IONIZABLE LIPIDOID COMPOSITIONS AND THERAPEUTIC USES THEREOF

RELATED APPLICATIONS

This application claims the benefit of priority to U.S. Provisional Patent Application serial number 63/538,946, filed September 18, 2023; U.S. Provisional Patent Application serial number 63/557,884, filed February 26, 2024; U.S. Provisional Patent Application serial number 63/654,580, filed May 31, 2024; and U.S. Provisional Patent Application serial number 63/676,004, filed July 26, 2024; the contents of each of which are incorporated herein by reference.

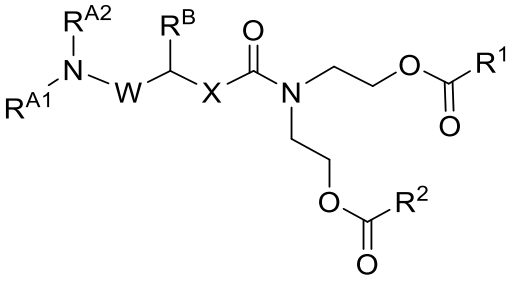
BACKGROUND

The effective targeted delivery of biologically active substances such as small molecule drugs, proteins, and nucleic acids represents a continuing medical challenge. In particular, the delivery of nucleic acids to cells is made difficult by their relative instability and low cell permeability. Thus, there exists a need to develop methods and compositions to facilitate the delivery of therapeutic and/or prophylactics, such as nucleic acids, to cells.

Lipid-containing nanoparticle compositions, liposomes, and lipoplexes can be effective transport vehicles into cells and/or intracellular compartments for biologically active substances such as small molecule drugs, proteins, and nucleic acids. Such compositions generally include one or more cationic and/or ionizable lipids, phospholipids including polyunsaturated lipids, structural lipids (e.g., sterols), and/or lipids containing polyethylene glycol (PEG lipids). There is a need to develop lipidoids useful in lipid-nanoparticle compositions that can deliver therapeutic agents, such as nucleic acid molecules, proteins, and small molecule drugs with safety, efficacy, and specificity.

SUMMARY

Provided here is a lipidoid having the structure of formula (X):



(X);

or a salt thereof;

wherein:

R^{A1} and R^{A2} are each independently H or alkyl;

or wherein R^{A1} and R^{A2}, taken together with the intervening nitrogen, form an optionally substituted heterocyclic ring;

R^B is H or alkyl;

X is a bond or $–CH_2–$;

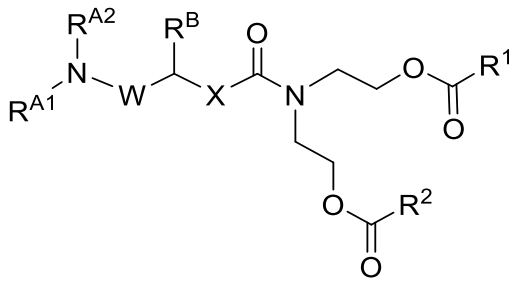
W is a bond, $–CH_2–$, or $–CH_2CH_2–$; and

R^1 and R^2 are each independently branched $(C_8\text{-}C_{30})$alkyl or linear $(C_8\text{-}C_{30})$alkenyl; wherein a branched $(C_8\text{-}C_{30})$alkyl may comprise more than one branch point, and a linear $(C_8\text{-}C_{30})$alkenyl may comprise more than one carbon-carbon double bond;

provided that

if R^B is H and R^{A1} and R^{A2} are both methyl, then R^1 and R^2 are each independently branched $(C_8\text{-}C_{30})$alkyl.

Provided herein is a lipidoid having the structure of formula (X):



(X);

or a salt thereof;

wherein:

R^{A1} and R^{A2} are each alkyl;

or wherein R^{A1} and R^{A2}, taken together with the intervening nitrogen, form an optionally substituted heterocyclic ring;

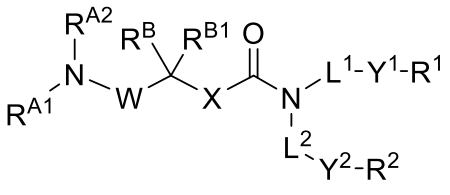
R^B is H or alkyl;

X is a bond or $–CH_2–$;

W is a bond, $–CH_2–$, or $–CH_2CH_2–$; and

R^1 and R^2 are each independently branched $(C_8\text{-}C_{30})$alkyl; wherein a branched $(C_8\text{-}C_{30})$alkyl may comprise more than one branch point.

In one aspect, provided here is a lipidoid having the structure of formula(I):



(I);

or a salt thereof;

wherein:

R^{A1} and R^{A2} are each independently H, alkyl, or hydroxyalkyl;

or wherein R^{A1} and R^{A2}, taken together with the intervening nitrogen, form an optionally substituted heterocyclic ring;

R^B and R^{B1} are each independently H, optionally substituted alkyl, alkenyl, cycloalkyl, arylalkyl, heteroarylalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, or thioalkyl;

or wherein R^B and R^{B1}, taken together with the intervening carbon, form an optionally substituted cycloalkyl or heterocyclic ring;

or R^{A1} and R^B taken together with the intervening N-CH atoms to which they are attached form an N-containing heterocyclic ring;

L^1 and L^2 are each independently $–CH_2CH_2–$, $–(CH_2)_3–$, $–(CH_2)_4–$, $–CH(CH_3)CH_2–$, or $–CH_2CH(CH_3)–$;

X is a bond, $–CH_2–$, or $–CH_2CH_2–$;

W is a bond, $–CH_2–$, or $–CH_2CH_2–$;

Y^1 and Y^2 are each independently $–O(C=O)–$, $–S(C=O)–$, or $–O(C=O)O–$; and

R^1 and R^2 are each independently linear $(C_8\text{-}C_{30})$alkyl, branched $(C_8\text{-}C_{30})$alkyl, linear $(C_8\text{-}C_{30})$alkenyl, branched $(C_8\text{-}C_{30})$alkenyl, linear $(C_8\text{-}C_{30})$alkynyl, or branched $(C_8\text{-}C_{30})$alkynyl; wherein a branched $(C_8\text{-}C_{30})$alkyl, a branched $(C_8\text{-}C_{30})$alkenyl, or a branched $(C_8\text{-}C_{30})$alkynyl may comprise more than one branch point, and a linear or branched $(C_8\text{-}C_{30})$alkenyl may comprise more than one carbon-carbon double bond, and a linear or

branched (C_8-C_{30})alkynyl may comprise more than one carbon-carbon triple bond;

provided that the compound is not:

L-Lysine-bis(O,O'-oleoyl-β-hydroxyethyl)amide;

L-Lysine-bis(O,O'-palmitoyl-β-hydroxyethyl)amide;

L-Lysine-bis(O,O'-myristoyl-β-hydroxyethyl)amide;

L-Ornithine-bis(O,O'-palmitoyl-β-hydroxyethyl)amide;

L-Ornithine-bis(O,O'-oleoyl-β-hydroxyethyl)amide;

L-Ornithine-bis(O,O'-myristoyl-β-hydroxyethyl)amide;

L-Arginine-bis(O,O'-palmitoyl-β-hydroxyethyl)amide;

L-Arginine-bis(O,O'-oleoyl-β-hydroxyethyl)amide;

L-Serine-bis(O,O'-oleoyl-β-hydroxyethyl)amide;

Glycine-bis(O,O'-palmitoyl-β-hydroxyethyl)amide;

Sarcosine-bis(O,O'-palmitoyl-β-hydroxyethyl)amide;

L-Histidine-bis(O,O'-palmitoyl-β-hydroxyethyl)amide;

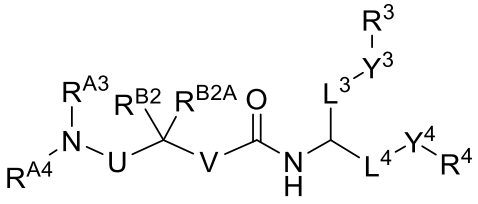
L-Glutamine-bis(O,O'-palmitoyl-β-hydroxyethyl)amide;

L-Glutamic acid-γ-N'-bis(O,O'-palmitoyl-β-hydroxyethyl)amide;

L-aspartic acid-β-N'-bis(O,O'-palmitoyl-β-hydroxyethyl)amide; or

L-aspartic acid-α-N'-bis(O,O'-palmitoyl-β-hydroxyethyl)amide.

In another aspect, provided here is a lipidoid having the structure of formula (II):



(II);

or a salt thereof;

wherein:

R^{A3} and R^{A4} are each independently H, alkyl, or hydroxyalkyl;

or wherein R^{A3} and R^{A4}, taken together with the intervening nitrogen, form an optionally substituted heterocycloalkyl ring;

R^{B2} and R^{B2A} are each independently H, optionally substituted alkyl, alkenyl, cycloalkyl, arylalkyl, heteroarylalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, or thioalkyl;

or wherein R^{B2} and R^{B2A}, taken together with the intervening carbon, form an optionally substituted cycloalkyl or heterocycloalkyl ring;

or R^{A3} and R^{B2} taken together with the intervening N-CH atoms to which they are attached form an N-containing heterocyclic ring;

L^3 and L^4 are each independently $–CH_2–$, $–CH_2CH_2–$, $–(CH_2)_3–$, $–(CH_2)_4–$, $–CH(CH_3)CH_2–$, or $–CH_2CH(CH_3)–$;

V is a bond, $–CH_2–$ or $–CH_2CH_2–$;

U is a bond, $–CH_2–$ or $–CH_2CH_2–$;

Y^3 and Y^4 are each independently $–O(C=O)–$, $–S(C=O)–$, or $–O(C=O)O–$; and

R^3 and R^4 are each independently linear (C_8-C_{30})alkyl, branched (C_8-C_{30})alkyl, linear (C_8-C_{30})alkenyl, branched (C_8-C_{30})alkenyl, linear (C_8-C_{30})alkynyl, or branched (C_8-C_{30})alkynyl; wherein a branched (C_8-C_{30})alkyl, a branched (C_8-C_{30})alkenyl, or a branched (C_8-C_{30})alkynyl may comprise more than one branch point, and a linear or branched (C_8-C_{30})alkenyl may comprise more than one carbon-carbon double bond, and a linear or branched (C_8-C_{30})alkynyl may comprise more than one carbon-carbon triple bond.

The disclosure provides nanoparticle compositions comprising a lipidoid of the disclosure.

In another aspect, the disclosure provides a nanoparticle composition, comprising a lipidoid of the disclosure, or a pharmaceutically acceptable salt thereof.

The disclosure also provides methods of delivering a therapeutic agent, comprising administering to a subject in need thereof an effective amount of a nanoparticle composition of the disclosure, wherein the nanoparticle composition comprises a therapeutic agent.

The disclosure also provides methods of vaccination, comprising administering to a subject in need thereof an effective amount of a nanoparticle composition of the disclosure, wherein the nanoparticle composition comprises an antigen.

Also provided herein are pharmaceutical compositions, comprising a nanoparticle composition of the disclosure, and a pharmaceutically acceptable carrier.

BRIEF DESCRIPTION OF THE DRAWINGS

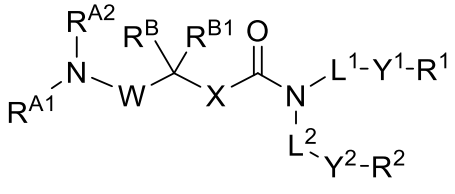
Figure 1 shows the *in vivo* LNP potency assessment by readout of hEPO mRNA expression for Series 100 lipids of the invention.

Figure 2 shows the *in vitro* LNP potency assessment by cellular EGFP mRNA expression with compositional modifications on Series 100 and Series 300 lipids.

CLAIMS

We claim:

1. A lipidoid having the structure of formula (I):



(I);

or a salt thereof;

wherein:

R^{A1} and R^{A2} are each independently H, alkyl, or hydroxyalkyl;

or wherein R^{A1} and R^{A2}, taken together with the intervening nitrogen, form an optionally substituted heterocyclic ring;

R^{B} and R^{B1} are each independently H, optionally substituted alkyl, alkenyl, cycloalkyl, arylalkyl, heteroarylalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, or thioalkyl;

or wherein R^{B} and R^{B1}, taken together with the intervening carbon, form an optionally substituted cycloalkyl or heterocyclic ring;

or R^{A1} and R^{B} taken together with the intervening N-CH atoms to which they are attached form an N-containing heterocyclic ring;

L^1 and L^2 are each independently $–CH_2CH_2–$, $–(CH_2)_3–$, $–(CH_2)_4–$, $–CH(CH_3)CH_2–$, or $–CH_2CH(CH_3)–$;

X is a bond, $–CH_2–$, or $–CH_2CH_2–$;

W is a bond, $–CH_2–$, or $–CH_2CH_2–$;

Y^1 and Y^2 are each independently –O(C=O)–, –S(C=O)–, or –O(C=O)O–; and

R^1 and R^2 are each independently linear $(C_8\text{-}C_{30})$alkyl, branched $(C_8\text{-}C_{30})$alkyl, linear $(C_8\text{-}C_{30})$alkenyl, branched $(C_8\text{-}C_{30})$alkenyl, linear $(C_8\text{-}C_{30})$alkynyl, or branched $(C_8\text{-}C_{30})$alkynyl; wherein a branched $(C_8\text{-}C_{30})$alkyl, a branched $(C_8\text{-}C_{30})$alkenyl, or a branched $(C_8\text{-}C_{30})$alkynyl may comprise more than one branch point, and a linear or branched $(C_8\text{-}C_{30})$alkenyl may comprise more than one carbon-carbon double bond, and a linear or branched $(C_8\text{-}C_{30})$alkynyl may comprise more than one carbon-carbon triple bond;

provided that the compound is not:

L-Lysine-bis(O,O'-oleoyl-β-hydroxyethyl)amide;
L-Lysine-bis(O,O'-palmitoyl-β-hydroxyethyl)amide;
L-Lysine-bis(O,O'-myristoyl-β-hydroxyethyl)amide;
L-Ornithine-bis(O,O'-palmitoyl-β-hydroxyethyl)amide;
L-Ornithine-bis(O,O'-oleoyl-β-hydroxyethyl)amide;
L-Ornithine-bis(O,O'-myristoyl-β-hydroxyethyl)amide;
L-Arginine-bis(O,O'-palmitoyl-β-hydroxyethyl)amide;
L-Arginine-bis(O,O'-oleoyl-β-hydroxyethyl)amide;
L-Serine-bis(O,O'-oleoyl-β-hydroxyethyl)amide;
Glycine-bis(O,O'-palmitoyl-β-hydroxyethyl)amide;
Sarcosine-bis(O,O'-palmitoyl-β-hydroxyethyl)amide;
L-Histidine-bis(O,O'-palmitoyl-β-hydroxyethyl)amide;
L-Glutamine-bis(O,O'-palmitoyl-β-hydroxyethyl)amide;
L-Glutamic acid-γ-N'-bis(O,O'-palmitoyl-β-hydroxyethyl)amide;
L-aspartic acid-β-N'-bis(O,O'-palmitoyl-β-hydroxyethyl)amide; or
L-aspartic acid-α-N'-bis(O,O'-palmitoyl-β-hydroxyethyl)amide.

2. The lipidoid of claim 1, wherein:

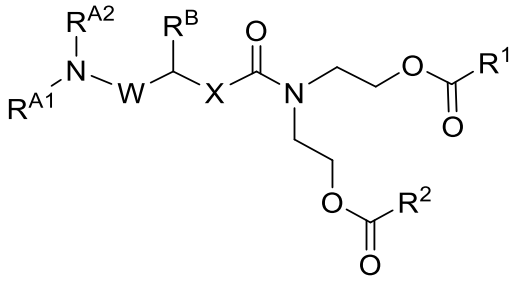
(i) R^{A1} and R^{A2} are each independently selected from H, methyl, ethyl, propyl, and isobutyl;

(ii) R^{A1} and R^{A2} are taken together with the intervening nitrogen, to form an optionally substituted 5-membered or 6-membered heterocyclic ring; or

(iii) R^{B} is alkyl, preferably methyl.

3. The lipidoid of claim 1 or 2, wherein R^1 and R^2 are each independently branched (C_{12}-C_{20})alkyl.

4. The lipidoid of claim 1, having the structure of formula (Xa):



(Xa);

or a salt thereof;

wherein:

R^{A1} and R^{A2} are each alkyl;

or wherein R^{A1} and R^{A2}, taken together with the intervening nitrogen, form an optionally substituted heterocyclic ring;

R^B is H or alkyl;

X is a bond or $–CH_2–$;

W is a bond, $–CH_2–$, or $–CH_2CH_2–$; and

R^1 and R^2 are each independently branched $(C_8\text{-}C_{30})$alkyl; wherein a branched $(C_8\text{-}C_{30})$alkyl may comprise more than one branch point.

5. The lipidoid of claim 4, wherein:

(i) R^{A1} and R^{A2} are each independently selected from methyl, ethyl, propyl, and isobutyl;

(ii) R^{A1} and R^{A2} are taken together with the intervening nitrogen, form an optionally substituted 5-membered or 6-membered heterocyclic ring;

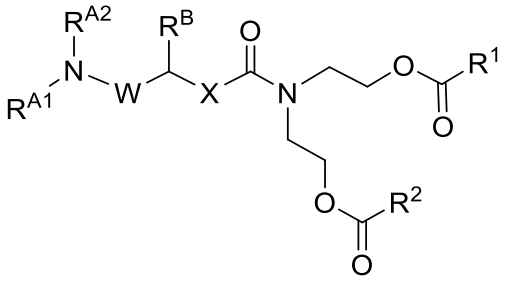
(iii) R^B is alkyl, preferably methyl;

(iv) R^1 and R^2 are each independently branched $(C_{12}\text{-}C_{20})$alkyl;

(v) when X is a bond, then W is $–CH_2–$ or $–CH_2CH_2–$; and when W is a bond, then X is $–CH_2–$; or

(vi) when X is a bond, then W is $–CH_2–$; and when W is a bond, then X is $–CH_2–$.

6. The lipidoid of claim 1, having the structure of formula (X):



(X);

or a salt thereof;

wherein:

R^{A1} and R^{A2} are each independently H or alkyl;

or wherein R^{A1} and R^{A2}, taken together with the intervening nitrogen, form an optionally substituted heterocyclic ring;

R^B is H or alkyl;

X is a bond or $–CH_2–$;

W is a bond, $–CH_2–$, or $–CH_2CH_2–$; and

R^1 and R^2 are each independently branched $(C_8\text{-}C_{30})$alkyl or linear $(C_8\text{-}C_{30})$alkenyl; wherein a branched $(C_8\text{-}C_{30})$alkyl may comprise more than one branch point, and a linear $(C_8\text{-}C_{30})$alkenyl may comprise more than one carbon-carbon double bond;

provided that

if R^B is H and R^{A1} and R^{A2} are both methyl, then R^1 and R^2 are each independently branched $(C_8\text{-}C_{30})$alkyl.

7. The lipidoid of claim 1, wherein:

(i) when R^B and R^{B1} are both H and R^{A1} and R^{A2} are both methyl, then R^1 and R^2 are each independently branched $(C_8\text{-}C_{30})$alkyl;

(ii) R^{A1} and R^{A2} are each independently selected from H, methyl, ethyl, propyl, and isobutyl; or

(iii) R^{A1} and R^{A2} are taken together with the intervening nitrogen, form an optionally substituted 5-membered or 6-membered heterocyclic ring;

(iv) R^{A1} is hydroxyalkyl; and R^{A2} is H; or R^{A1} is $–CH_2CH_2OH$;

(v) R^B is H, optionally substituted alkyl, arylalkyl, heteroarylalkyl, hydroxyalkyl, or aminoalkyl;

(vi) R^B is H, methyl, $–CH_2Ph$, $–CH_2OH$, $–(CH_2)_4NH_2$, or $–CH_2$(imidazolyl), preferably methyl

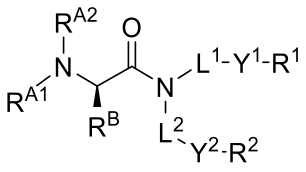
(vii) R^{B1} is hydrogen;

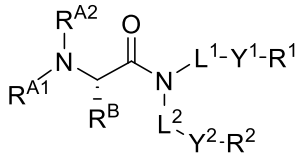
(viii) R^{B} or R^{B1} is alkyl, preferably methyl;

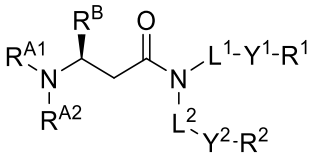
(ix) at least one of X and W is a bond; or

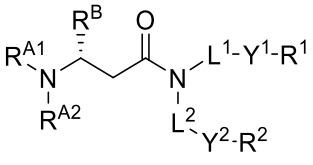
(x) X and W are both a bond.

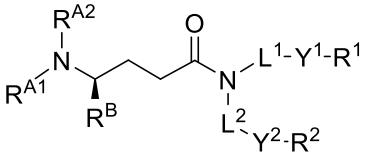
8. The lipidoid of claim 1, having the structure of formula (Ia), (Ib), (Ic), (Id), (Ie), (If), or (Ig):

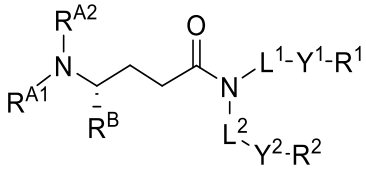

(Ia);

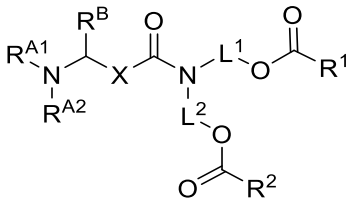

(Ib);


(Ic);


(Id);


(Ie);

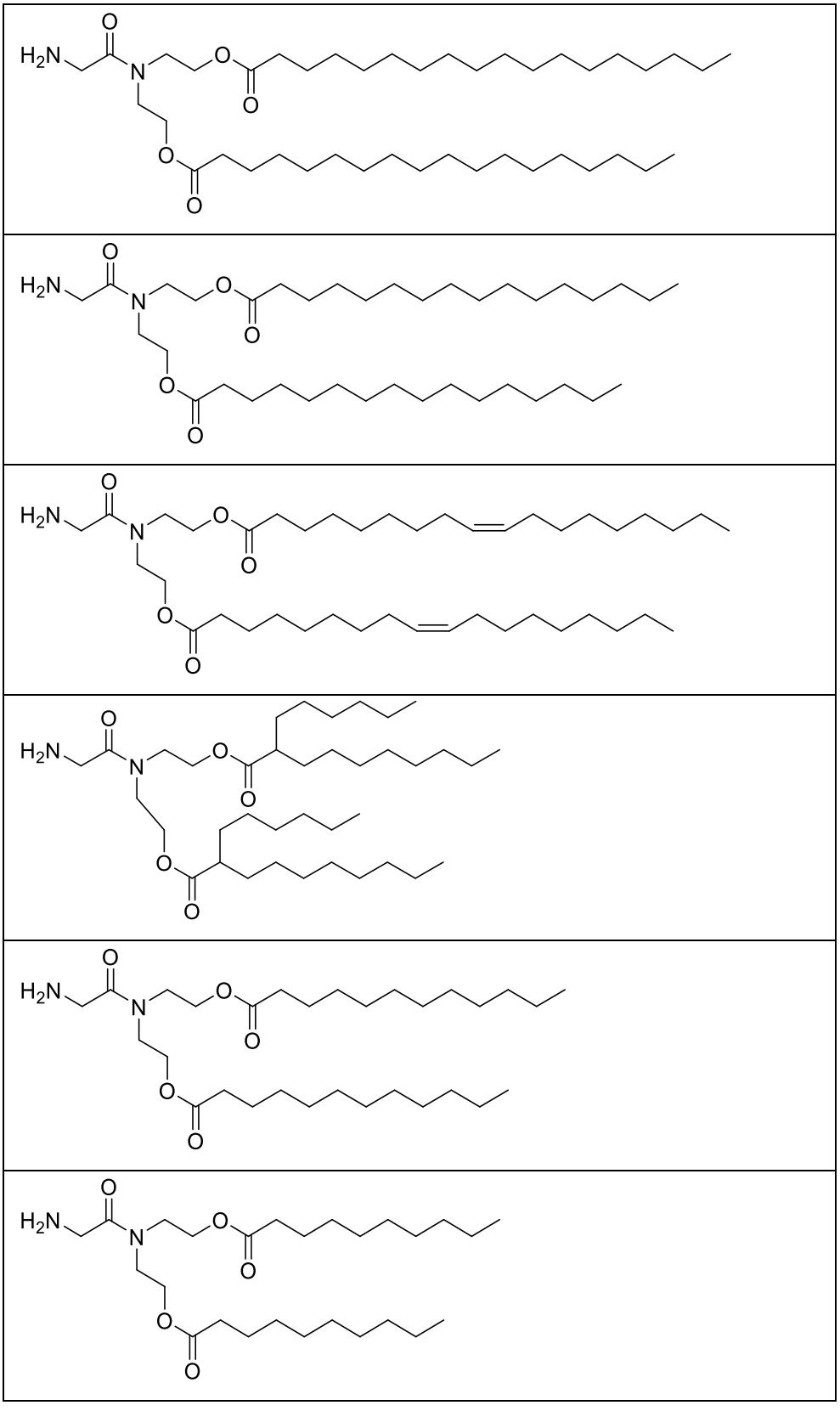

(If);

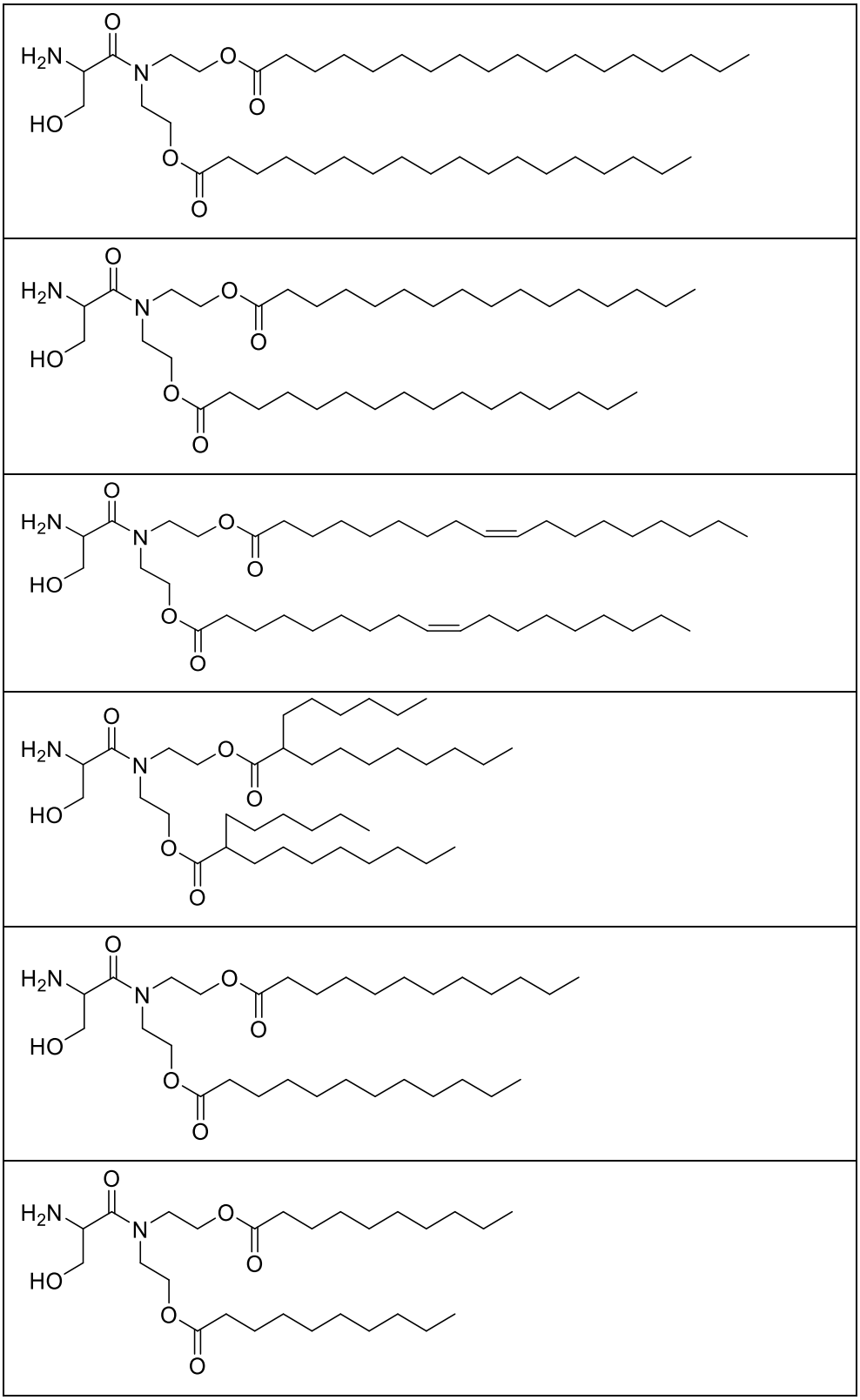

(Ig);

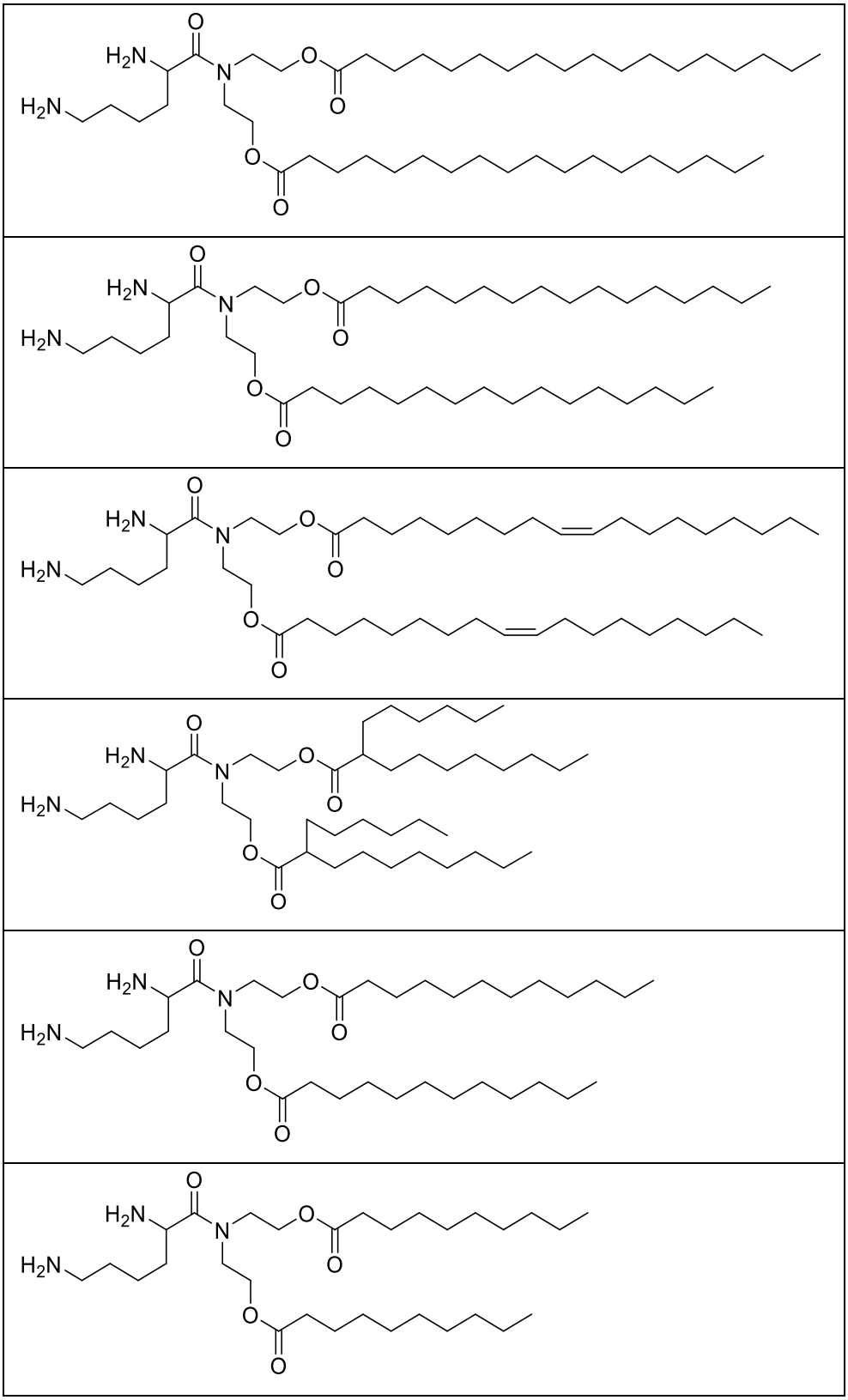
or a salt thereof;

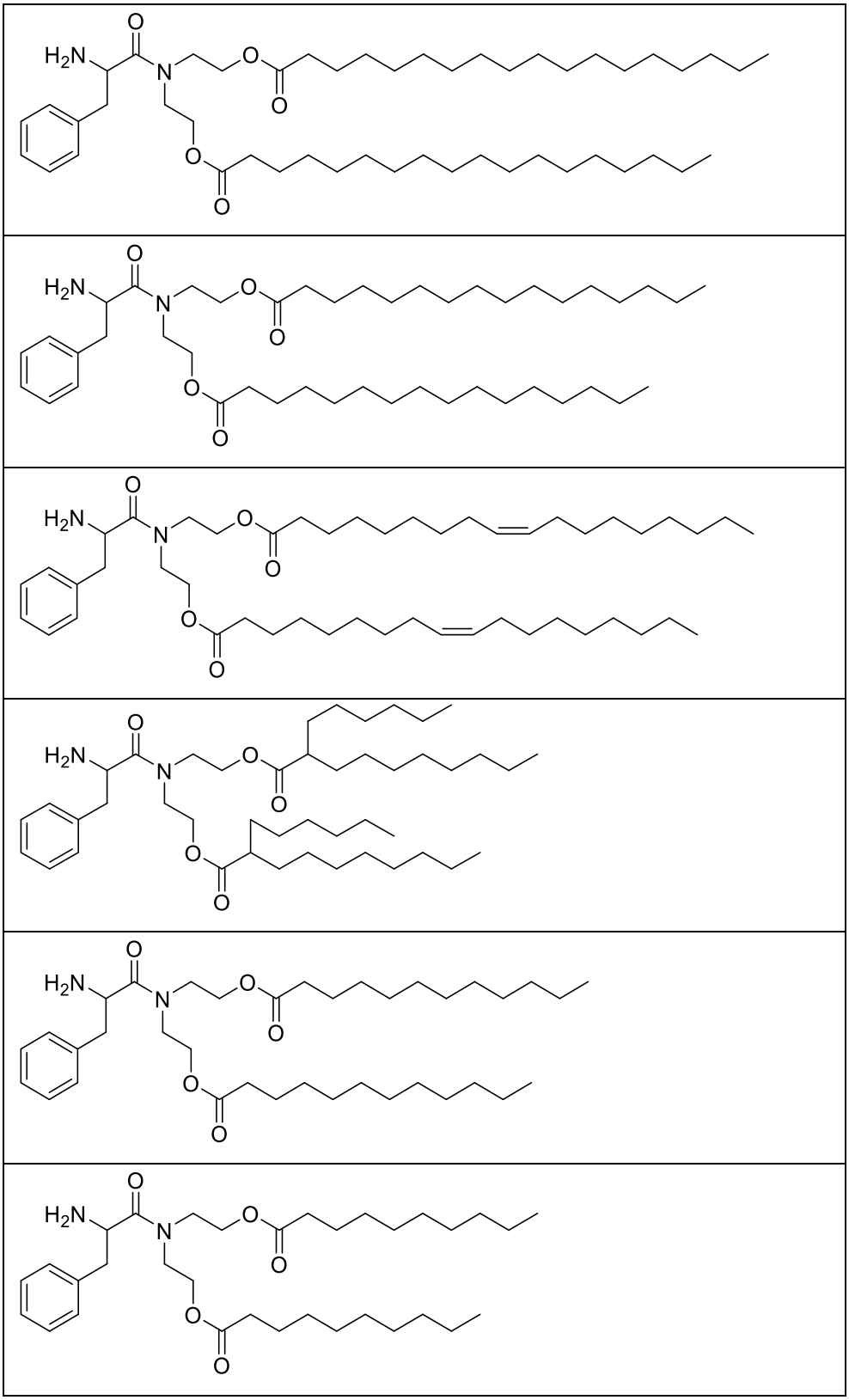
wherein the lipidoid has the absolute stereochemistry shown.

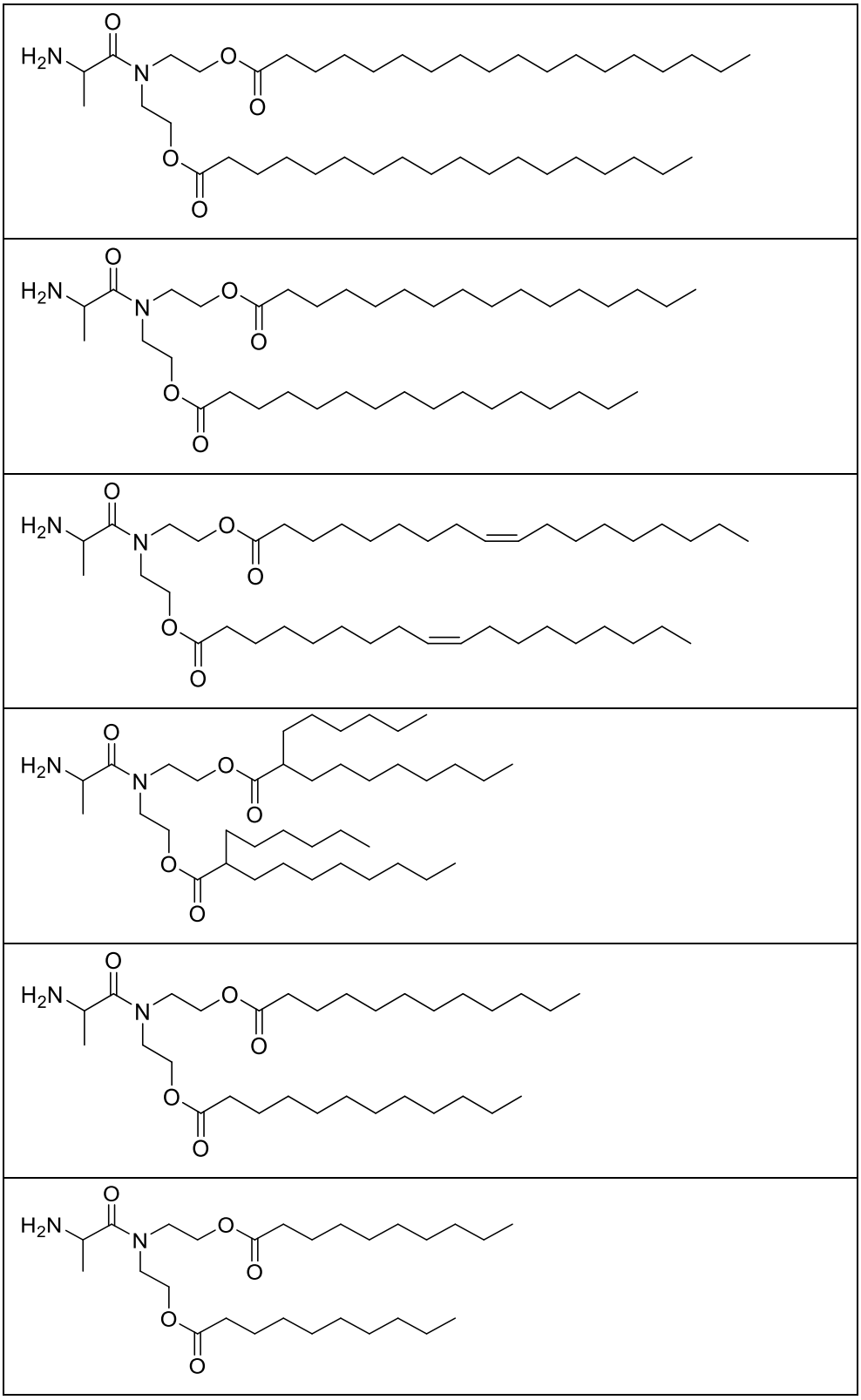
9. The lipidoid of claim 1, selected from the following table:

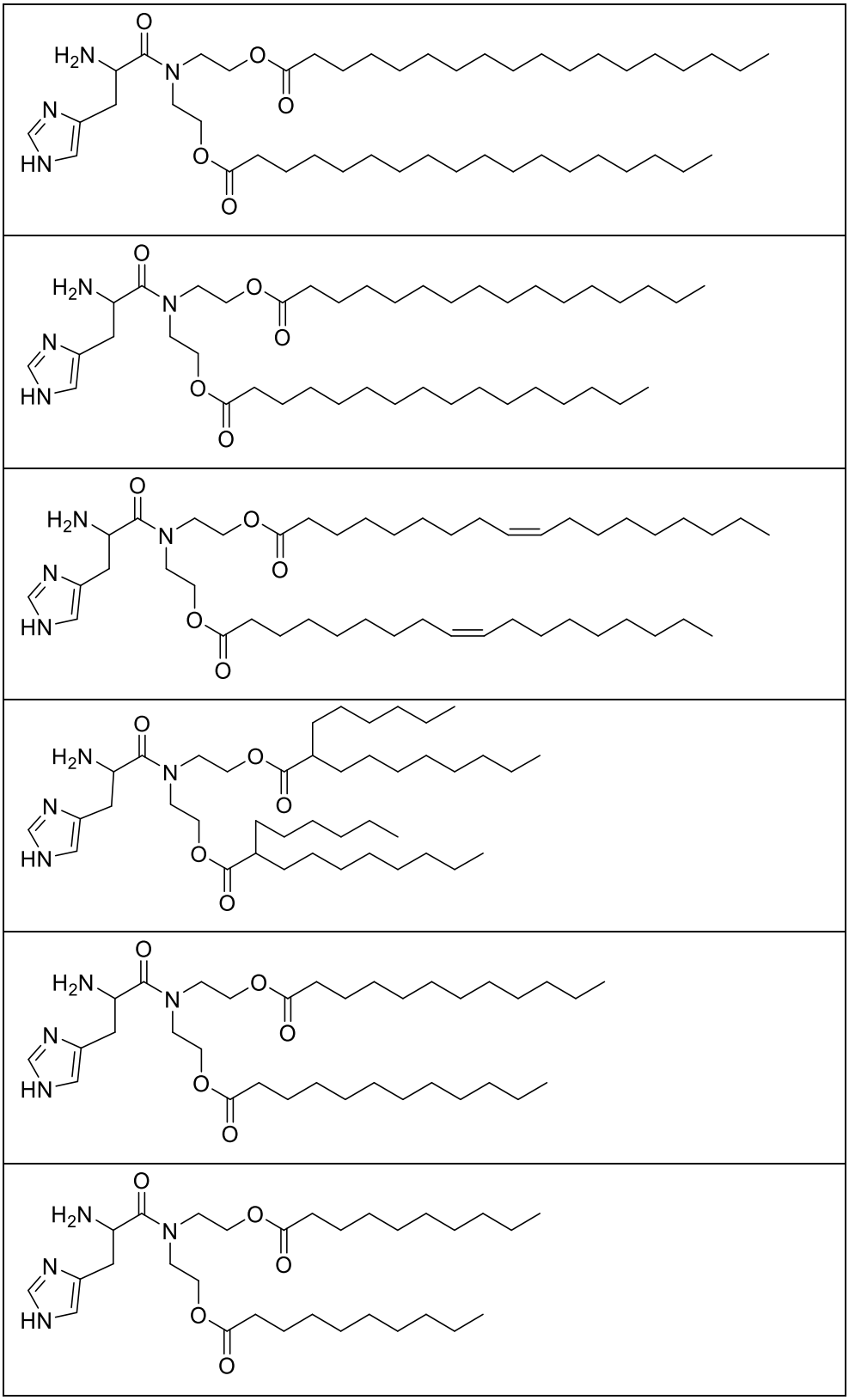


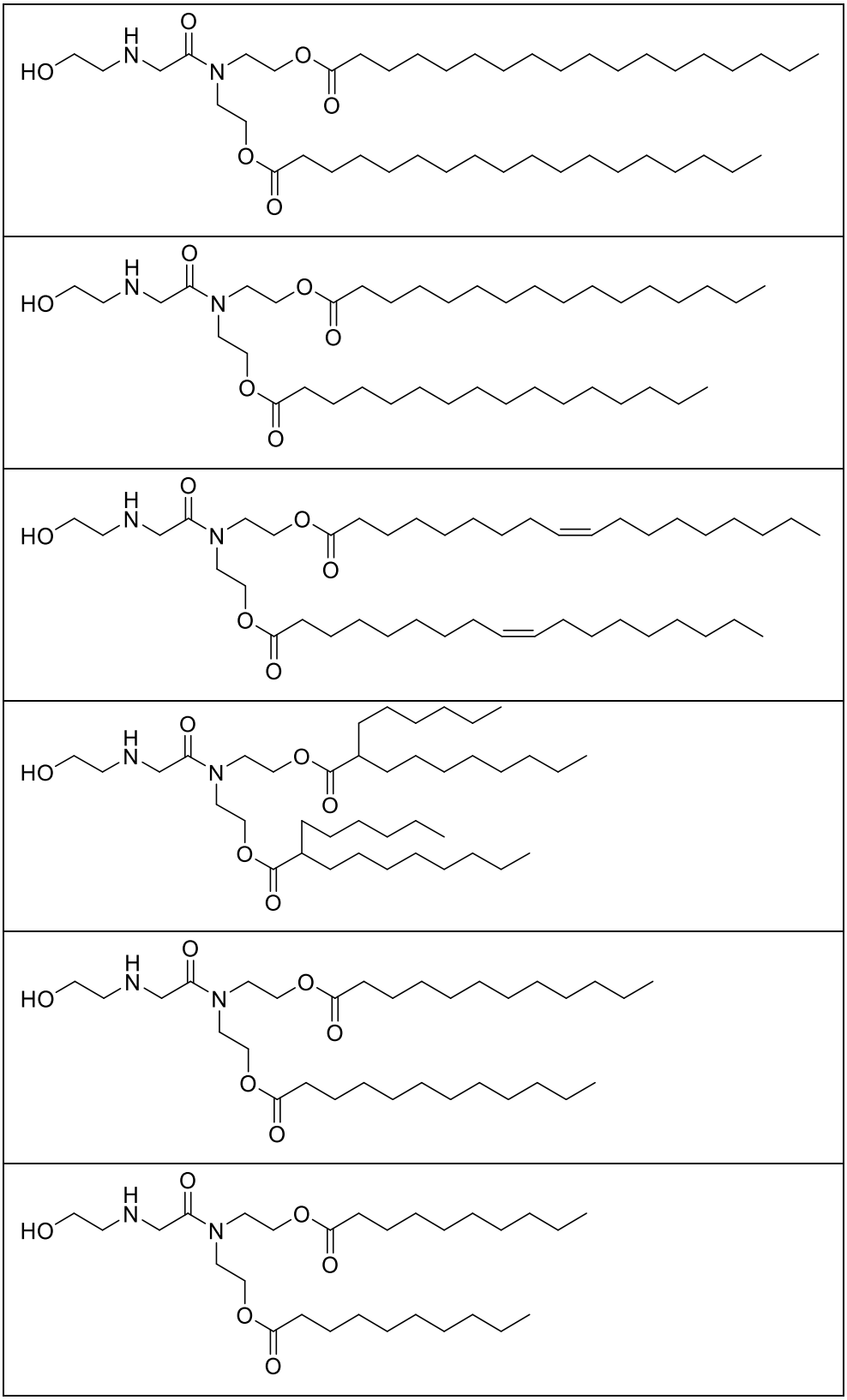


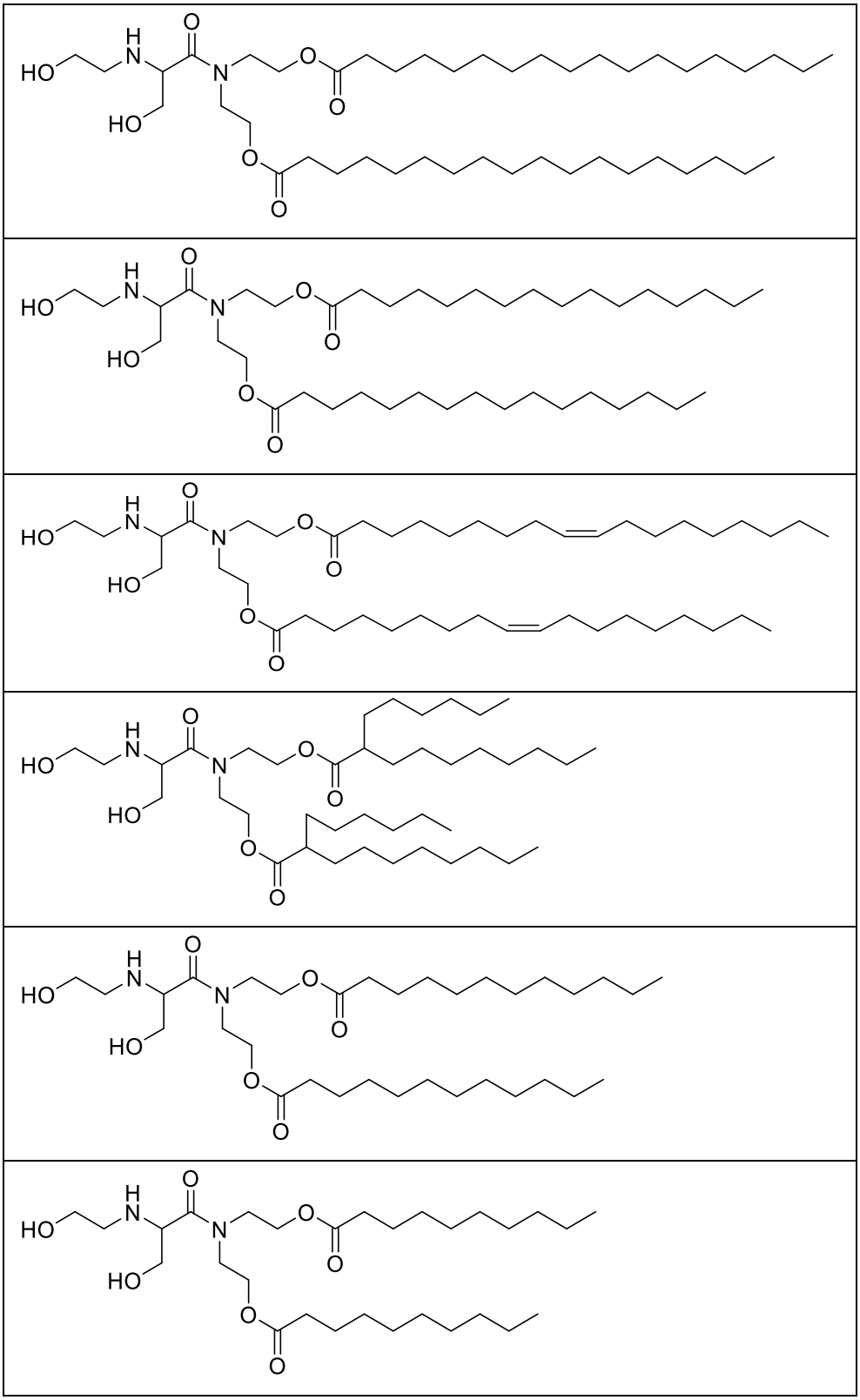


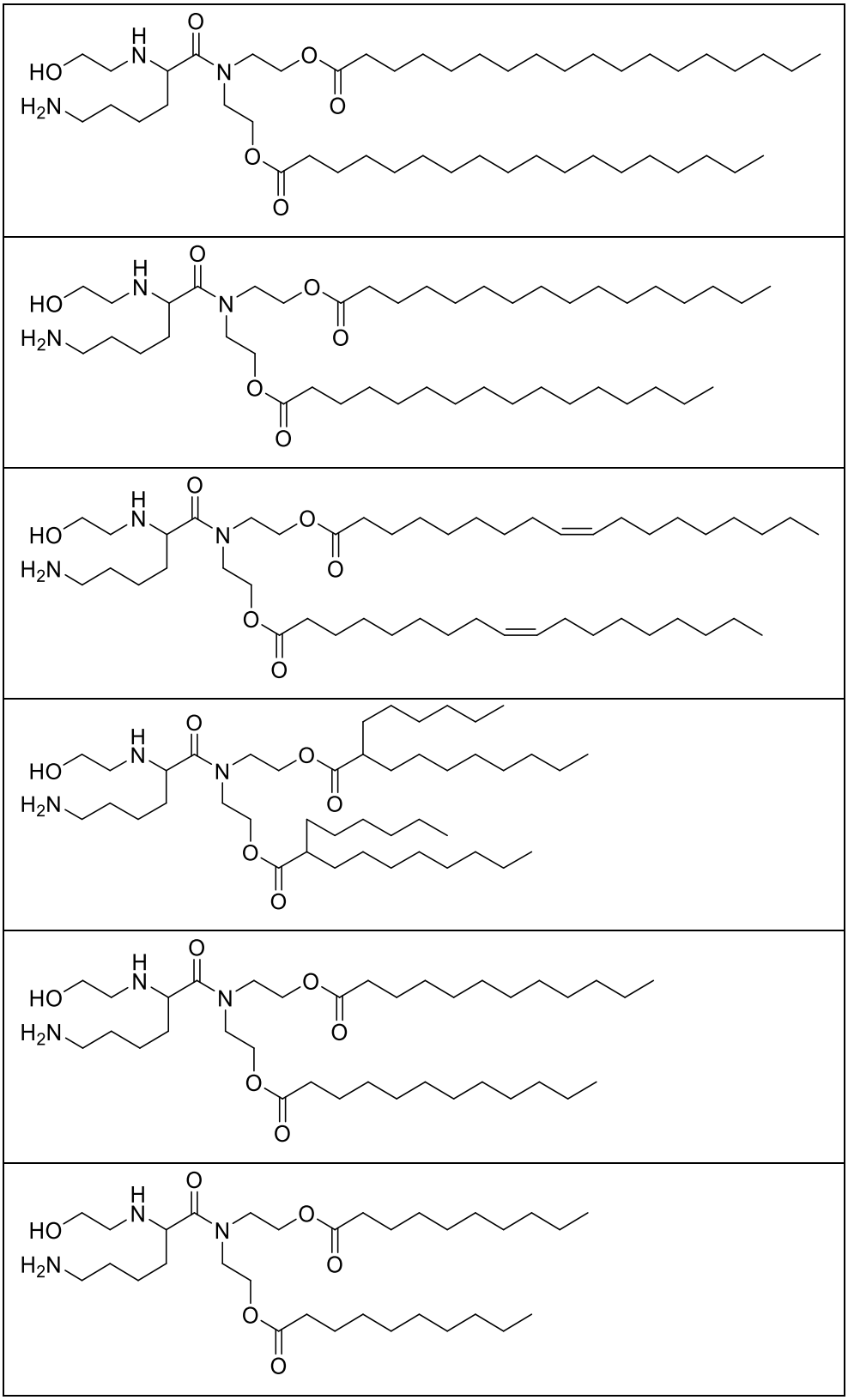


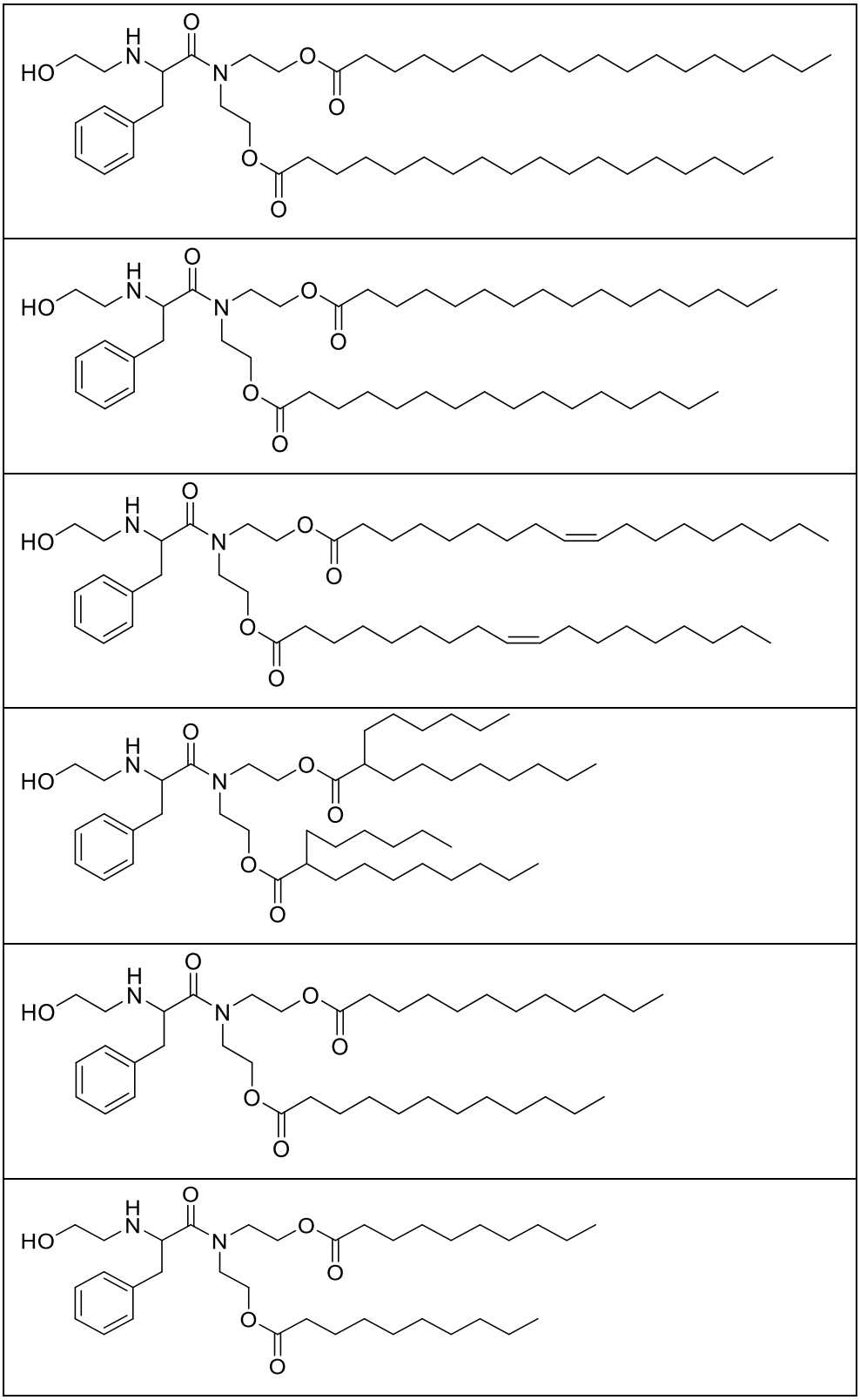


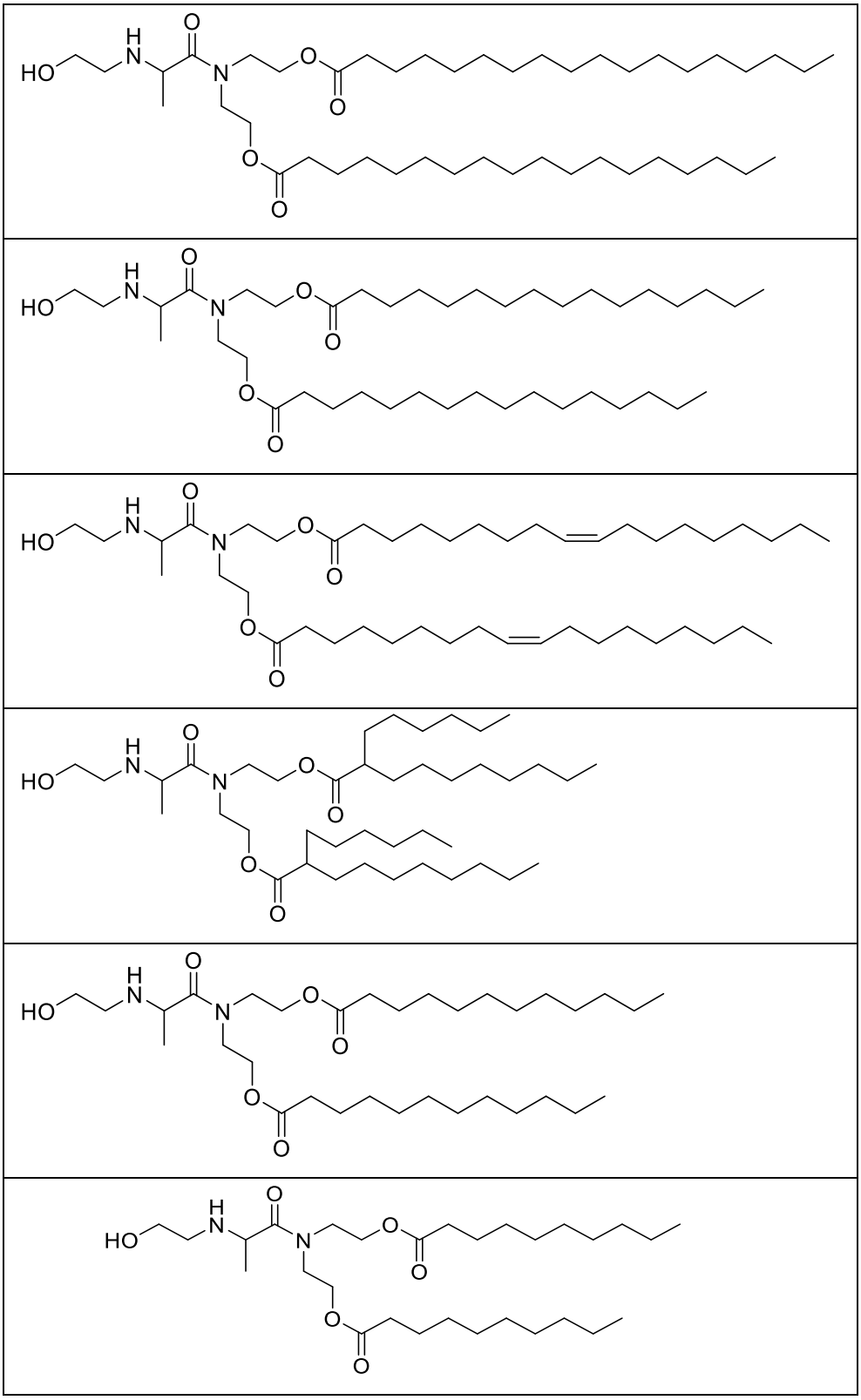


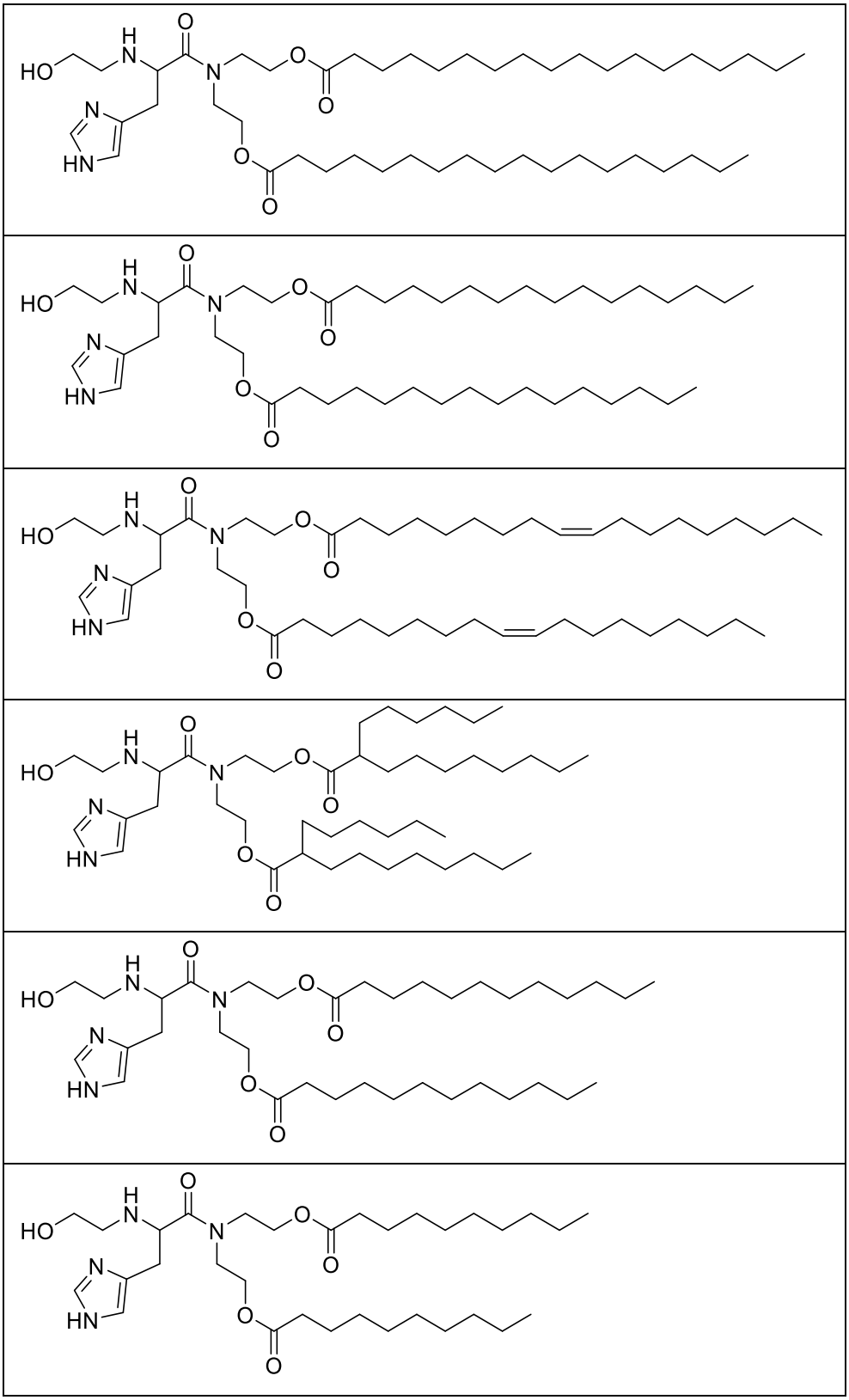


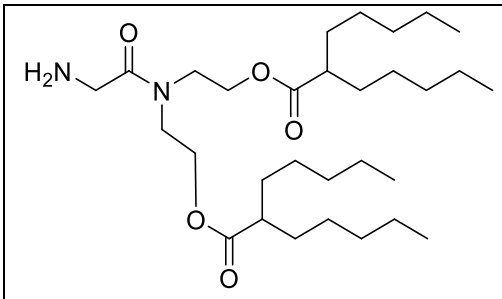
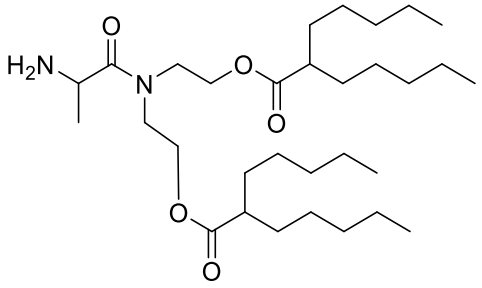
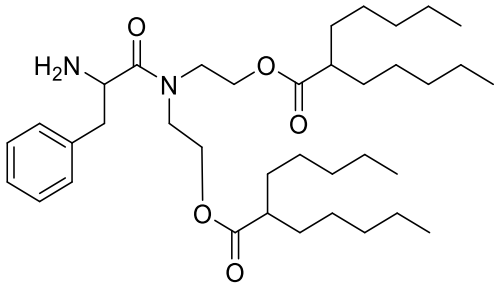
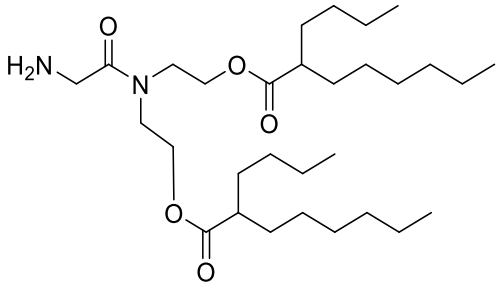
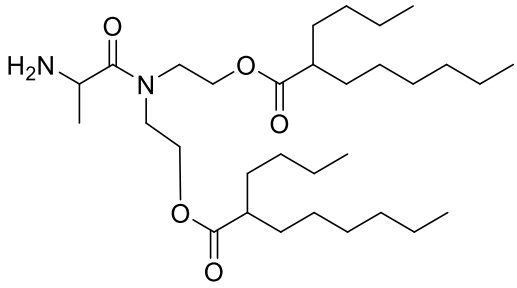
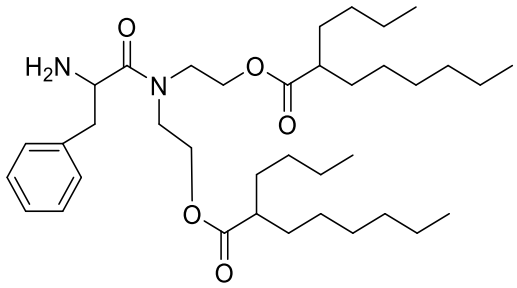


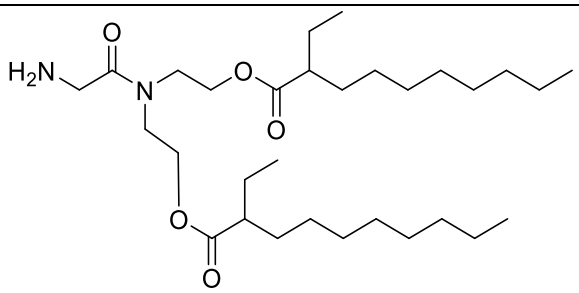


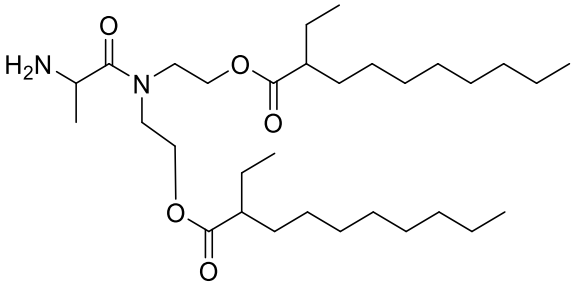


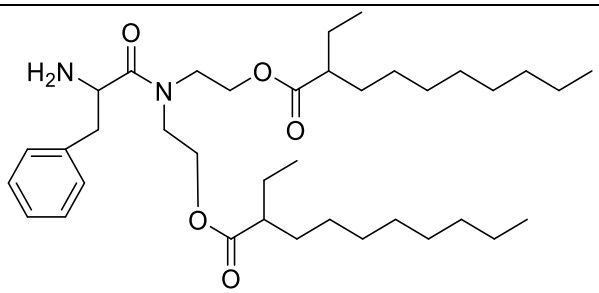


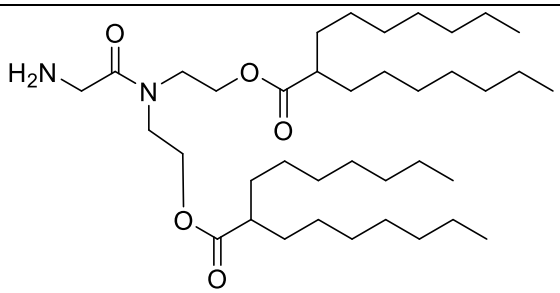


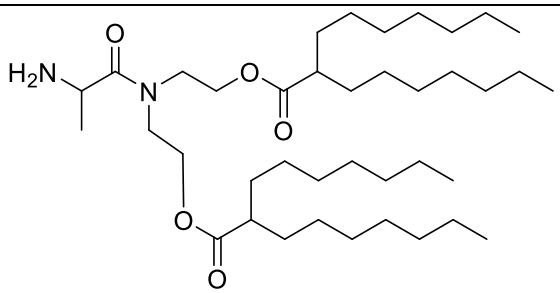







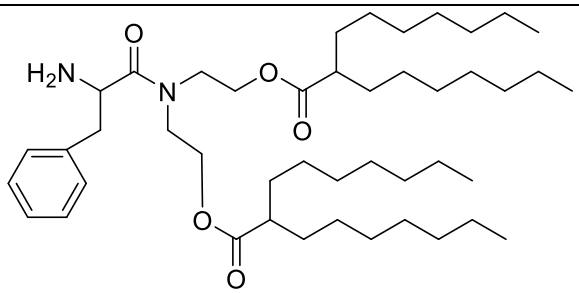


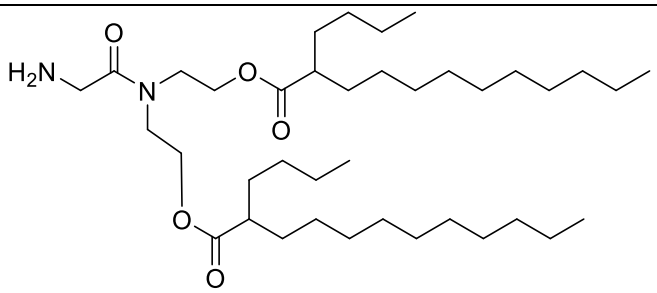


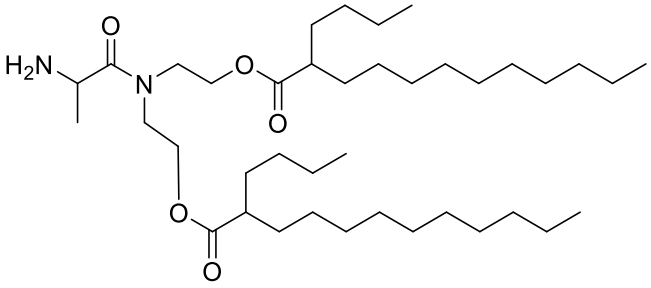


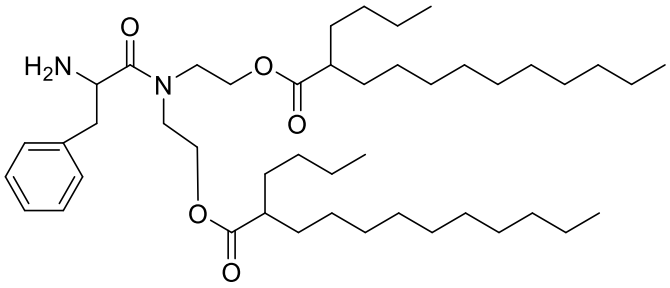


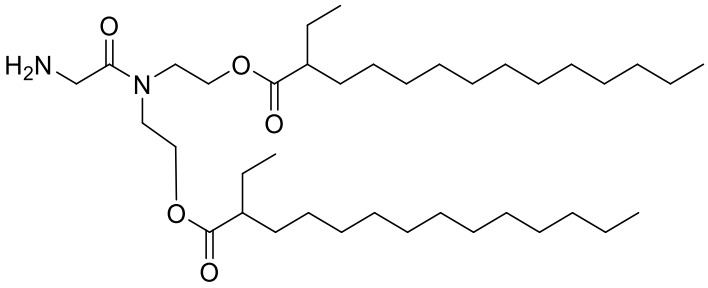


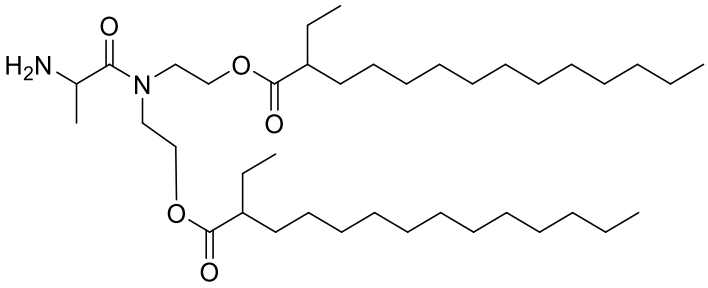


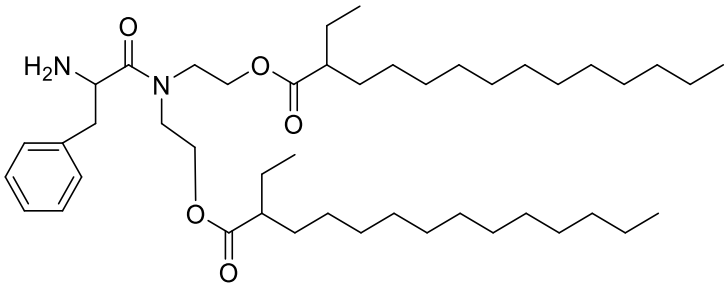


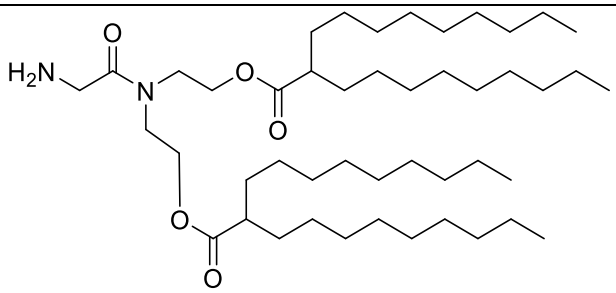


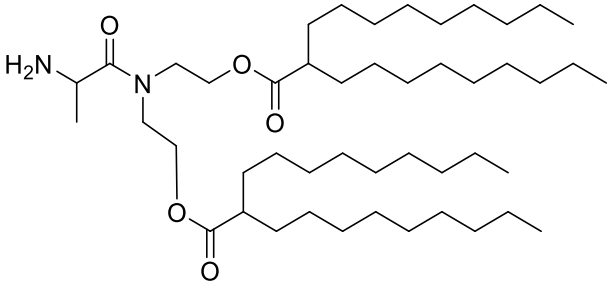


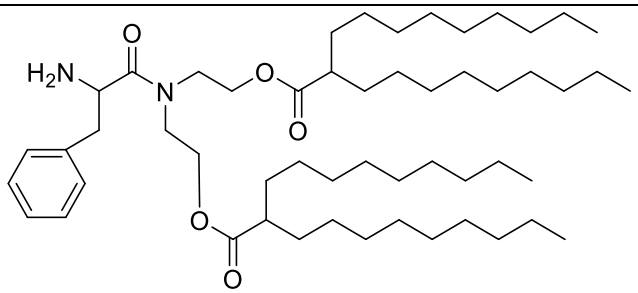


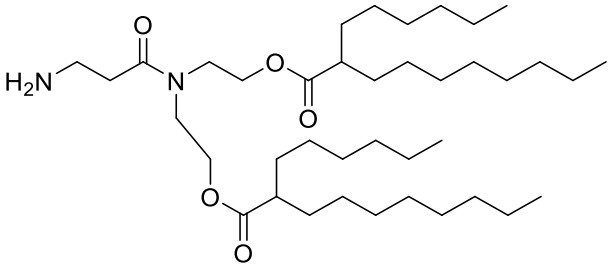


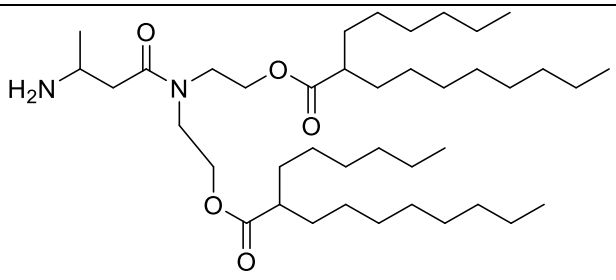


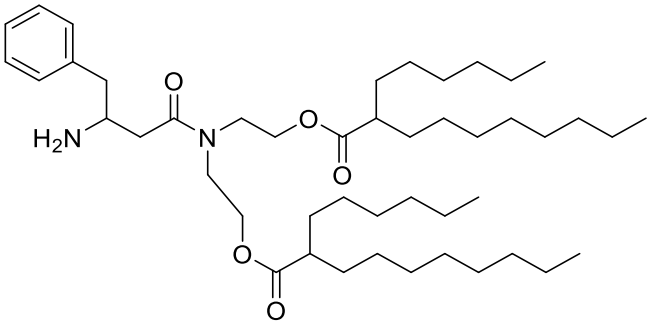


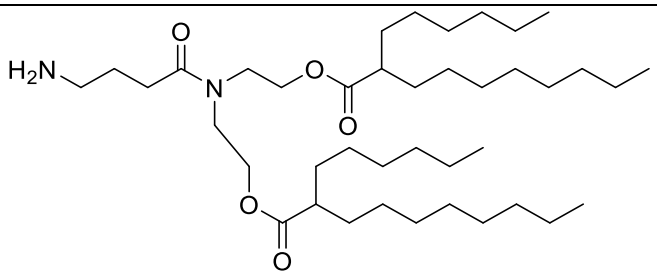


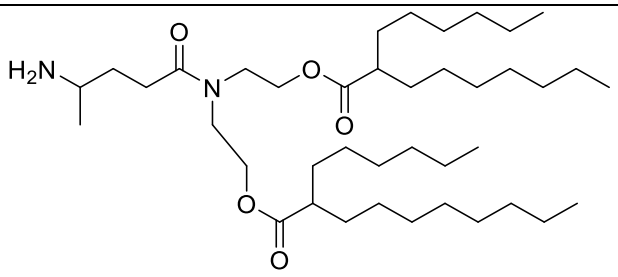


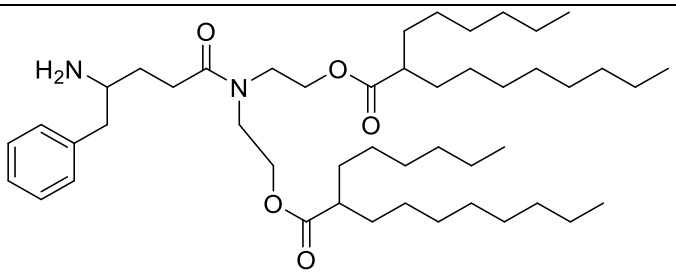


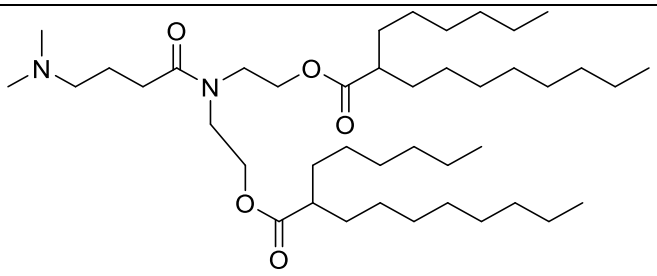


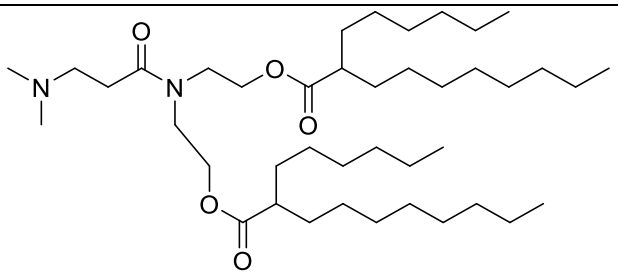


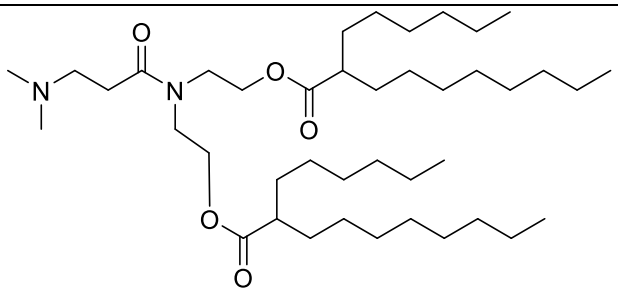


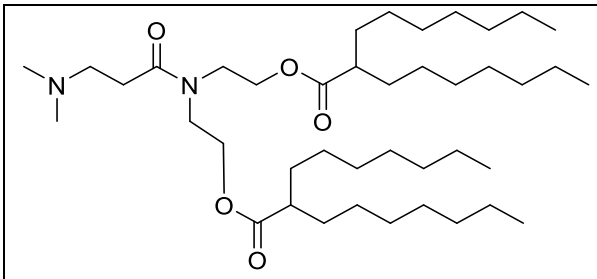
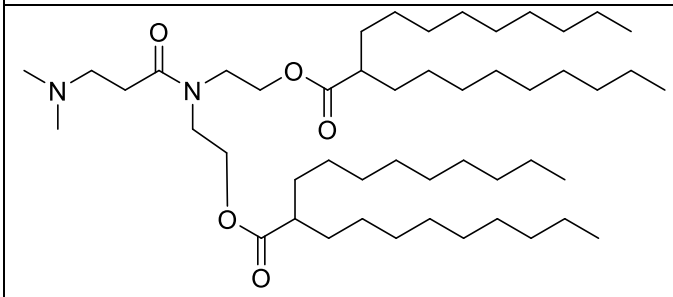
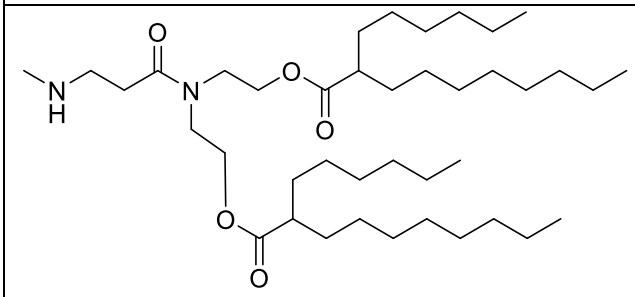
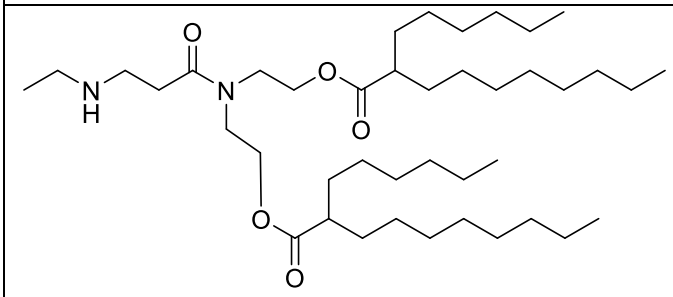
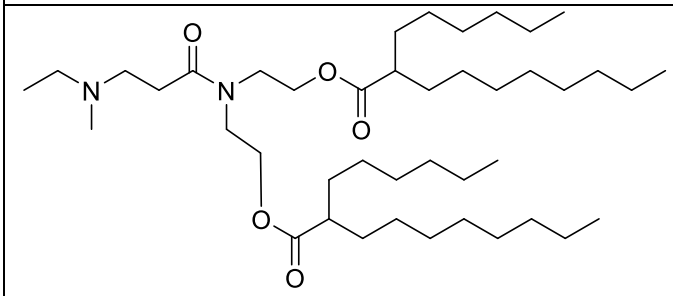
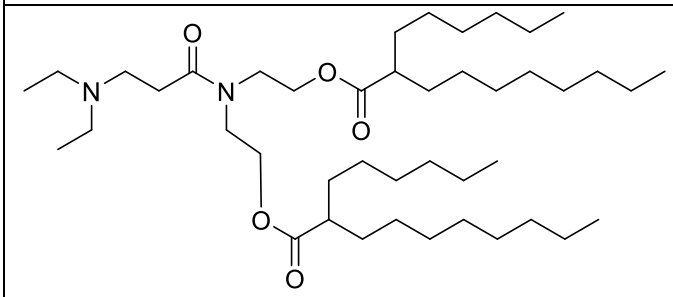


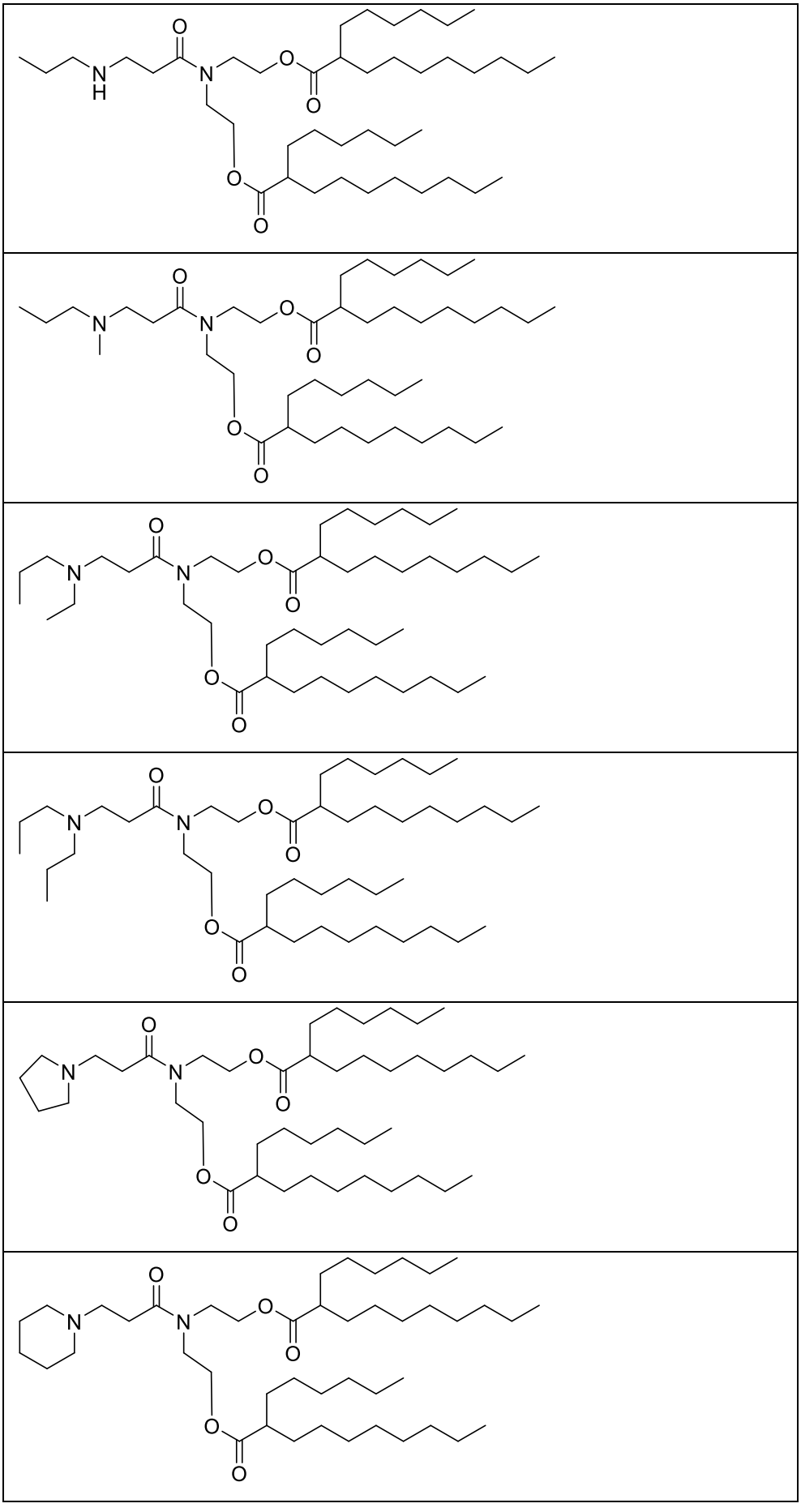


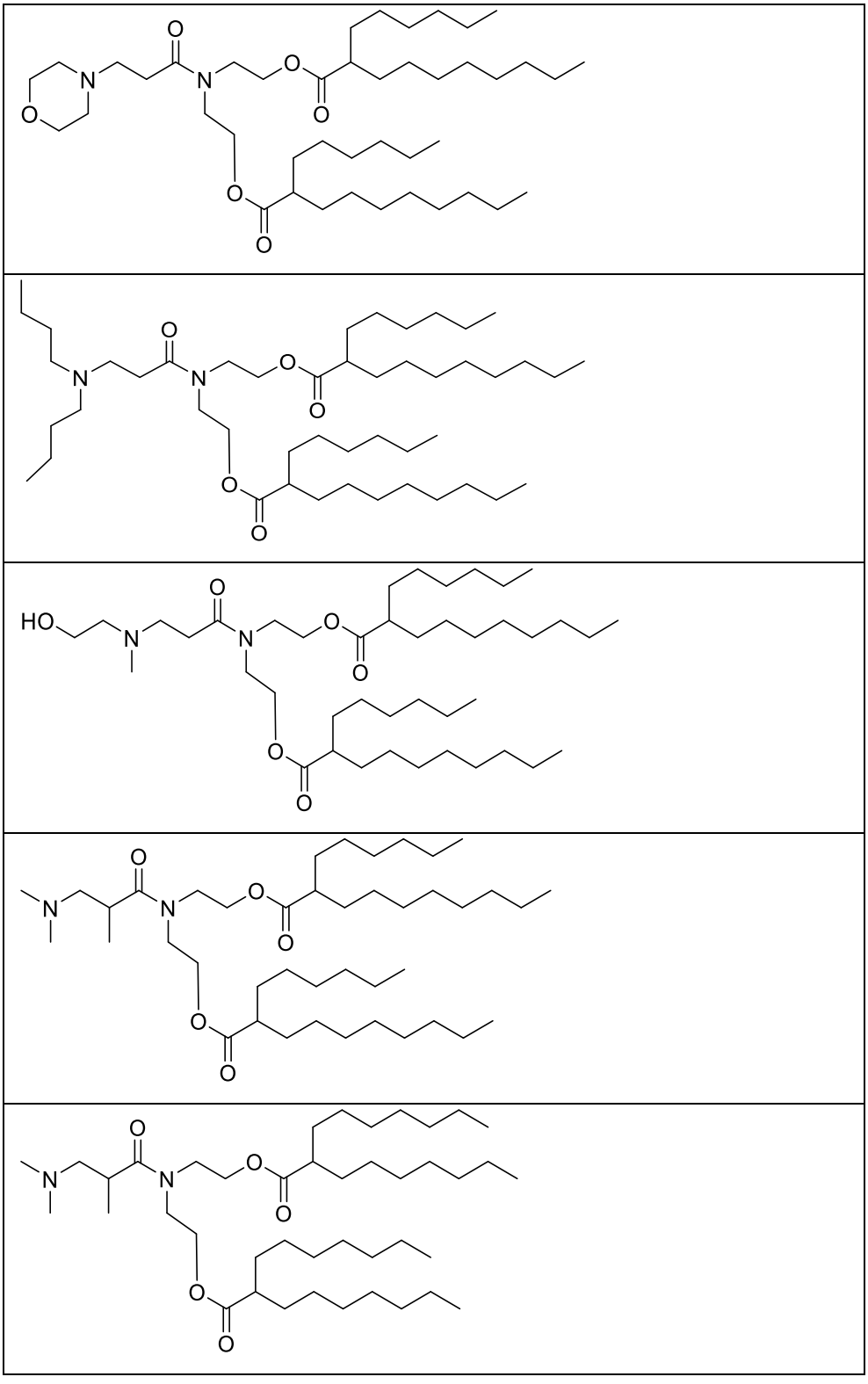


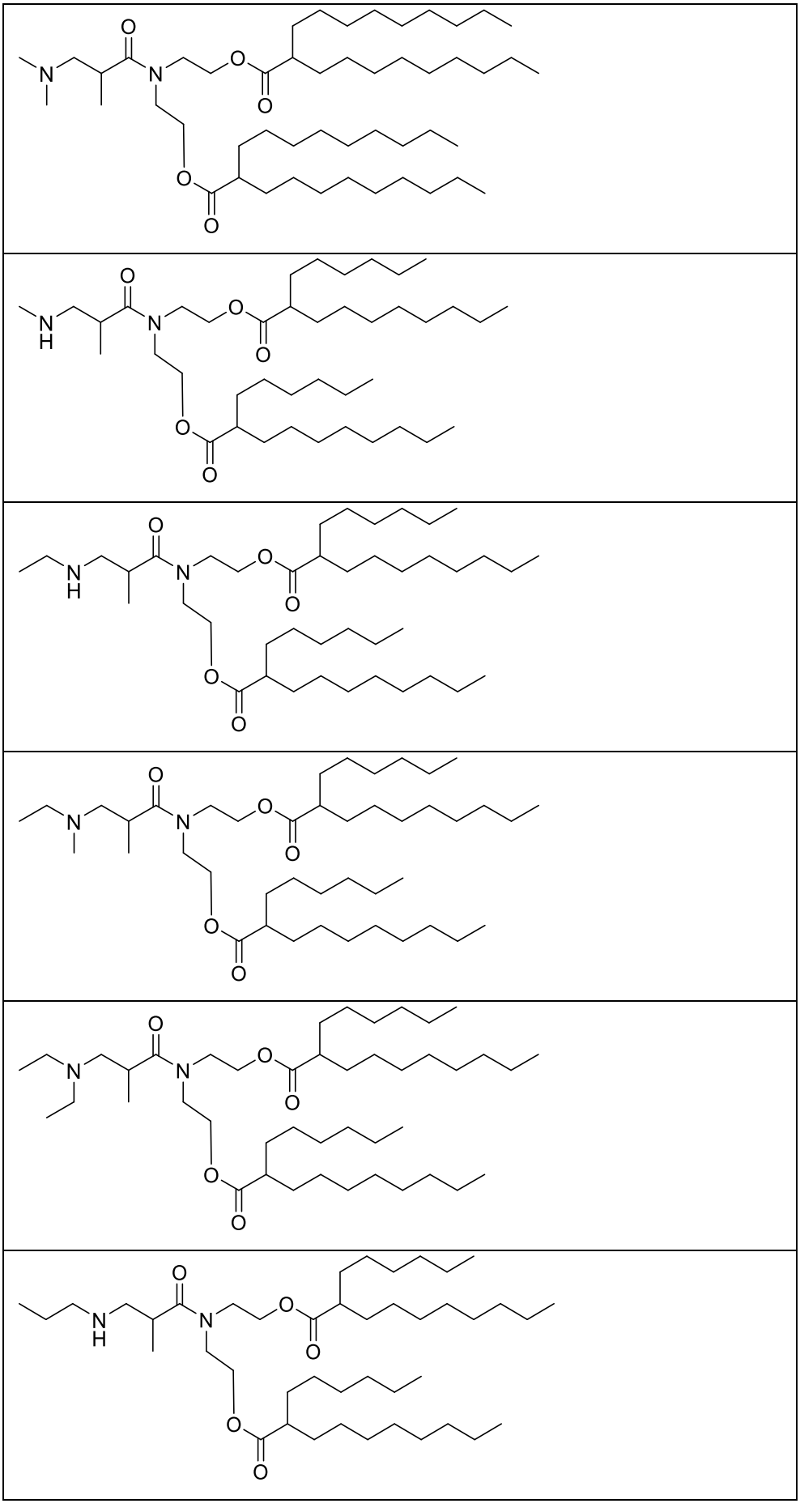


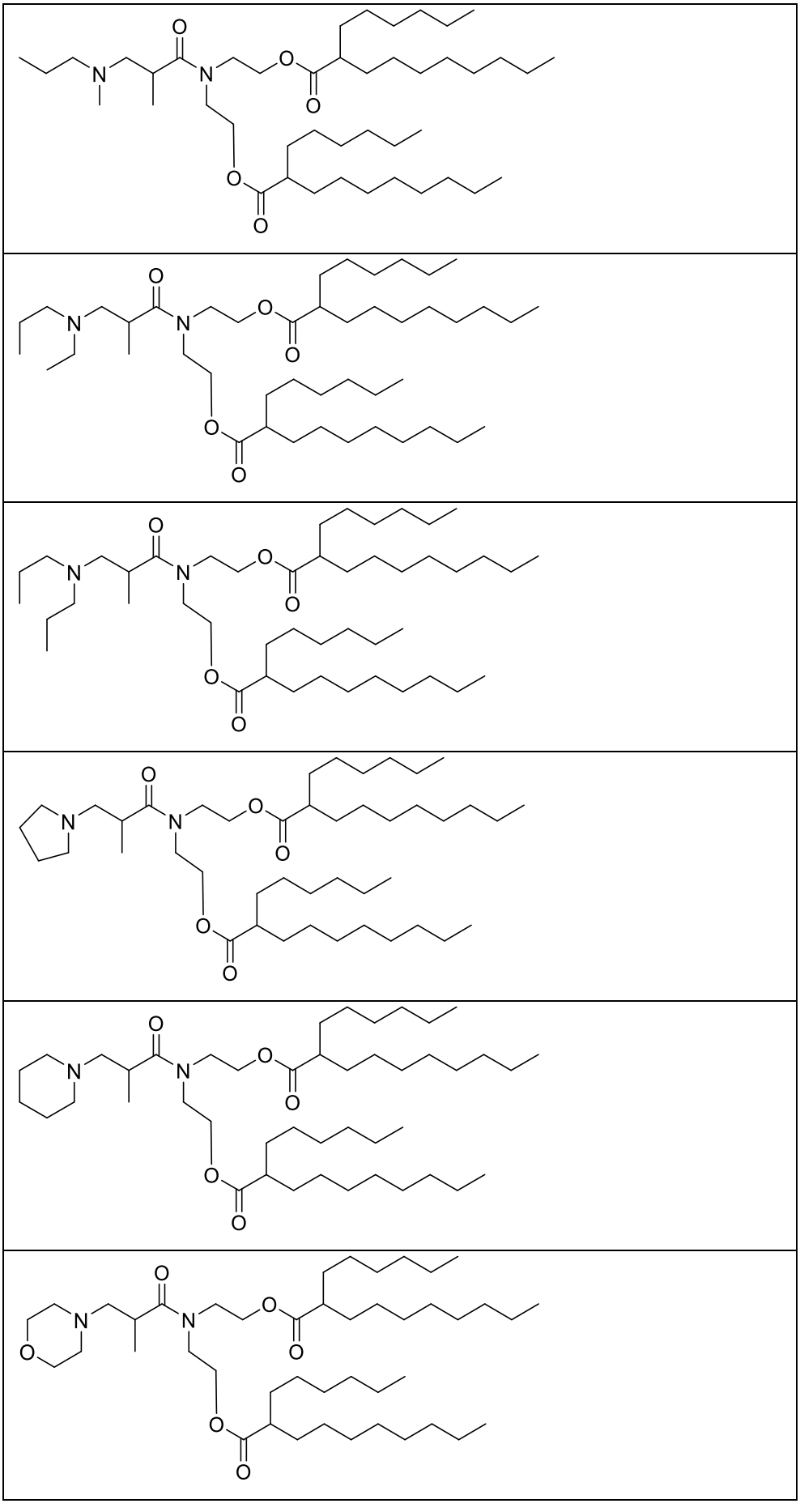


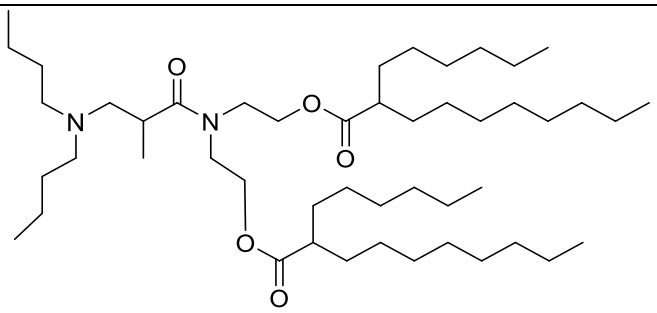
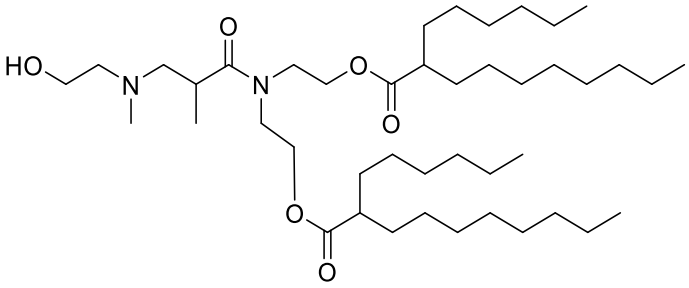
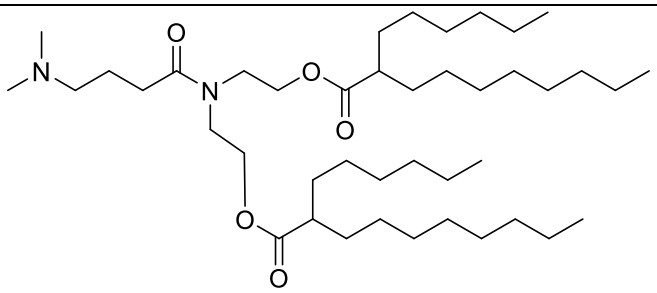
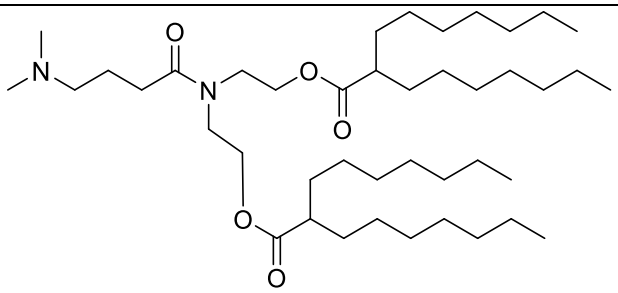
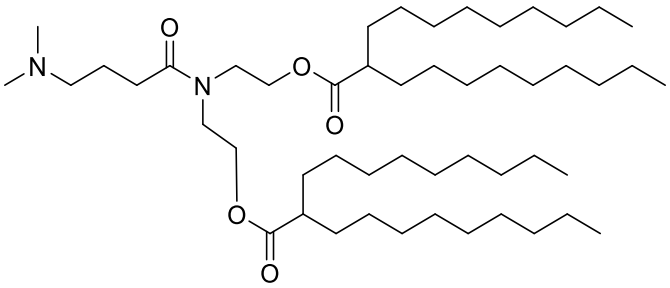







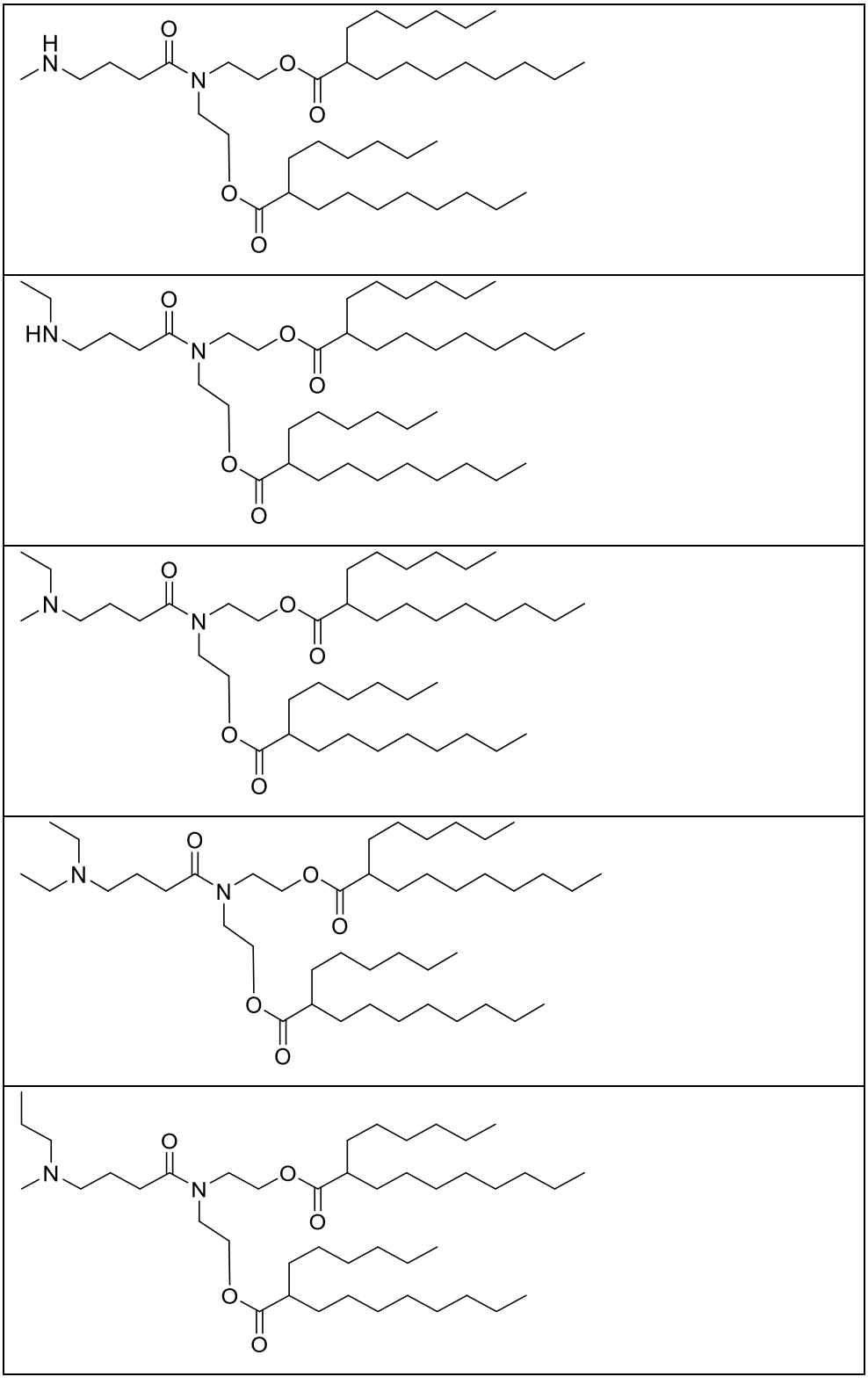


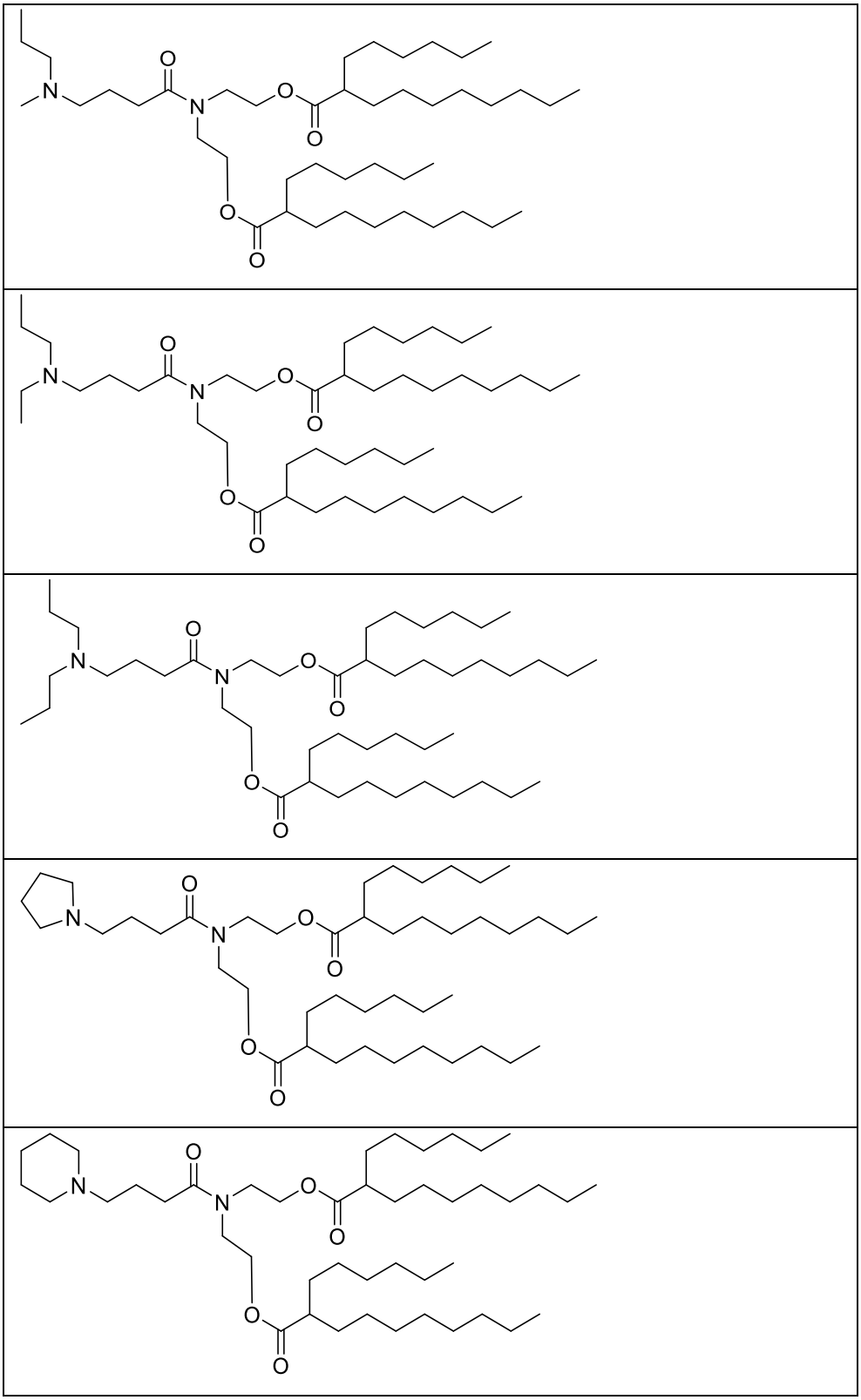


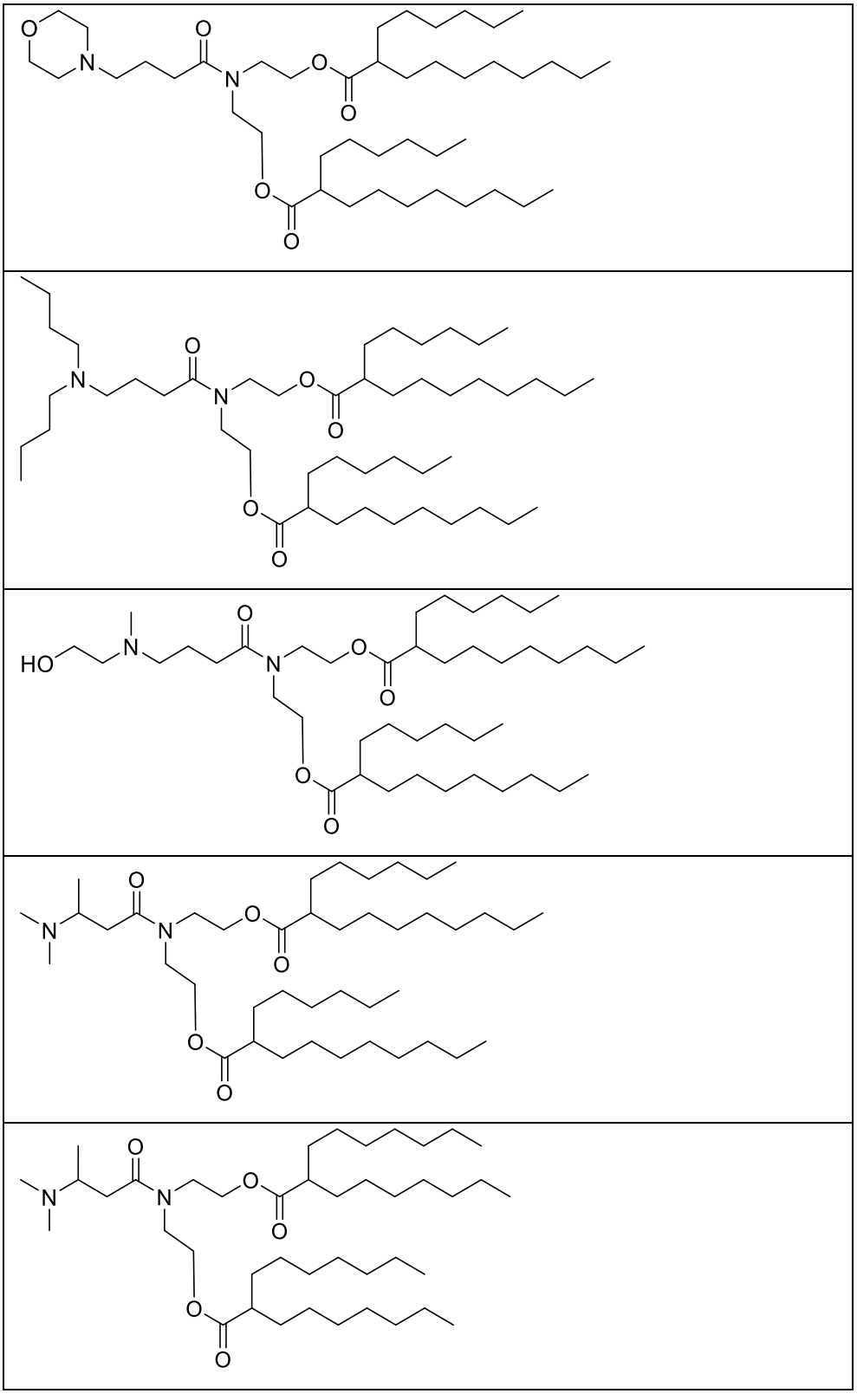


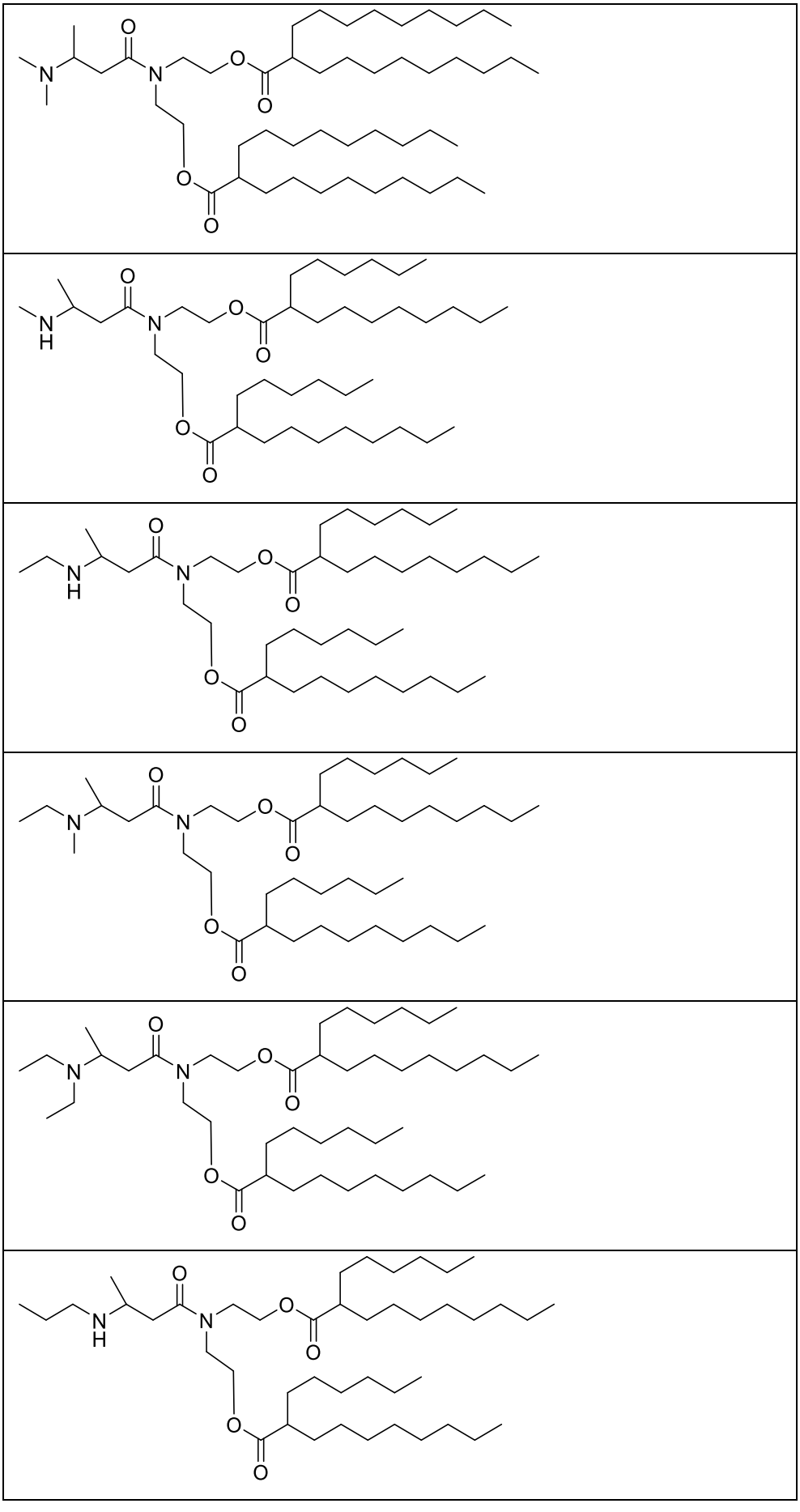


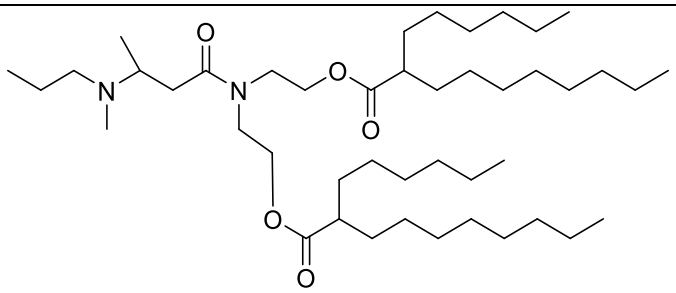
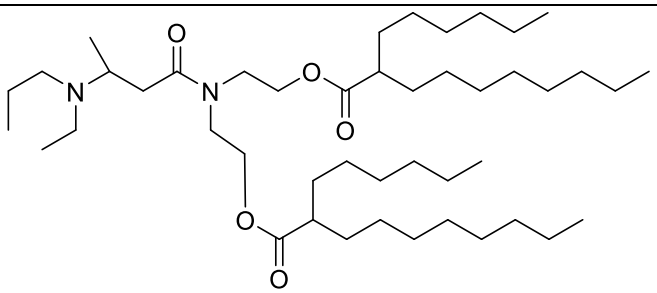
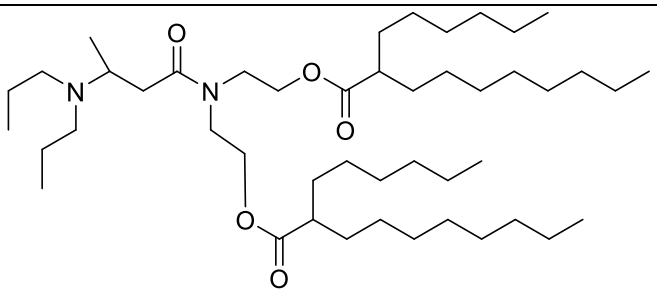
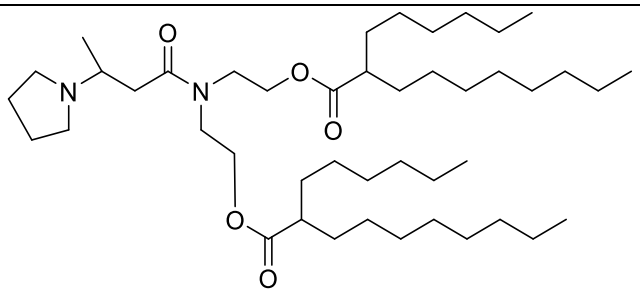
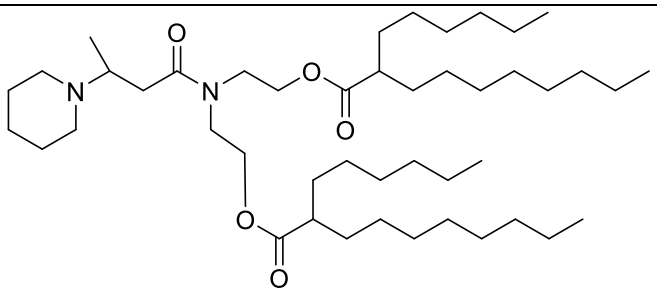
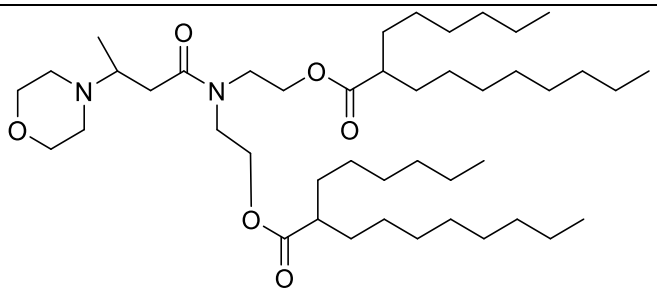






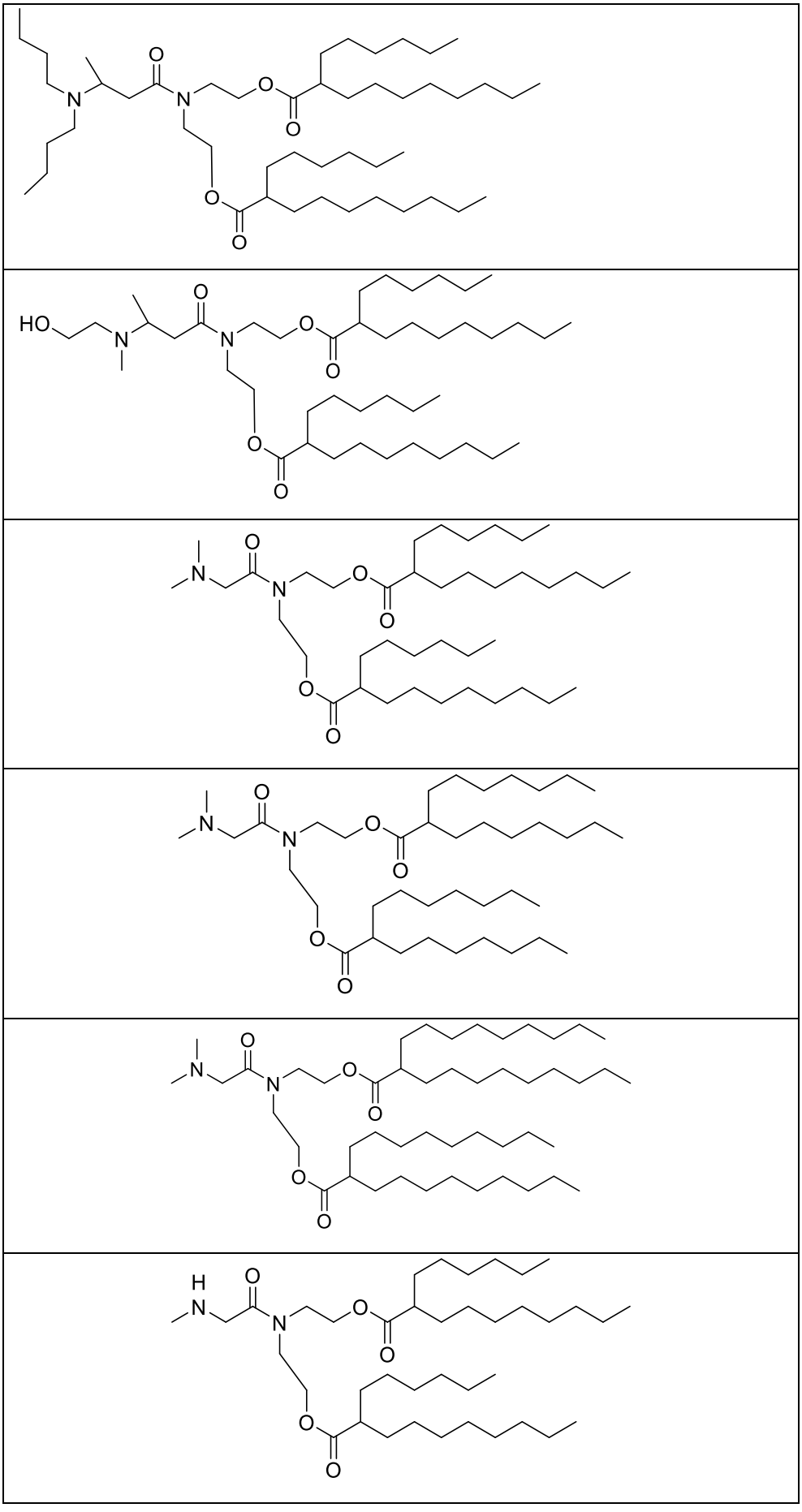


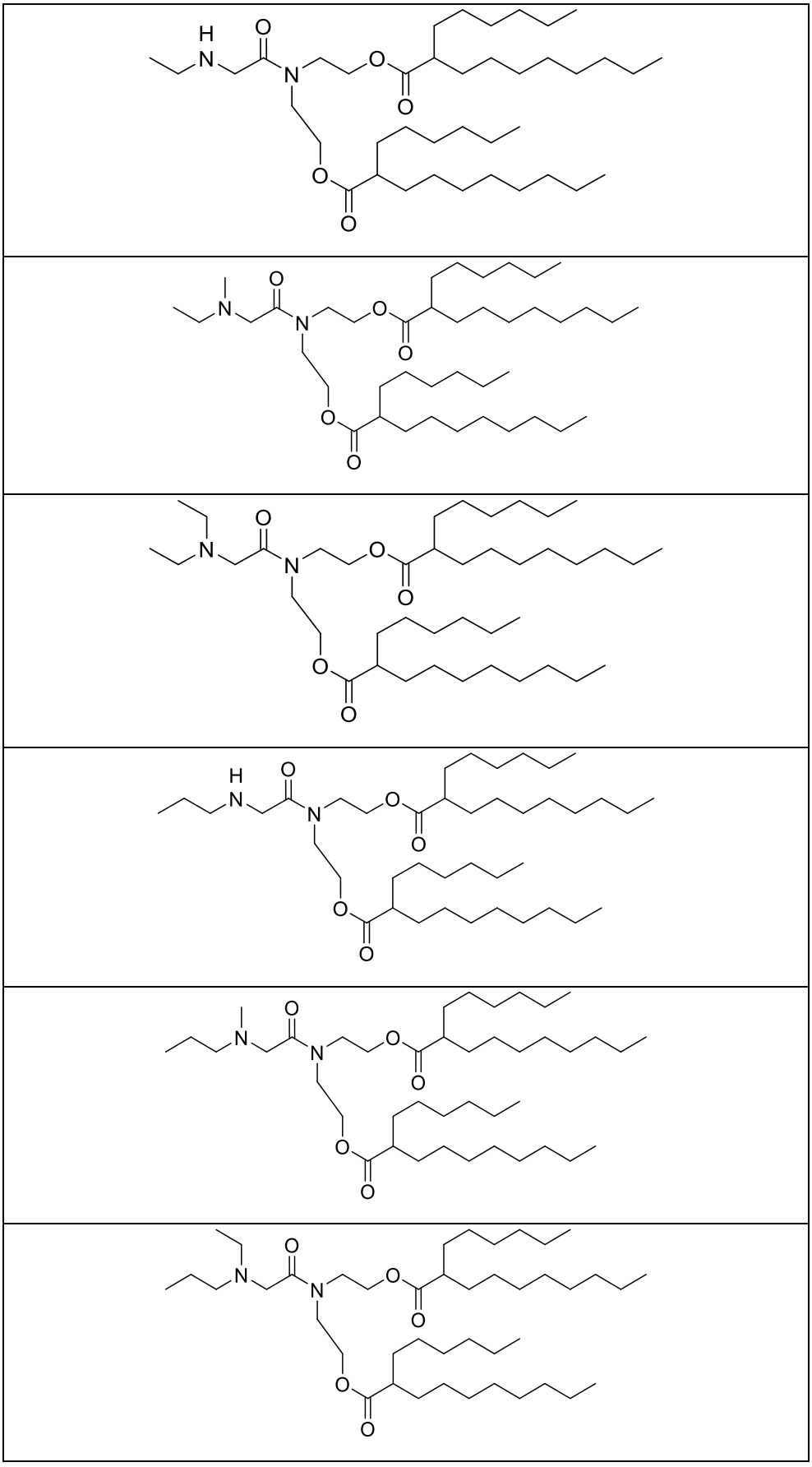


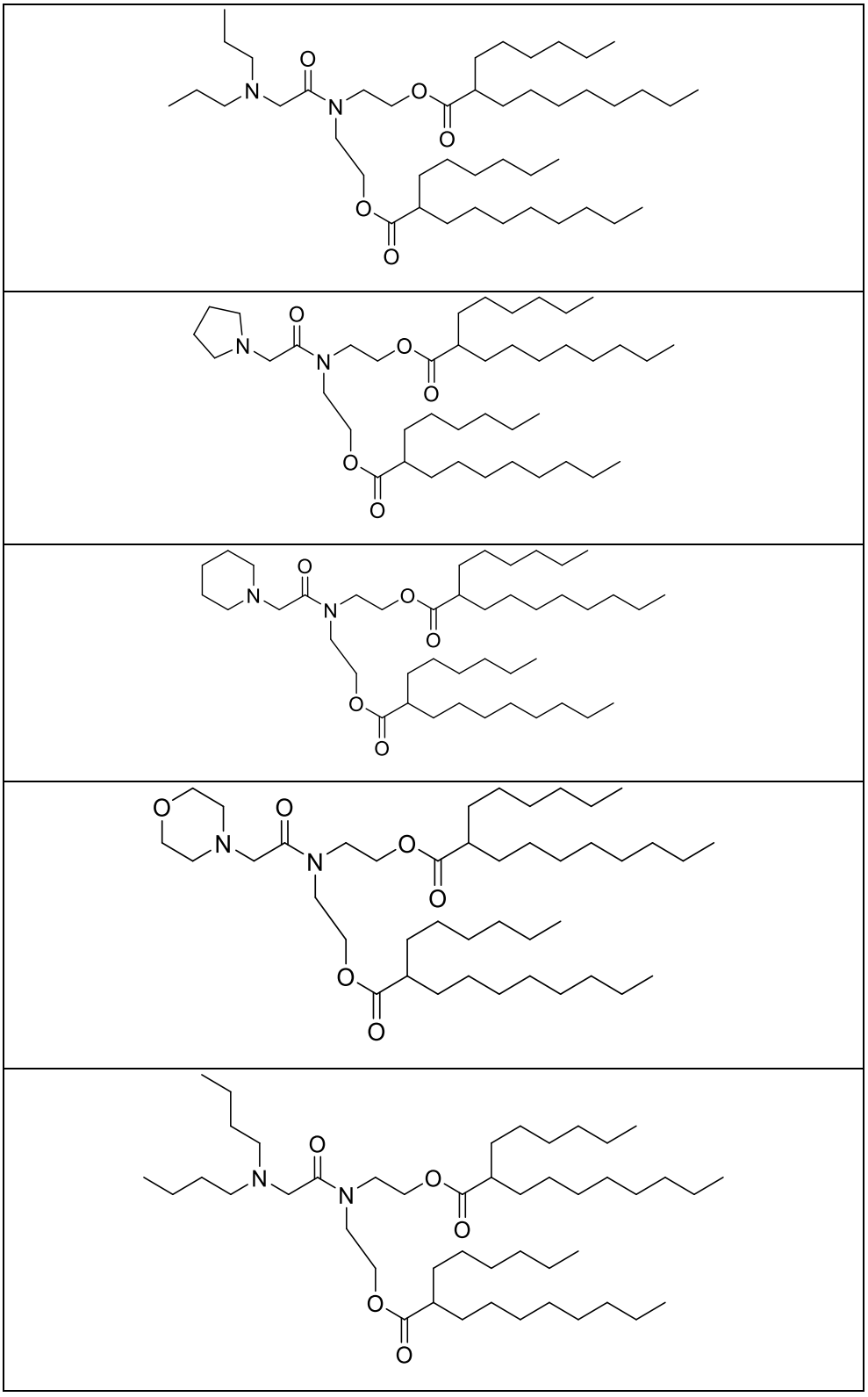


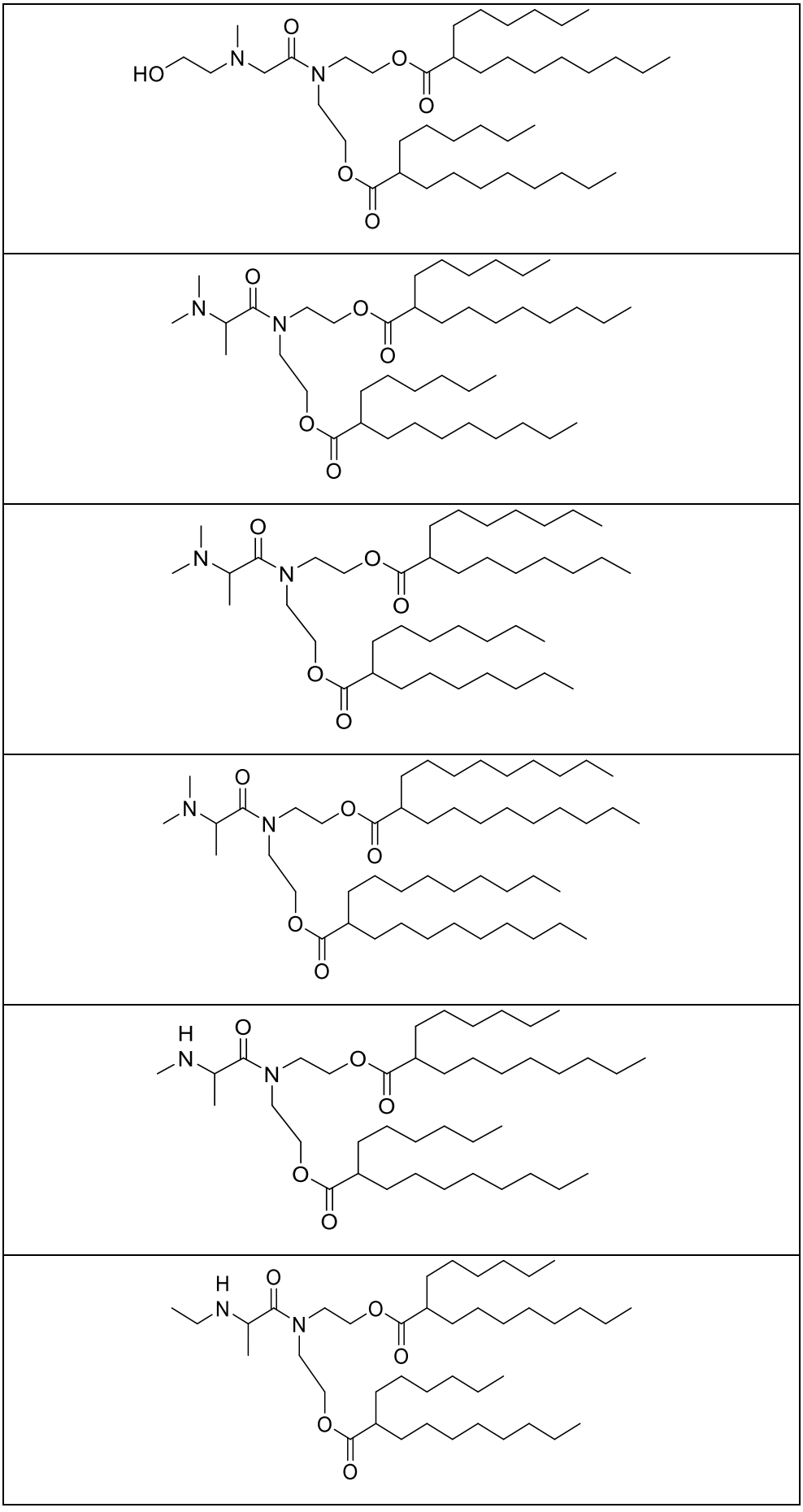


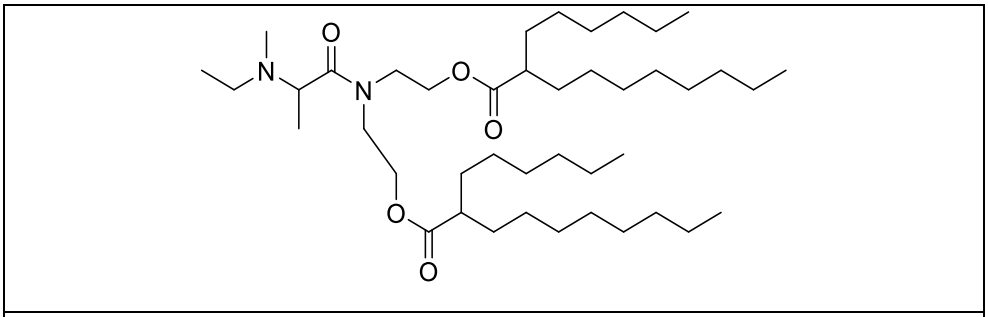







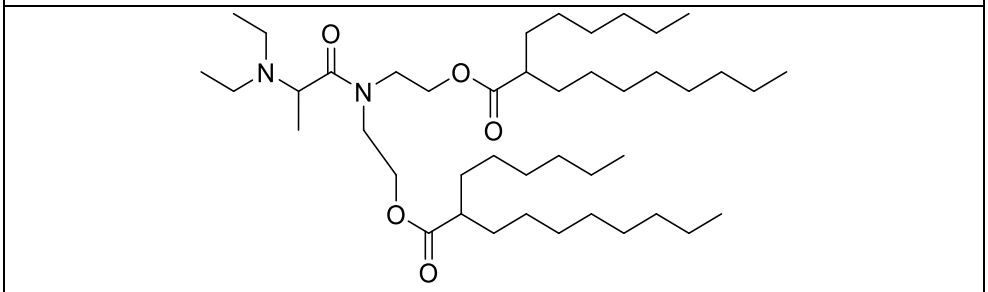


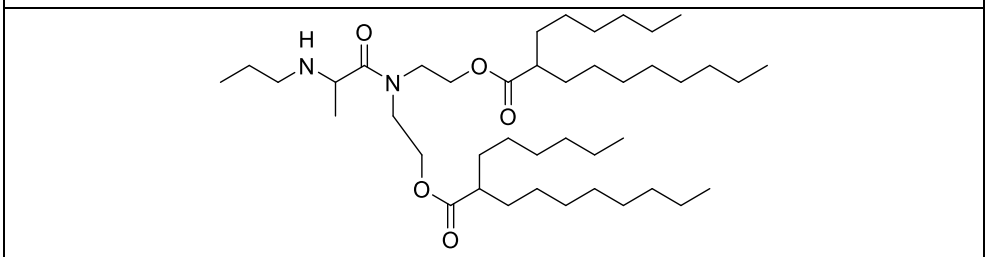


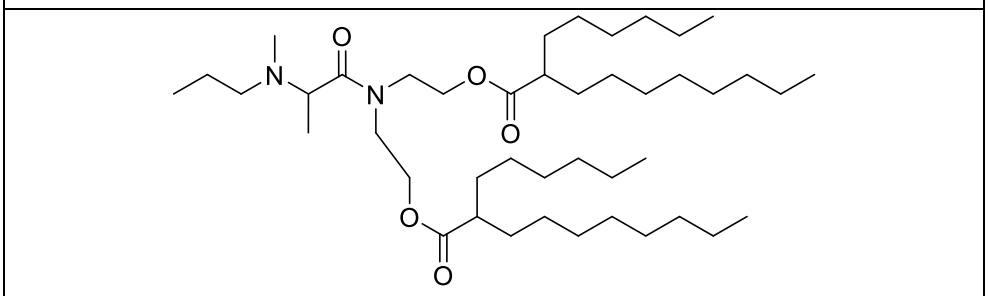


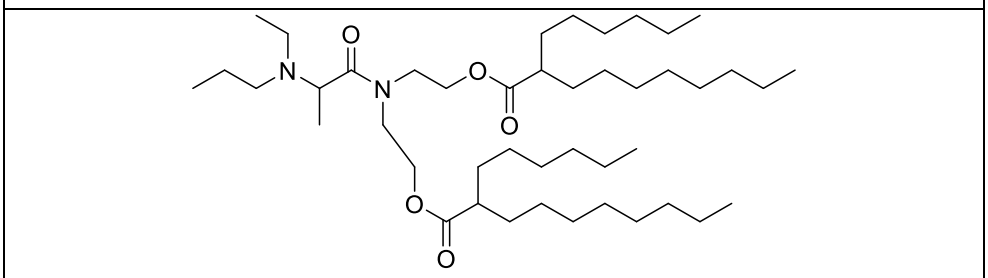


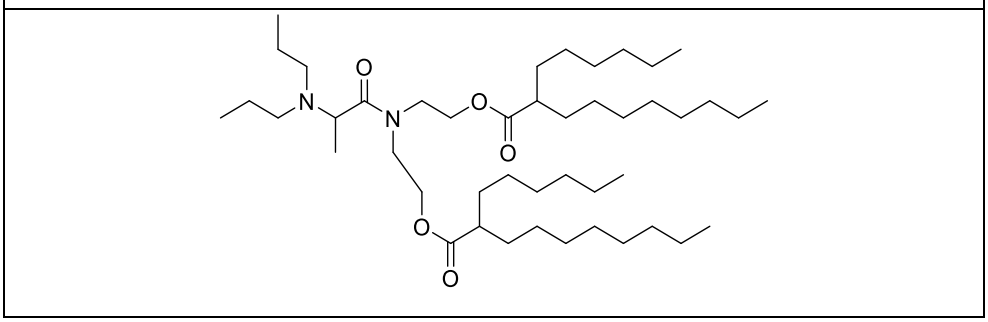


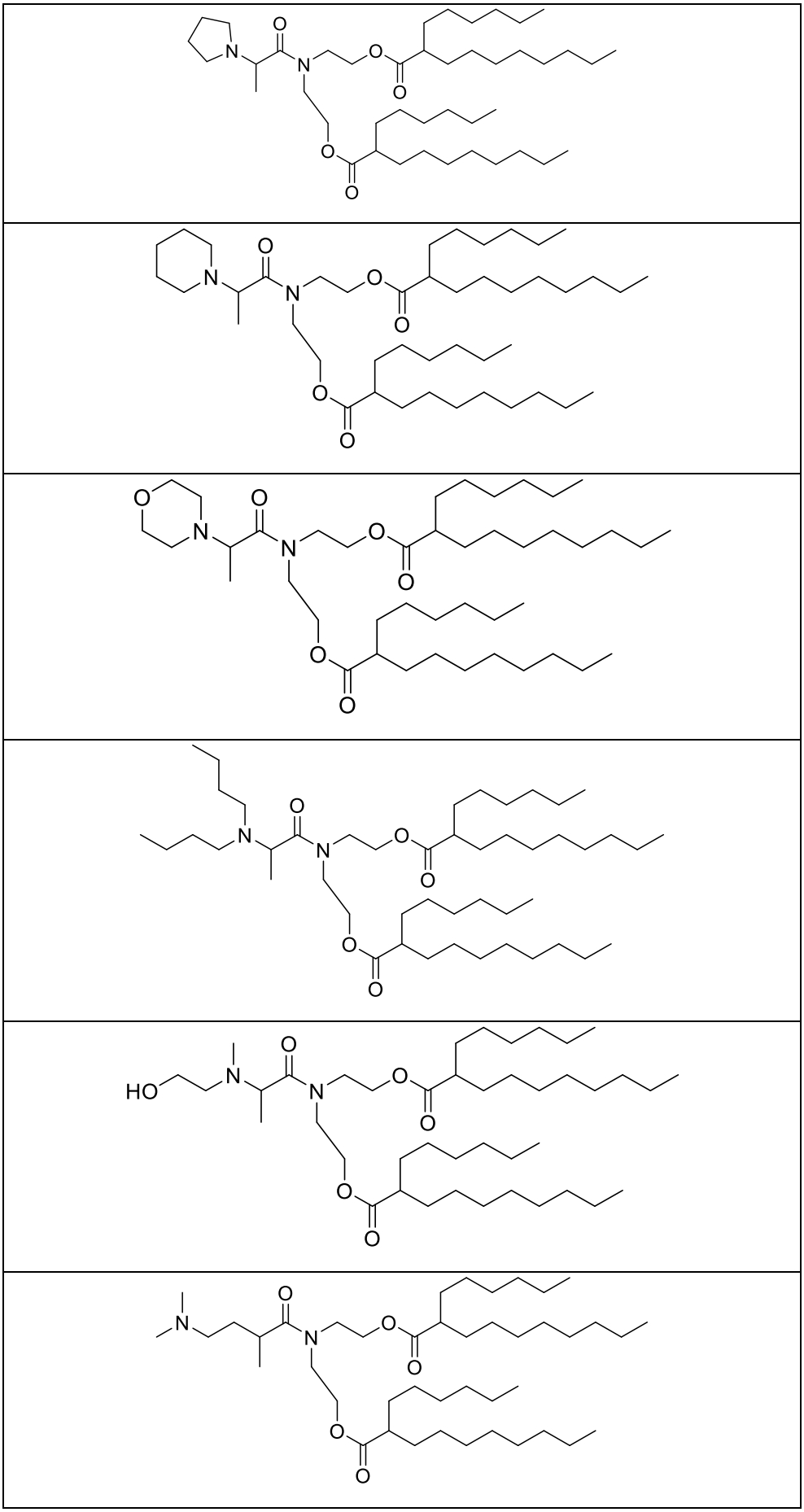


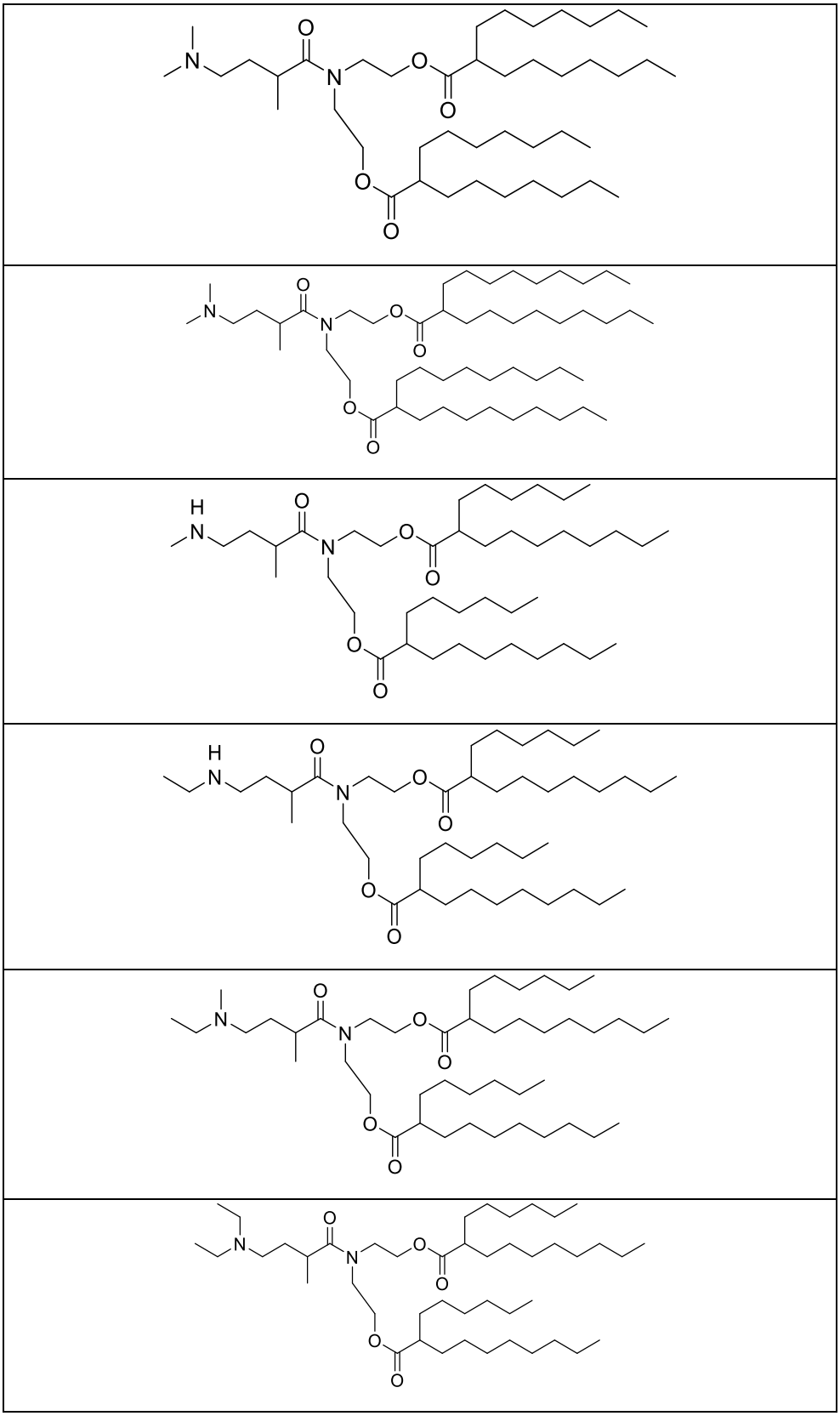


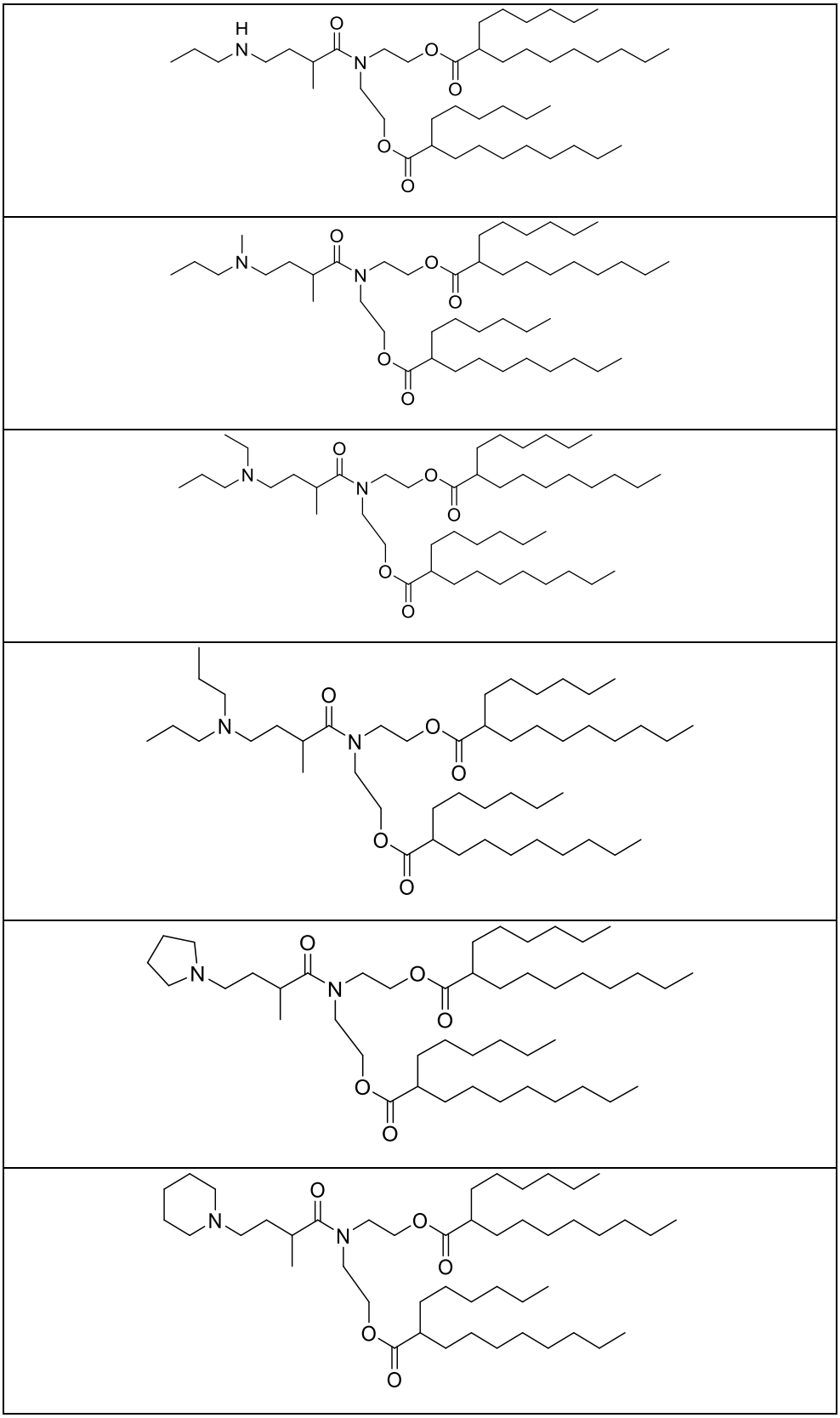


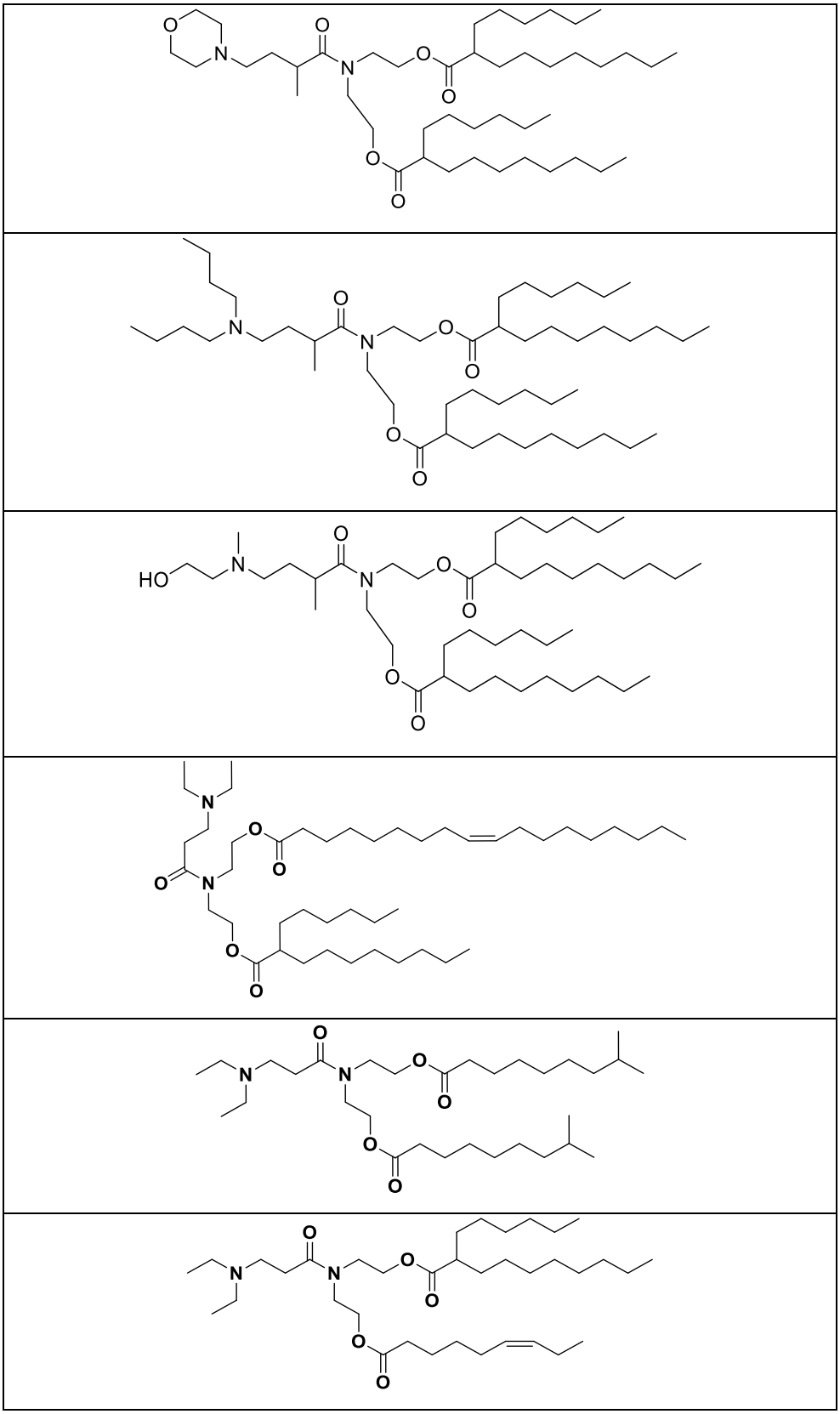


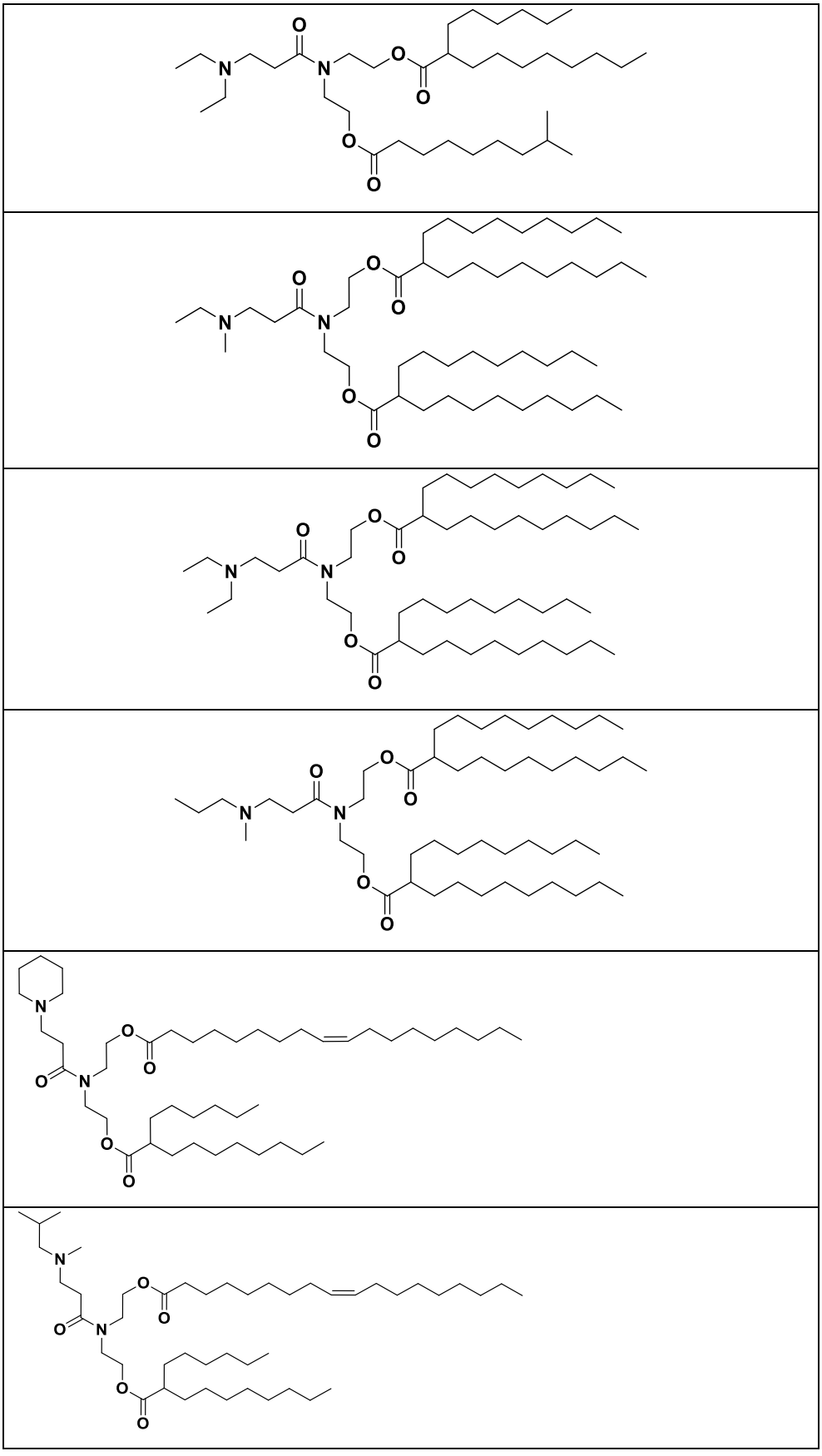


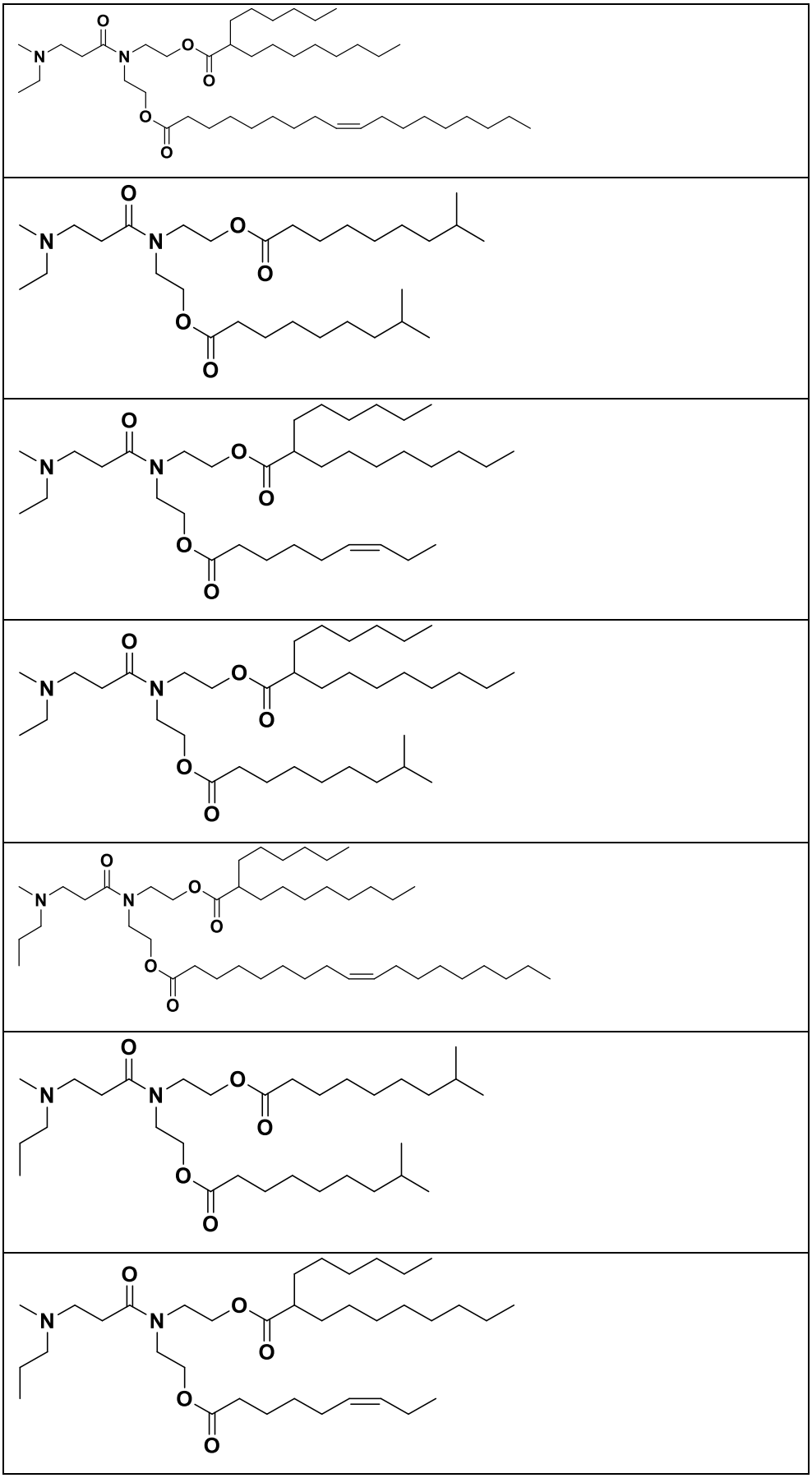


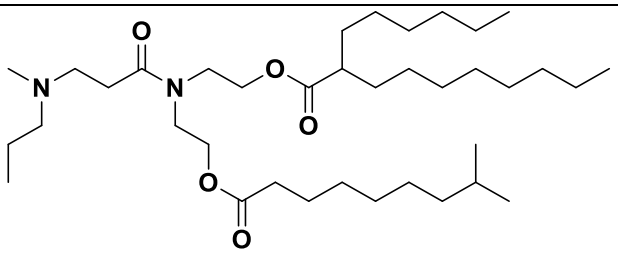
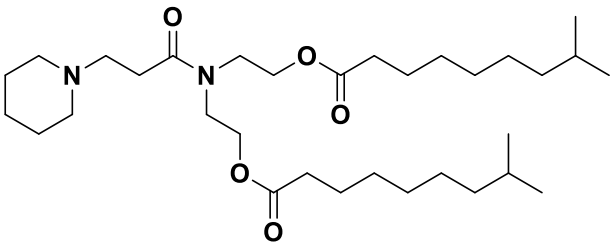
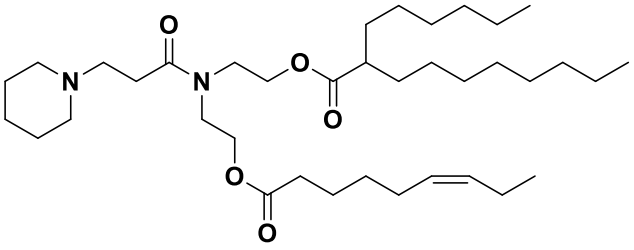
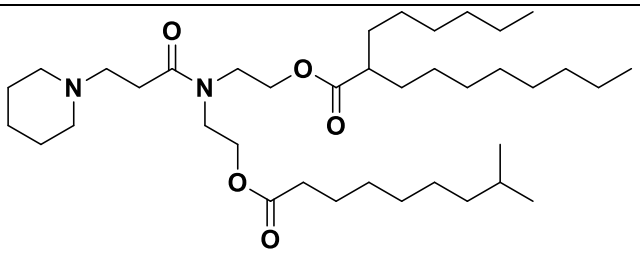
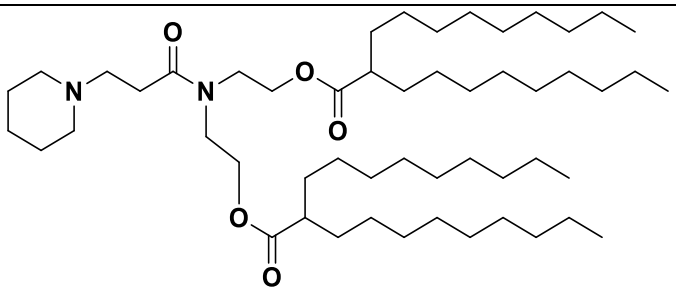
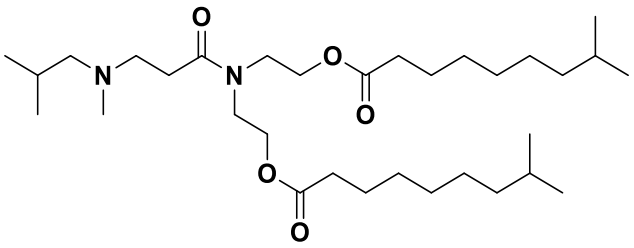


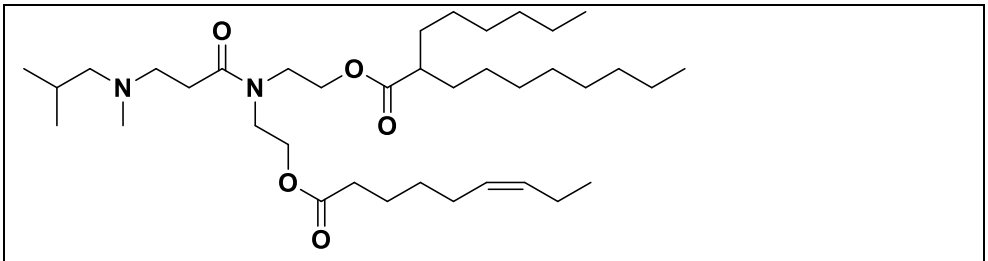


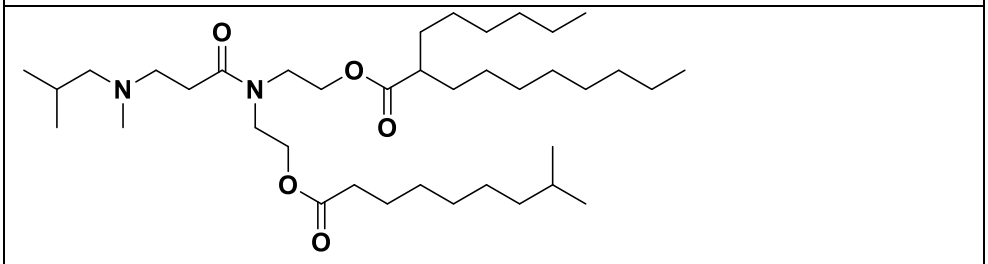


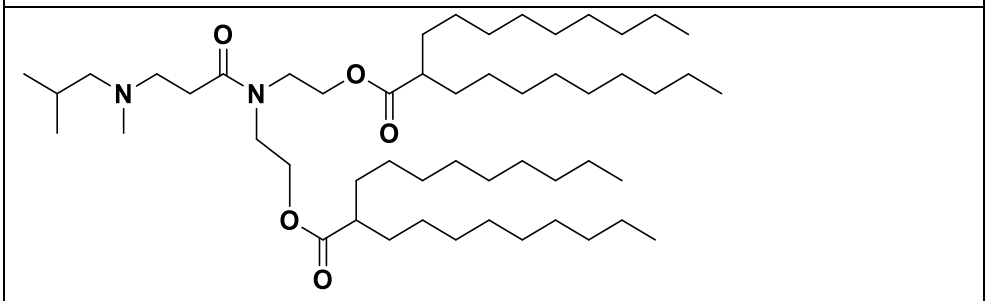


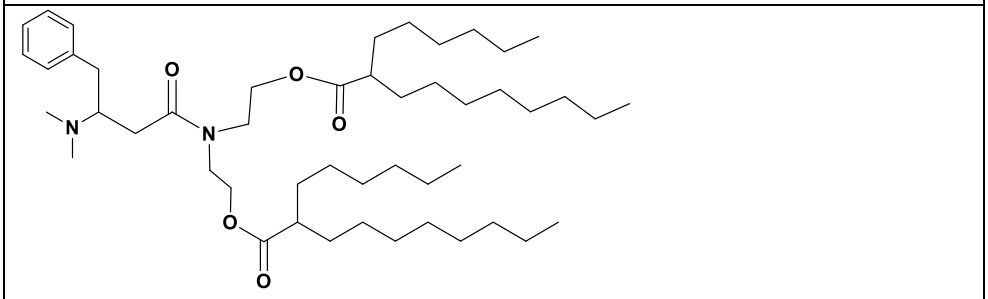


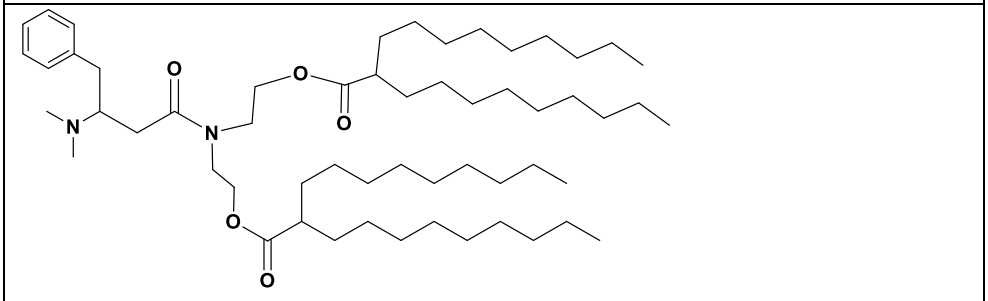







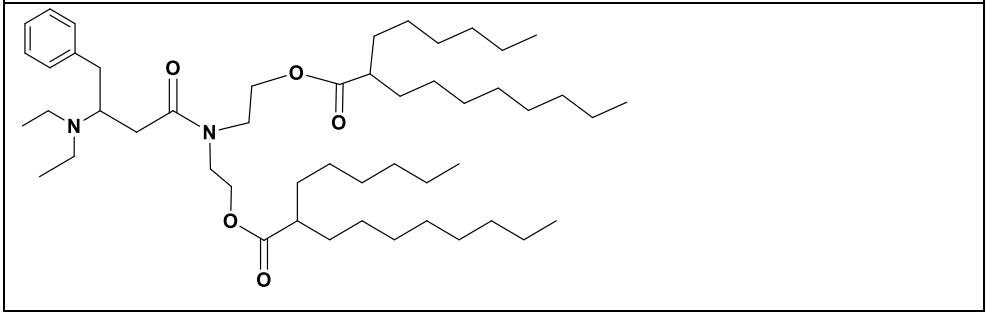


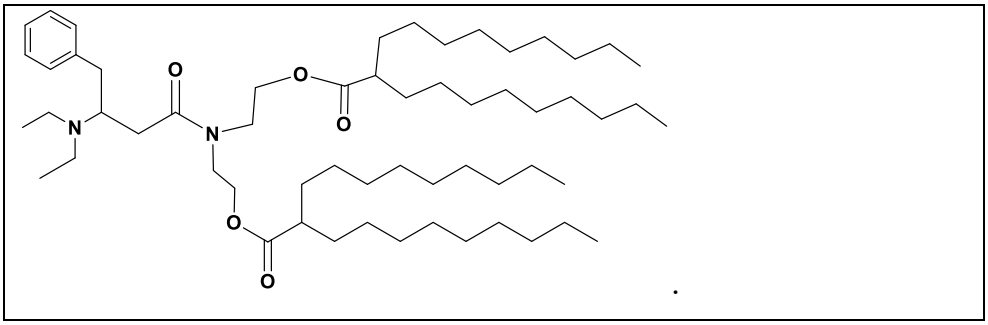




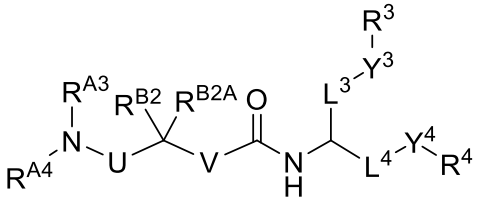








10. A lipidoid having the structure of formula (II):



(II);

or a salt thereof;

wherein:

R^{A3} and R^{A4} are each independently H, alkyl, or hydroxyalkyl;

or wherein R^{A3} and R^{A4}, taken together with the intervening nitrogen, form an optionally substituted heterocycloalkyl ring;

R^{B2} and R^{B2A} are each independently H, optionally substituted alkyl, alkenyl, cycloalkyl, arylalkyl, heteroarylalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, or thioalkyl;

or wherein R^{B2} and R^{B2A}, taken together with the intervening carbon, form an optionally substituted cycloalkyl or heterocycloalkyl ring;

or R^{A3} and R^{B2} taken together with the intervening N-CH atoms to which they are attached form an N-containing heterocyclic ring;

L^3 and L^4 are each independently $–CH_2–$, $–CH_2CH_2–$, $–(CH_2)_3–$, $–(CH_2)_4–$, $–CH(CH_3)CH_2–$, or $–CH_2CH(CH_3)–$;

V is a bond, $–CH_2–$ or $–CH_2CH_2–$;

U is a bond, $–CH_2–$ or $–CH_2CH_2–$;

Y^3 and Y^4 are each independently –O(C=O)–, –S(C=O)–, or –O(C=O)O–; and

R^3 and R^4 are each independently linear (C_8-C_{30})alkyl, branched (C_8-C_{30})alkyl, linear (C_8-C_{30})alkenyl, branched (C_8-C_{30})alkenyl, linear (C_8-C_{30})alkynyl, or branched (C_8-C_{30})alkynyl; wherein a branched (C_8-C_{30})alkyl, a branched (C_8-C_{30})alkenyl, or a branched (C_8-C_{30})alkynyl may comprise more than one branch point, and a linear or branched (C_8-C_{30})alkenyl may comprise more

than one carbon-carbon double bond, and a linear or branched (C_8-C_{30})alkynyl may comprise more than one carbon-carbon triple bond.

11. The lipidoid of claim 10, wherein:

(i) R^{A3} and R^{A4} are each H;

(ii) R^{A3} is hydroxyalkyl; and R^{A4} is H;

(iii) R^{A3} is $–CH_2CH_2OH$;

(iv) R^{B2} is H, optionally substituted alkyl, arylalkyl, heteroarylalkyl, hydroxyalkyl, or aminoalkyl;

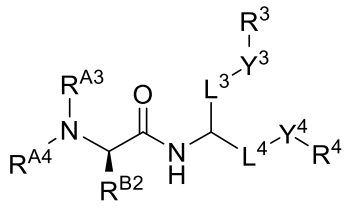
(v) R^{B2} is H, methyl, $–CH_2Ph$, $–CH_2OH$, $–(CH_2)_4NH_2$, or $–CH_2$(imidazolyl), preferably methyl;

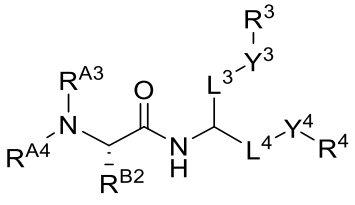
(vi) R^{B2A} is hydrogen;

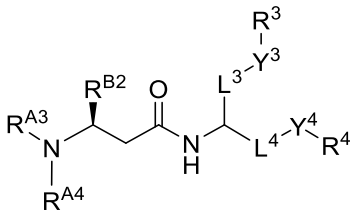
(vii) at least one of U and V is a bond; or

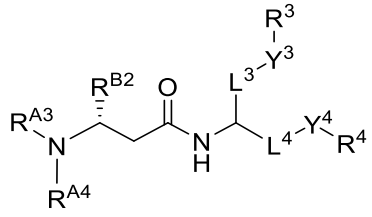
(viii) U and V are both a bond.

12. The lipidoid of claim 10, having the structure of formula (IIa), (IIb), (IIc), (IId), (IIe), or (IIf):

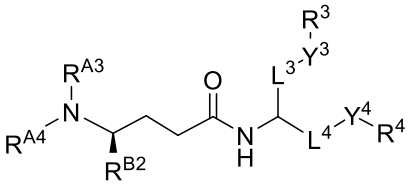

(IIa);


(IIb);

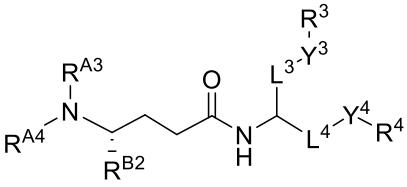

(IIc);



(IId);



(IIe);



(IIf);

or a salt thereof;

wherein the lipidoid has the absolute stereochemistry shown.

13. The lipidoid of any one of claims 10-12, wherein:

(i) U is a bond;

(ii) Y^3 and Y^4 are each –O(C=O)–;

(iii) L^3 and L^4 each represent $–CH_2–$;

(iv) R^3 and R^4 are each independently linear (C_8-C_{24})alkyl, branched (C_8-C_{24})alkyl, linear (C_8-C_{24})alkenyl, or branched (C_8-C_{24})alkenyl;

(v) R^3 and R^4 are each independently linear (C_8-C_{24})alkyl or linear (C_8-C_{24})alkenyl;

(vi) R^3 and R^4 are each independently linear (C_8-C_{24})alkyl;

(vii) R^3 and R^4 are each independently linear (C_9-C_{17})alkyl;

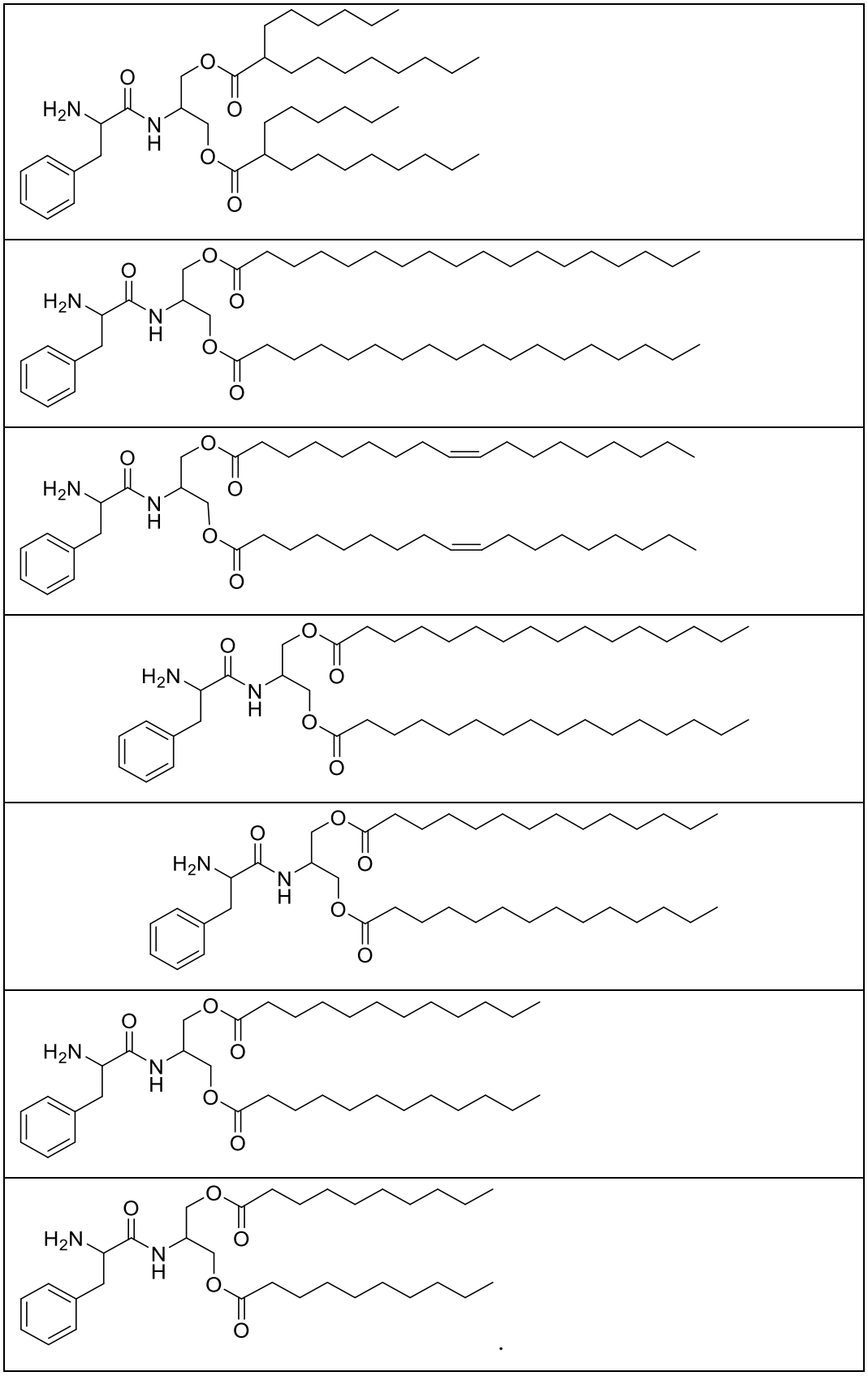
(viii) R^3 and R^4 are each independently a linear (C_8-C_{24})alkenyl;

(ix) R^3 and R^4 are each independently a linear (C_{17})alkenyl;

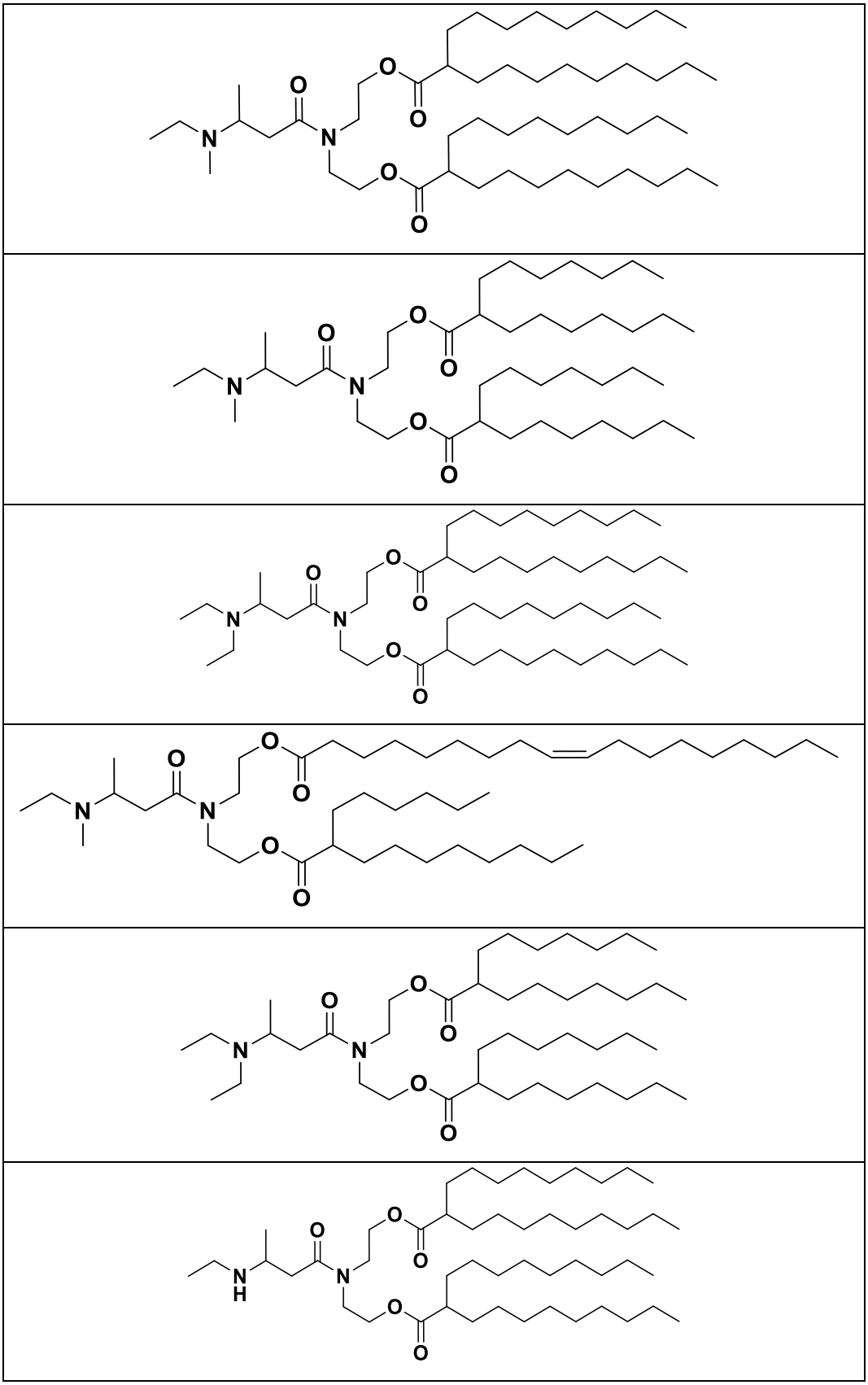
(x) R^3 and R^4 are each independently branched (C_8-C_{24})alkyl; or

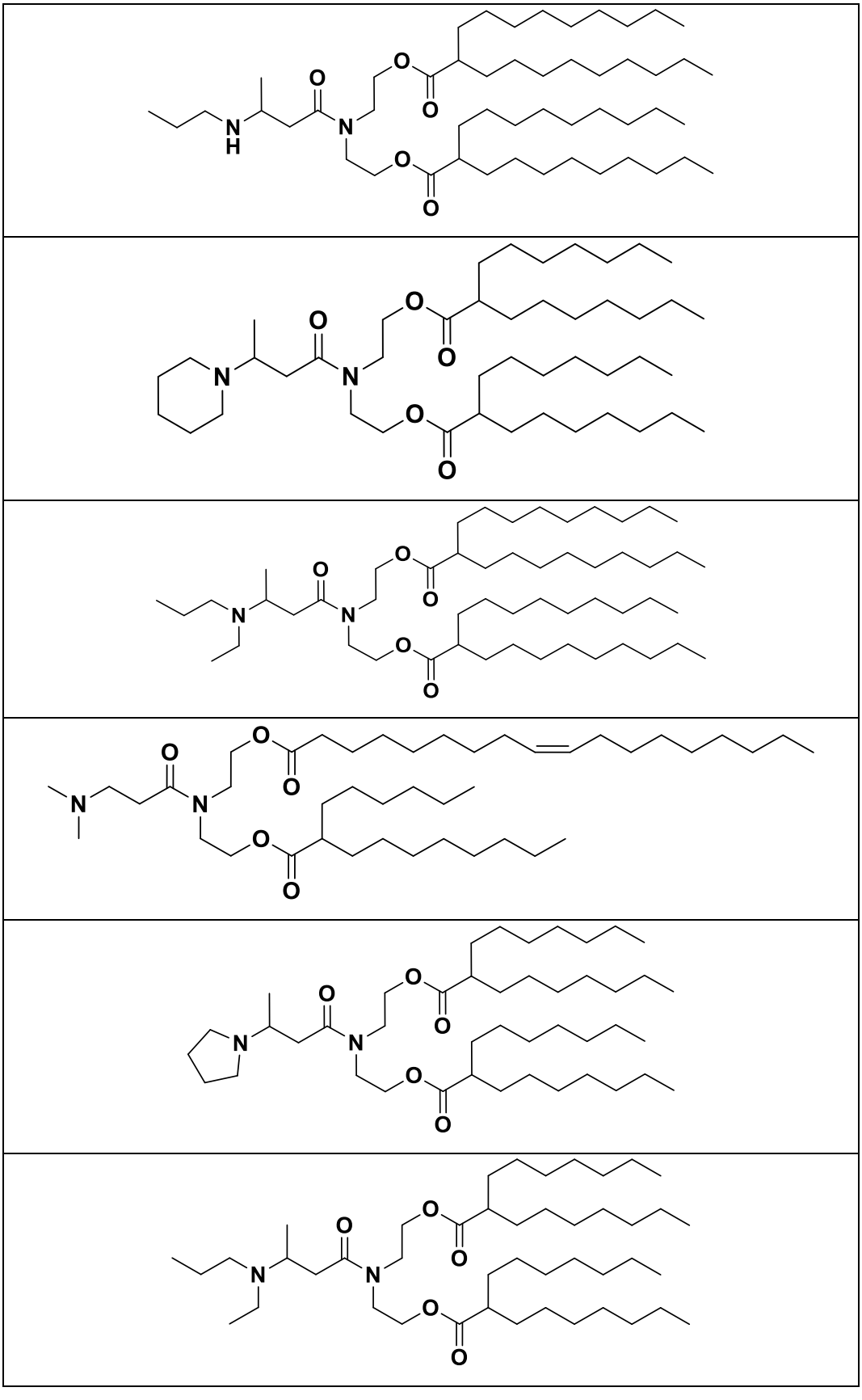
(xi) R^3 and R^4 are each independently a branched (C_{15}-C_{19})alkyl.

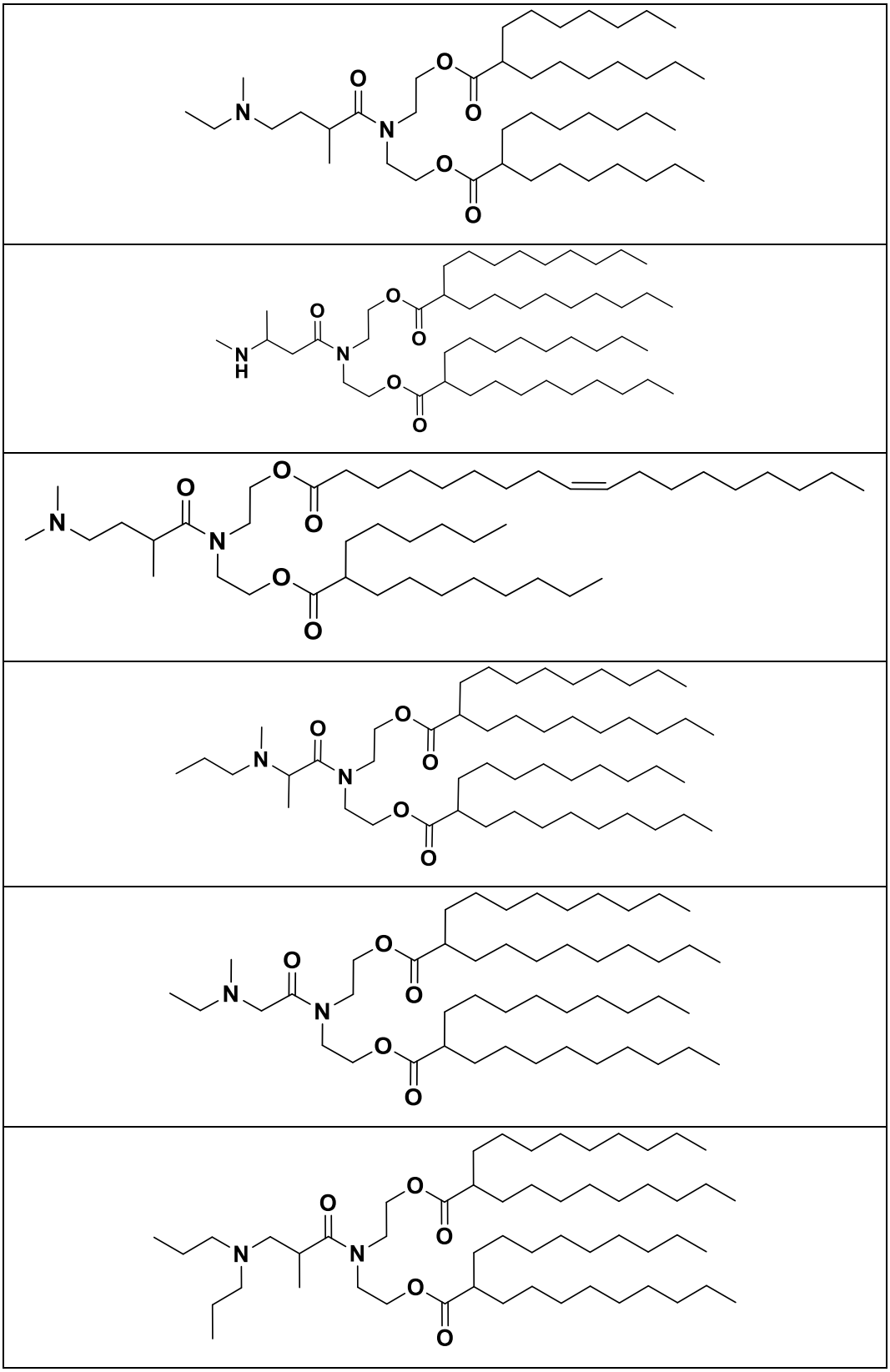
14. The lipidoid of claim 10, selected from the following table:

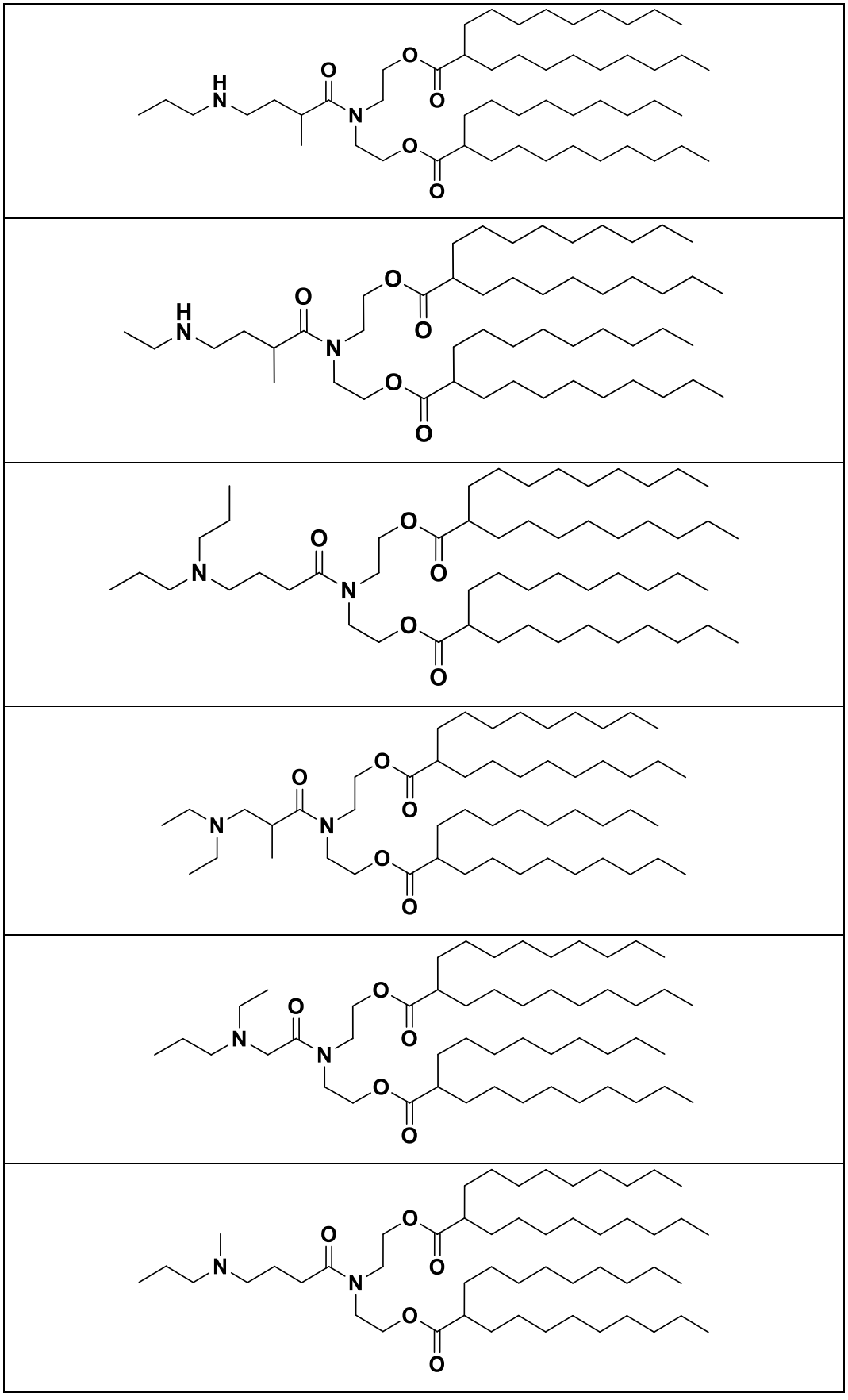


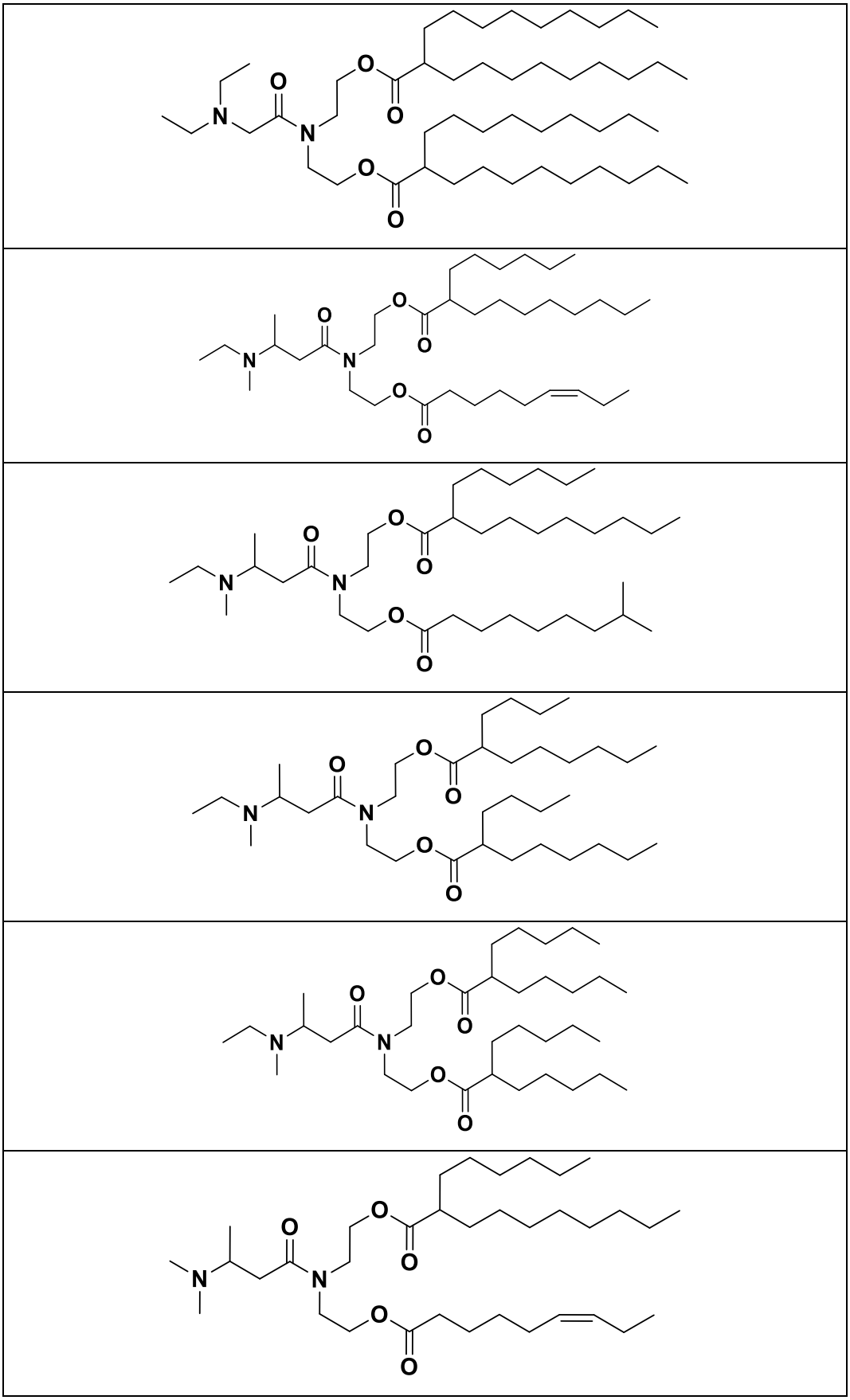
15. The lipidoid of claim 1, selected from the following table:

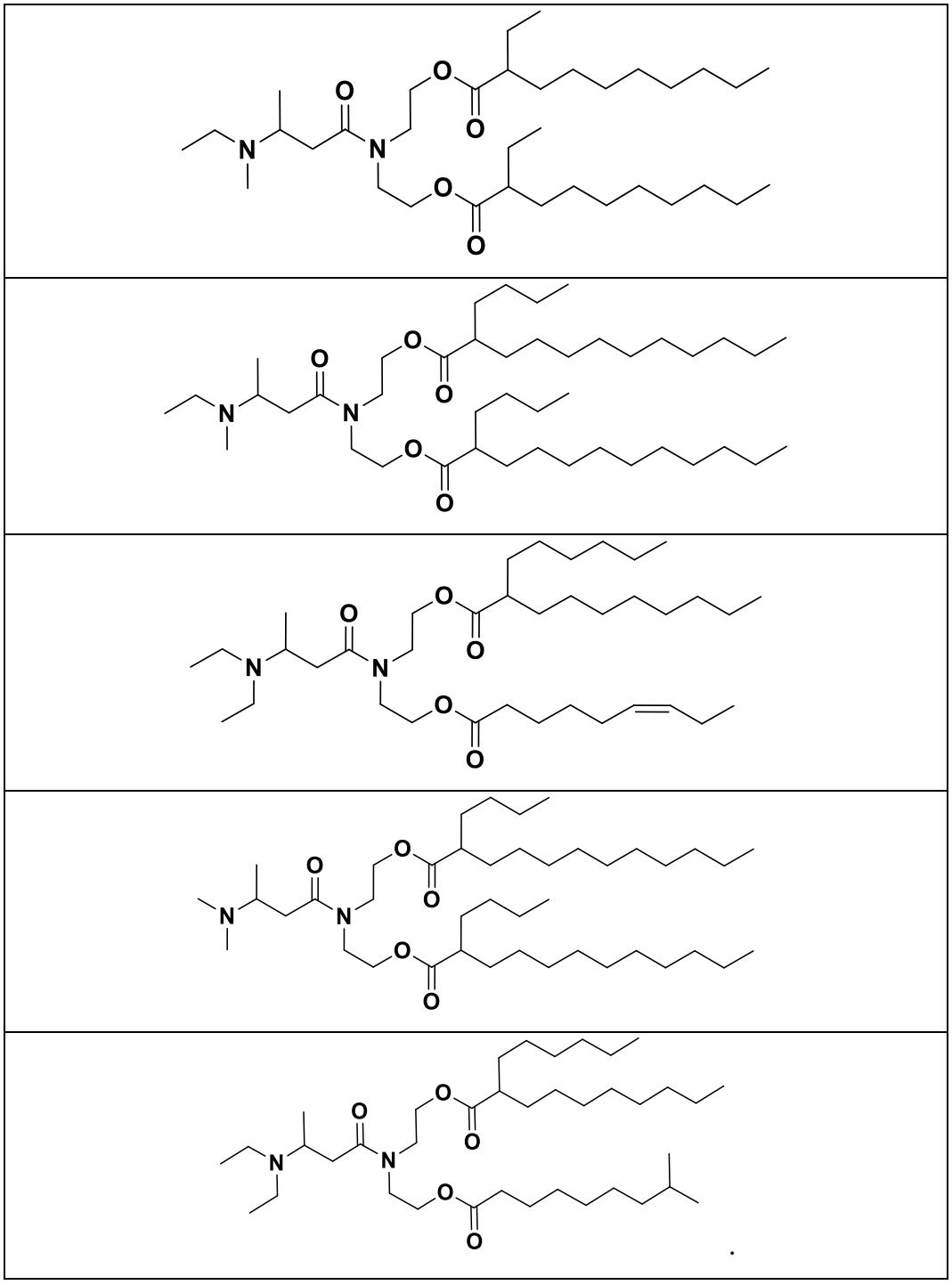




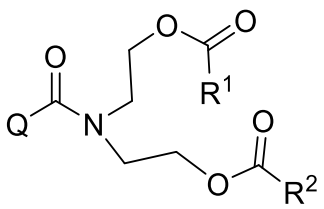






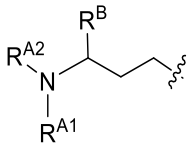
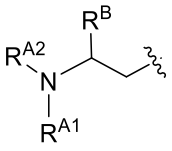
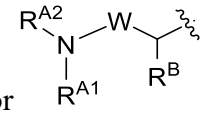


16. The lipidoid of claim 1, having the structure of Formula (Iz):

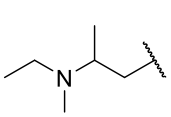
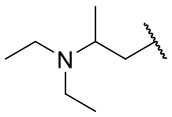
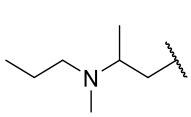
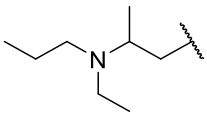
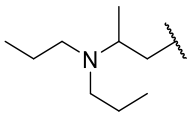
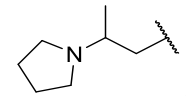
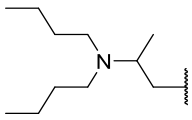
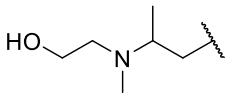
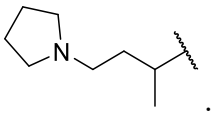


(Iz)

or a salt thereof,

wherein Q is , , or .

17. The lipidoid of claim 16, wherein Q is selected from:

, , , , , , , , and .

18. A nanoparticle composition, comprising a lipidoid of any one of claims 1-17, or a pharmaceutically acceptable salt thereof.

19. The nanoparticle composition of claim 18, further comprising a PEGylated lipid, a sterol, a phospholipid, and/or a neutral lipid.

20. The nanoparticle composition of claim 18 or 19, further comprising a therapeutic agent, wherein the therapeutic agent is a protein, a small molecule drug, or a nucleic acid molecule, such as a plasmid, an immunostimulatory oligonucleotide, an antisense oligonucleotide, an antagomir, an aptamer, a deoxyribozyme (DNAzyme), or a ribozyme.

21. The nanoparticle composition of claim 20, wherein the nucleic acid molecule is DNA or RNA, preferably mRNA.

22. The nanoparticle composition of any one of claims 18-21, further comprising an antigen, wherein the antigen is a protein or a nucleic acid.