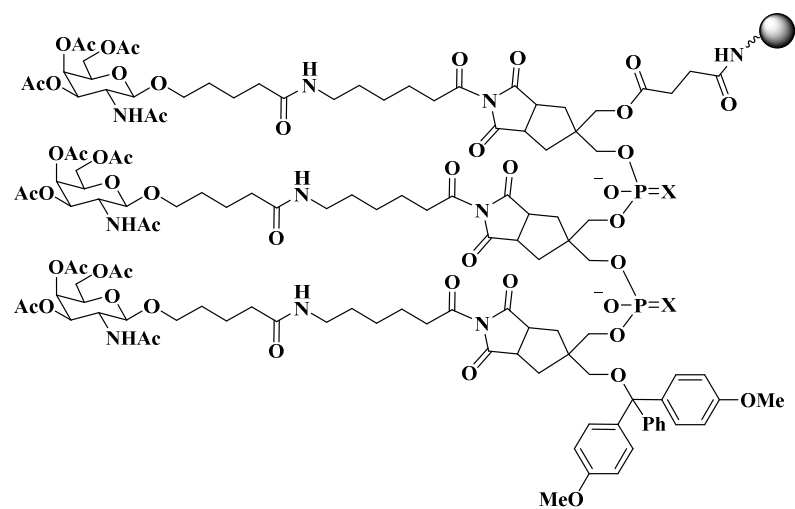


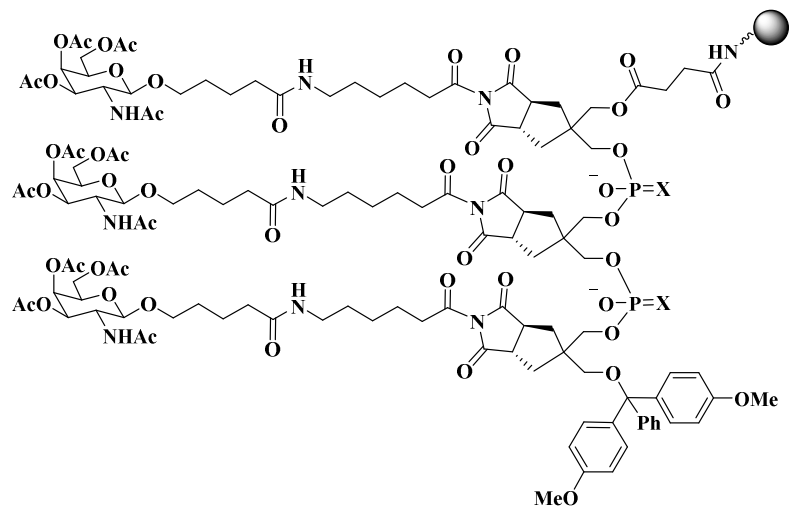
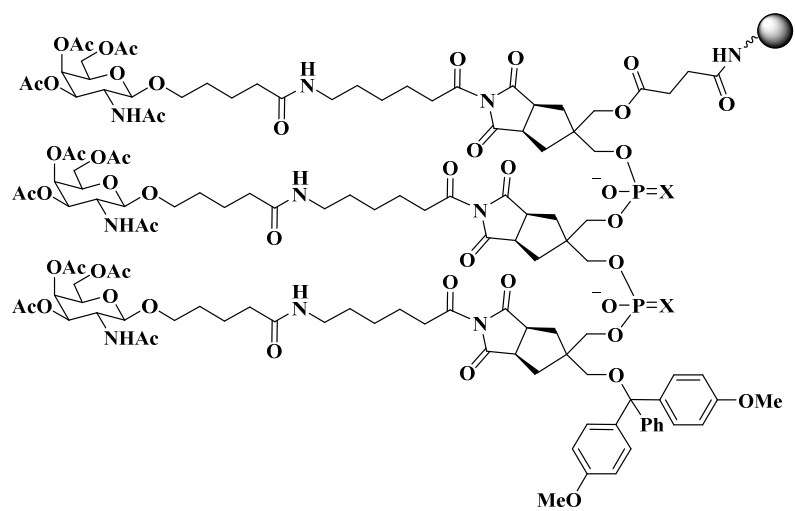
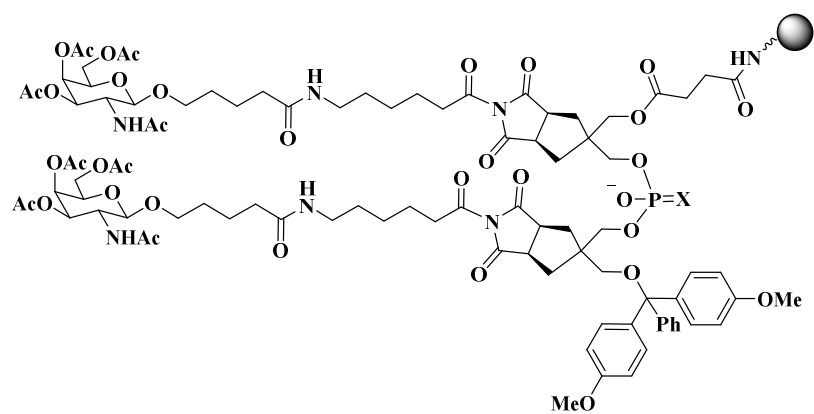


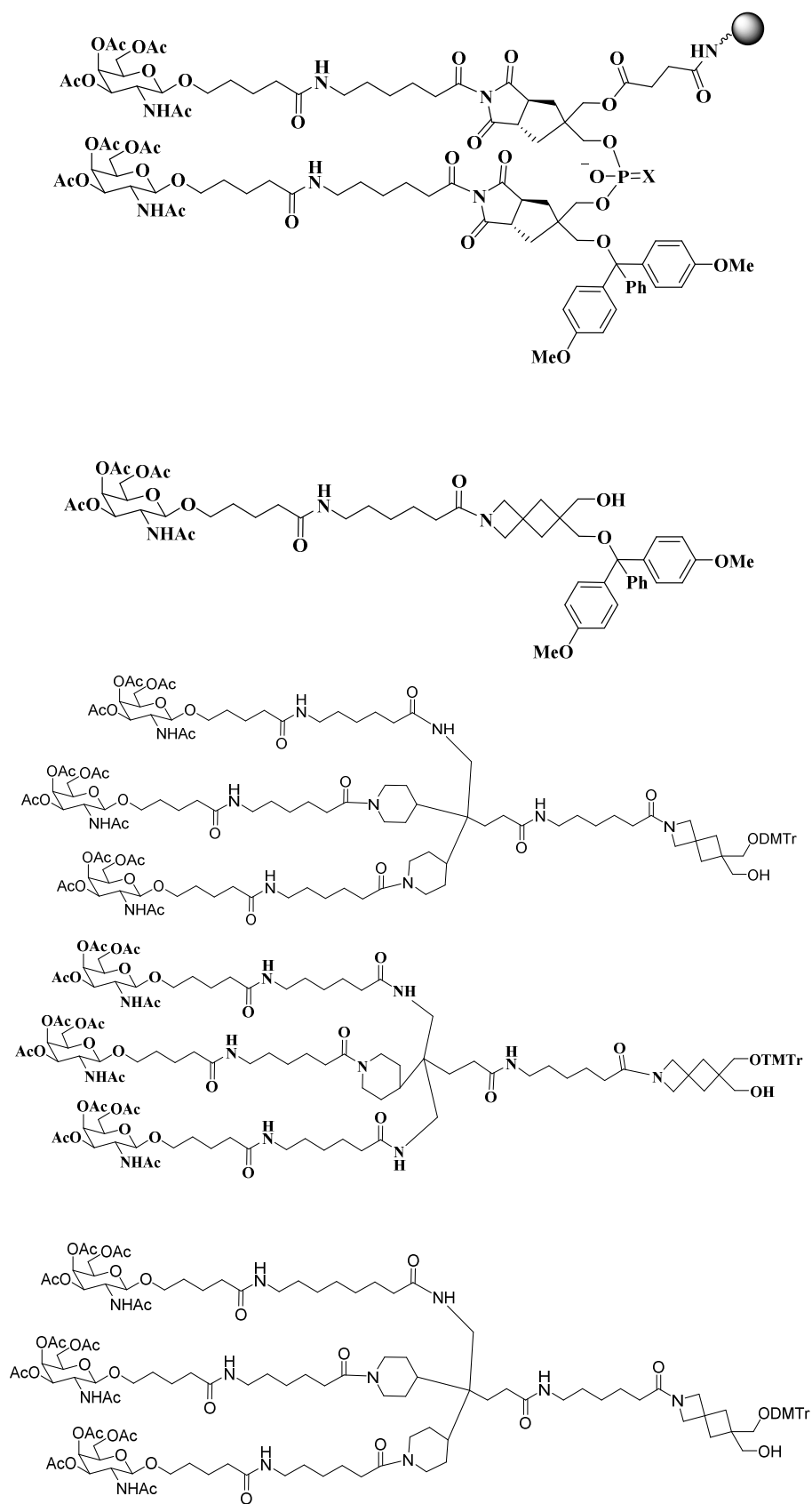


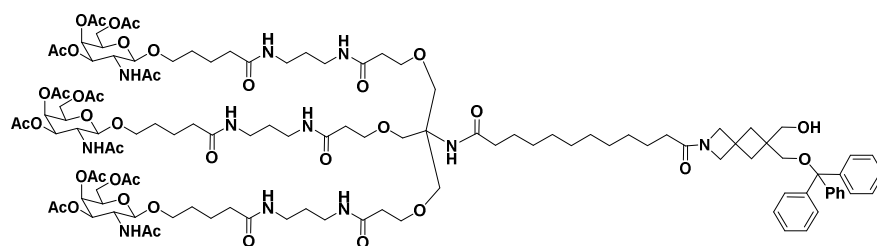
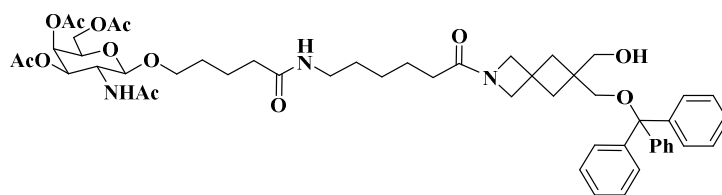
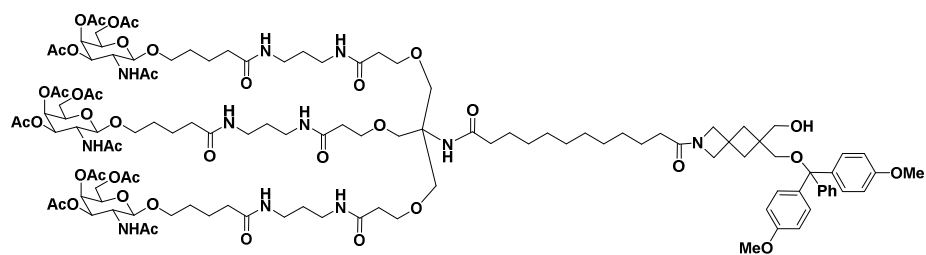
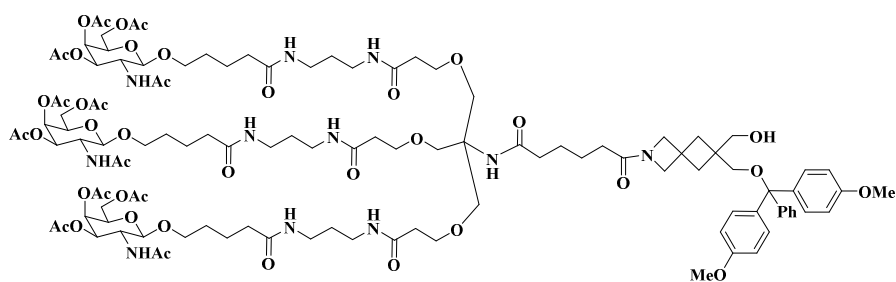
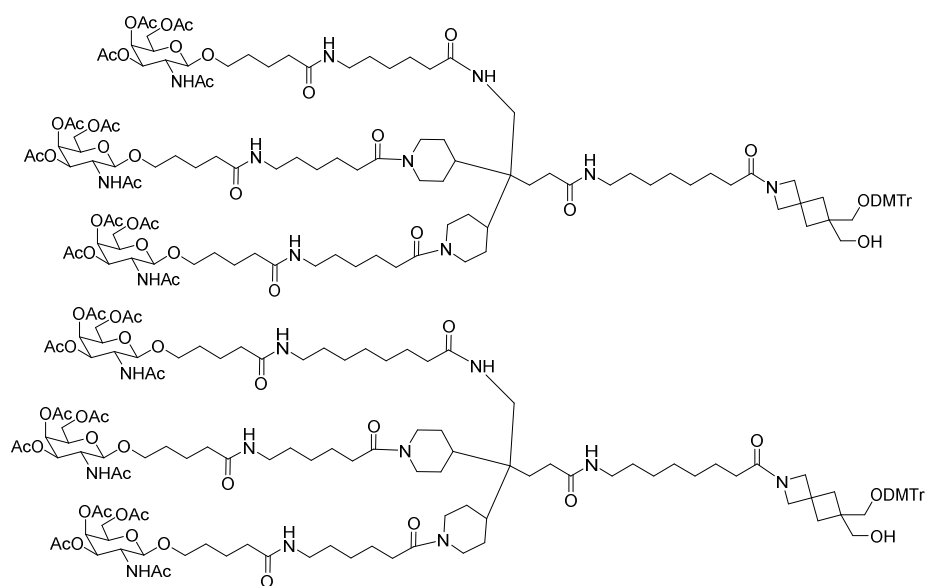


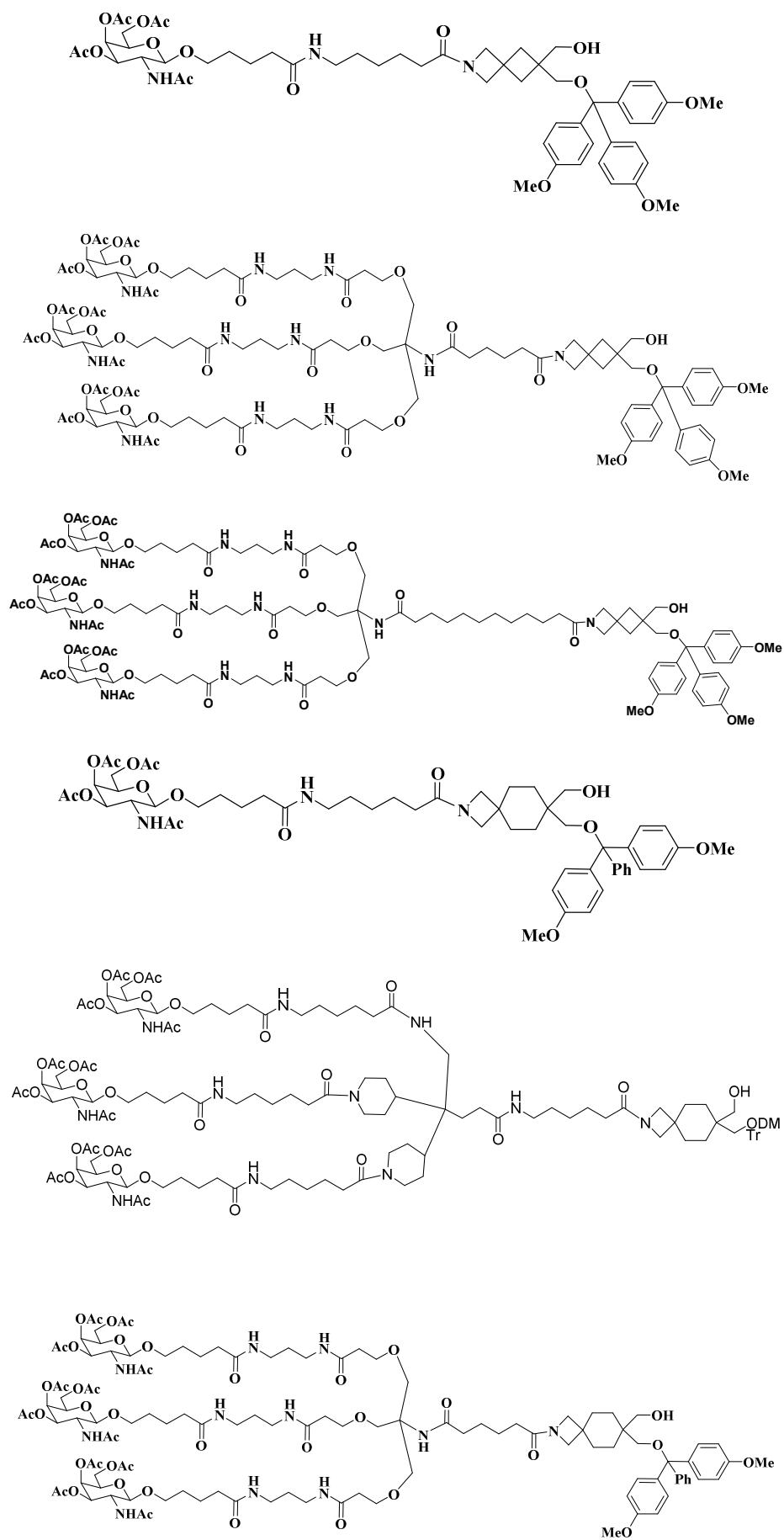


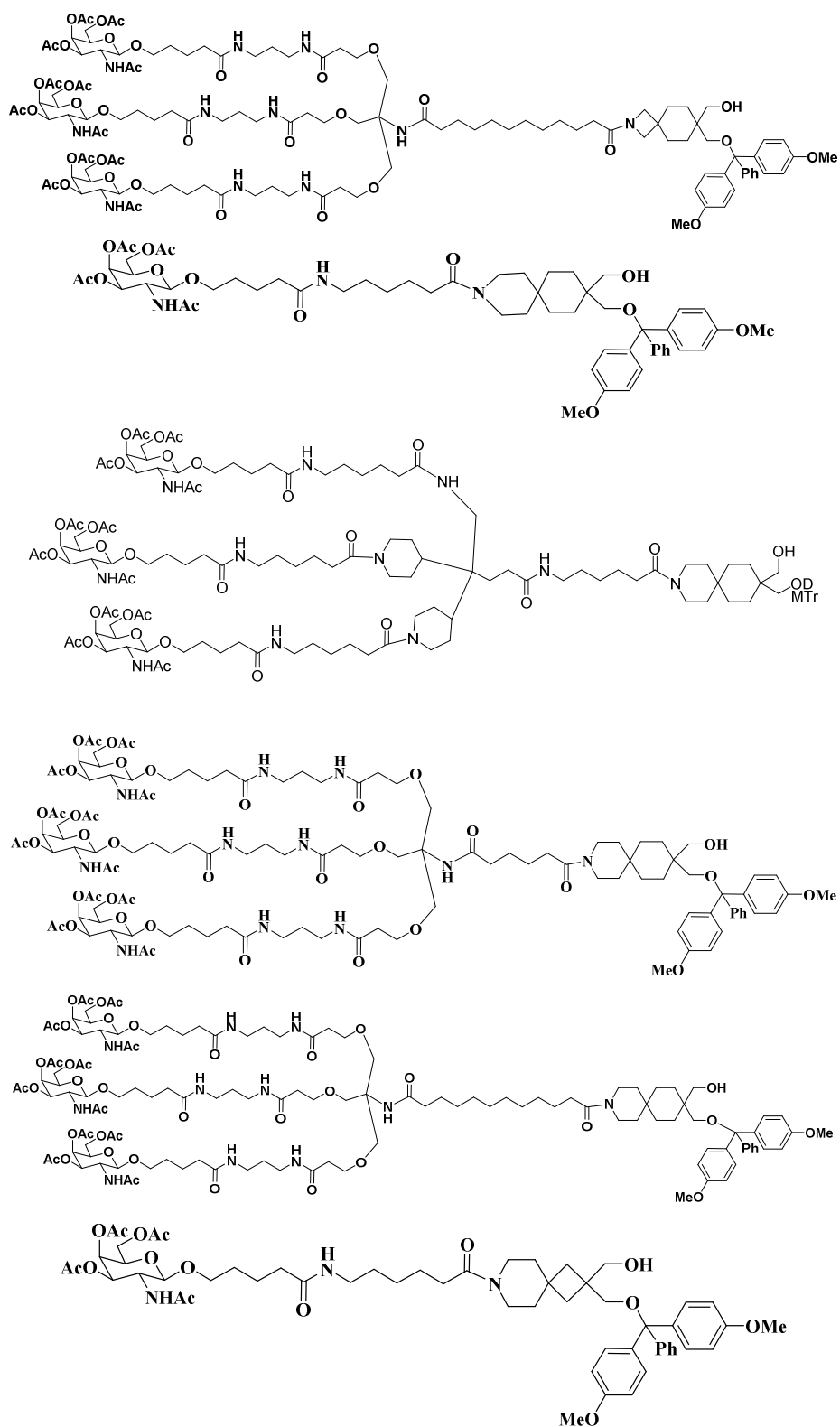


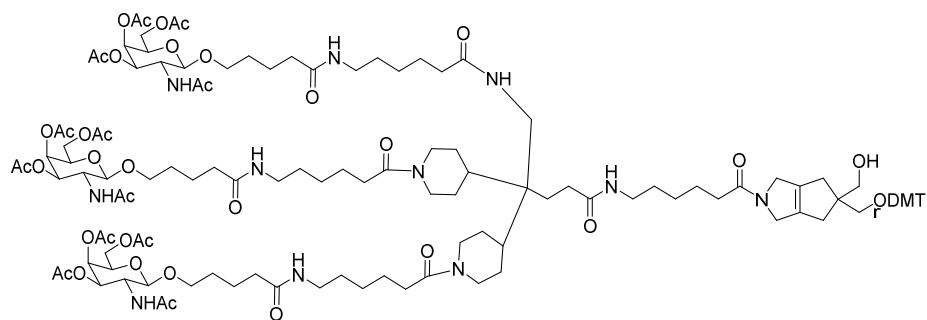
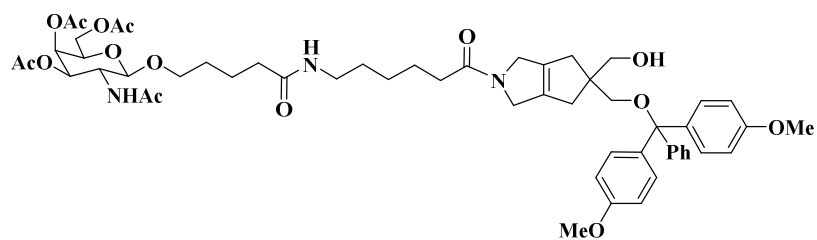
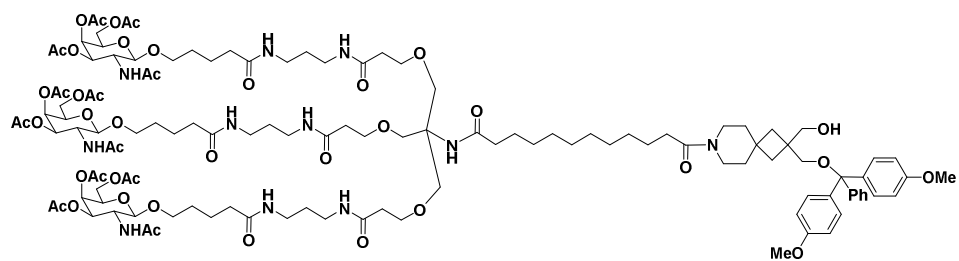
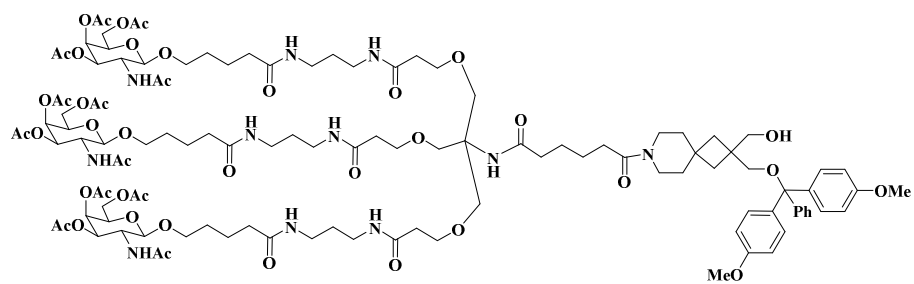
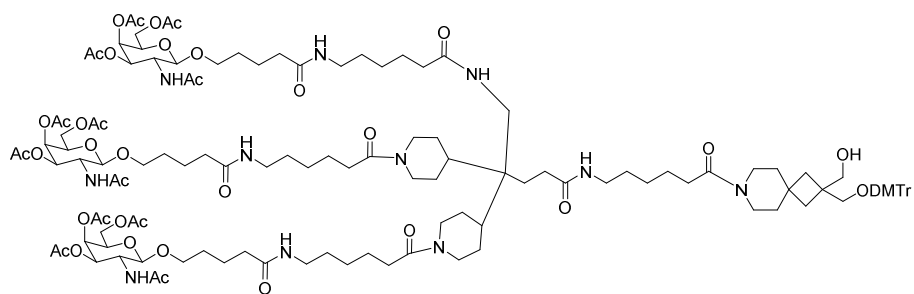


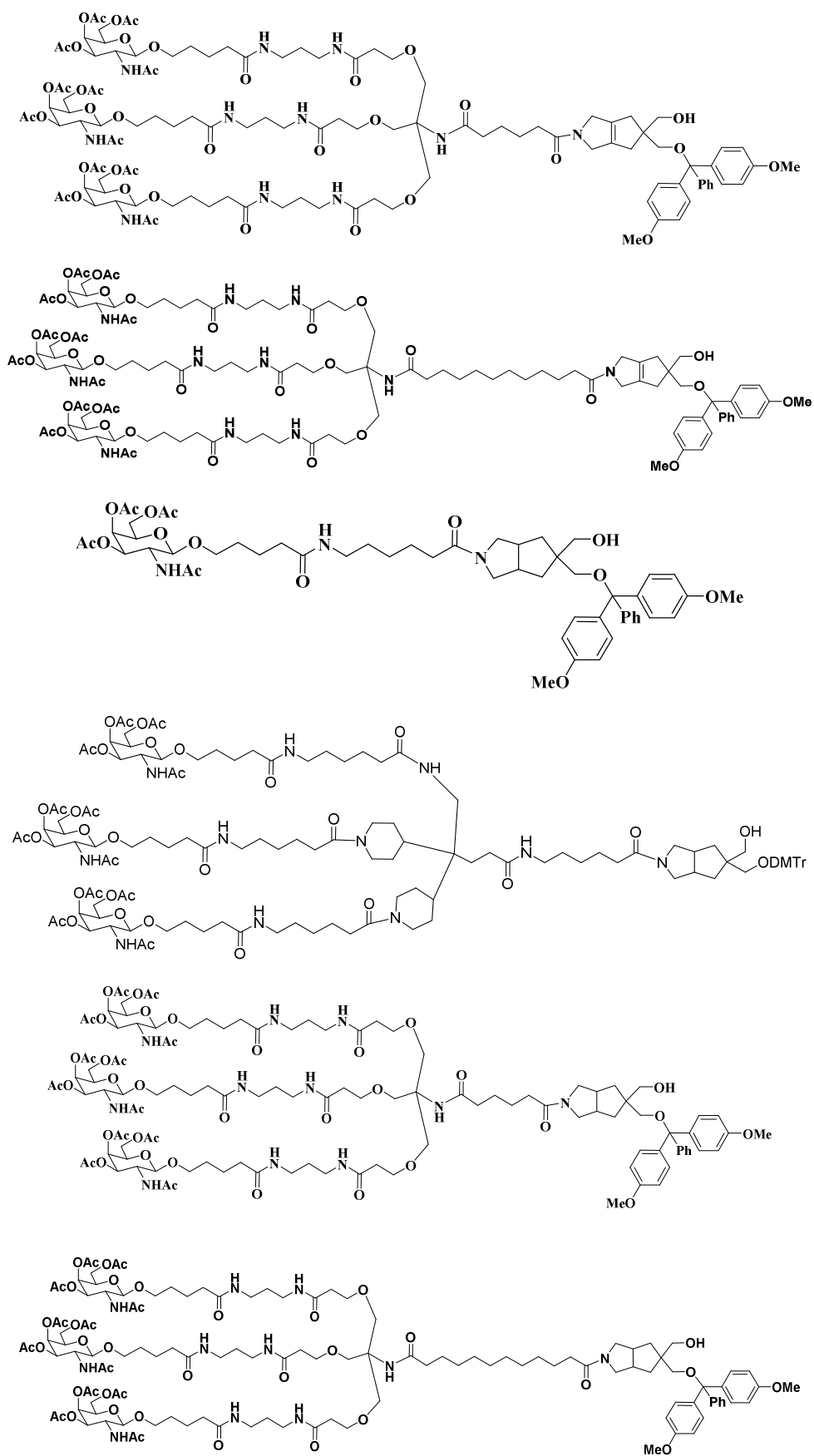


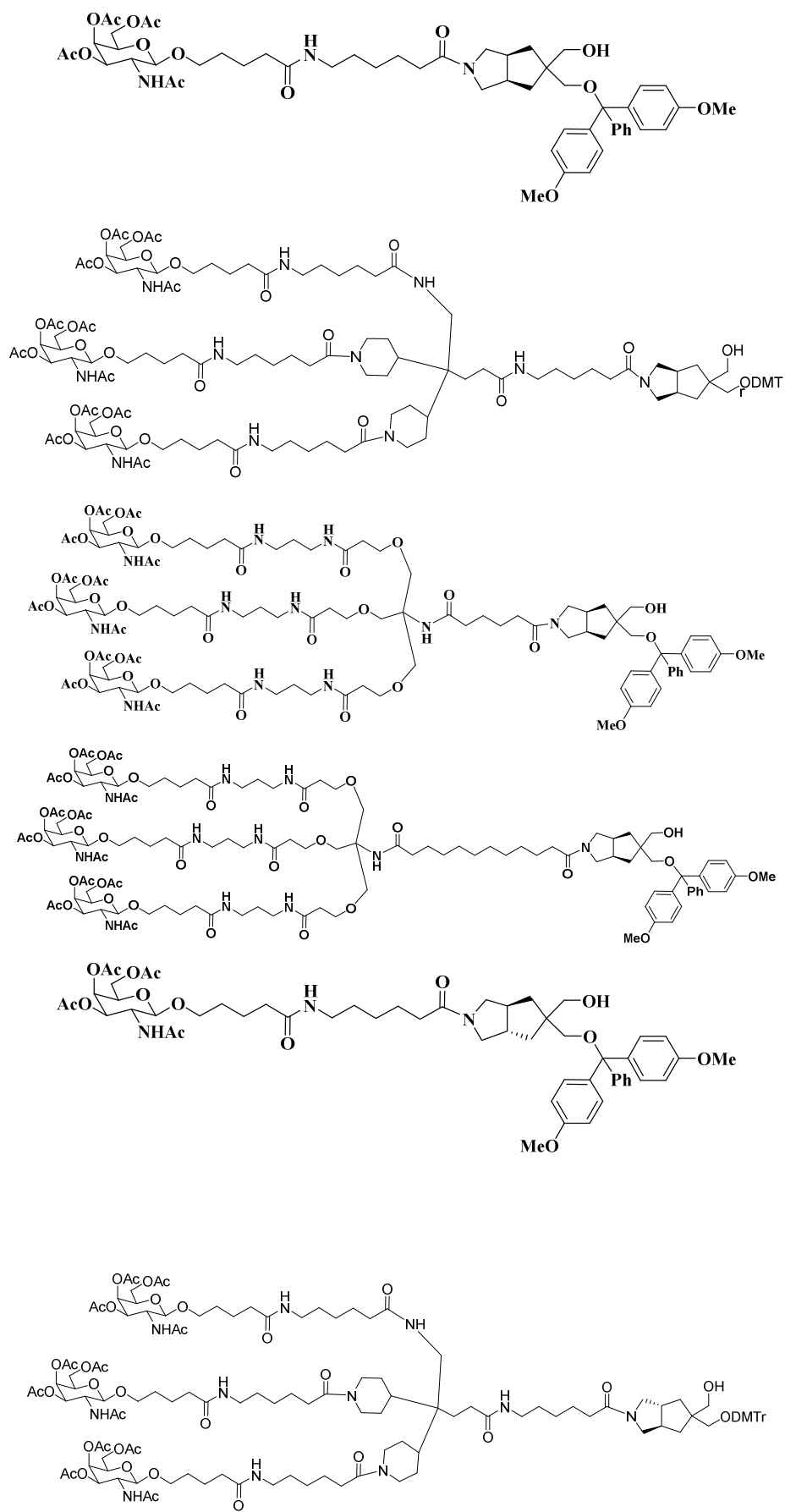


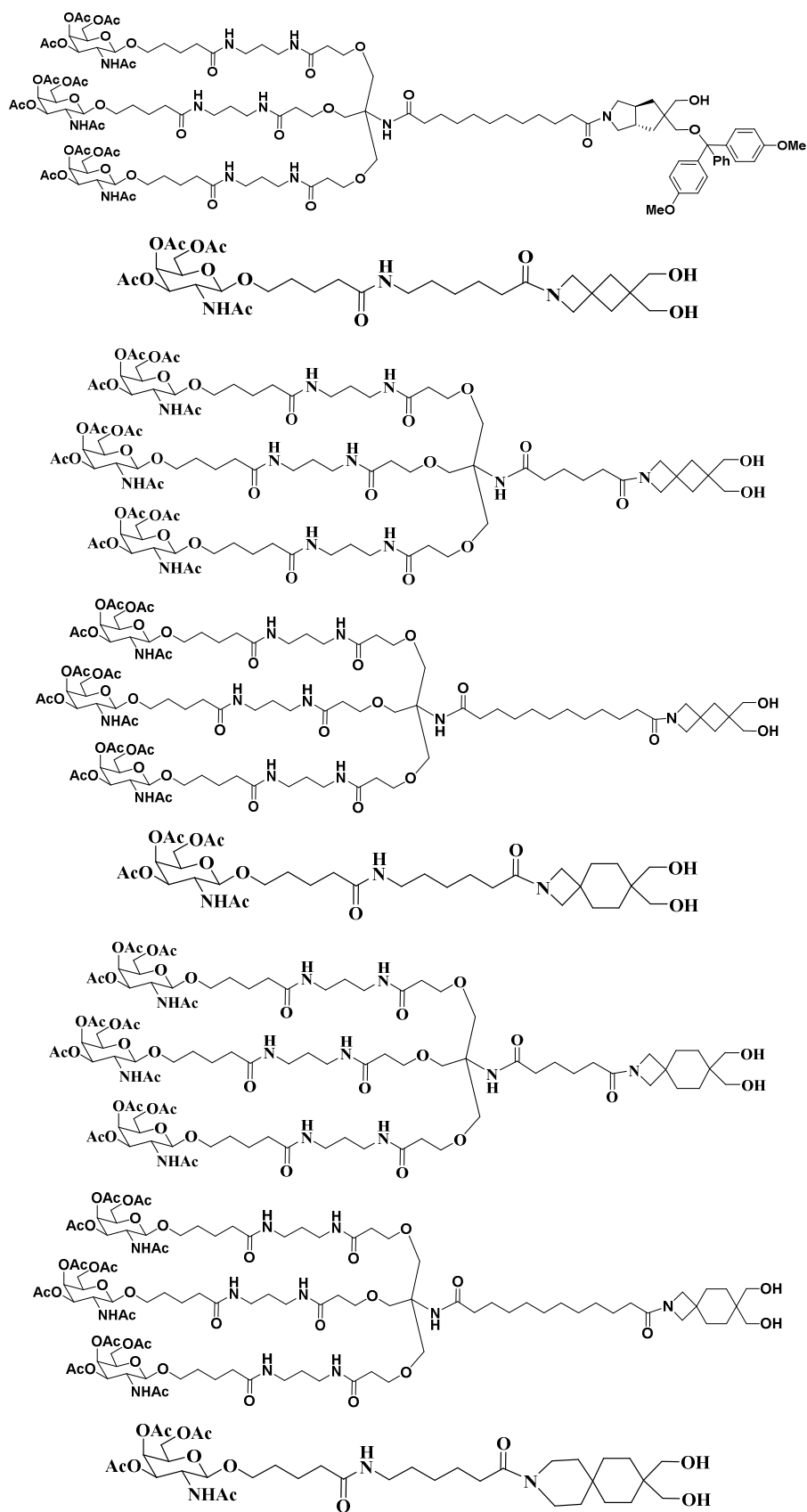


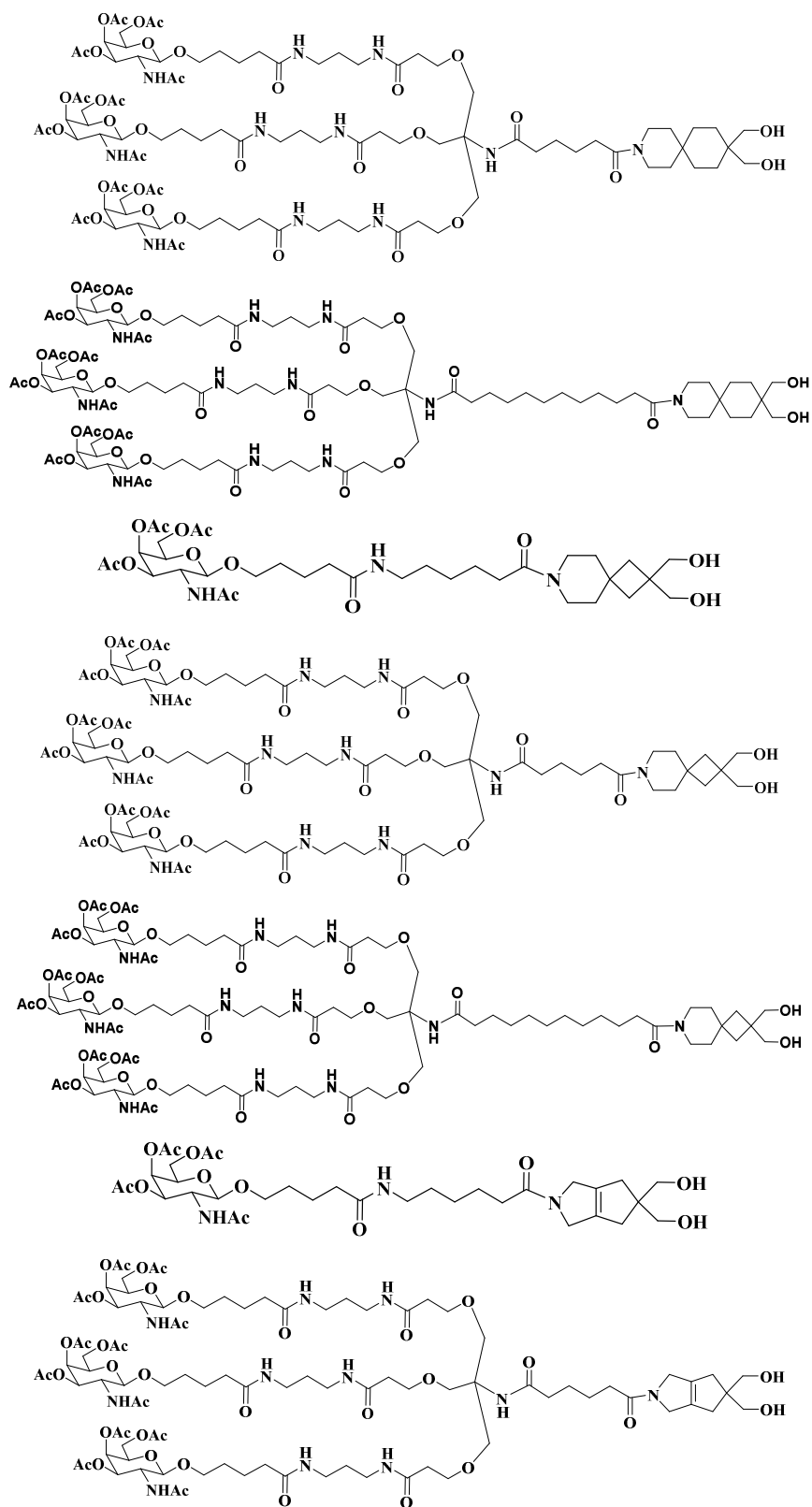


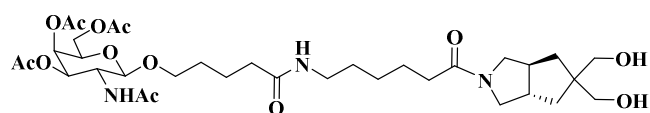
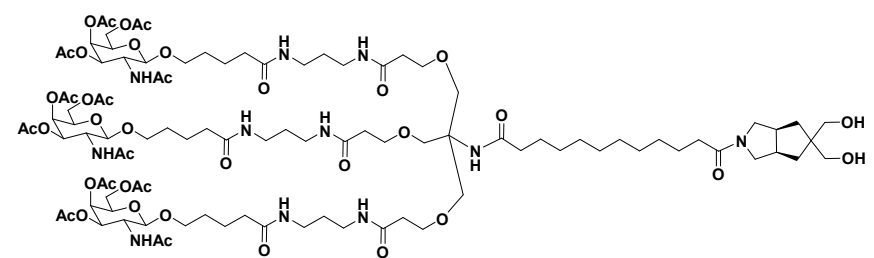
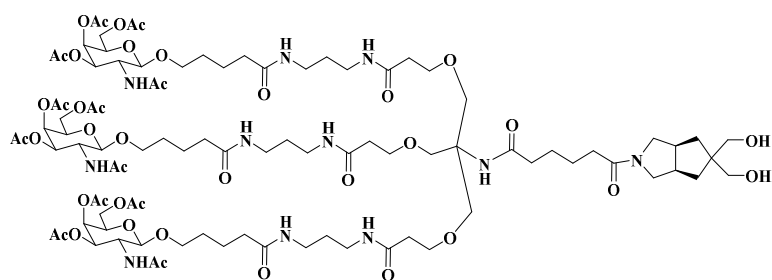
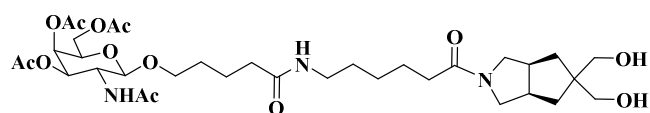
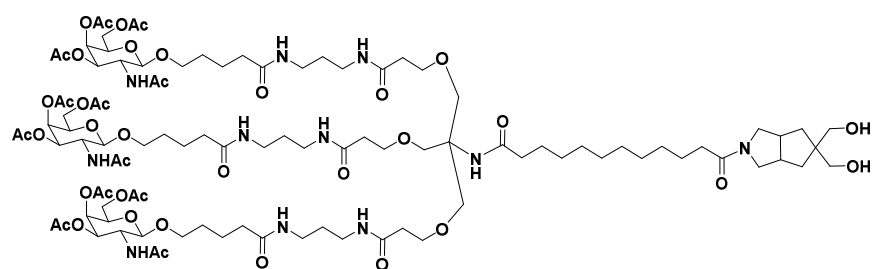
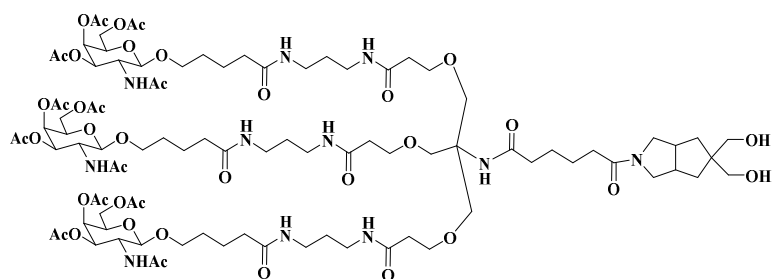
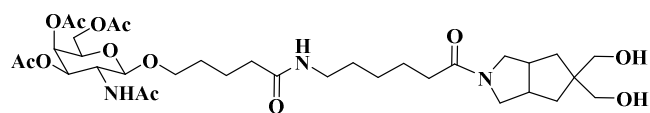
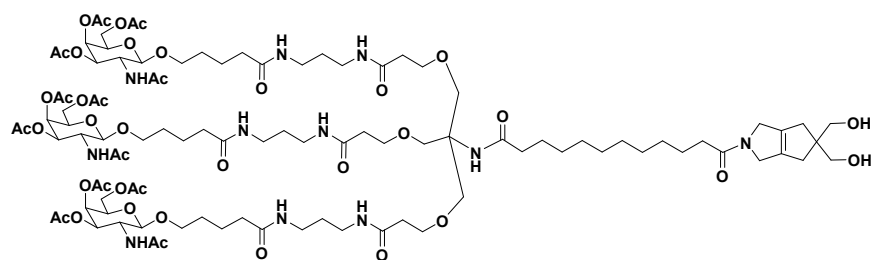


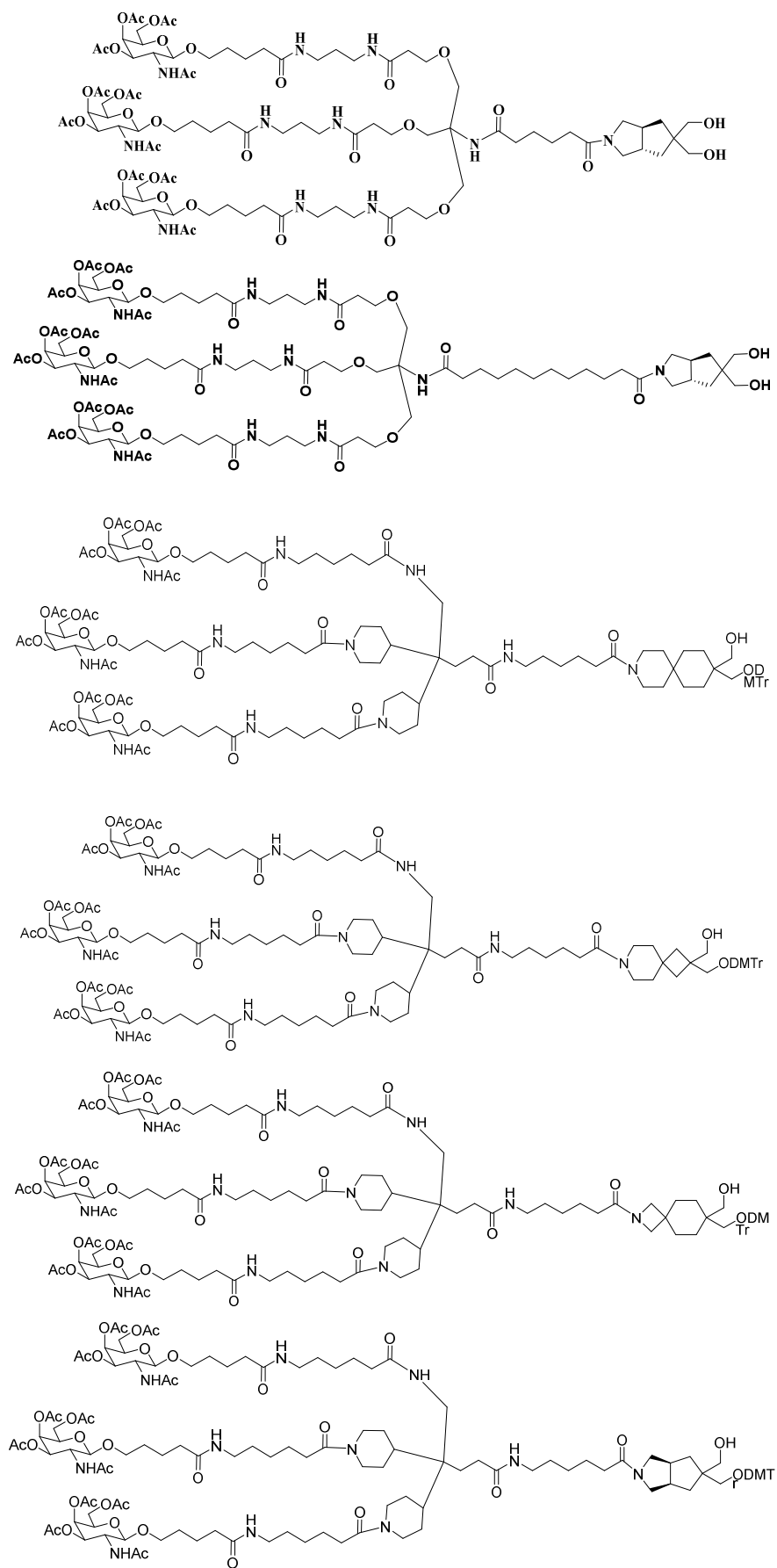


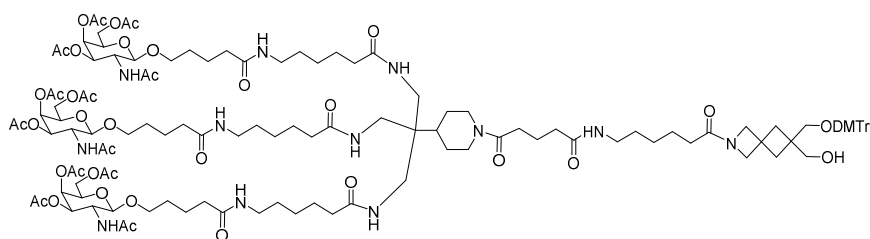
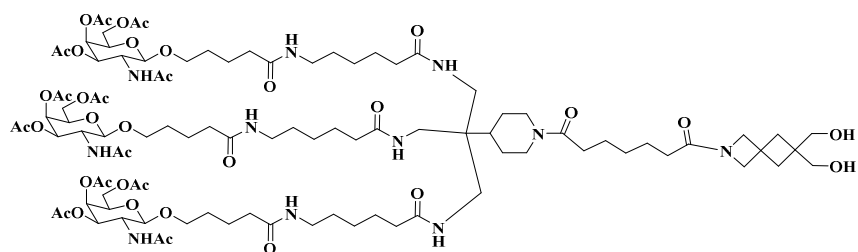
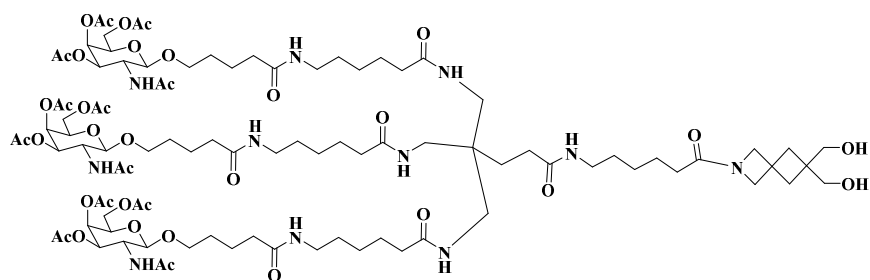
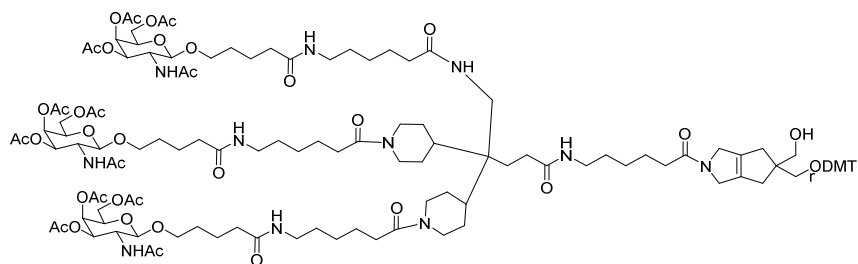
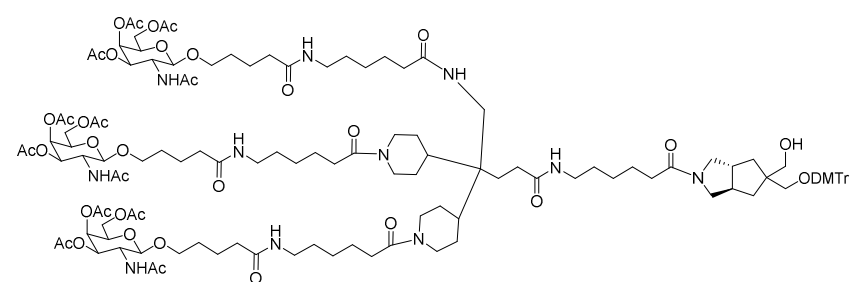


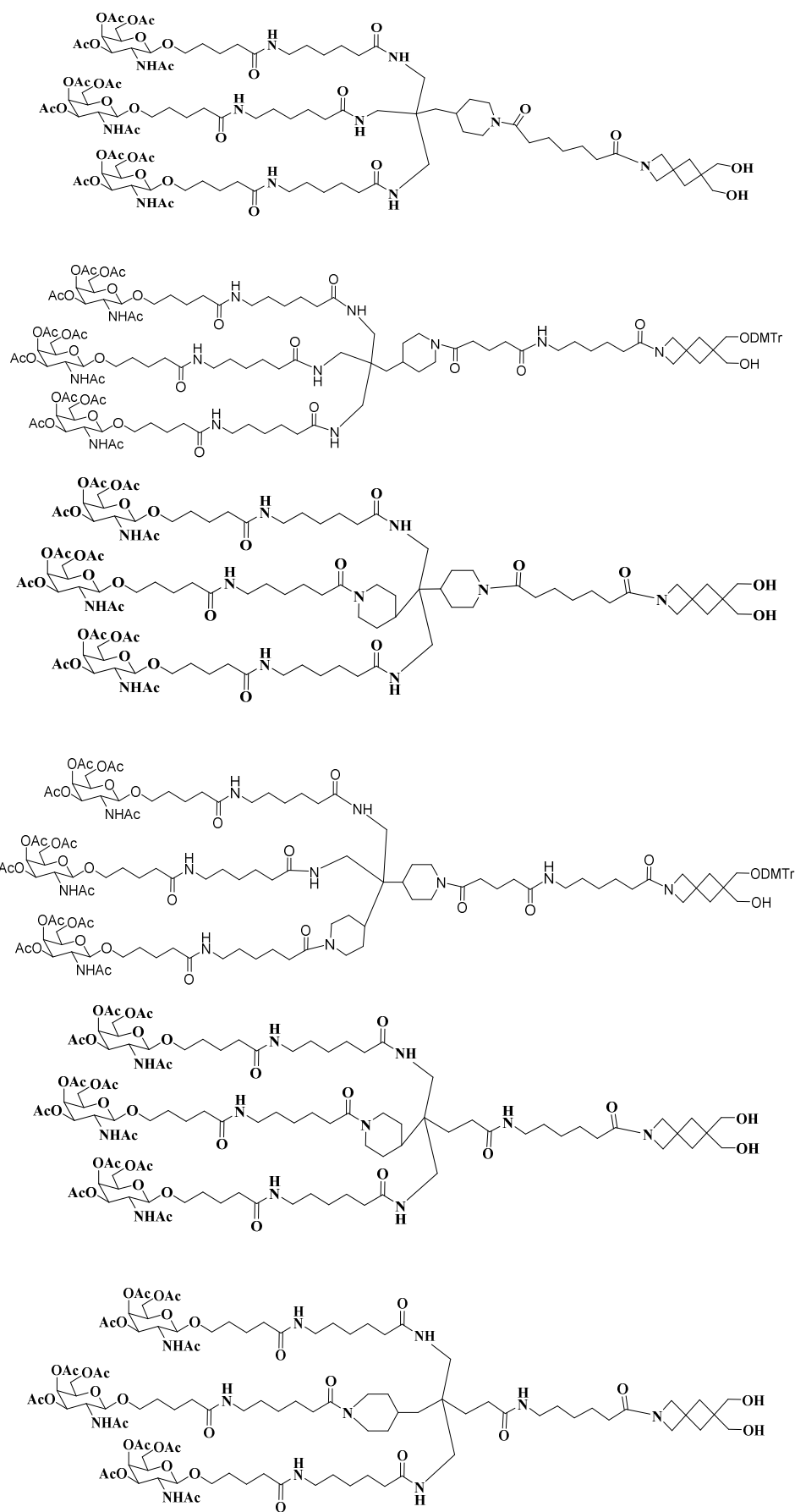


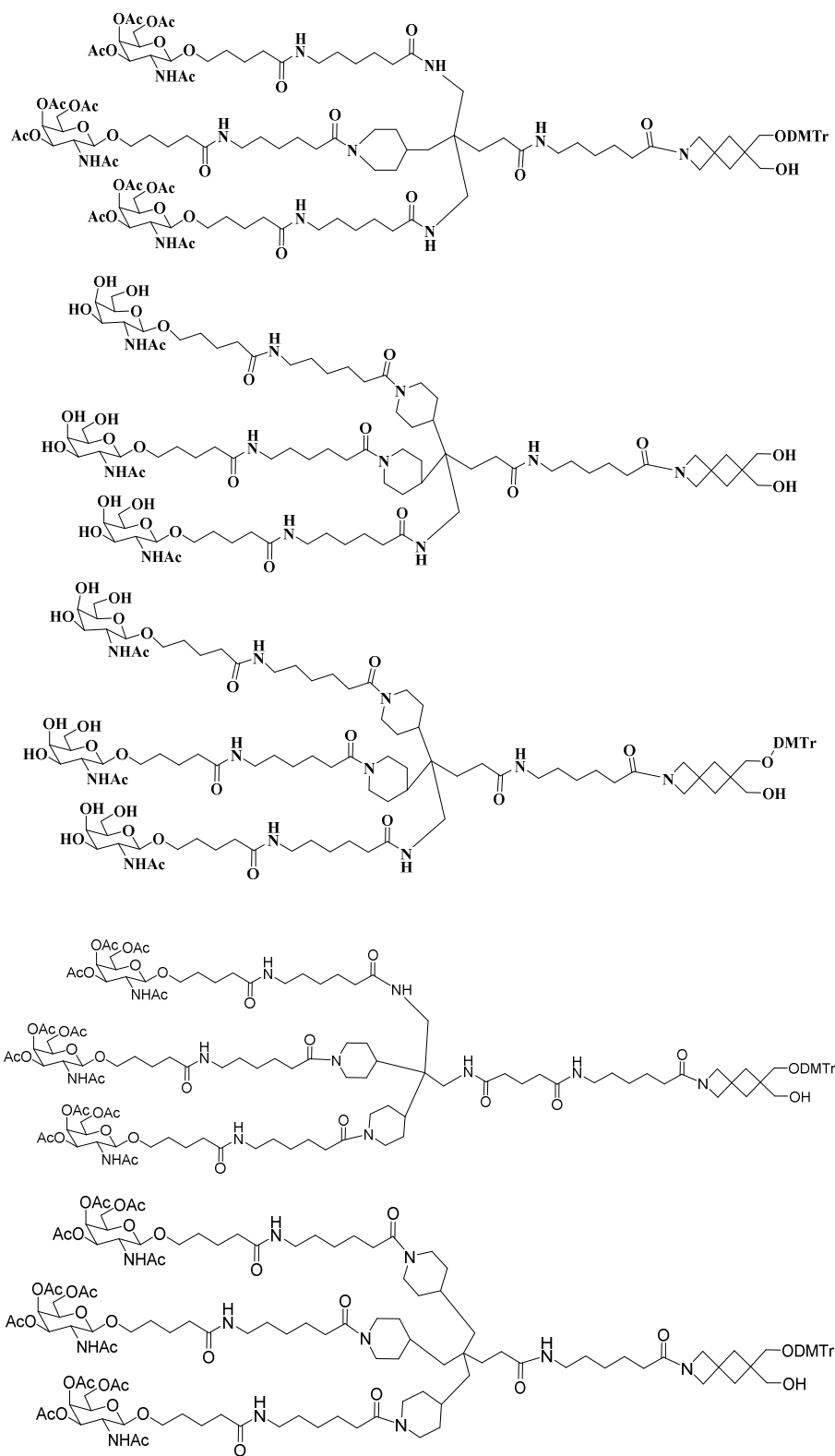


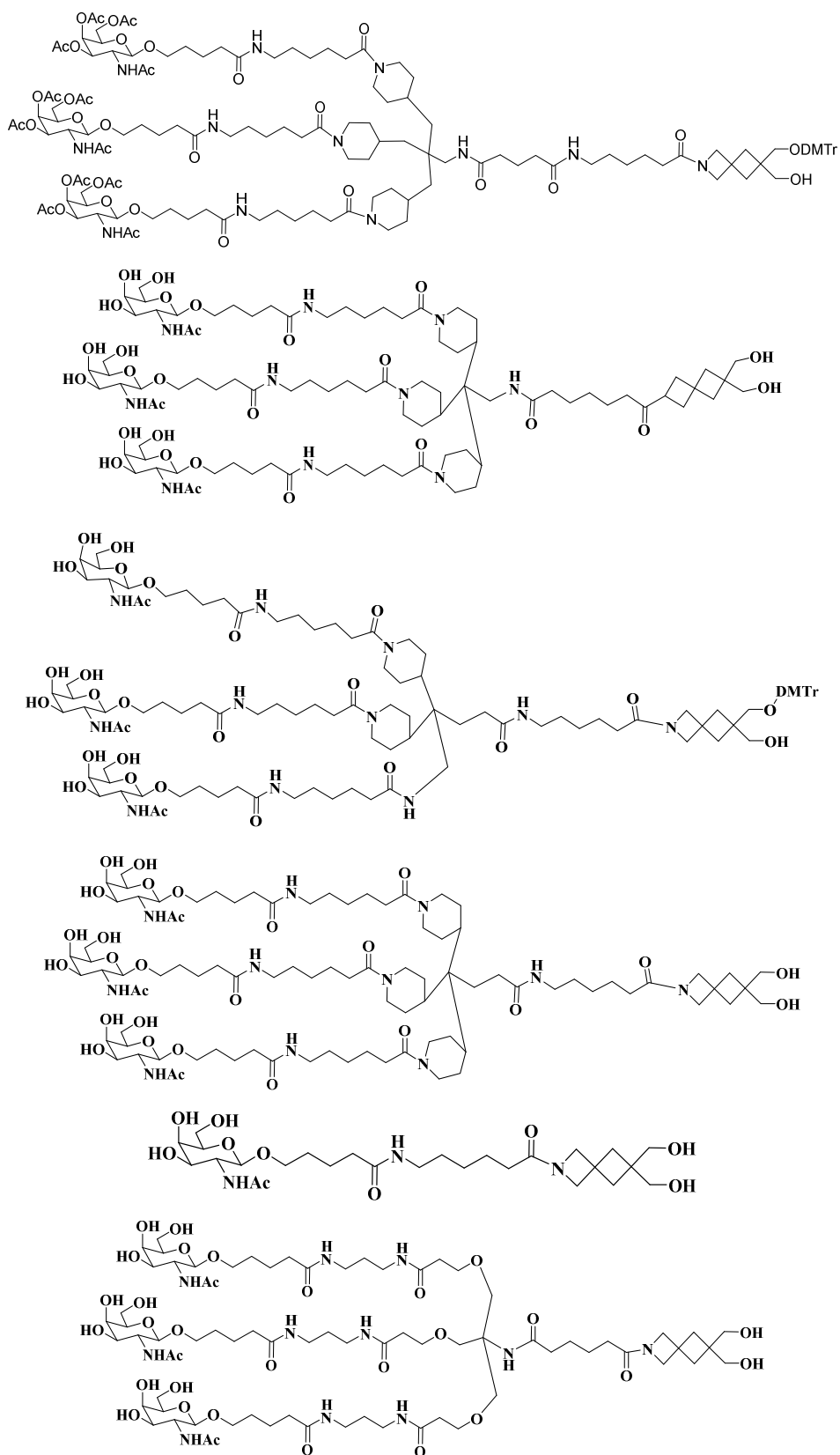


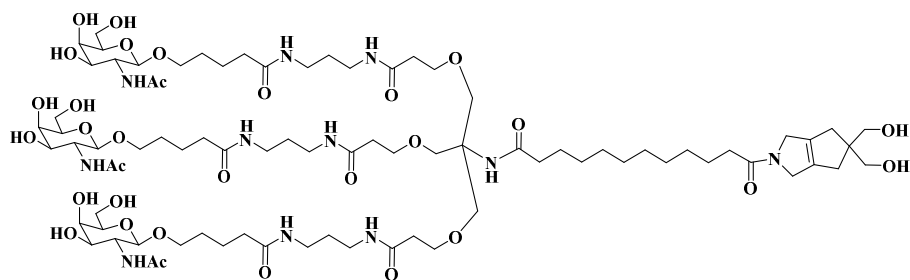
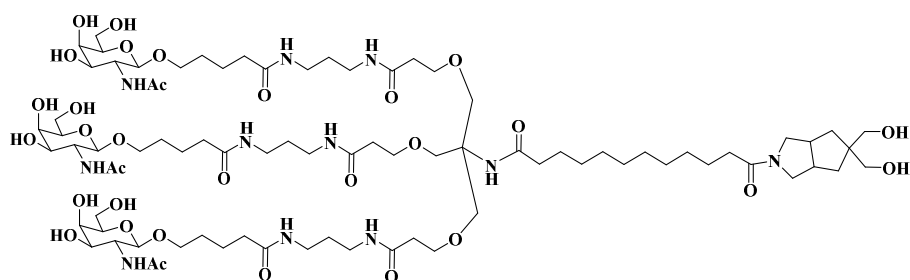
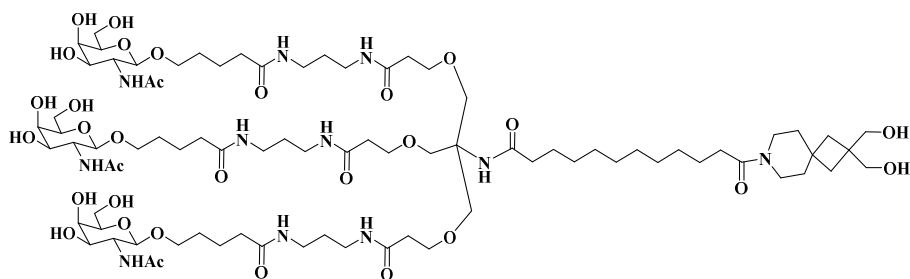
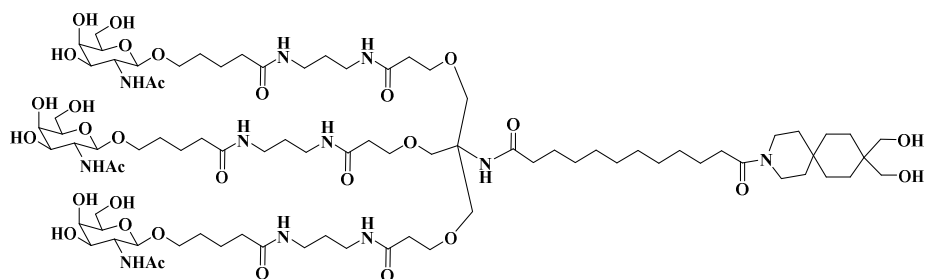
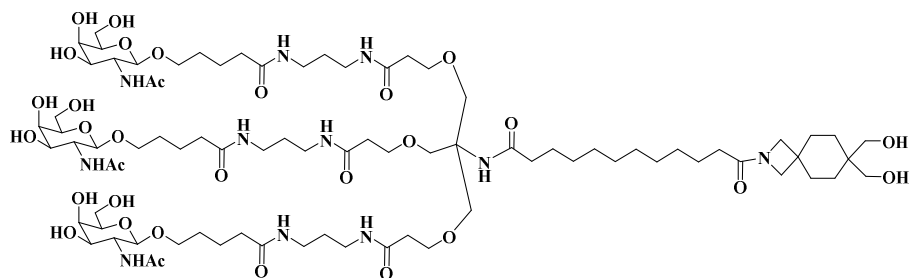
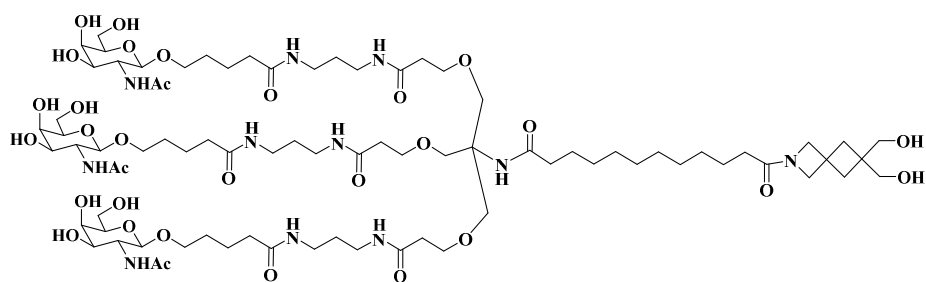


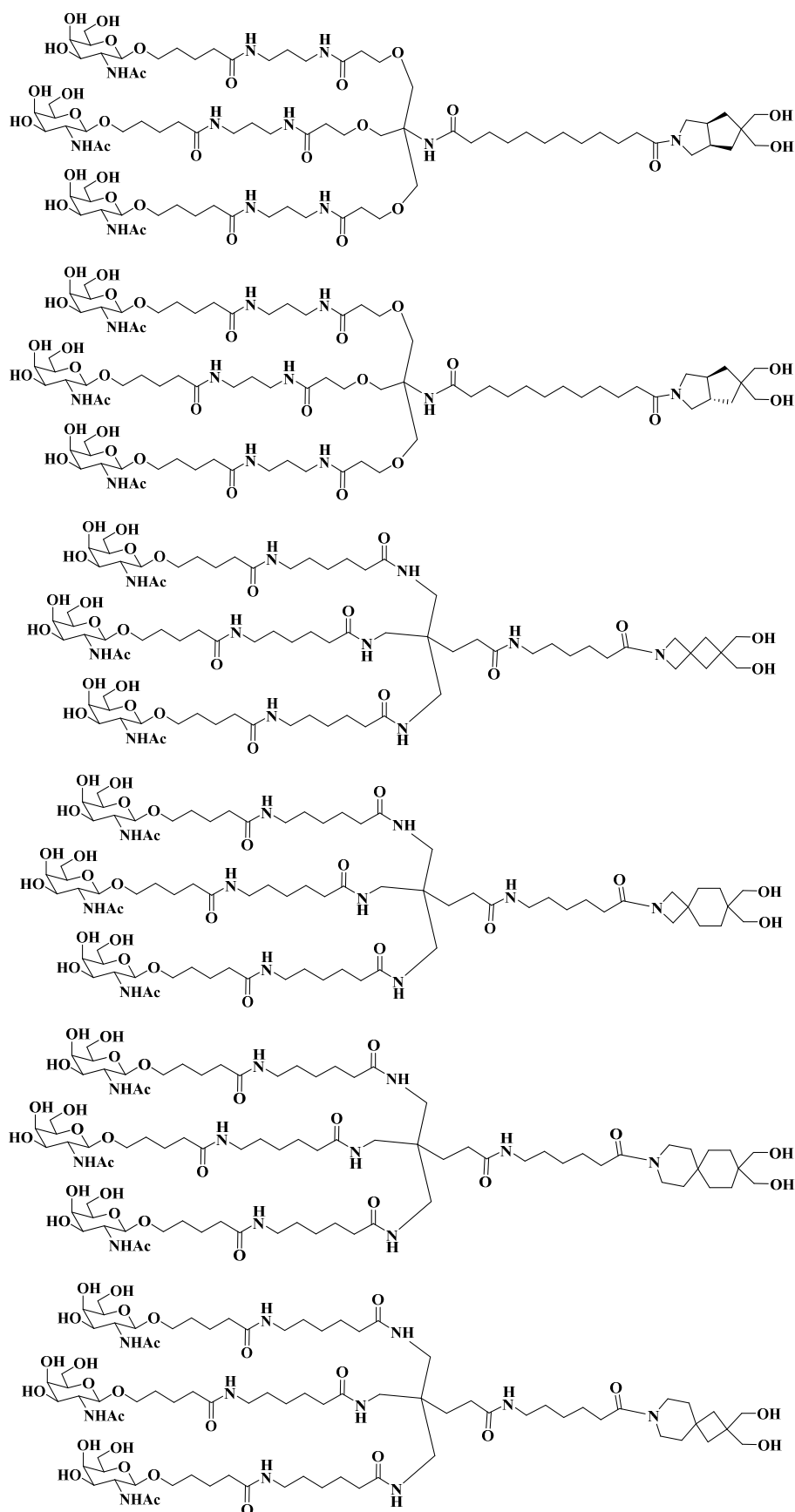


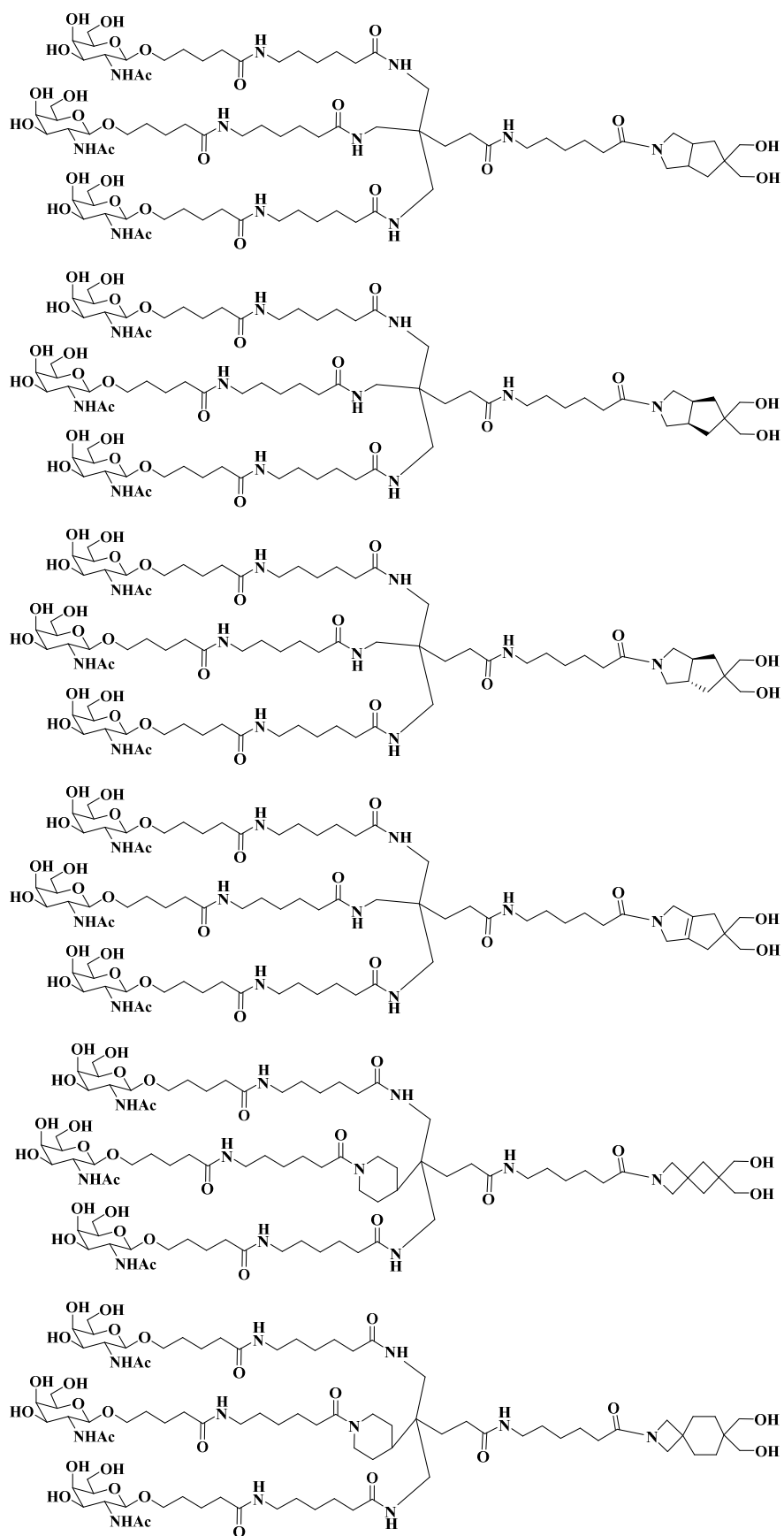


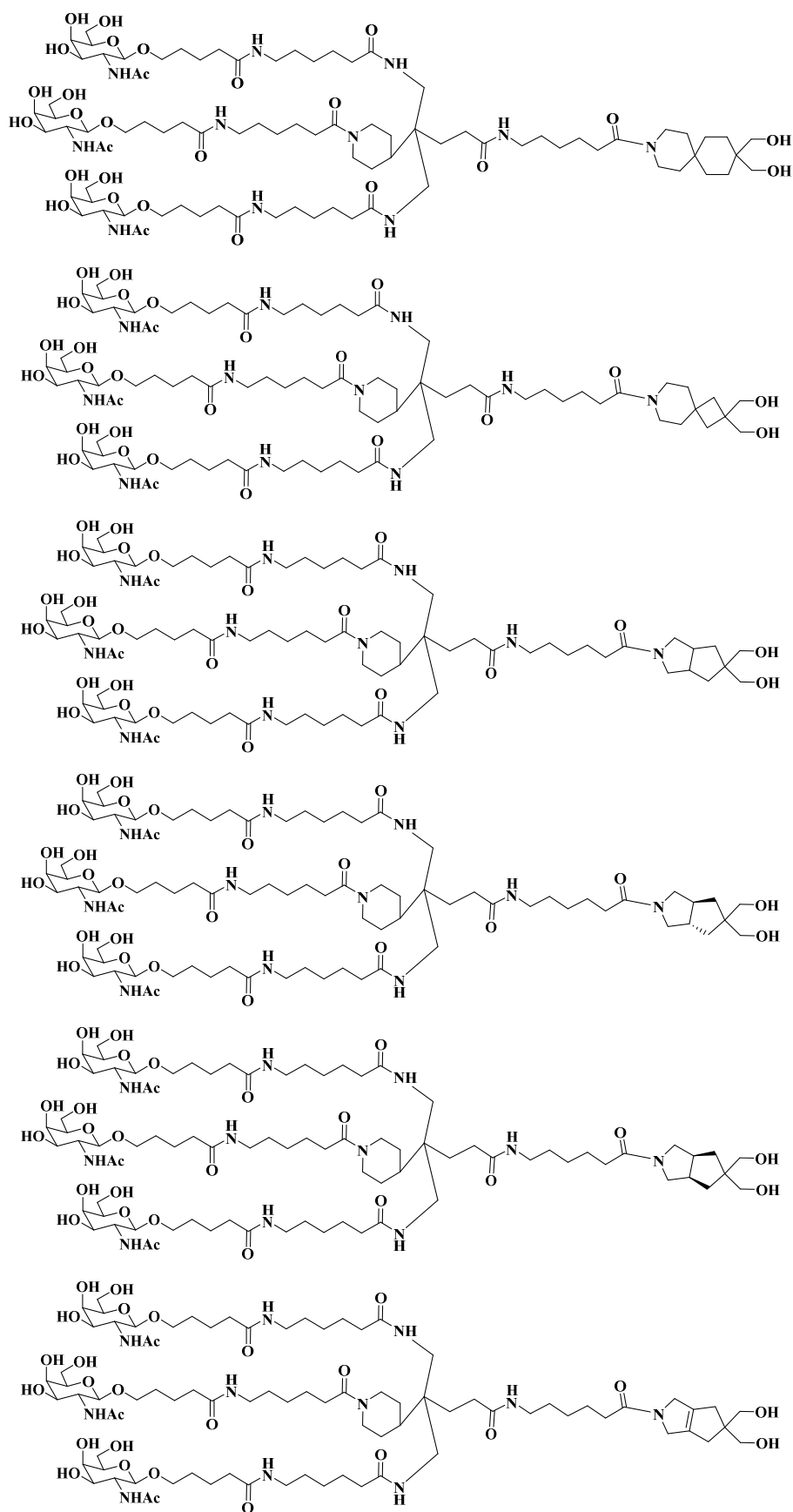


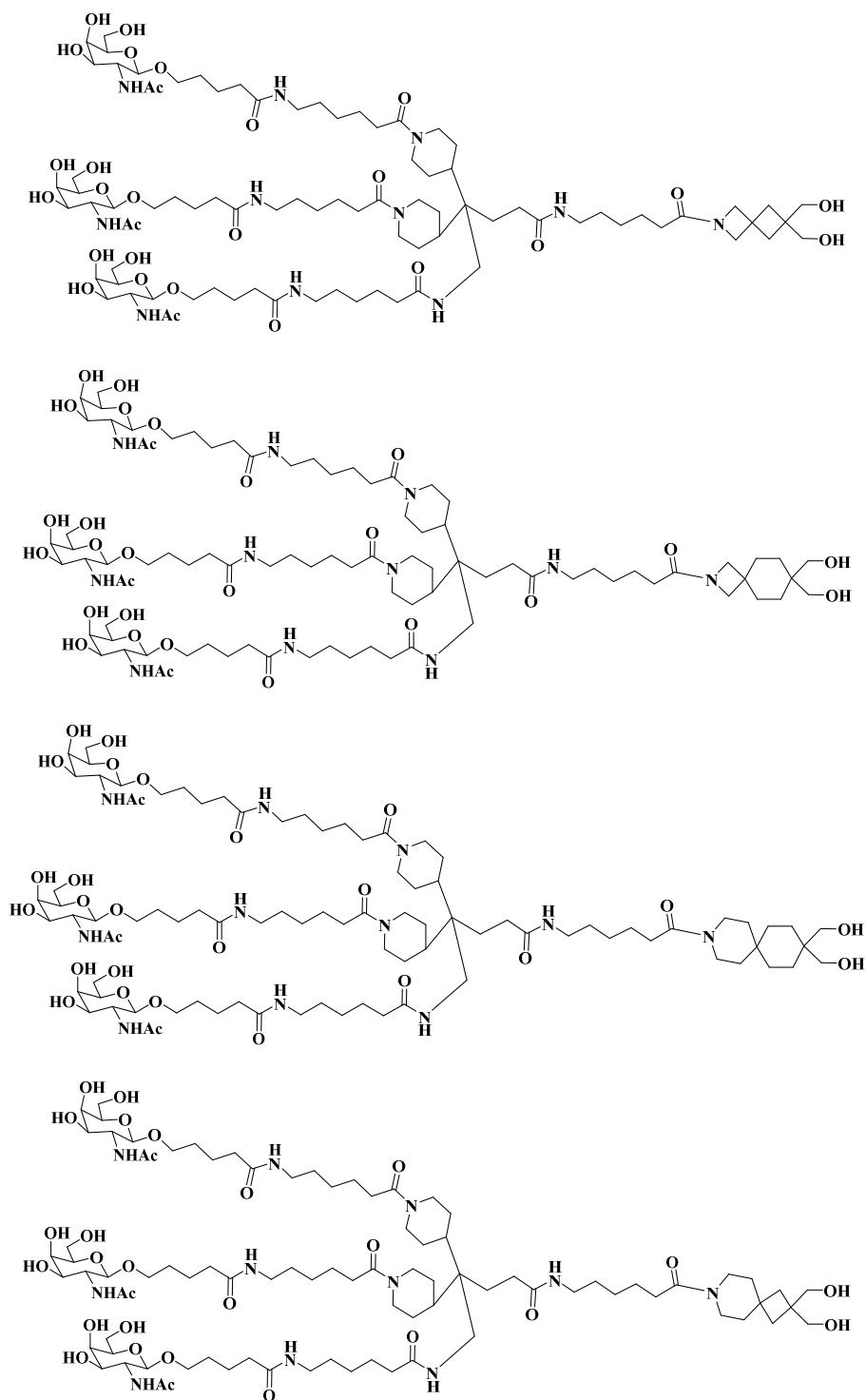


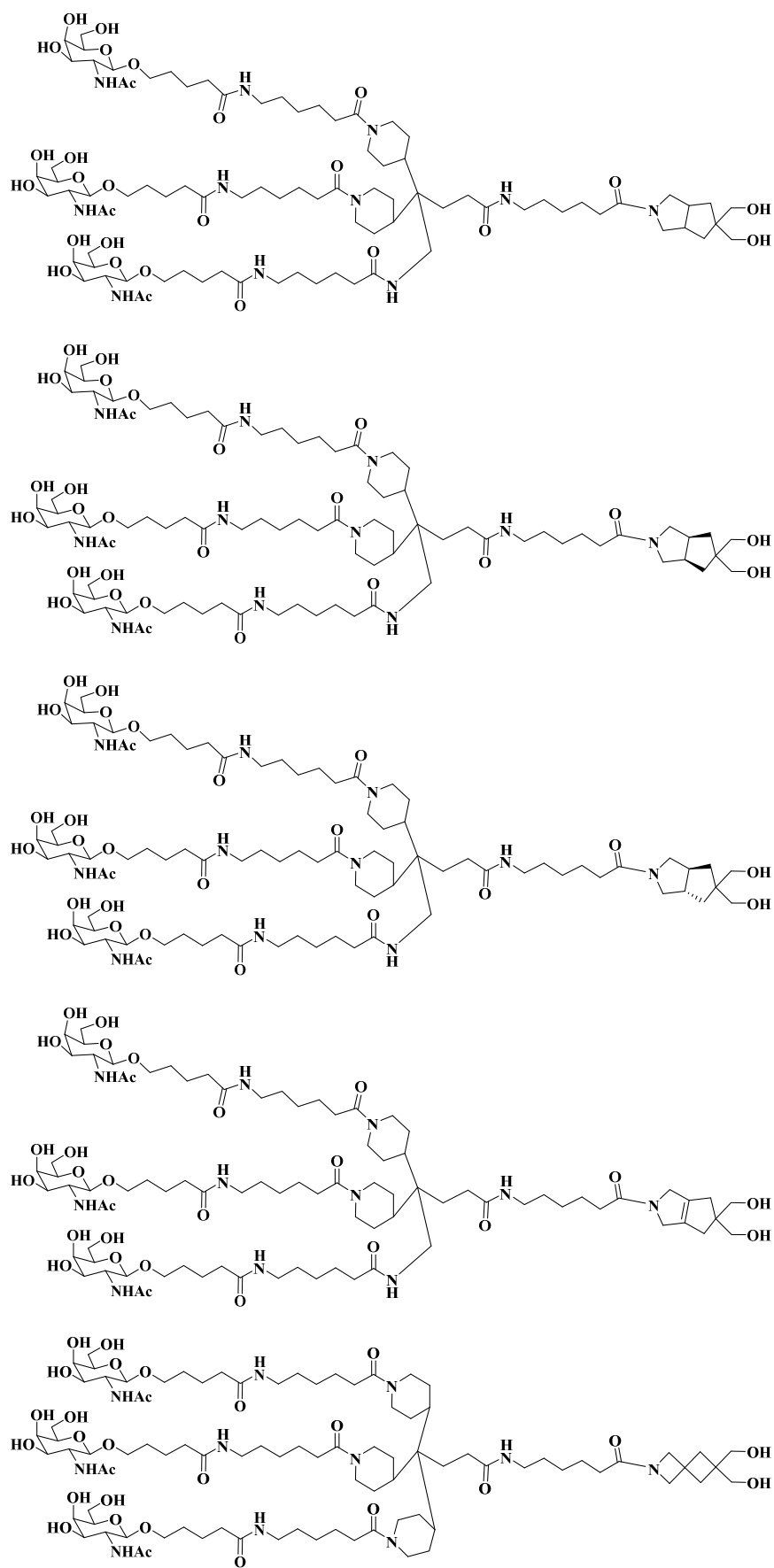


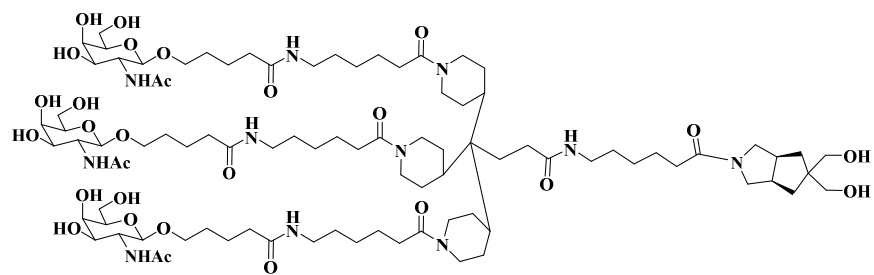
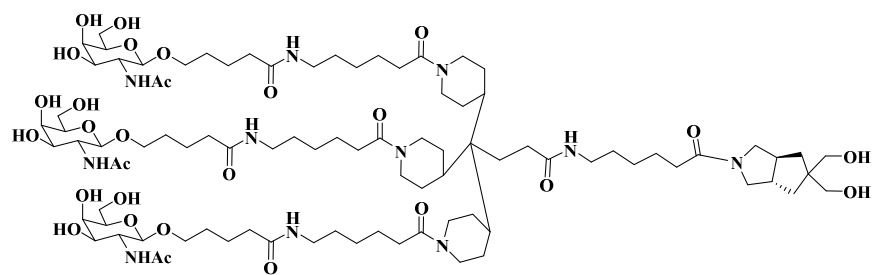
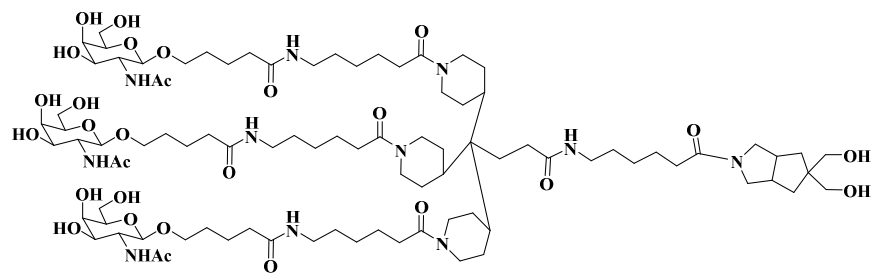
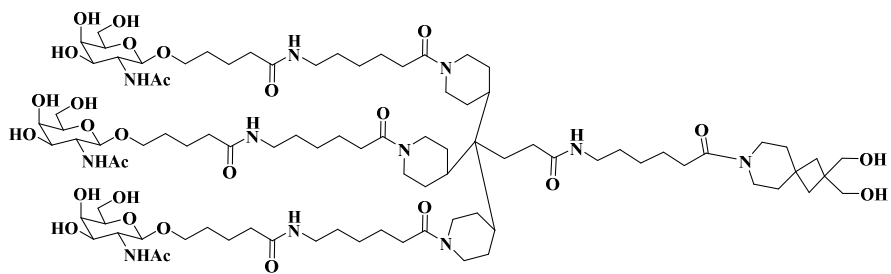
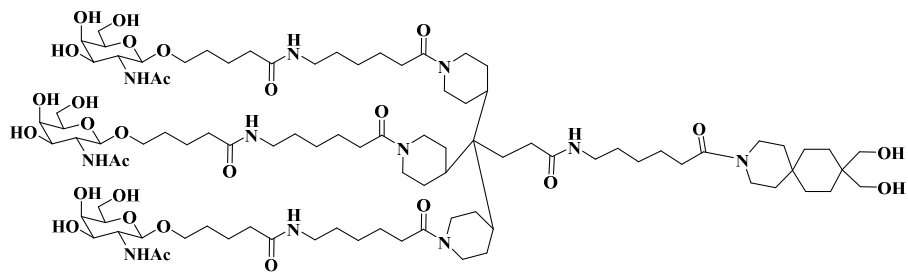
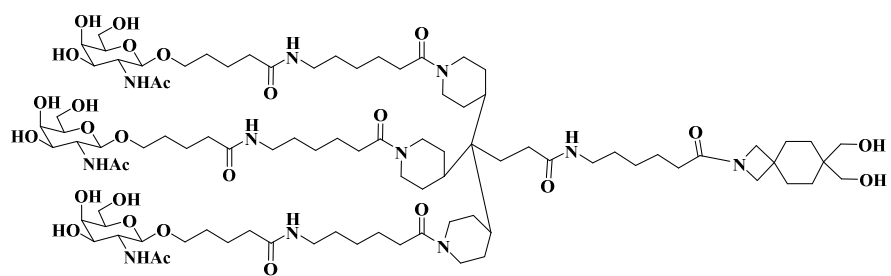


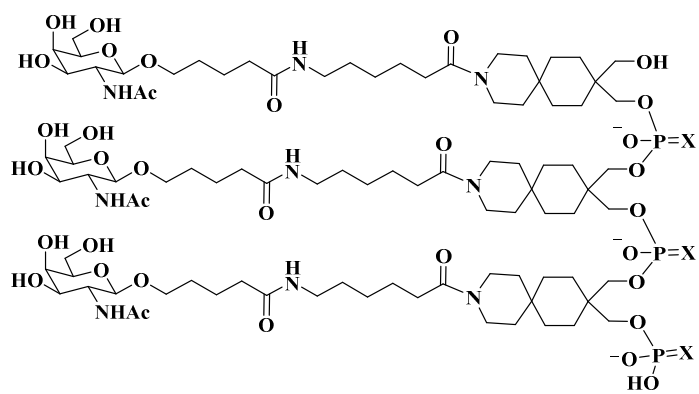
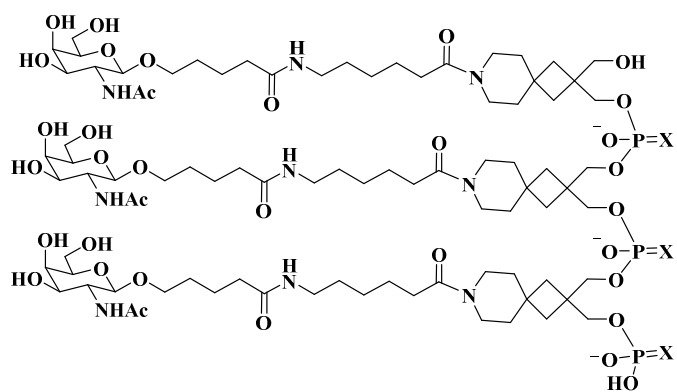
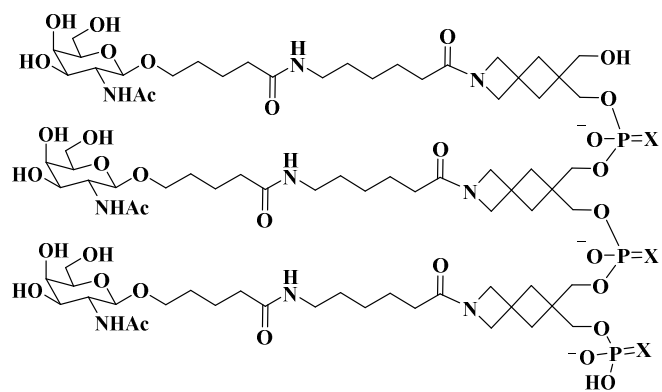
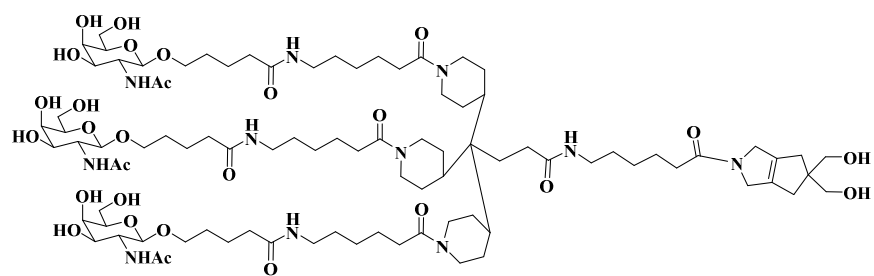


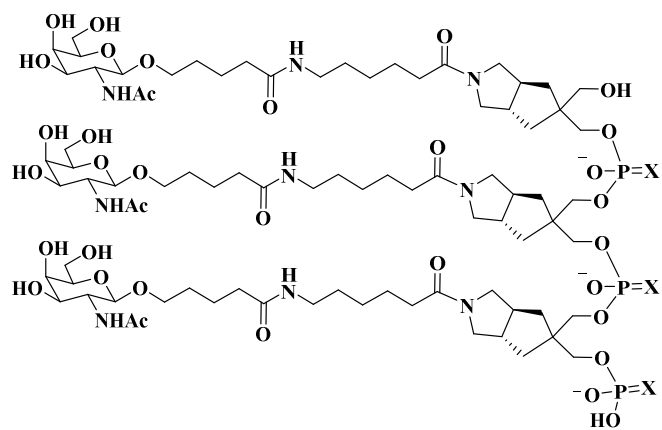
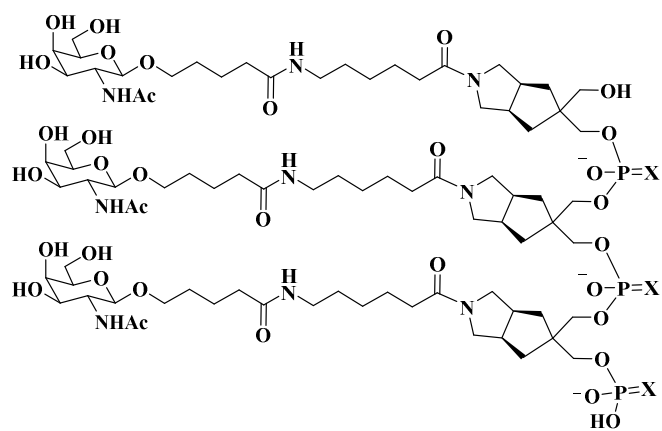
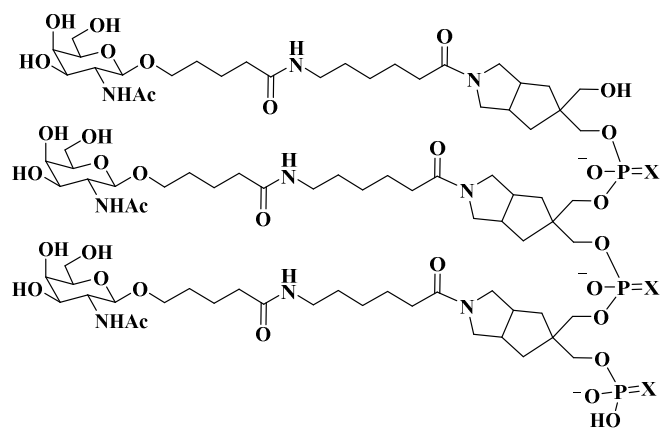
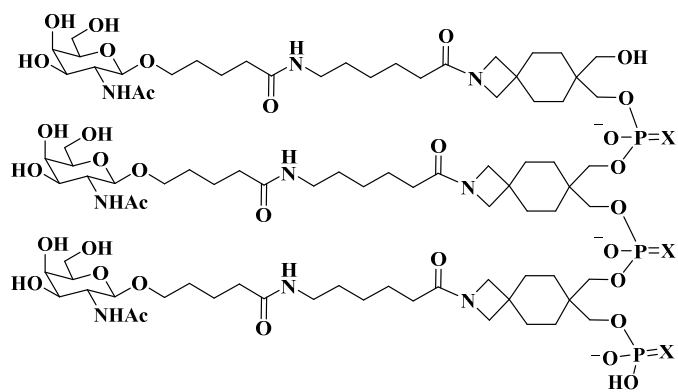


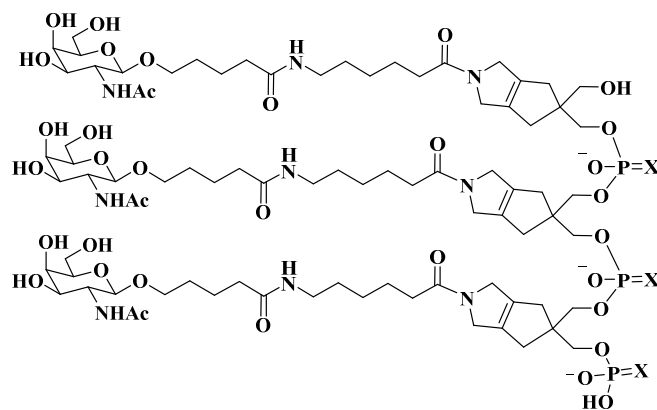










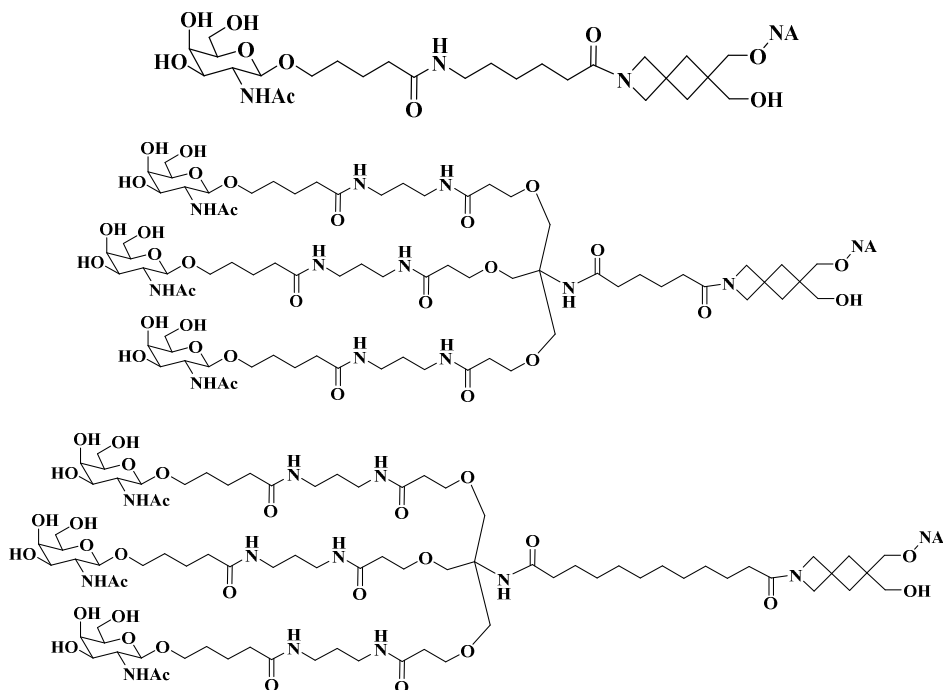


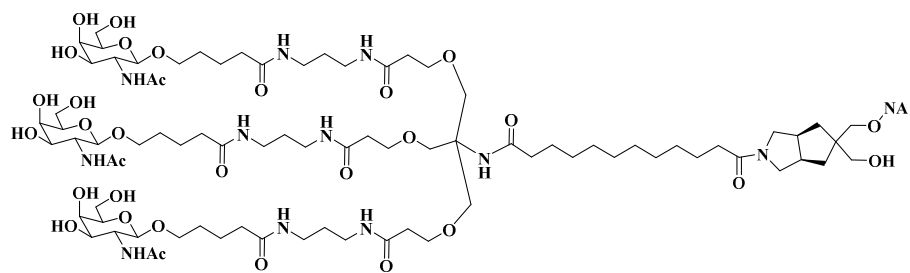
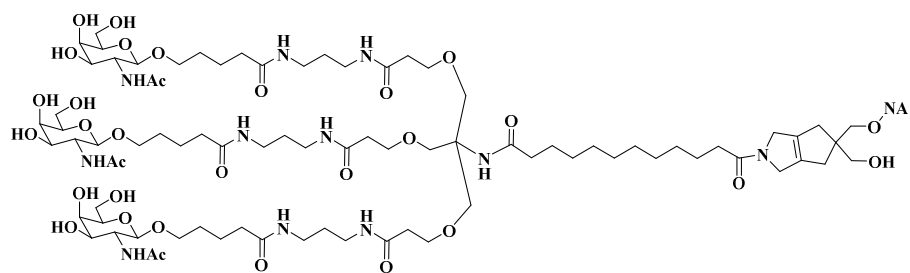
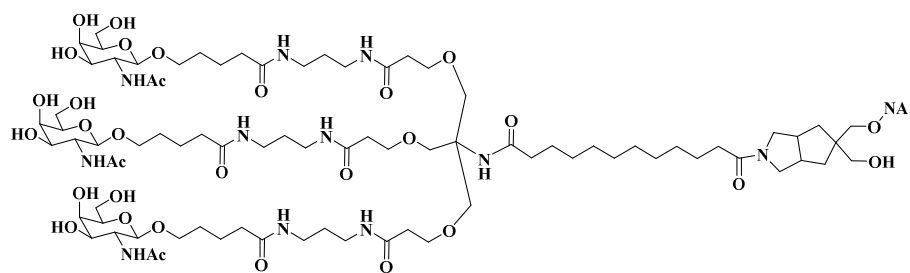
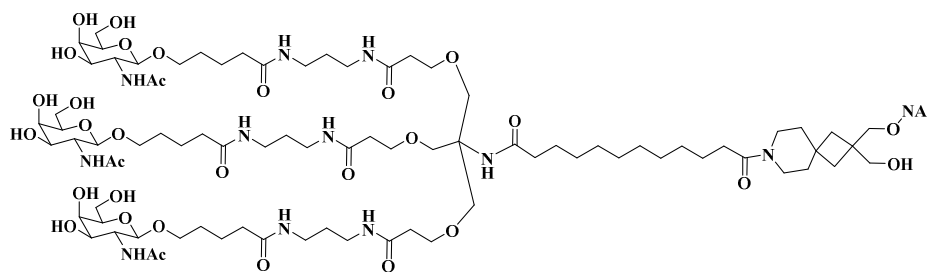
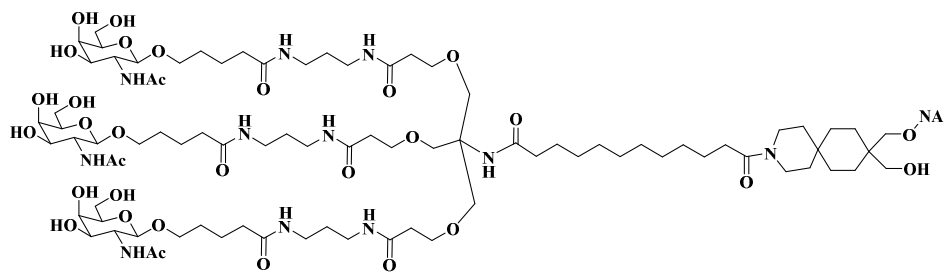
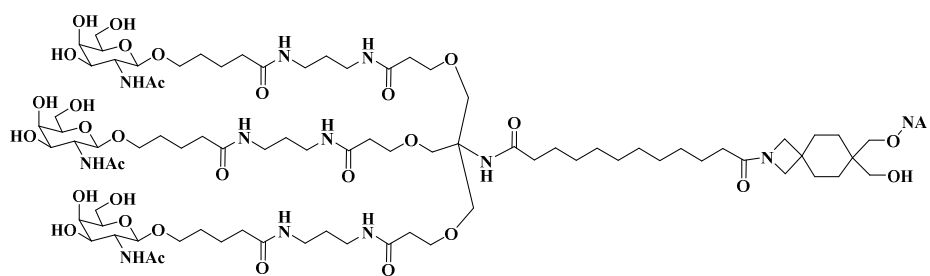
X is O or S.

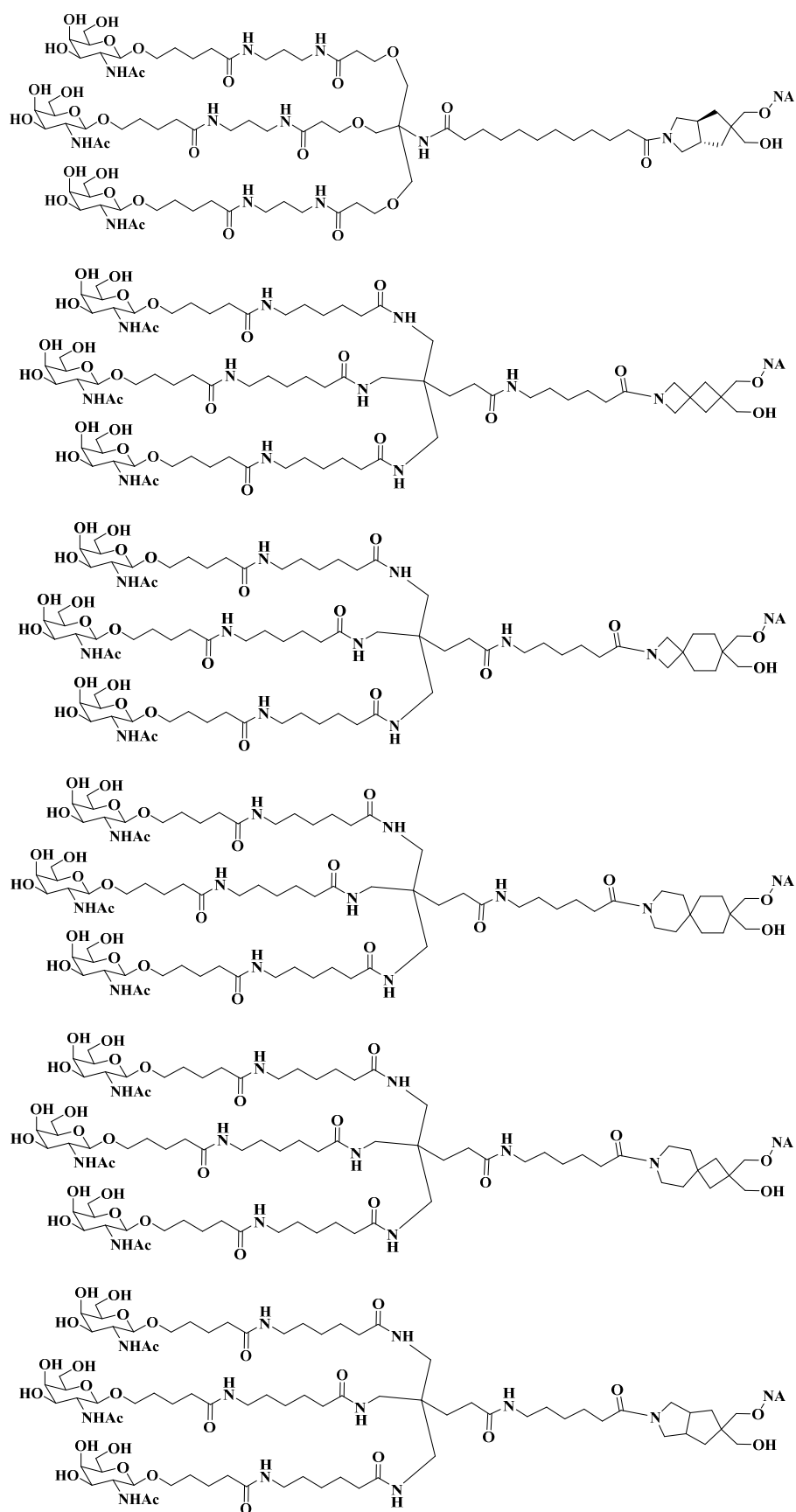
12. A targeting ligand of any one of claims 1-11, linked to a therapeutic agent, for use as medicament.

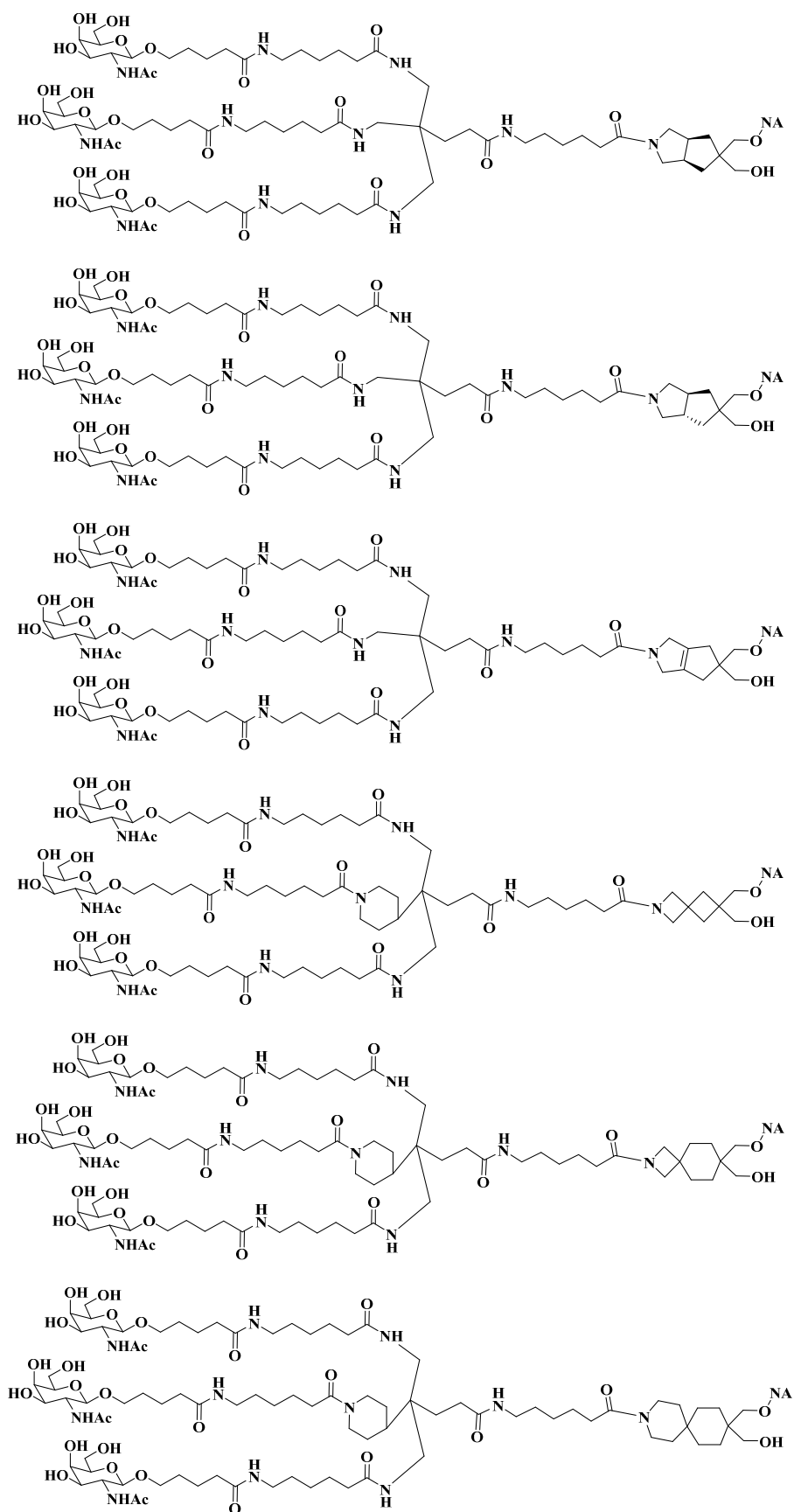
13. A therapeutic compound or pharmaceutically acceptable salt thereof, comprising at least one therapeutic oligonucleotide, and the oligonucleotide conjugate to the targeting ligand of any one of claims 1-11.

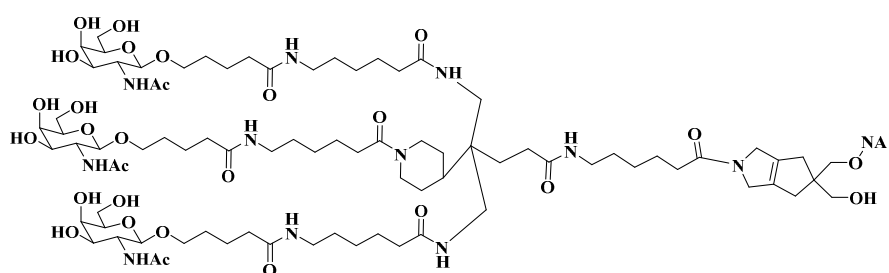
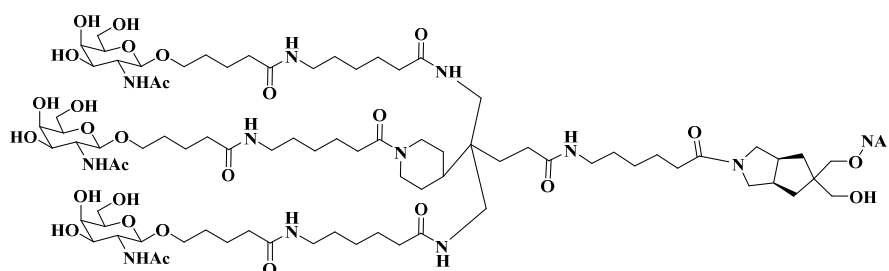
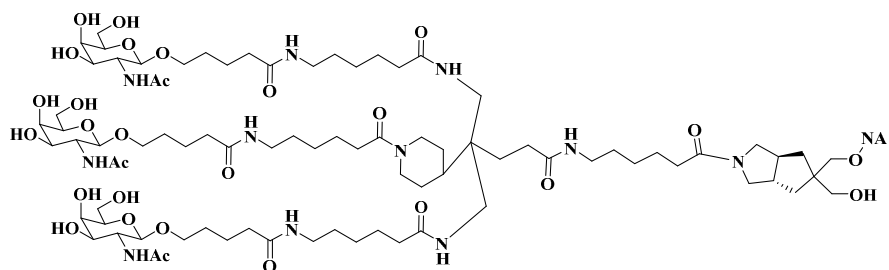
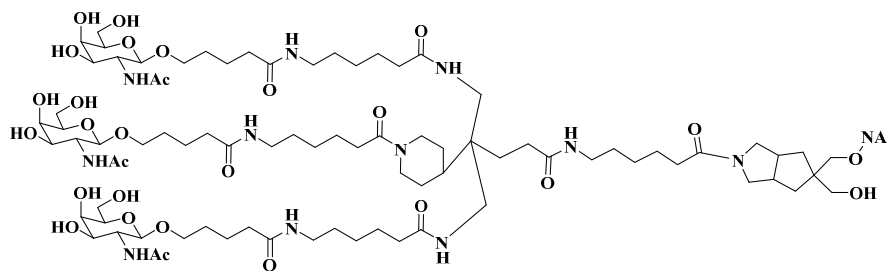
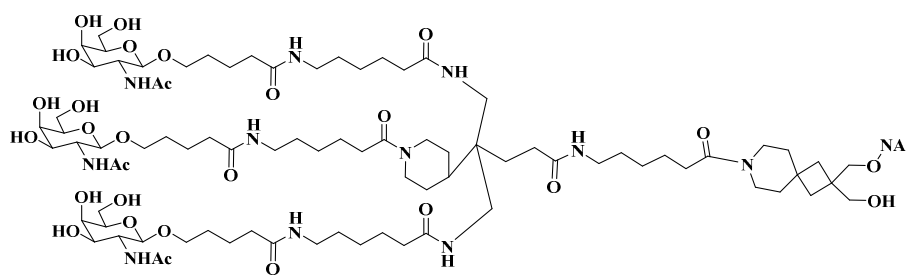
14. The therapeutic compound or pharmaceutically acceptable salt thereof of claim 13, wherein the therapeutic compound is:

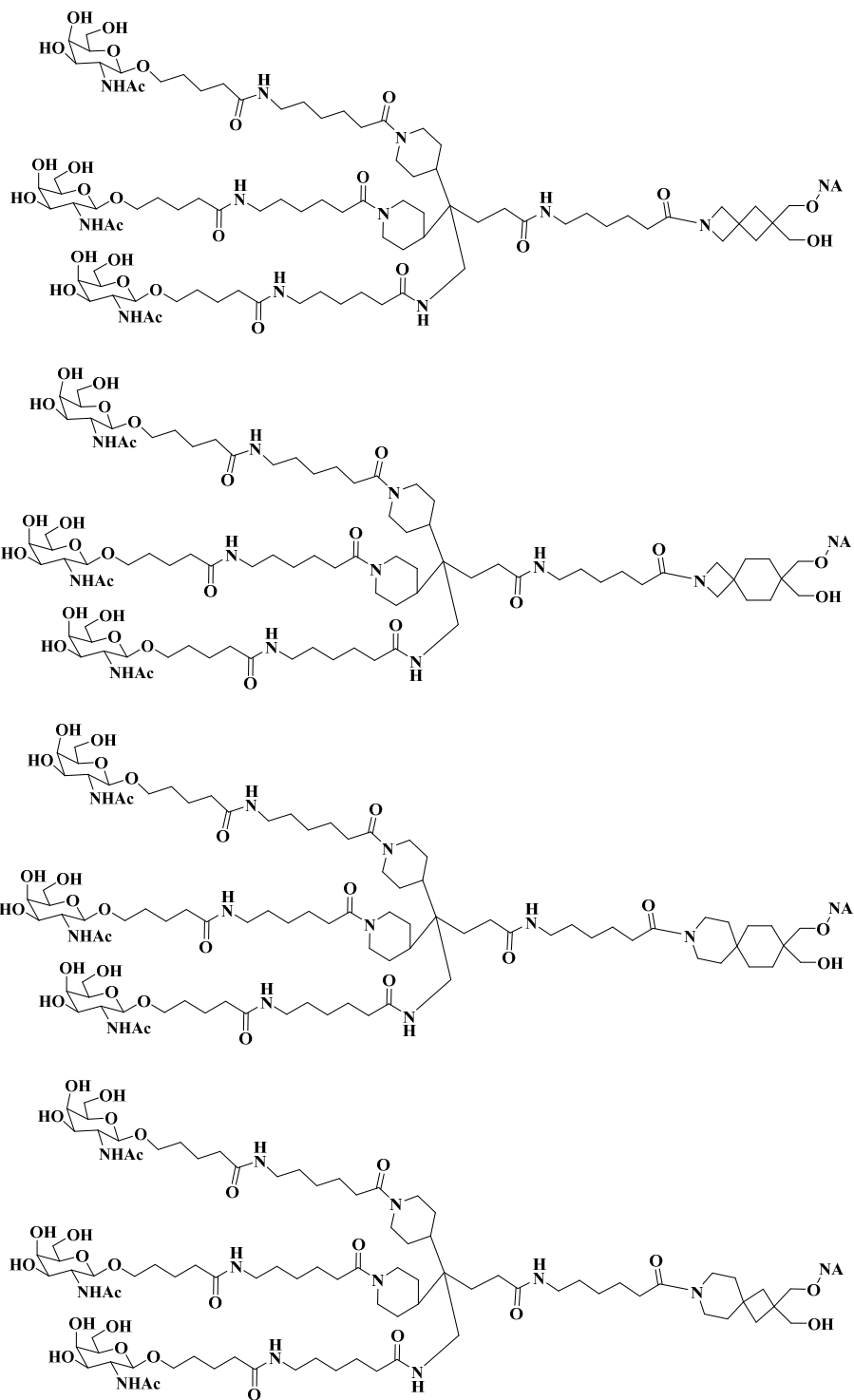


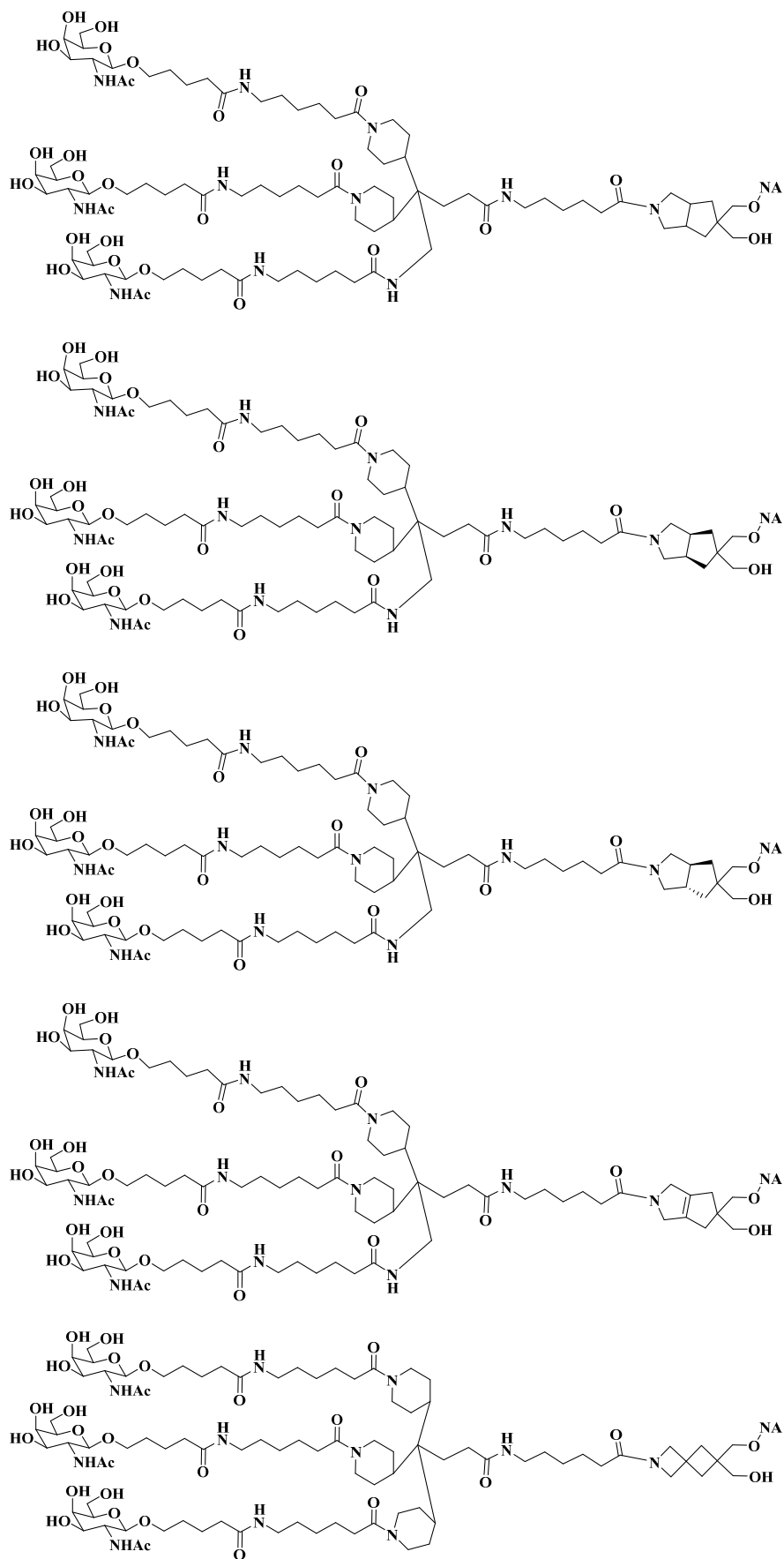


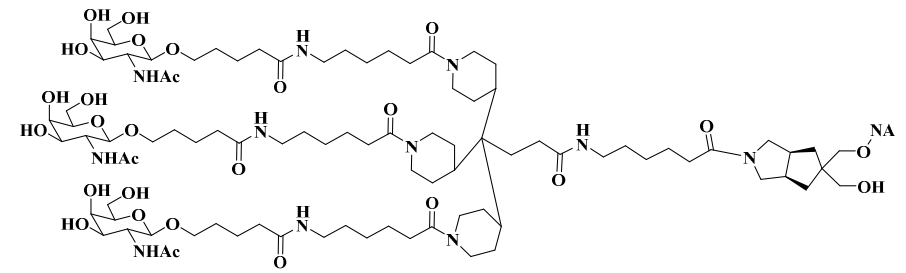
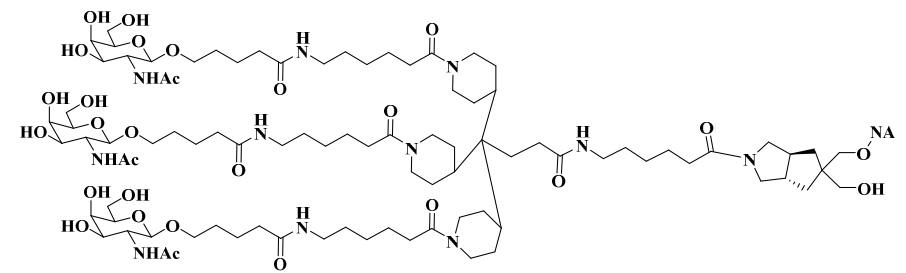
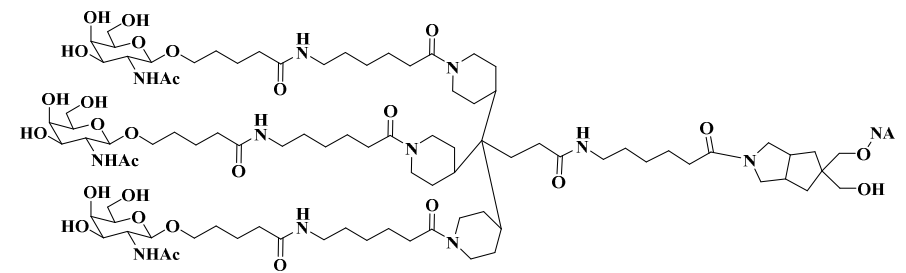
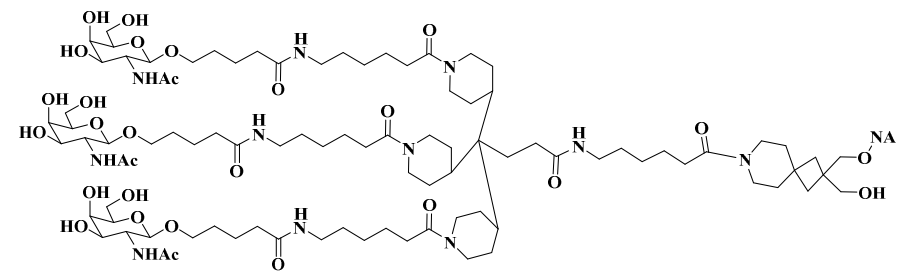
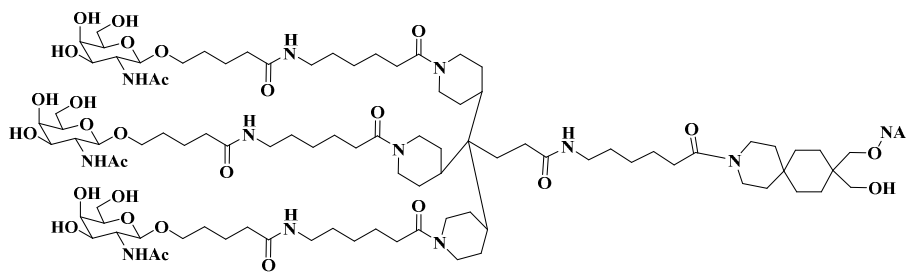
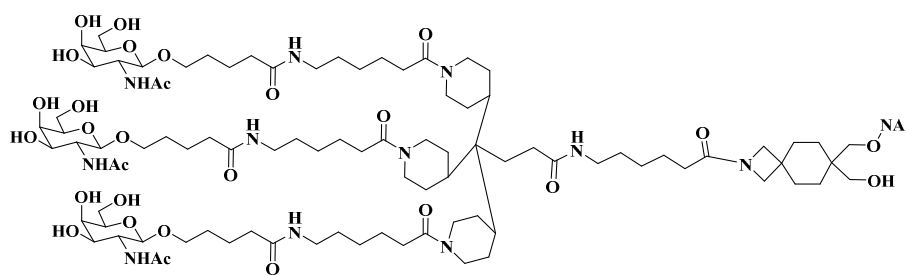


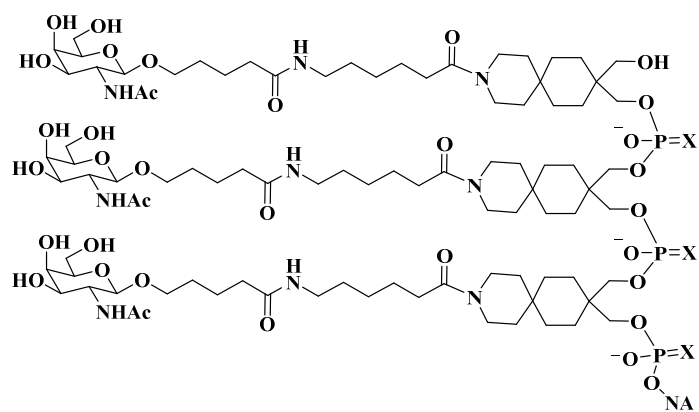
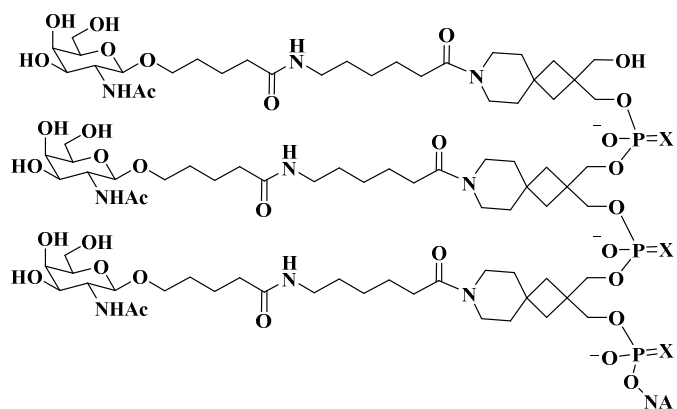
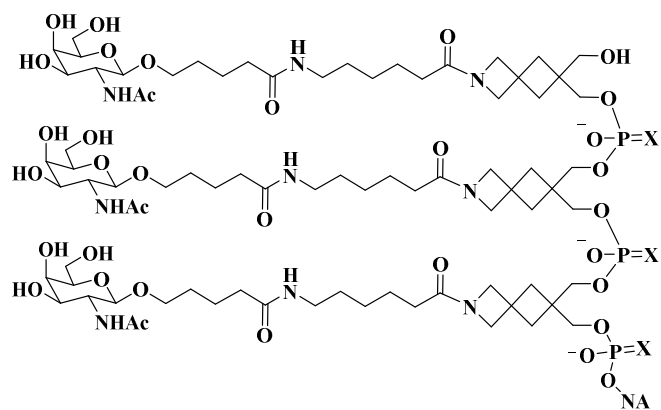
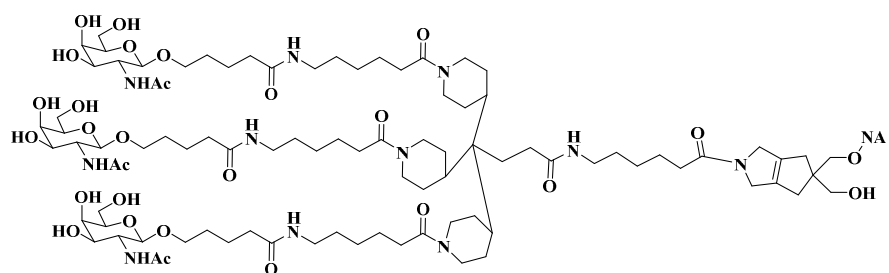


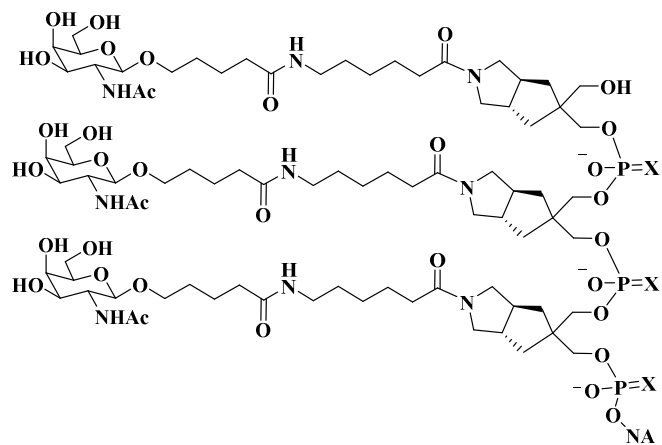
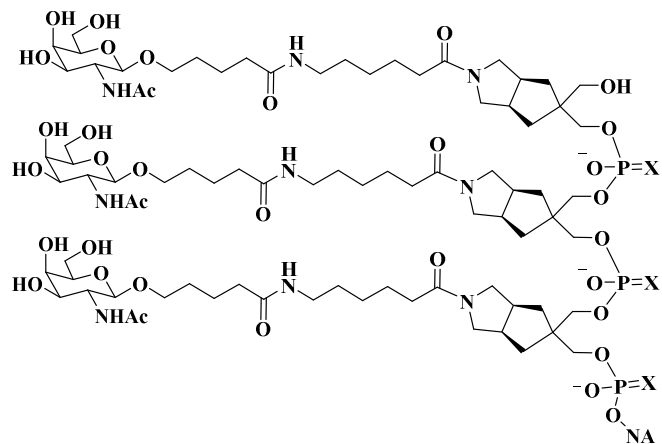
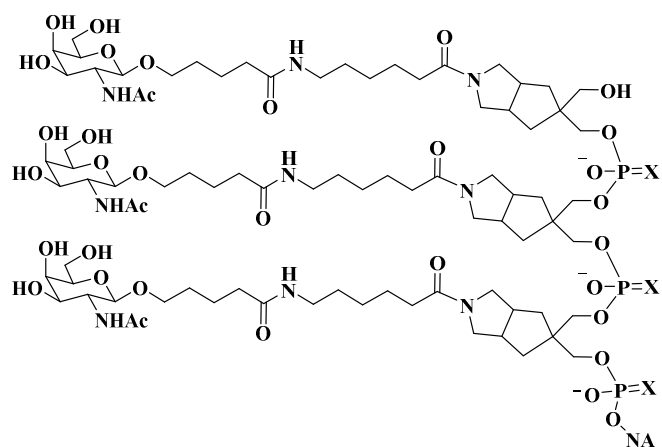
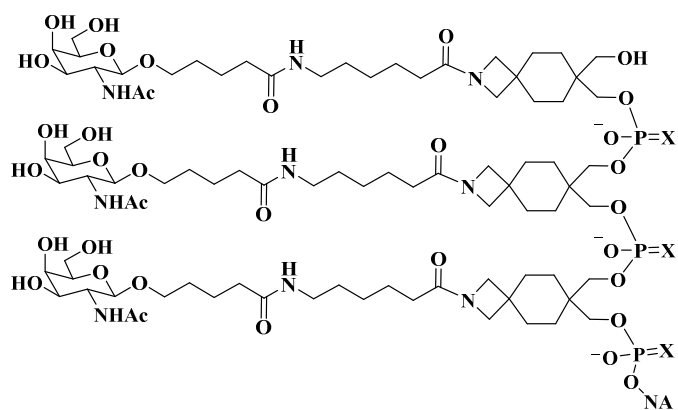


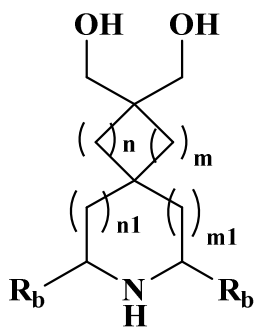




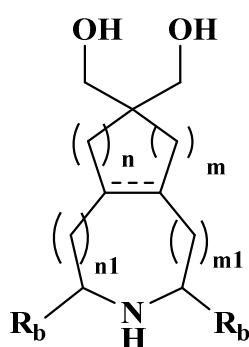




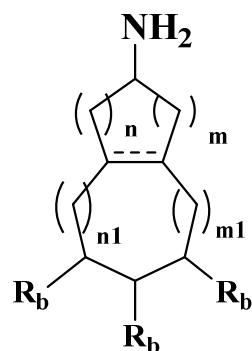




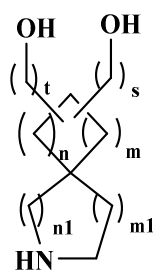
(V-a)



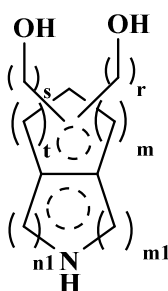
(V-b)



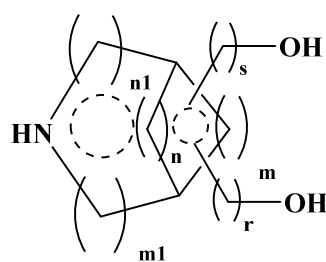
(V-c)



(VI-a)



(VI-b)



(VI-c)

(i) in the formula (V-a), (V-b), (V-c):

 is a single or double bond;

R_b is independently selected from the group of hydrogen and oxo;

each of m and n is independently selected from 1, 2, 3; 4 and 5

each of $m1$ and $n1$ is each independently selected from 0, 1, 2, 3 and 4;

(ii) in the formula (VI-a), (VI-b), or (VI-c),

m is independently selected from 0, 1, 2, 3; 4 and 5;

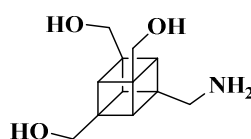
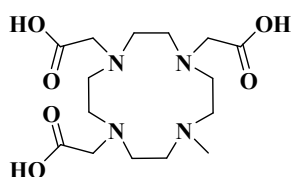
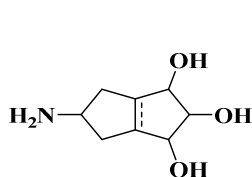
n is independently selected from 1, 2, 3; 4 and 5;

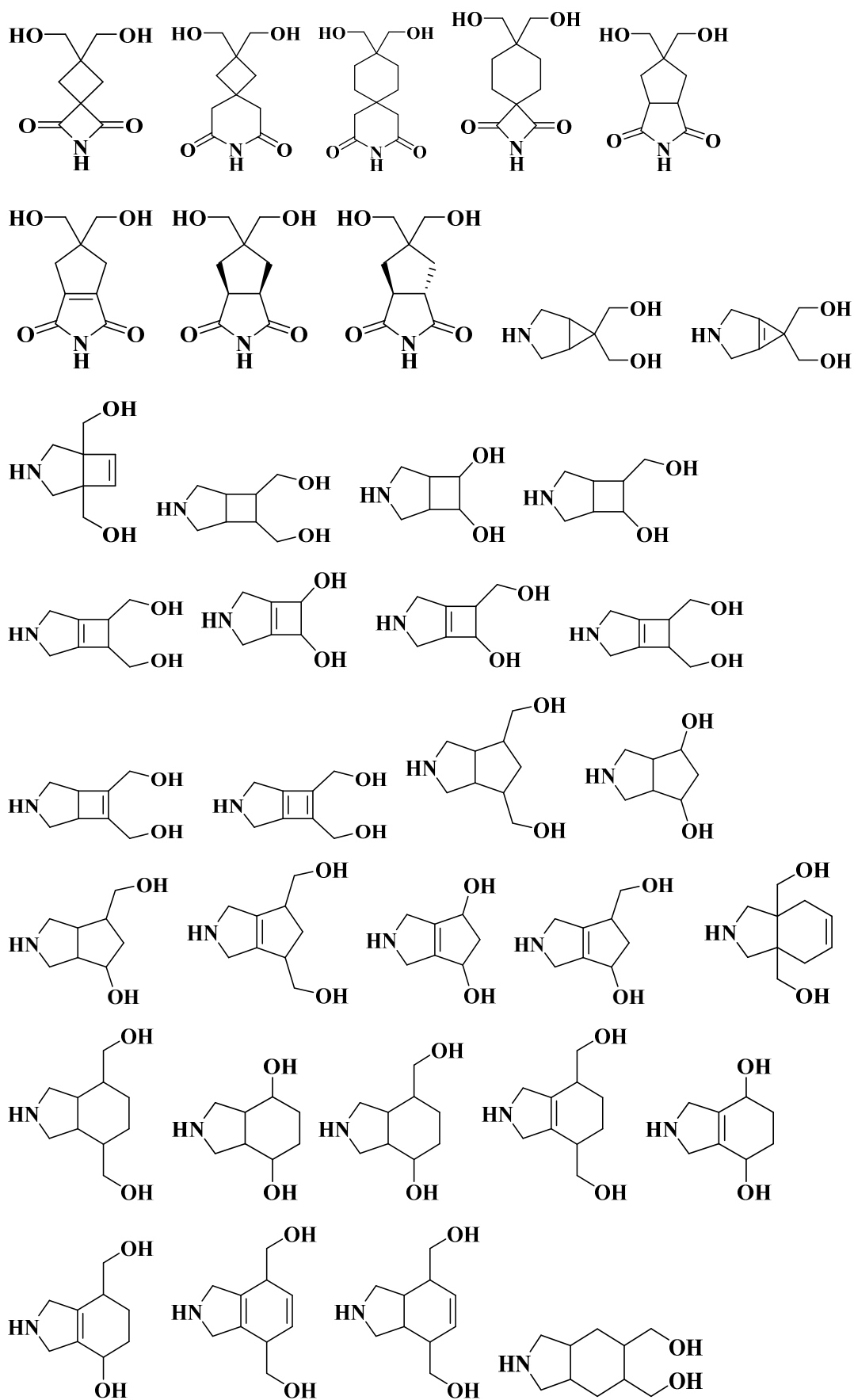
each of r , s and t is independently selected from 0, 1 and 2;

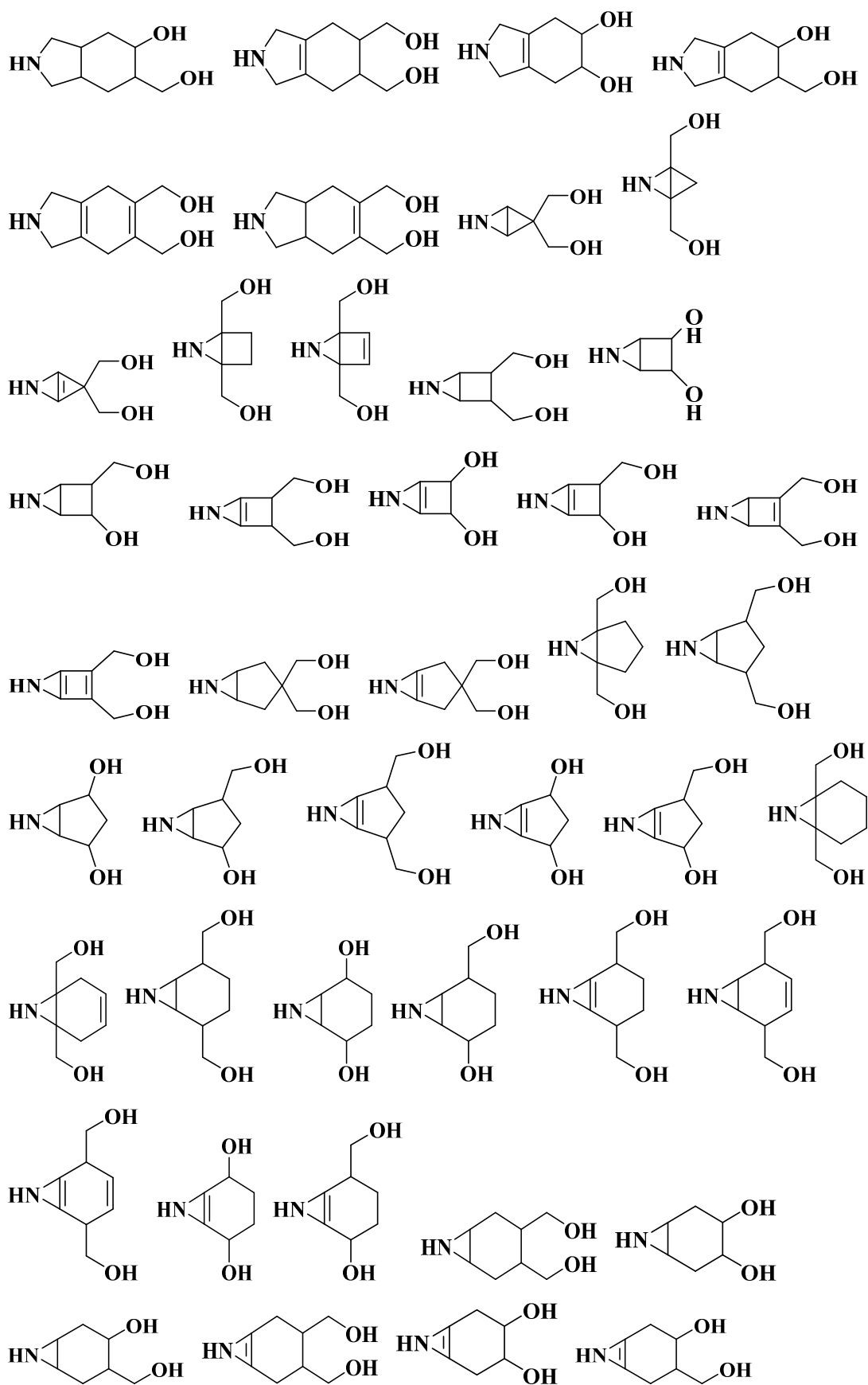
in the formula (VI-a), $m1$ and $n1$ is each independently selected from 0, 1, 2, 3 and 4,

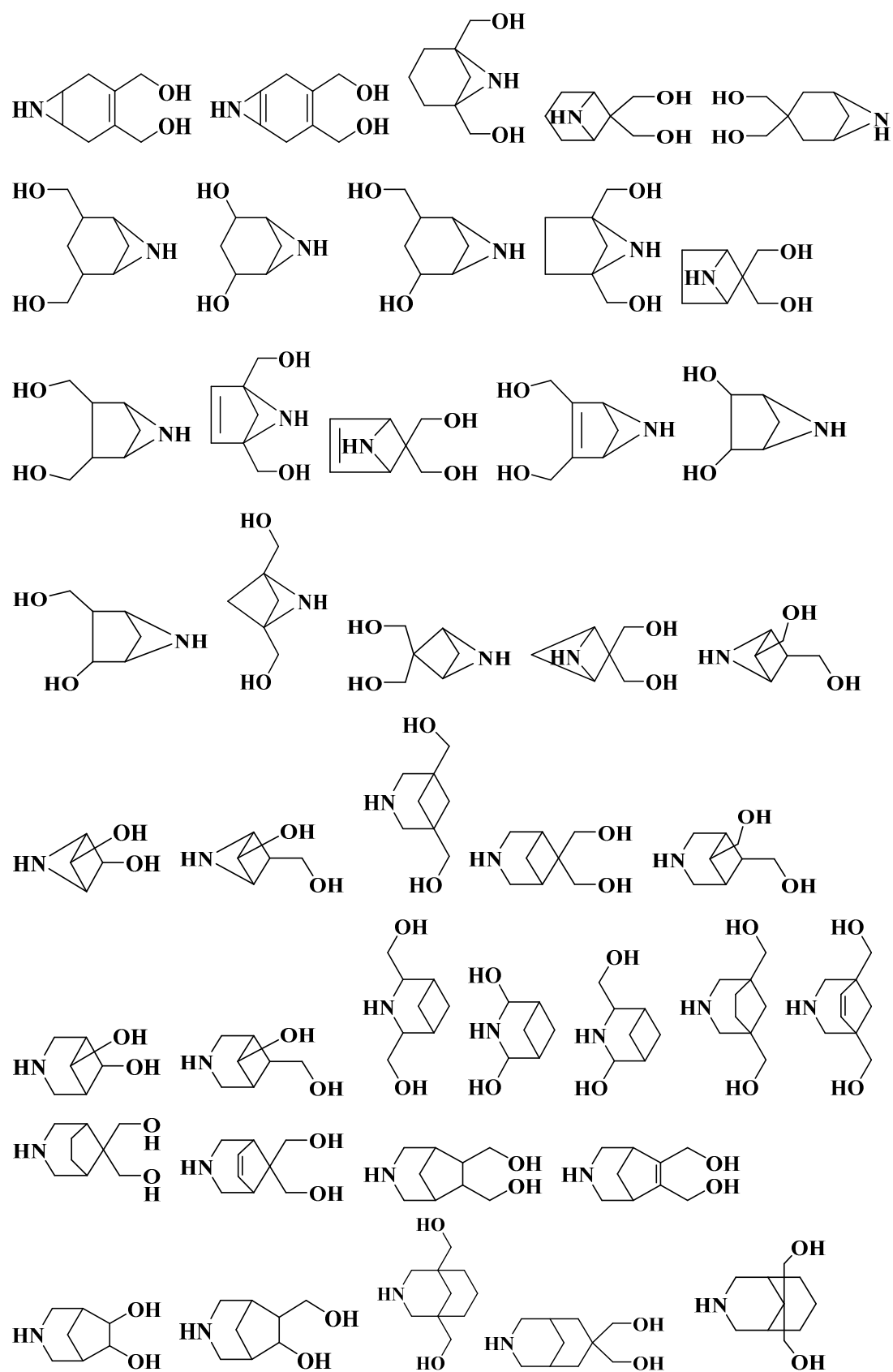
and in the formula (VI-b) or (VI-c), $m1$ is 1, $n1$ is 0, 2, 3 or 4.

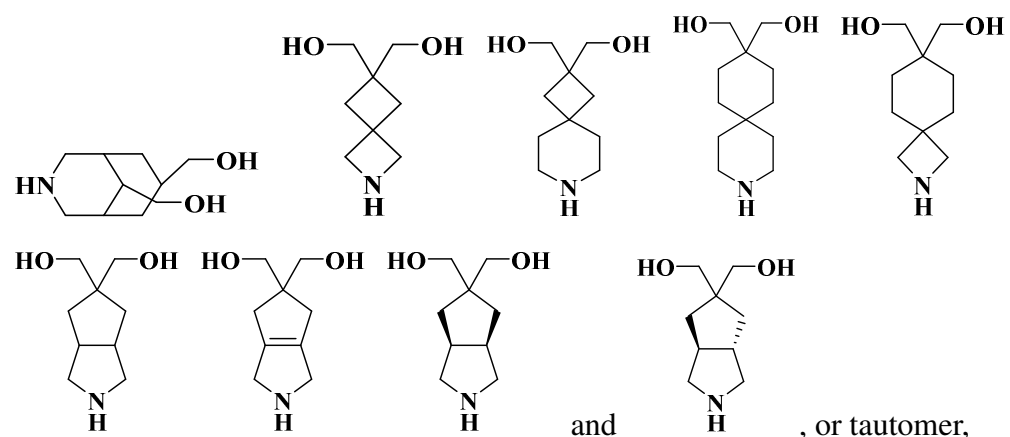
20. A compound having the following structure:











and , or tautomer,
pharmaceutically acceptable salt thereof.