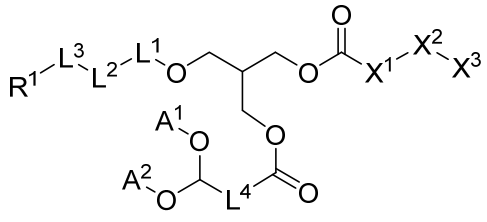
Claims

We claim:

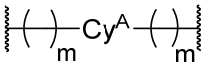
1. A compound of Formula I:



(I)

or a pharmaceutically acceptable salt thereof, wherein:

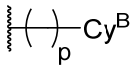
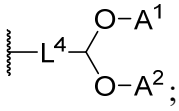
L^1 is a covalent bond, -C(O)-, or -OC(O)-;

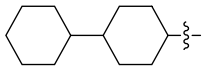
L^2 is a covalent bond, an optionally substituted bivalent saturated or unsaturated, straight or branched C_1-C_{12} hydrocarbon chain, or ;

Cy^A is an optionally substituted ring selected from phenylene and 3- to 7-membered saturated or partially unsaturated carbocyclene;

each m is independently 0, 1, or 2;

L^3 is a covalent bond, -C(O)-, -C(O)O-, -OC(O)-, -O-, or -OC(O)O-;

R^1 is , an optionally substituted saturated or unsaturated, straight or branched C_1-C_{20} hydrocarbon chain wherein 1-3 methylene units are optionally and independently replaced with –O- or –NR-, or ;

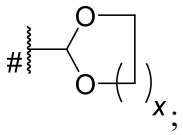
Cy^B is an optionally substituted ring selected from 3- to 12-membered saturated or partially unsaturated carbocyclyl, 1-adamantyl, 2-adamantyl, , sterolyl, and phenyl;

p is 0, 1, 2, or 3;

each L^4 is independently a bivalent saturated or unsaturated, straight or branched C_1-C_6 hydrocarbon chain;

each A^1 and A^2 is independently an optionally substituted C_1-C_{20} aliphatic or -L^5-R^5;

or A^1 and A^2, together with their intervening atoms, may form an optionally substituted ring:



where

x is selected from 1 or 2; and

represents the point of attachment to L^4;

each L^5 is independently a bivalent saturated or unsaturated, straight or branched C_1-C_{20} hydrocarbon chain, wherein 1-3 methylene units are optionally and independently replaced with -O- or -NR-;

each R^5 is independently an optionally substituted group selected from a 5- to 10-membered aryl ring or a 3- to 8-membered carbocyclic ring ;

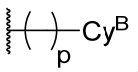
X^1 is a covalent bond, –O–, or –NR–;

X^2 is a covalent bond or an optionally substituted, bivalent saturated or unsaturated, straight or branched, C_1-C_{12} hydrocarbon chain, wherein 1-3 methylene units are optionally and independently replaced with -O-, -NR-, or $–Cy^C-$;

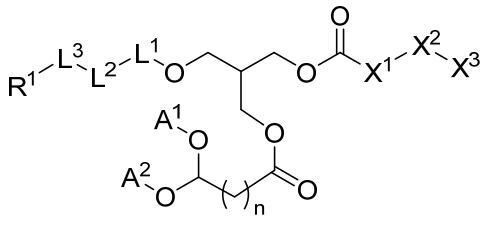
Cy^C is an optionally substituted ring selected from 3- to 7- membered saturated or partially unsaturated carbocyclene, phenylene, 3- to 7-membered saturated or partially unsaturated heterocyclene having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and 5- to 6-membered heteroarylene having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

X^3 is hydrogen or an optionally substituted ring selected from 3- to 7-membered saturated or partially unsaturated carbocyclyl, phenyl, 3- to 7-membered saturated or partially unsaturated heterocyclyl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or 5- to 6-membered heteroaryl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and

each R is independently hydrogen or an optionally substituted C_1-C_6 aliphatic group;

provided that when L^3 is a covalent bond, then R^1 must be .

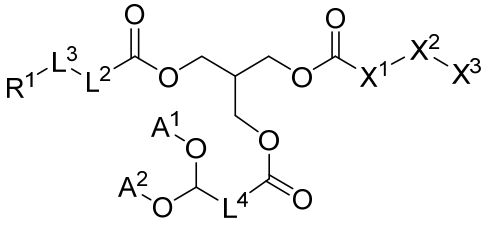
2. The compound of claim 1, wherein the compound is of Formula (II):



(II)

or a pharmaceutically acceptable salt thereof, wherein n is 1, 2, 3 or 4.

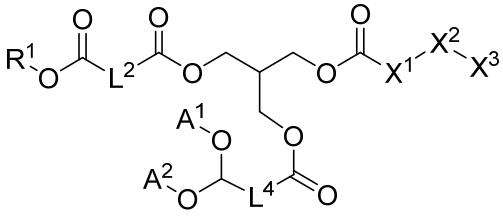
3. The compound of claim 1, wherein the compound is of Formula (III):



(III)

or a pharmaceutically acceptable salt thereof.

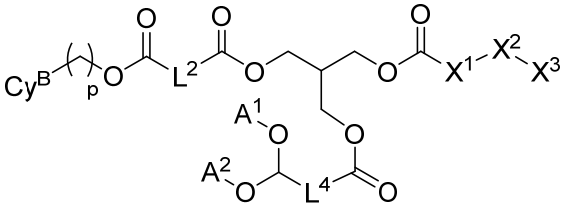
4. The compound of claim 1, wherein the compound is of Formula (IIIA):



(IIIA)

or a pharmaceutically acceptable salt thereof.

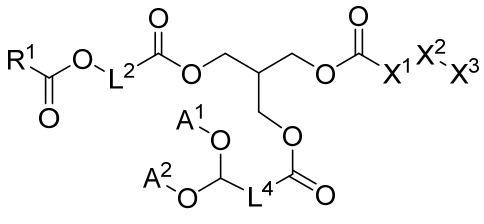
5. The compound of claim 1, wherein the compound is of Formula (IIIB):



(IIIB)

or a pharmaceutically acceptable salt thereof.

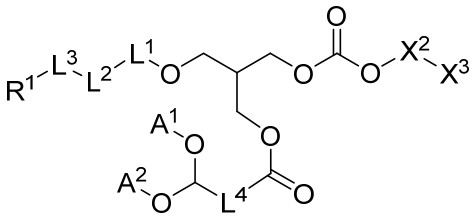
6. The compound of claim 1, wherein the compound is of Formula (IIIC):



(IIIC)

or a pharmaceutically acceptable salt thereof.

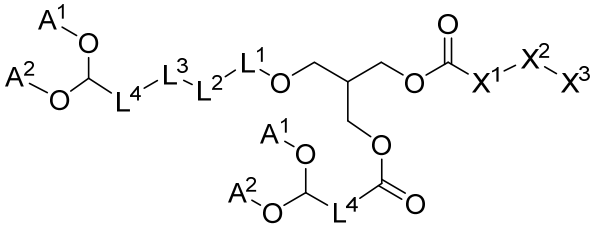
7. The compound of claim 1, wherein the compound is of Formula (IV):



(IV)

or a pharmaceutically acceptable salt thereof.

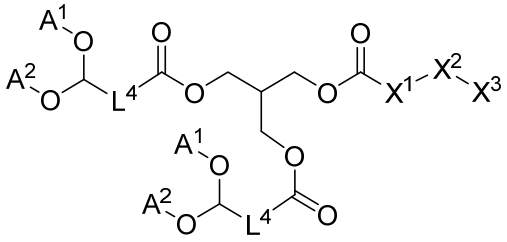
8. The compound of claim 1, wherein the compound is of Formula (V):



(V)

or a pharmaceutically acceptable salt thereof.

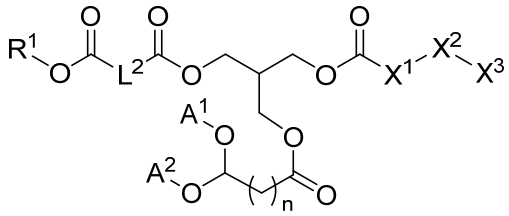
9. The compound of claim 1, wherein the compound is of Formula (VA):



(VA)

or a pharmaceutically acceptable salt thereof.

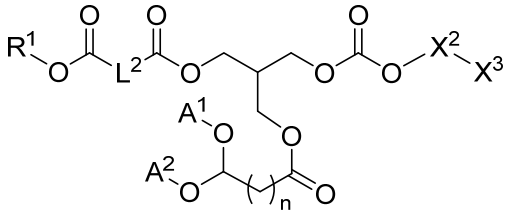
10. The compound of claim 1, wherein the compound is of Formula (VI):



(VI)

or a pharmaceutically acceptable salt thereof, wherein n is 1, 2, 3 or 4.

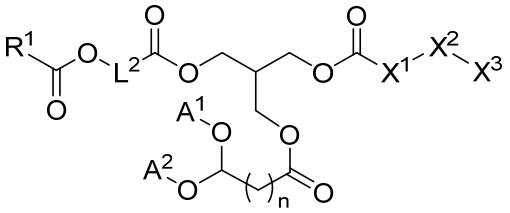
11. The compound of claim 1, wherein the compound is of Formula (VIA):



(VIA)

or a pharmaceutically acceptable salt thereof, wherein n is 1, 2, 3 or 4.

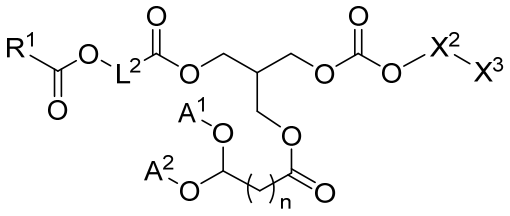
12. The compound of claim 1, wherein the compound is of Formula (VII):



(VII)

or a pharmaceutically acceptable salt thereof, wherein n is 1, 2, 3 or 4.

13. The compound of claim 1, wherein the compound is of Formula (VIIA):



(VIIA)

or a pharmaceutically acceptable salt thereof, wherein n is 1, 2, 3 or 4.

14. The compound of any one of claims 1, 2, 7 or 8, wherein L^1 is –C(O)-.

15. The compound of any one of claims 1, 2, 7 or 8, wherein L^1 is –OC(O)-.

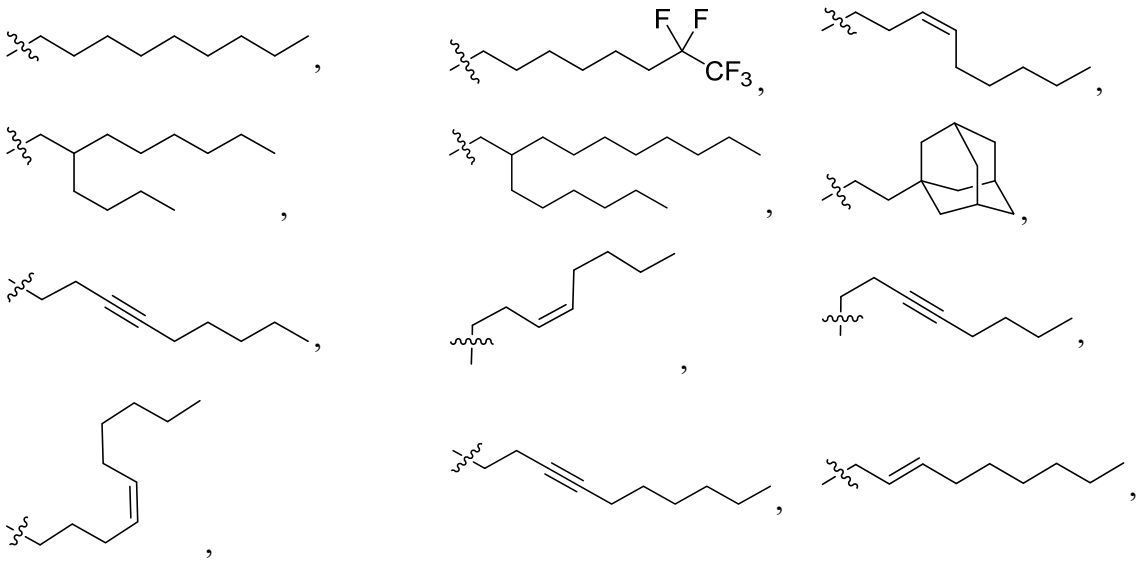
16. The compound of any one of claims 1-8 and 10-15, wherein L^2 is an optionally substituted bivalent saturated or unsaturated, straight or branched C_4-C_8 hydrocarbon chain.

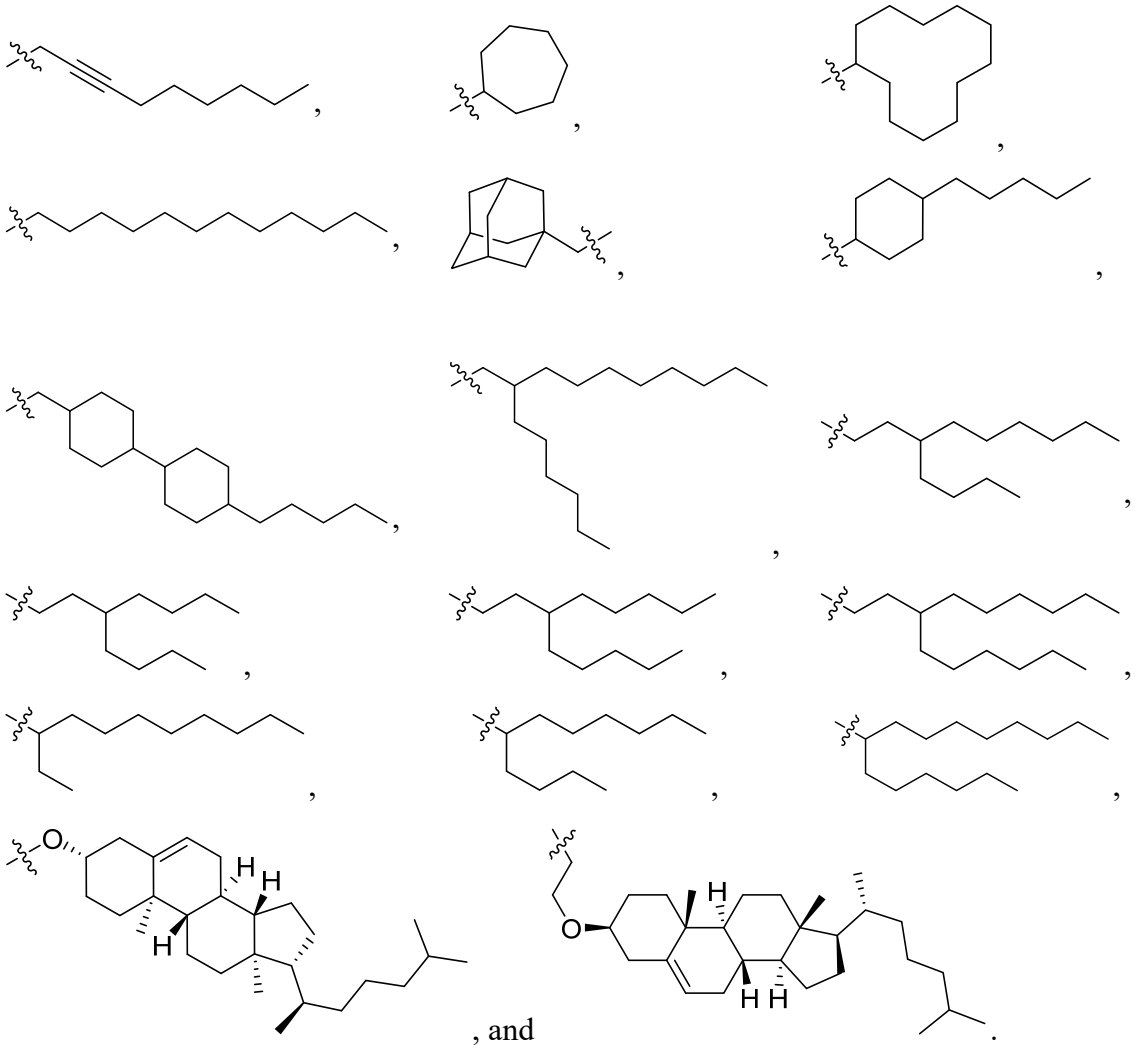
17. The compound of any one of claims 1-3, 7, 8 or 14-16, wherein L^3 is -C(O)O-.

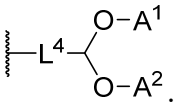
18. The compound of any one of claims 1-3, 7, 8 or 14-16, wherein L^3 is –OC(O)-.

19. The compound of any one of claims 1-4, 6, 7 or 10-18, wherein R^1 is a saturated or unsaturated, straight or branched C_6-C_{20} hydrocarbon chain optionally substituted with 1-6 fluorine atoms.

20. The compound of any one of claims 1-4, 6, 7, or 10-18, wherein R^1 is selected from:



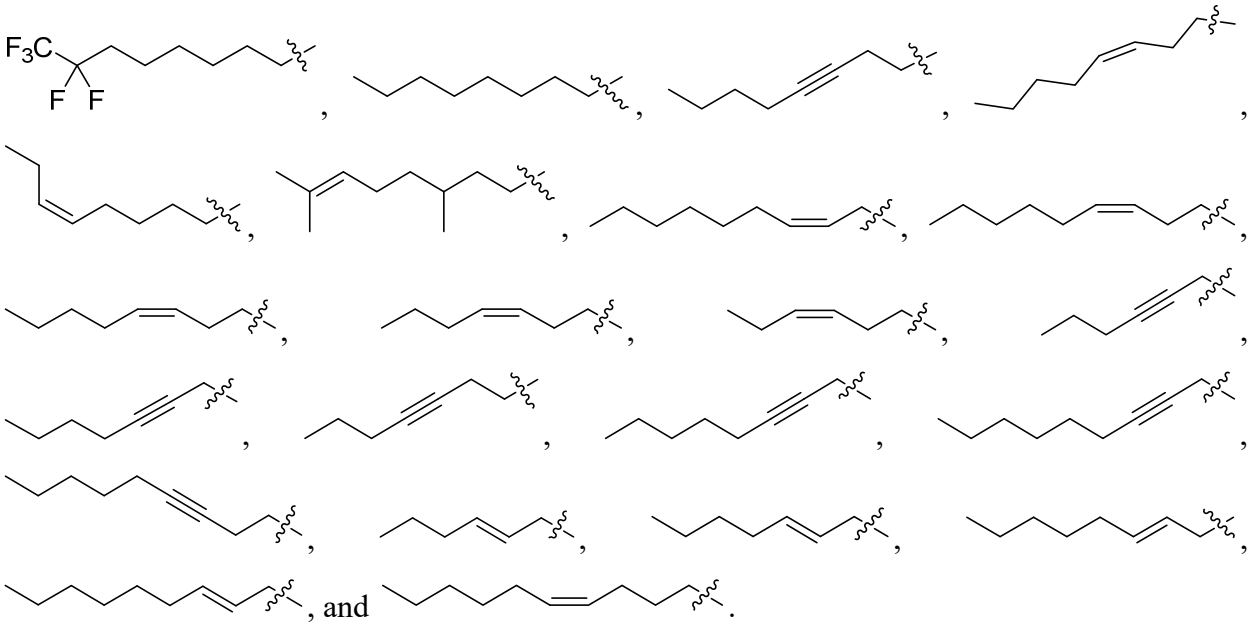


21. The compound of any one of claims 1-4, 6, 7, or 10-18, wherein R^1 is .

22. The compound of any one of claims 1-21, wherein each A^1 is independently an optionally substituted C_1-C_{20} aliphatic.

23. The compound of any one of claims 1-22, wherein each A^2 is independently an optionally substituted C_1-C_{20} aliphatic.

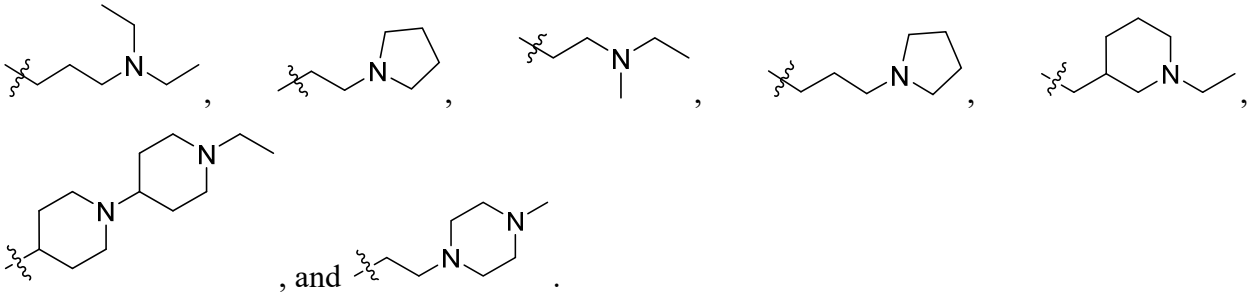
24. The compound of any one of claims 1-23, wherein each of A^1 and A^2 is independently selected from:



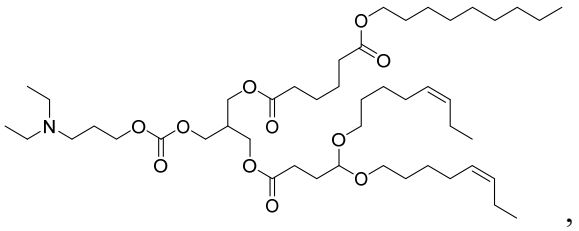
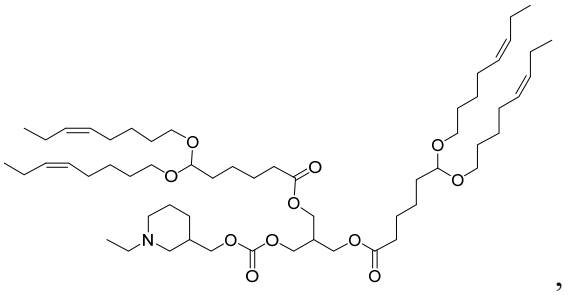
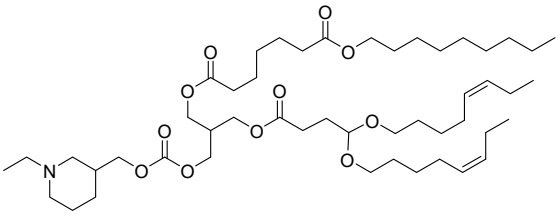
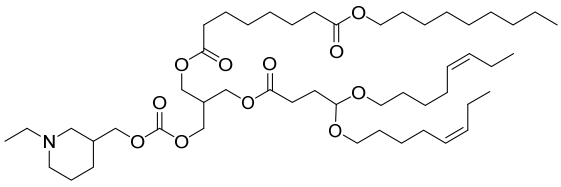
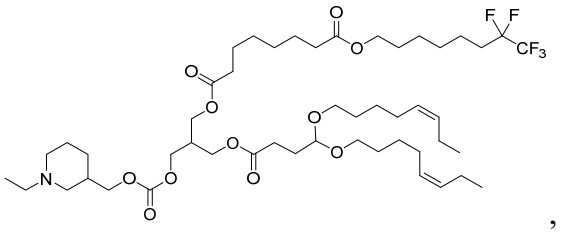
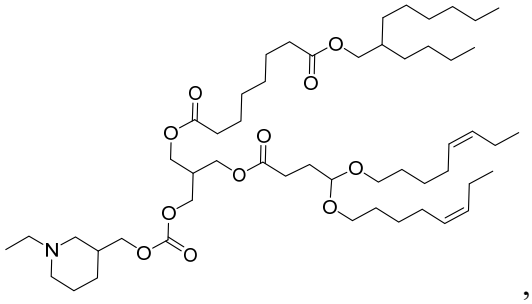
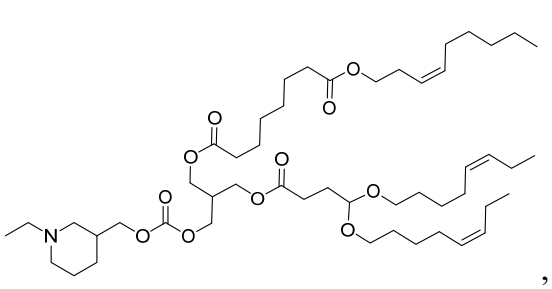
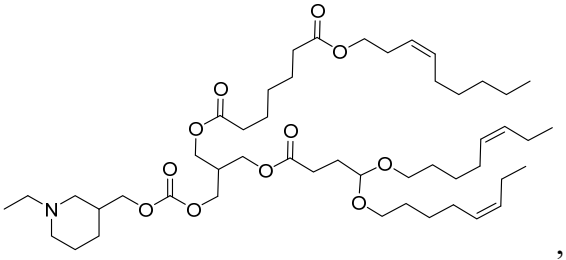
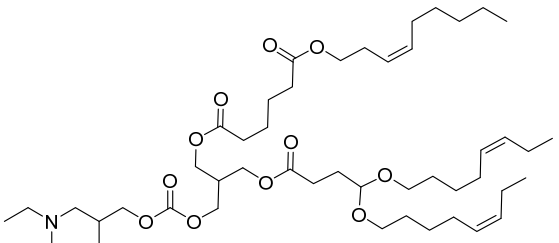
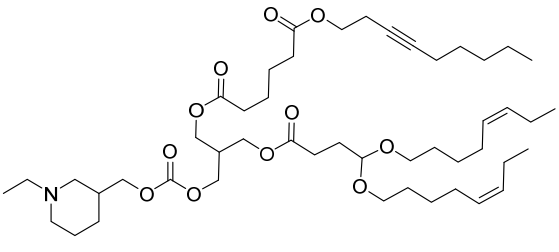
25. The compound of any one of claims 1-6, 8-10, 12 or 14-24, wherein X^1 is –O-.

26. The compound of any one of claims 1-25, wherein X^3 is optionally substituted 3- to 7-membered saturated or partially unsaturated heterocyclyl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

27. The compound of any one of claims 1-25, wherein $-X^2-X^3$ is selected from:

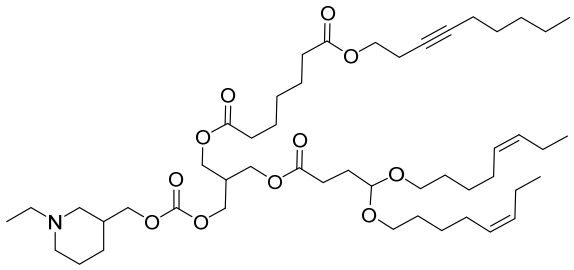
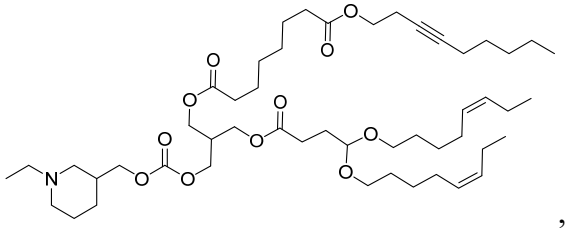
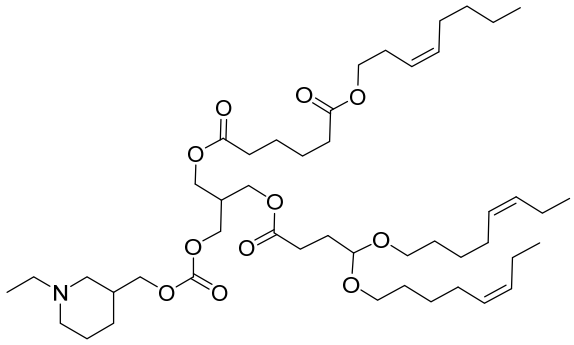
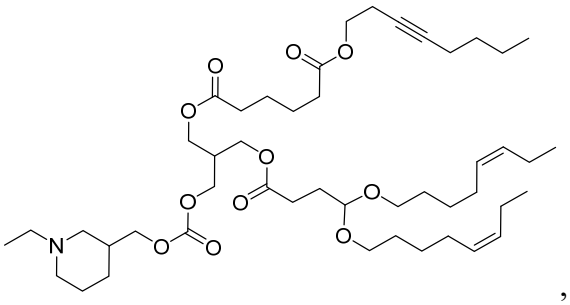
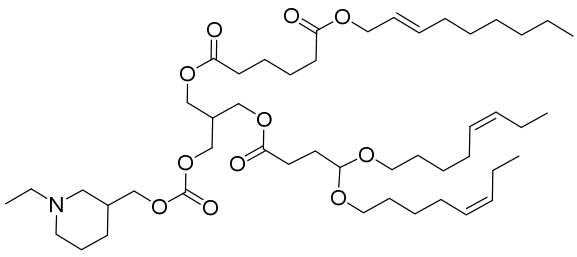
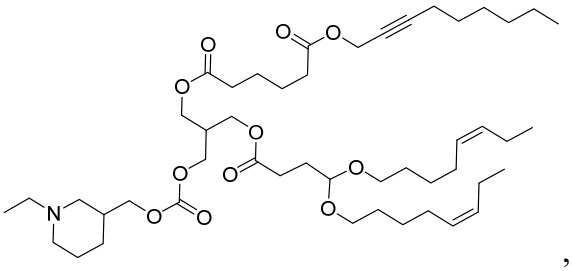
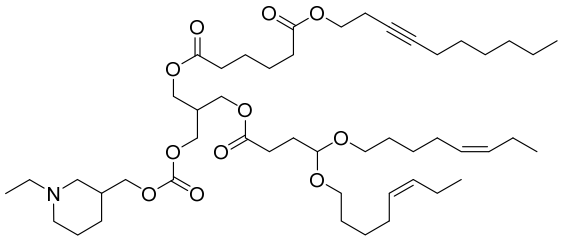
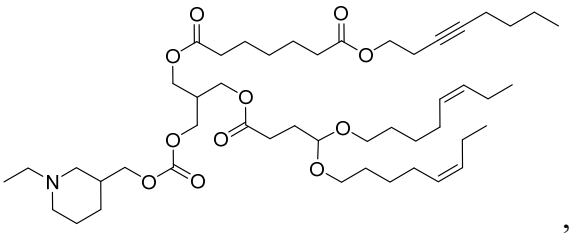


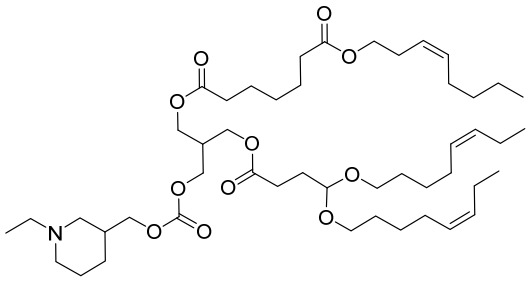
28. The compound of claim 1, wherein the compound is selected from:


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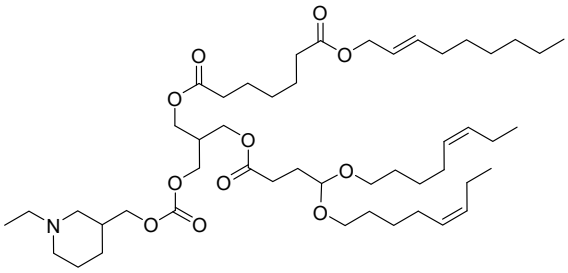
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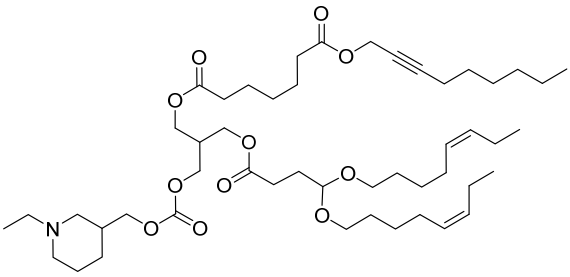

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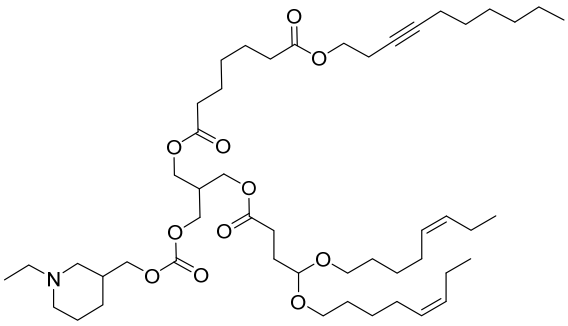
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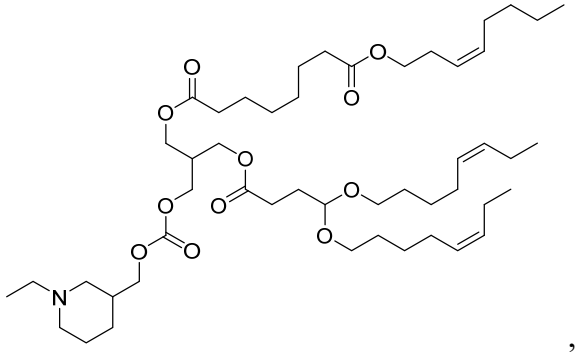
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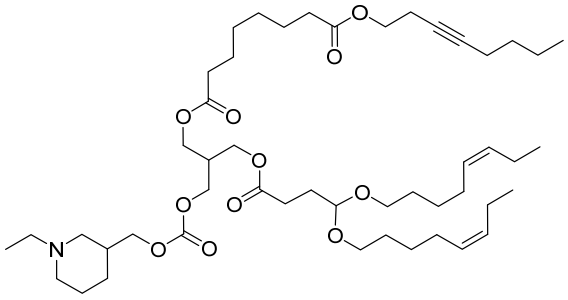
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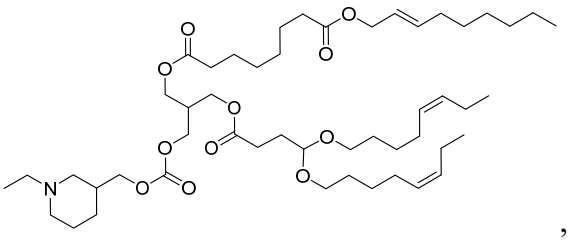
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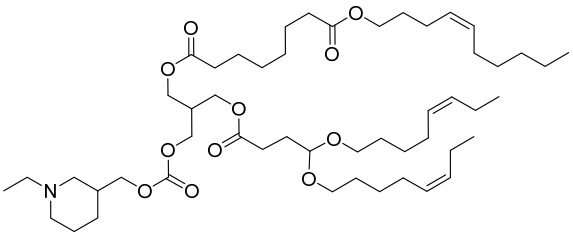
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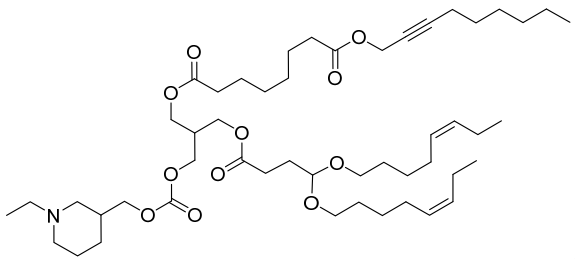
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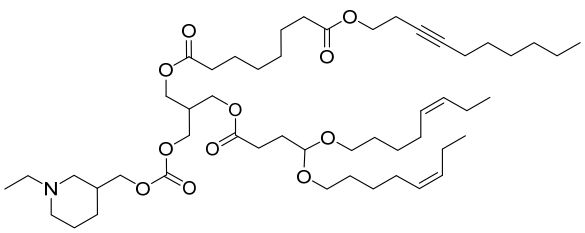
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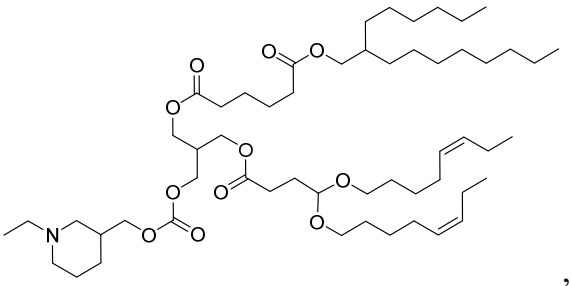
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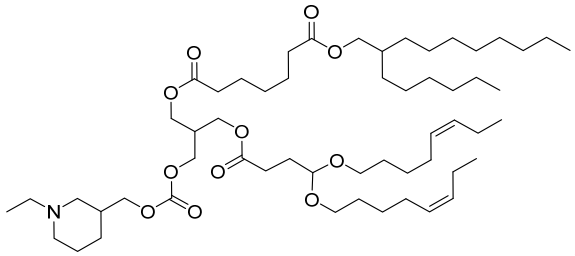
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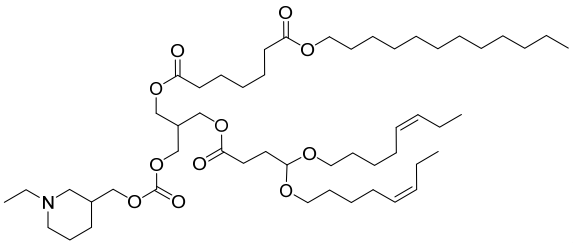
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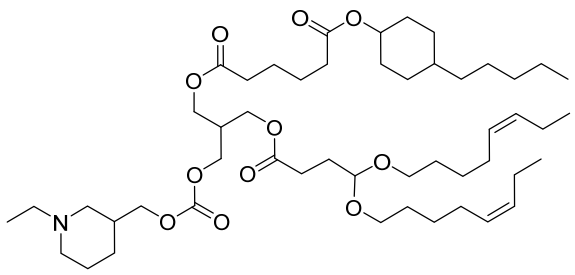
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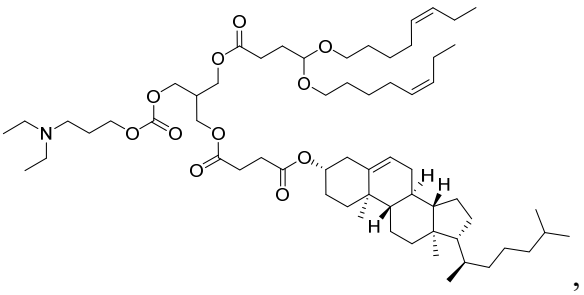
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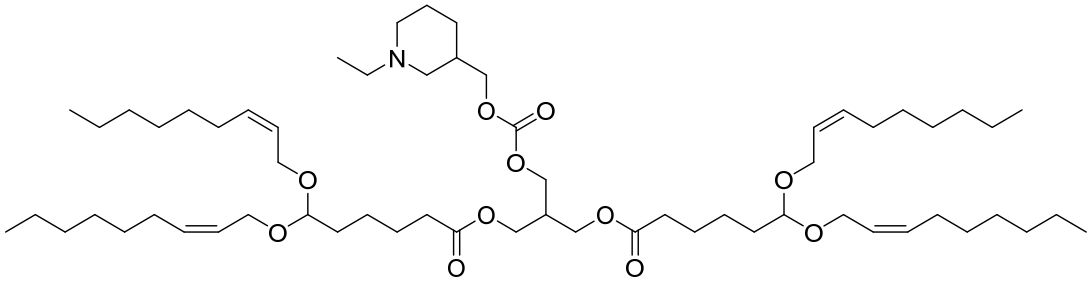
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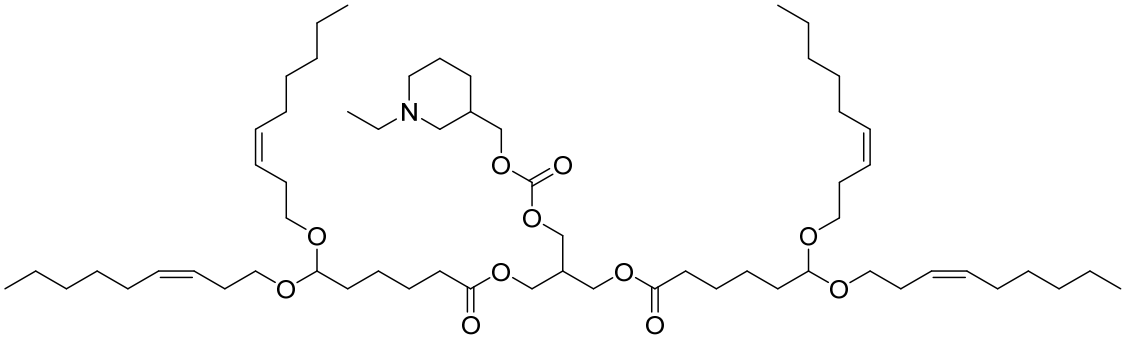
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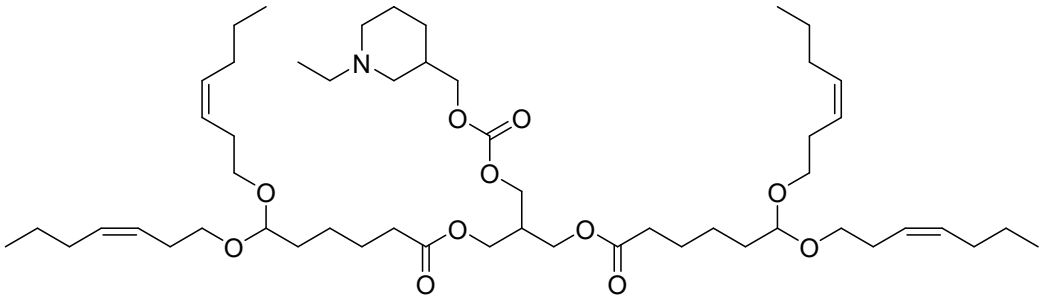
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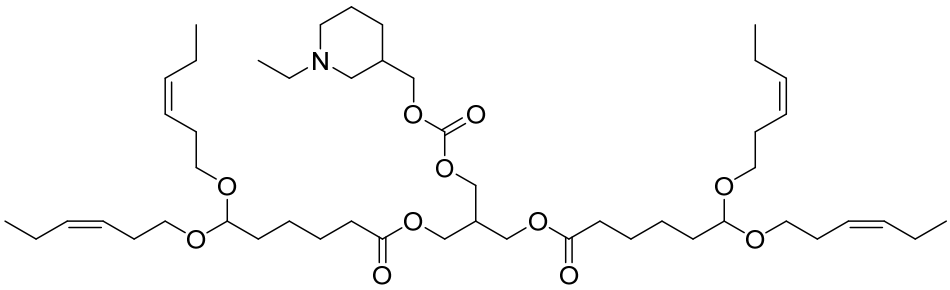
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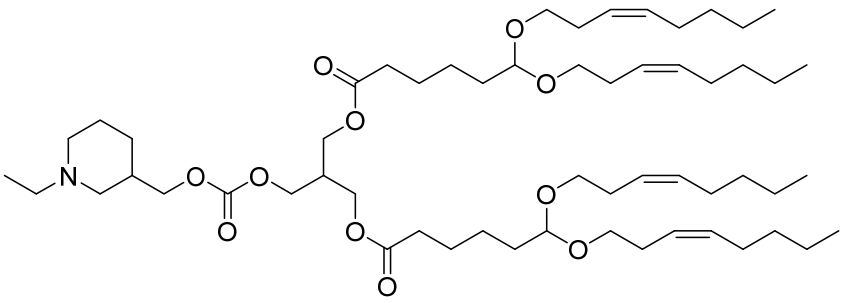
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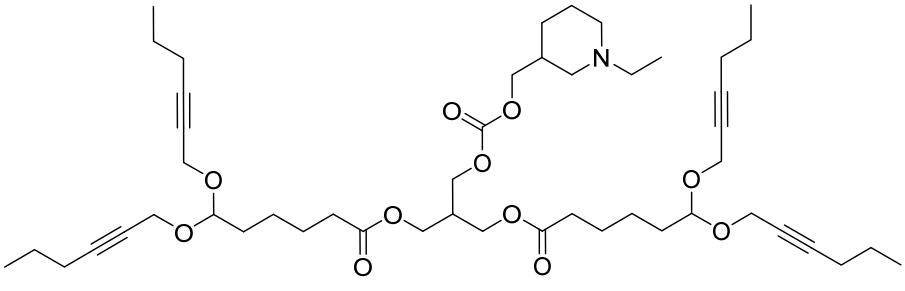
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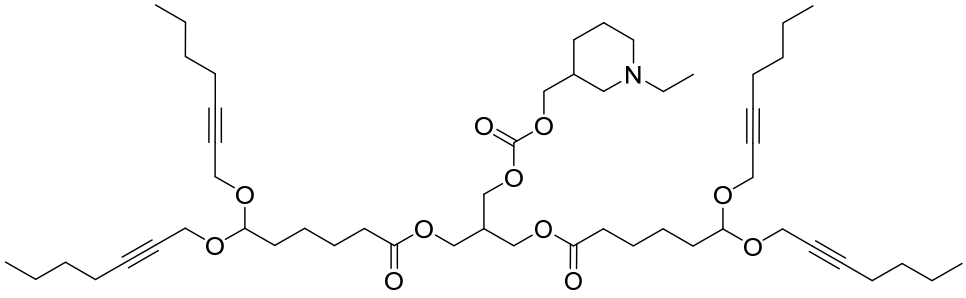
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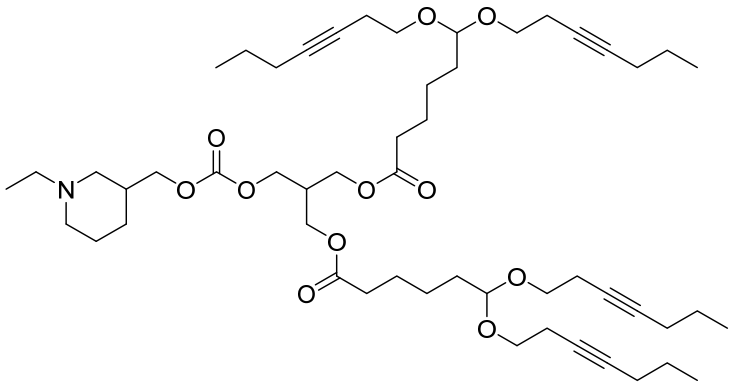
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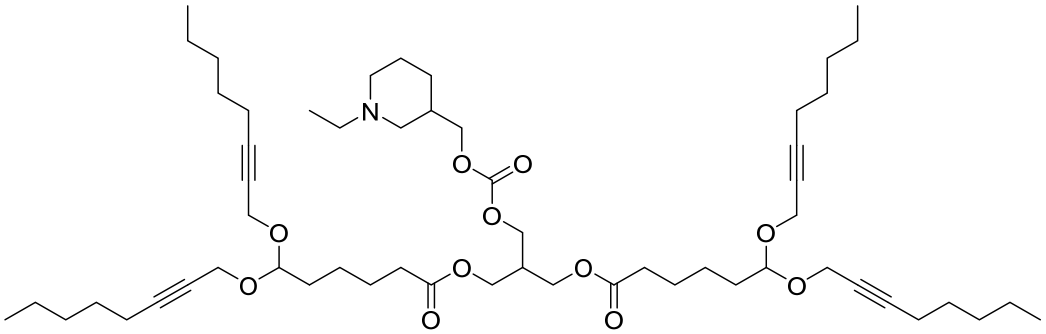
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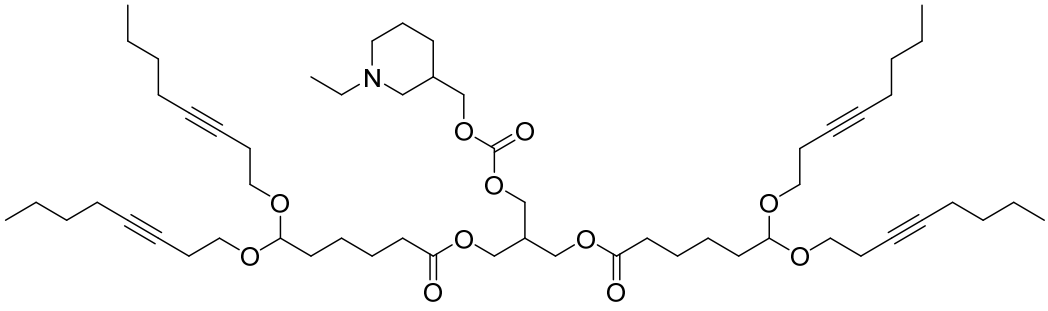
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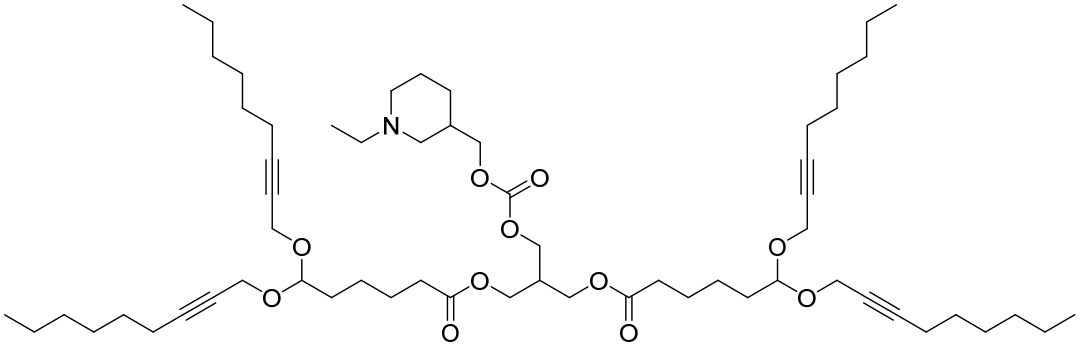
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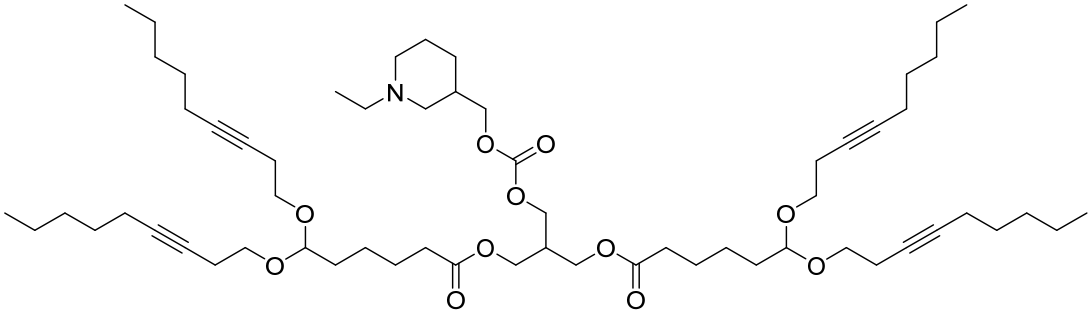
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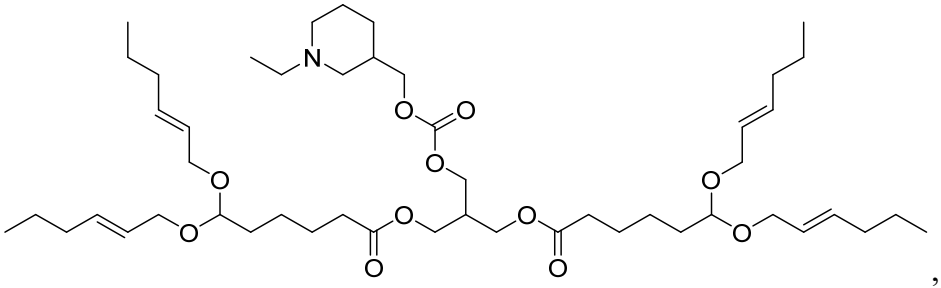
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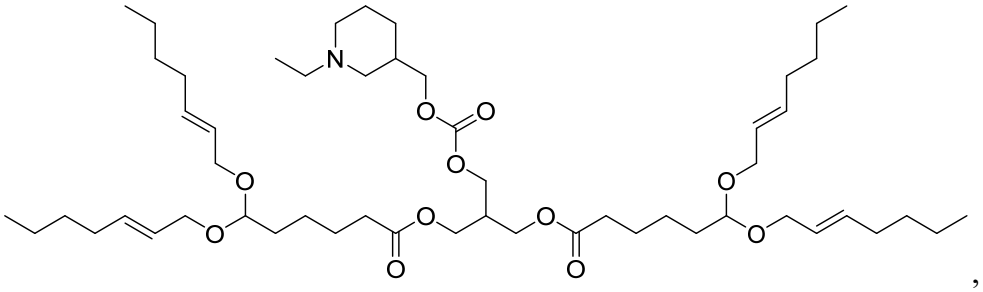
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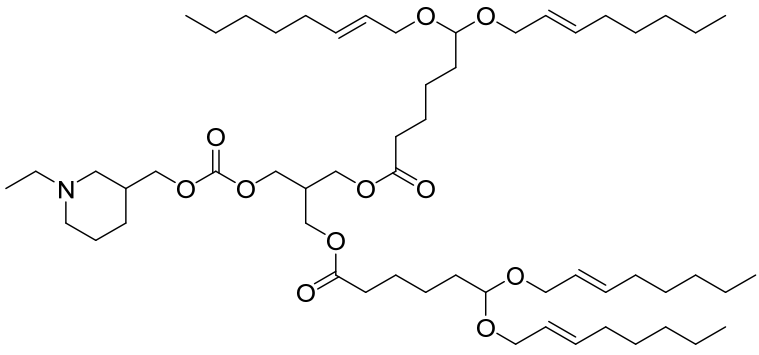
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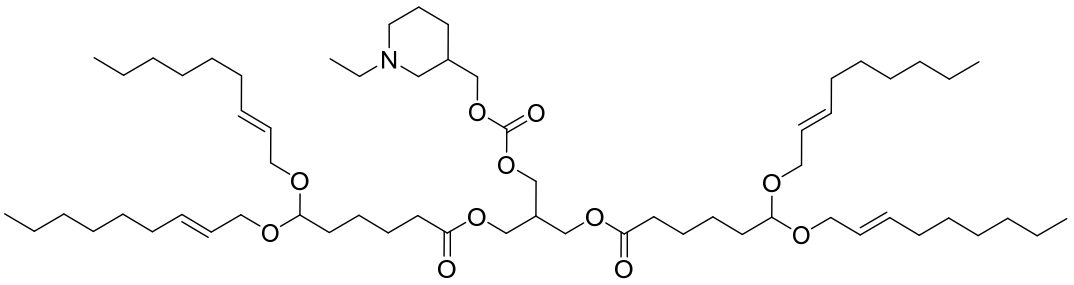
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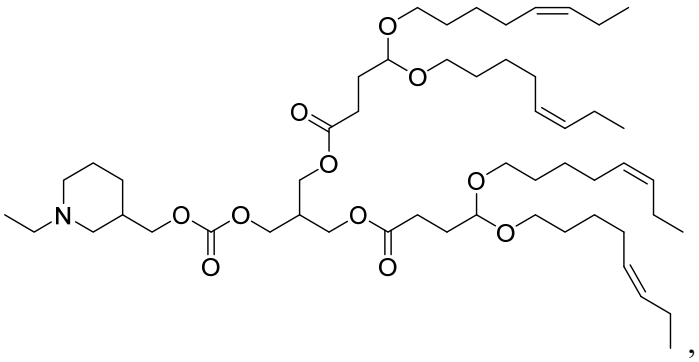
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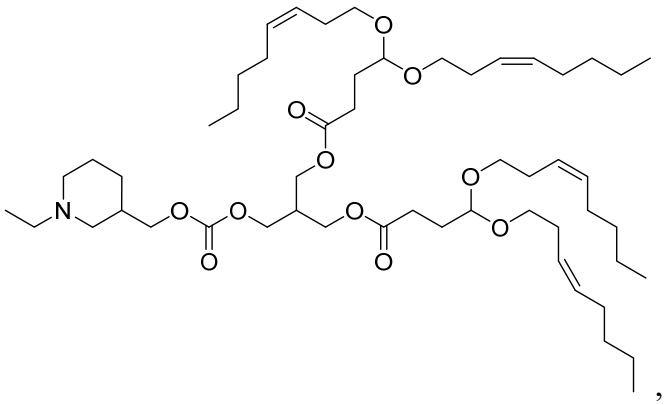
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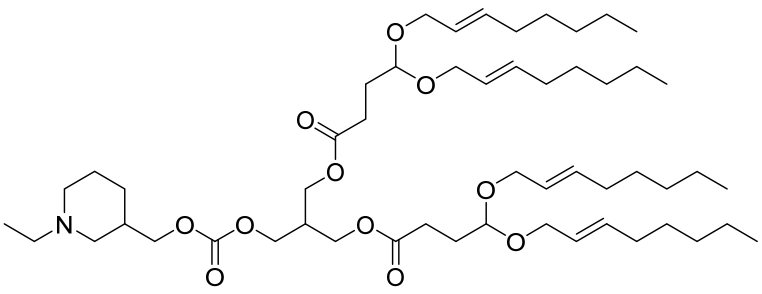
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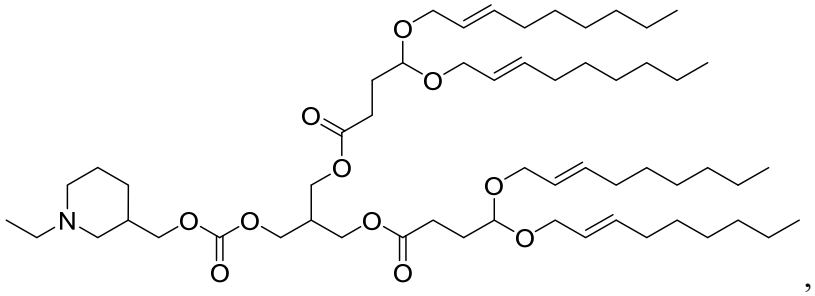
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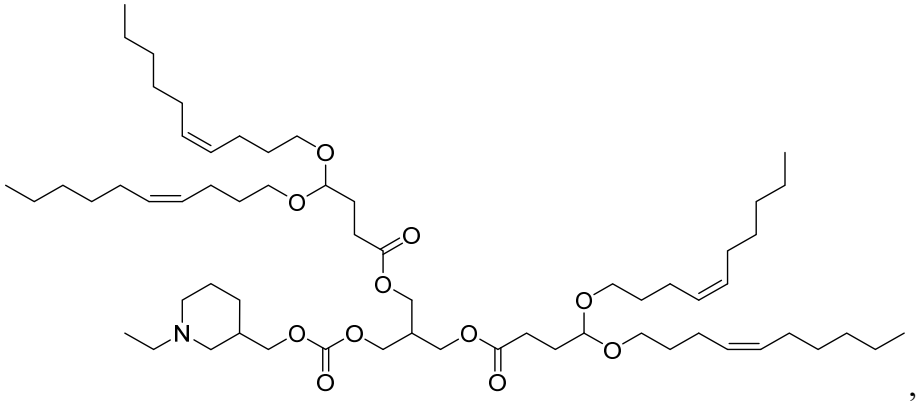
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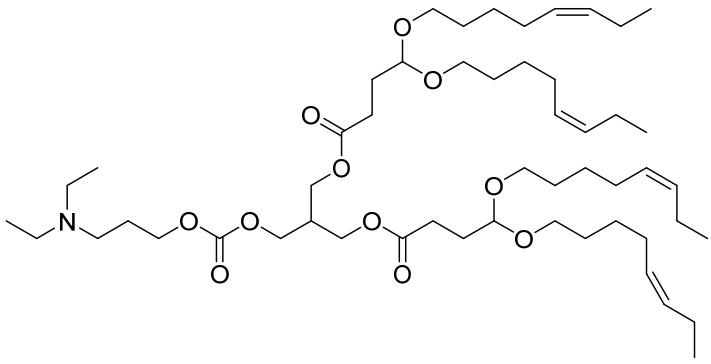
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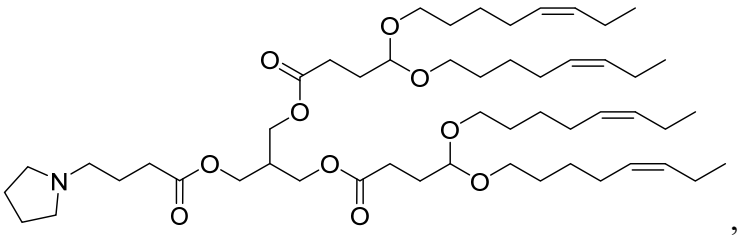
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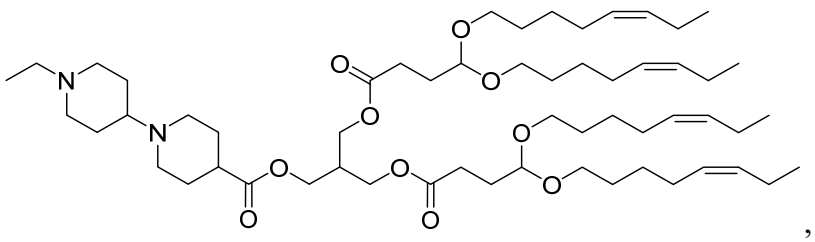
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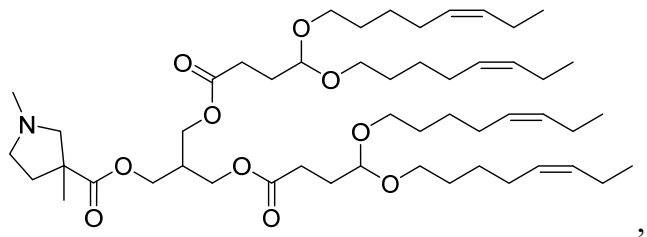
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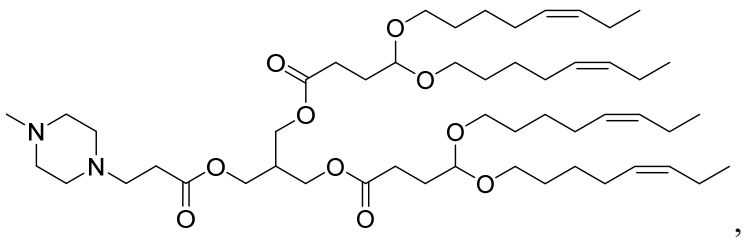
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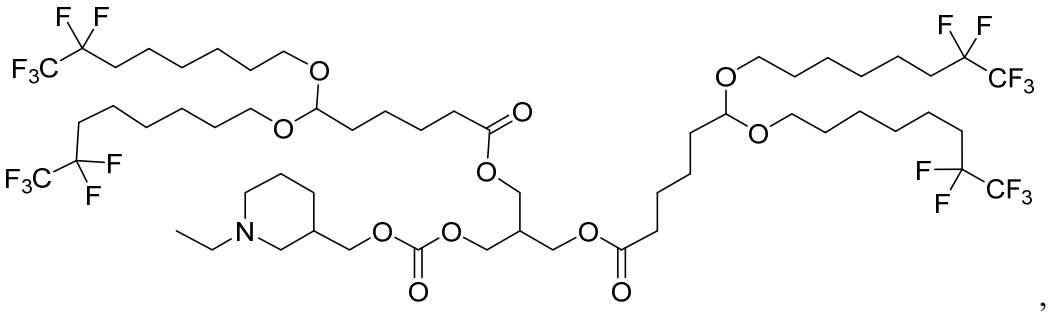
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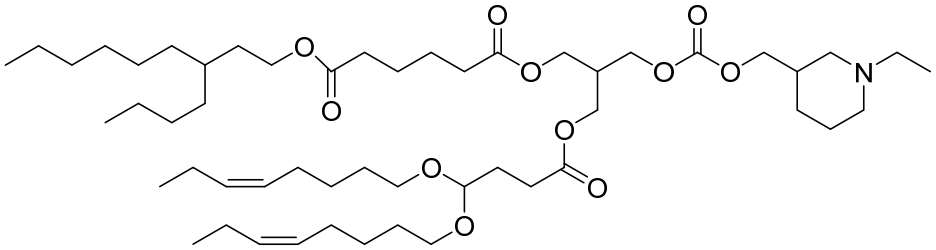
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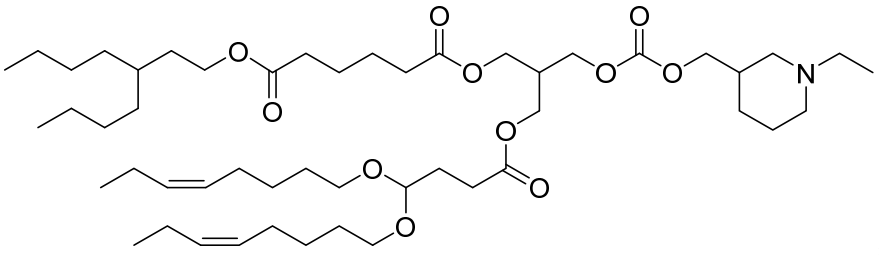
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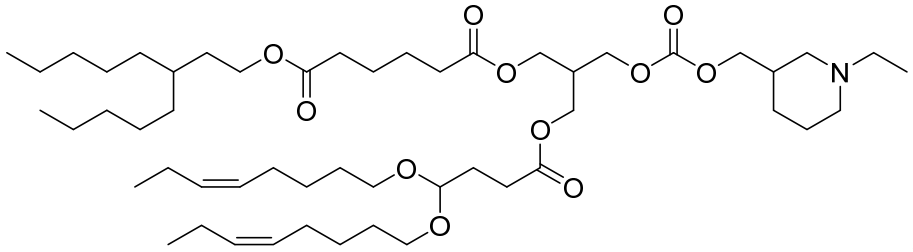
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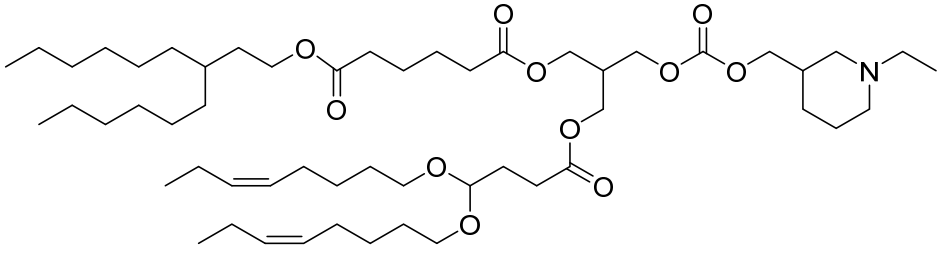
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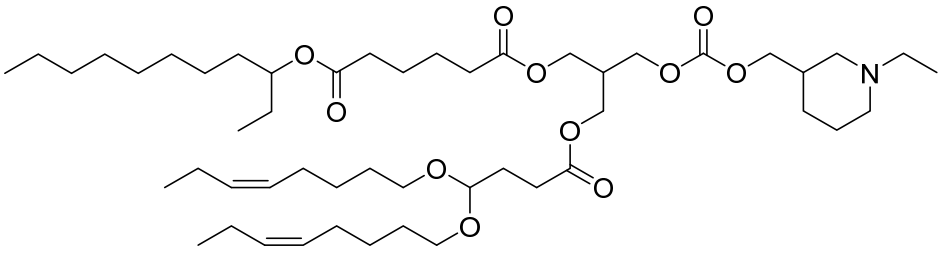
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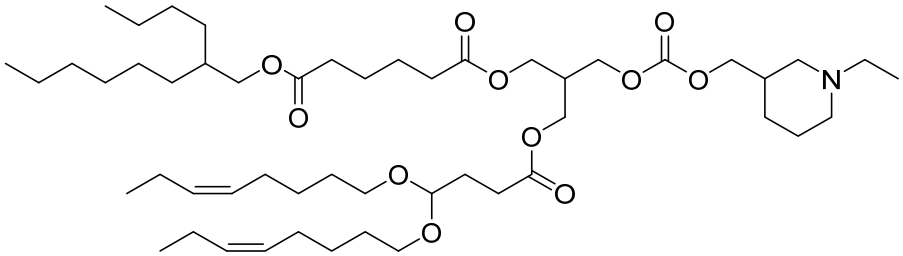
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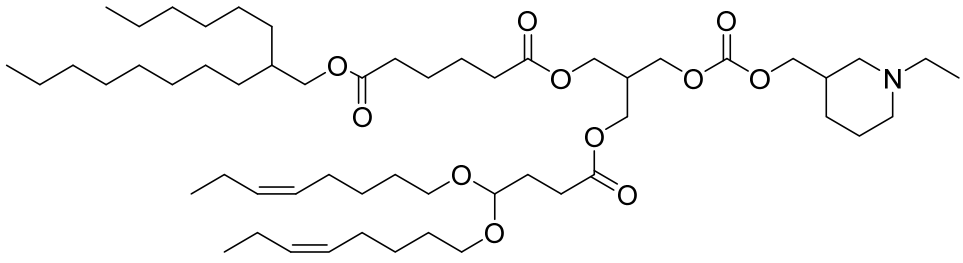
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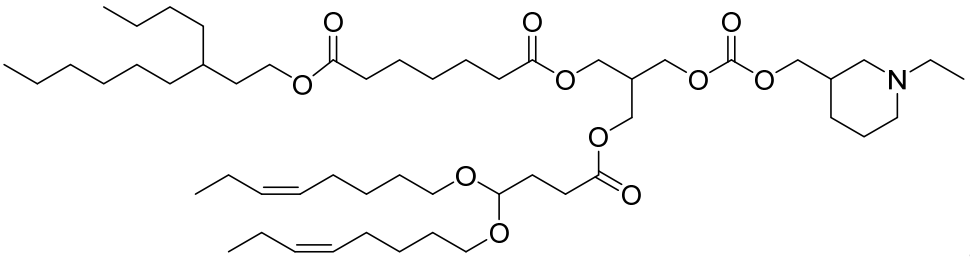
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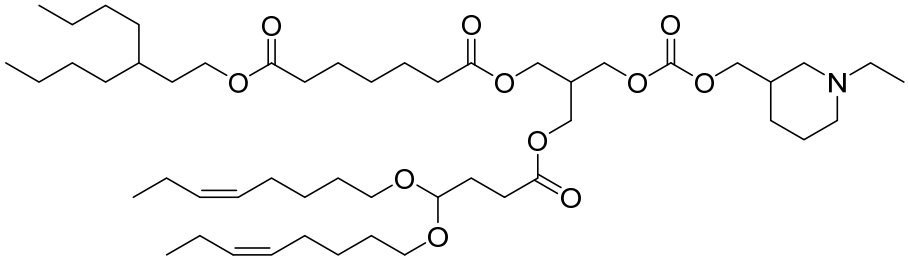
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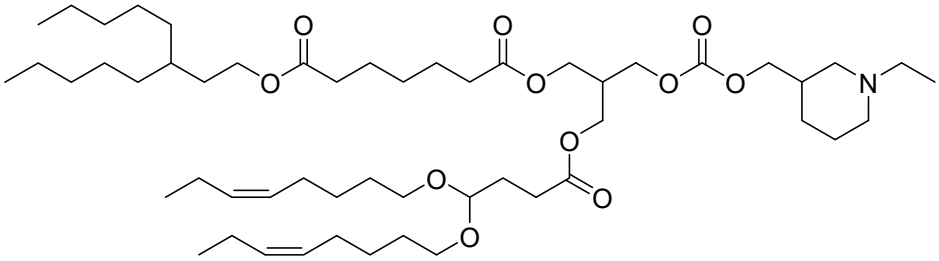
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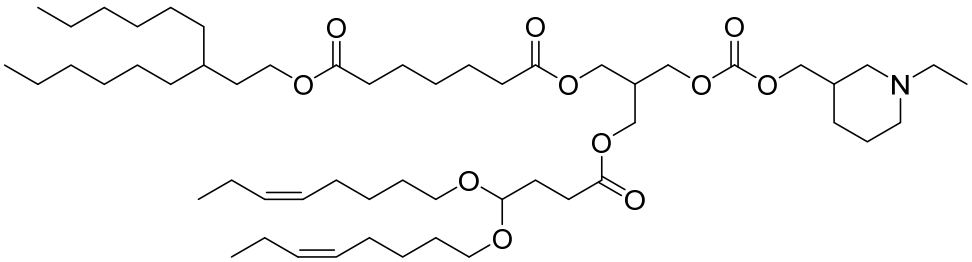
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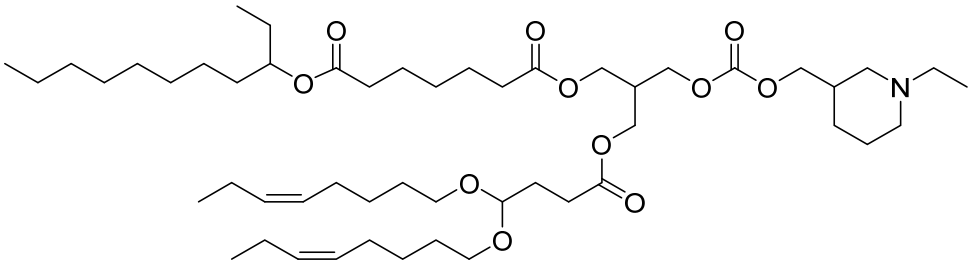
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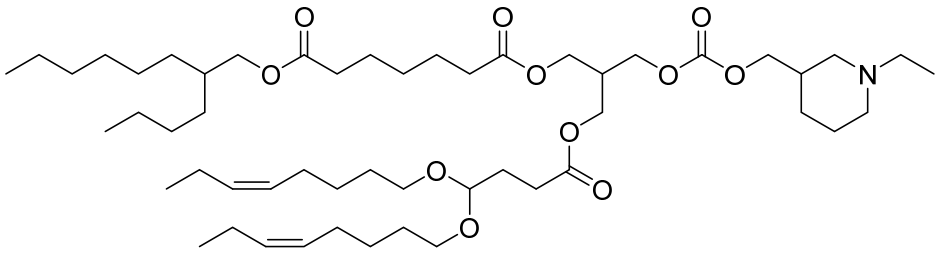
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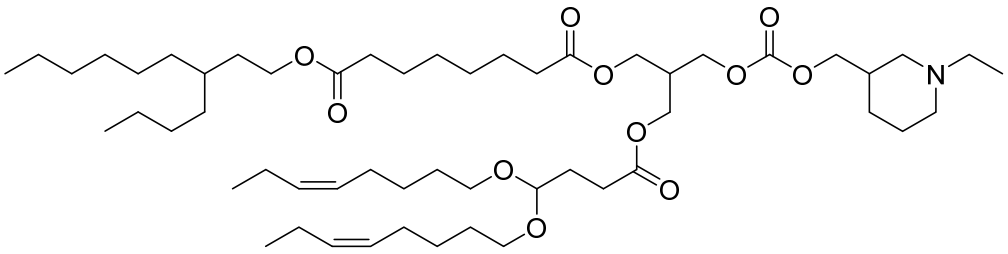
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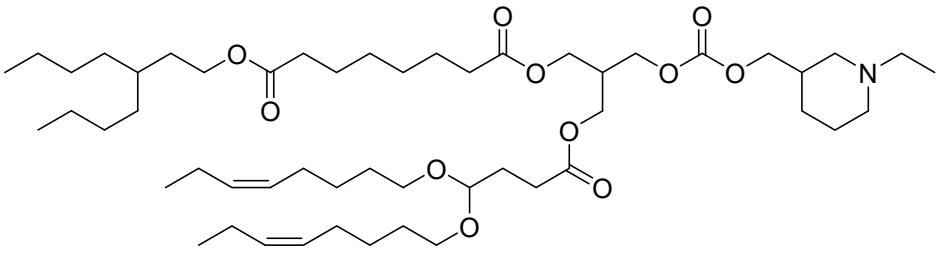
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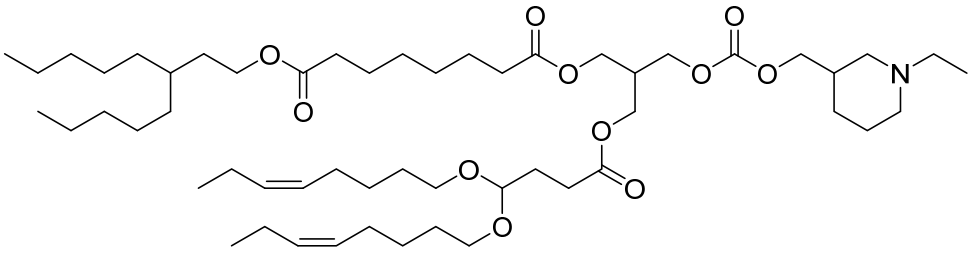
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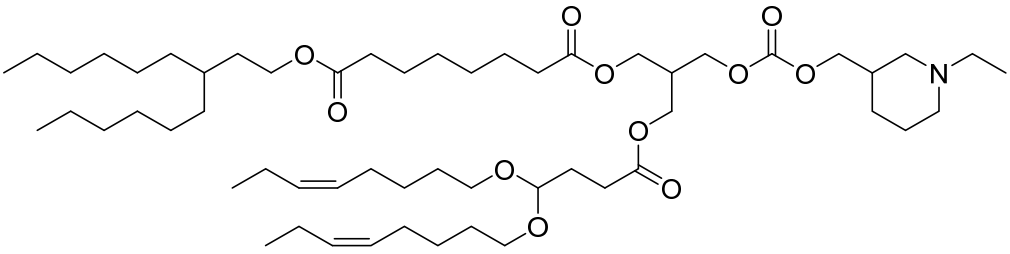
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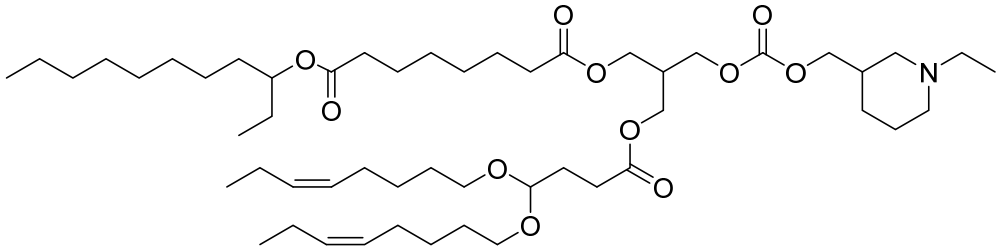
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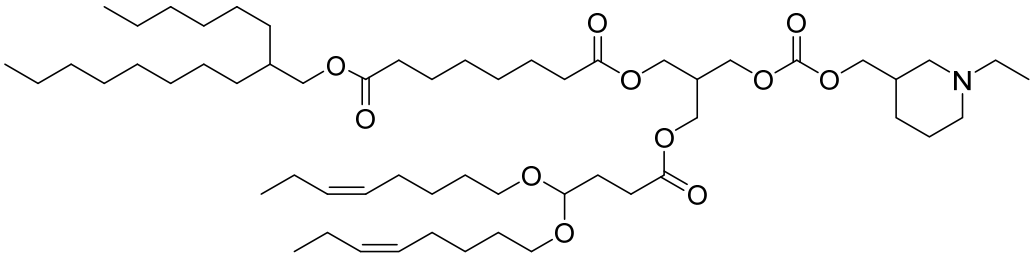
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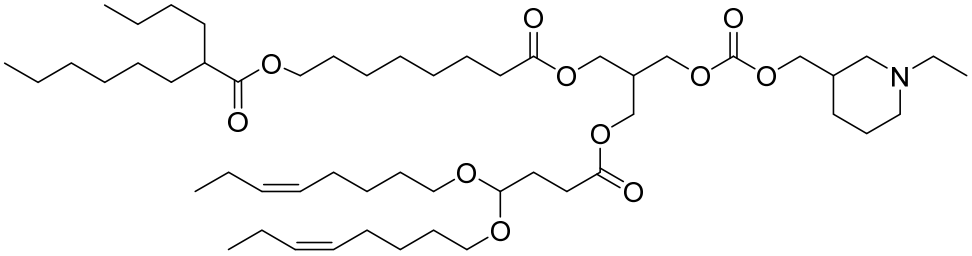
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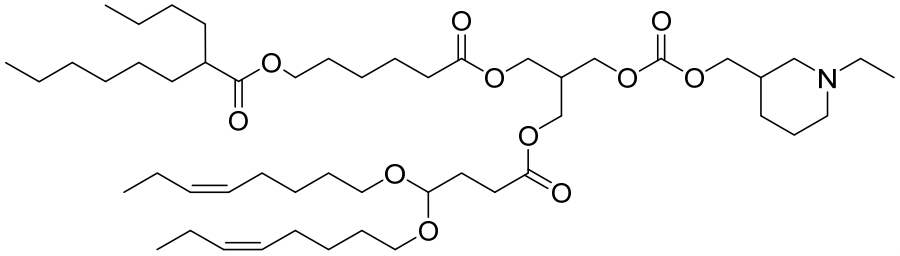
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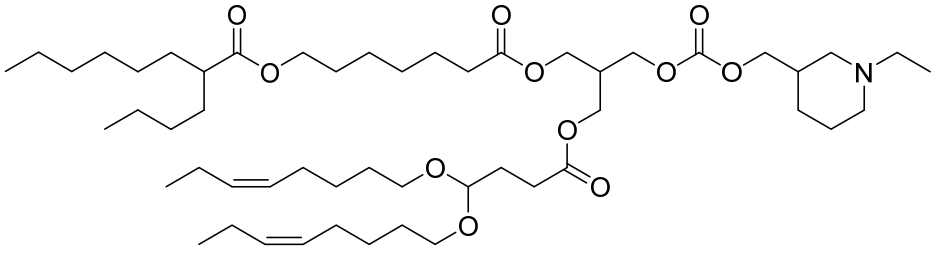
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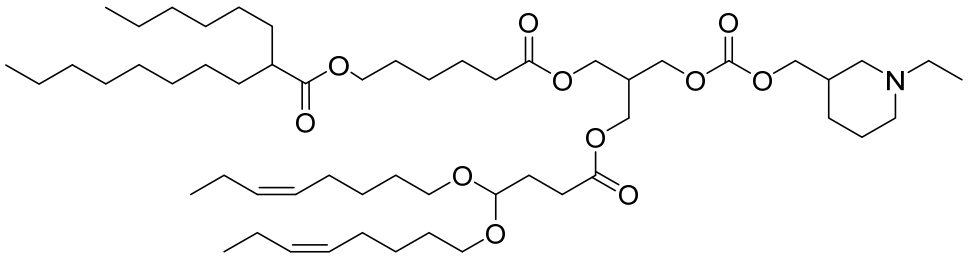
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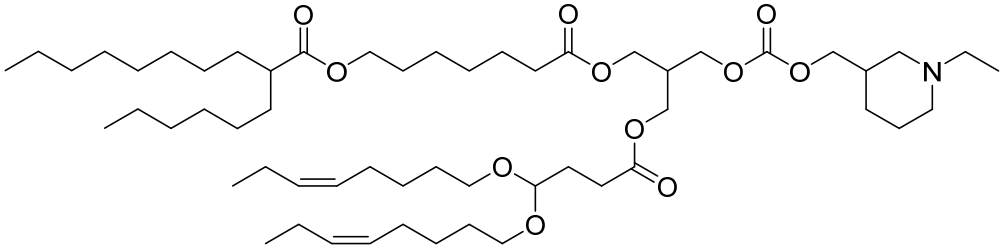
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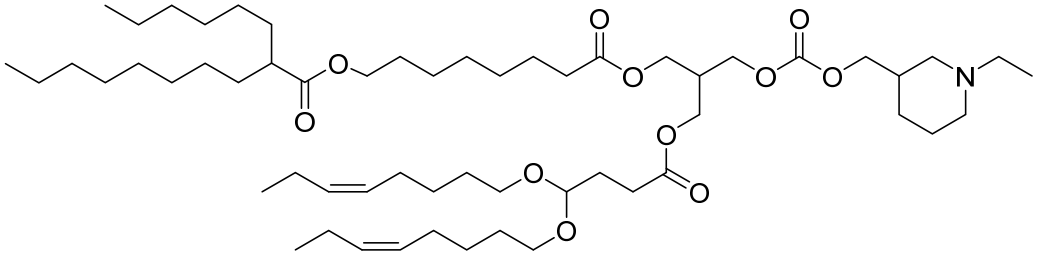


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and



or a pharmaceutically acceptable salt thereof.

29. A lipid nanoparticle (LNP) preparation comprising an ionizable lipid according to any one of claims 1-28.

30. A lipid nanoparticle (LNP) preparation comprising:
an ionizable lipid according to any one of claims 1-28;
a phospholipid;
a cholesterol; and
a conjugate-linker lipid (e.g., polyethylene glycol lipid).

31. The LNP preparation of claim 29 or claim 30, further comprising a therapeutic and/or prophylactic agent.

32. The LNP preparation of claim 31, wherein the therapeutic and/or prophylactic agent is or comprises one or more nucleic acids.

33. The LNP preparation of claim 32, wherein the one or more nucleic acids is or comprises RNA.

34. The LNP preparation of claim 32, wherein the one or more nucleic acids is or comprises DNA.

35. The LNP preparation of any one of claims 31-34, wherein the LNP preparation is formulated to deliver the therapeutic and/or prophylactic agent to target cells.

36. The LNP preparation of claim 35, wherein the target cells are or comprise spleen cells (e.g., splenic B cells, splenic T cells, splenic monocytes), liver cells (e.g., hepatocytes), bone marrow cells (e.g., bone marrow monocytes), immune cells, muscle cells (e.g., myocytes), heart cells (e.g., cardiomyocytes), kidney cells, or cells in the central nervous system.

37. The LNP preparation of claim 35, wherein the target cells are or comprise hematopoietic stem cells (HSCs).

38. A pharmaceutical composition comprising a LNP preparation of any one of claims 29-37 and a pharmaceutically acceptable excipient.

39. Use of the LNP preparation of any one of claims 29-37 in the manufacture of a medicament for treating a disease or a disorder in a subject in need thereof, wherein the disease or disorder comprises cancer, autoimmune disease, infectious disease, organ transplant, organ failure, protein deficiency, or a combination thereof.

40. Use of the LNP preparation of any one of claims 29-37 in the manufacture of a medicament for delaying and/or arresting progression of a disease or a disorder in a subject in need thereof,

wherein the disease or disorder comprises cancer, autoimmune disease, infectious disease, organ transplant, organ failure, protein deficiency, or a combination thereof.

41. A method of delivering a therapeutic and/or prophylactic agent to a mammalian cell derived from a subject, the method comprising contacting the cell of the subject having been administered the LNP preparation of any one of claims 29-37.

42. A method of producing a polypeptide of interest in a mammalian cell, the method comprising contacting the cell with the LNP preparation of any one of claims 31-37, wherein the therapeutic and/or prophylactic agent is or comprises an mRNA, and wherein the mRNA encodes the polypeptide of interest, whereby the mRNA is capable of being translated in the cell to produce the polypeptide of interest.

43. A method of inhibiting production of a polypeptide of interest in a mammalian cell, the method comprising contacting the cell with the LNP preparation of any one of claims 31-37, wherein the therapeutic and/or prophylactic agent is or comprises an RNA, whereby the RNA is capable of inhibiting production of the polypeptide of interest.

44. Use of the LNP nanoparticle composition of any one of claims 29-37 in the manufacture of a medicament to deliver a therapeutic and/or prophylactic agent to a mammalian organ, wherein the mammalian organ is contacted with the medicament, whereby the therapeutic and/or prophylactic agent is delivered to the organ.

45. Use of the LNP preparation of any one of claims 29-37 in the manufacture of a vaccine.

46. Use of a LNP preparation comprising a compound of any one of claims 1-28, or a pharmaceutically acceptable salt thereof, or a LNP composition of any one of claims 29-37 in the manufacture of a medicament for inducing an adaptive immune response in a subject wherein the subject has a disease or disorder comprising cancer, autoimmune disease, infectious disease, organ transplant, organ failure, protein deficiency, or a combination thereof and wherein the disease or disorder is responsive to the adaptive immune response induced by the medicament.