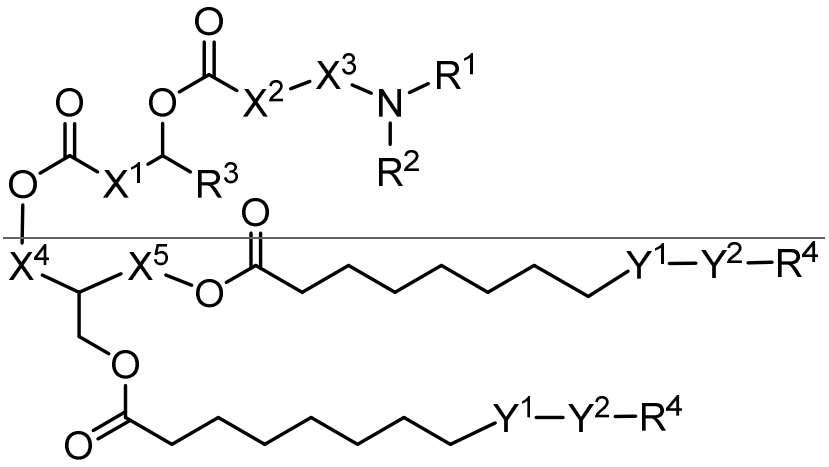
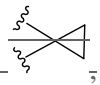
What is claimed is:

1. A compound of ~~Formula IA;~~



~~(IA)~~

~~wherein, independently for each occurrence,~~

~~X^1 is C_{1-3} alkylene or~~  ;

~~X^2 is selected from O, NH, NMe, and a bond,~~

~~X^3 is C_{2-4} alkylene,~~

~~X^4 is C_1 alkylene or a bond,~~

~~X^5 is C_1 alkylene or a bond,~~

~~R^1 is C_{1-3} alkyl,~~

~~R^2 is C_{1-3} alkyl, or~~

~~R^2 taken together with the nitrogen atom and either R^1 or a carbon atom of X^3 form a 4-membered, 5-membered, or 6-membered ring,~~

~~Y^1 is selected from a bond, –CH=CH–, –(C=O)O–, and –O(C=O)–,~~

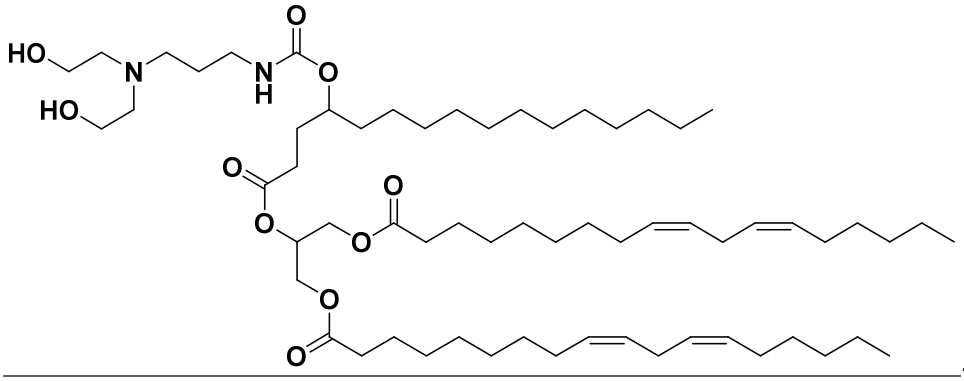
~~Y^2 is selected from –CH_2–CH=CH– and C_3-C_4 alkylene,~~

~~R^3 is selected from H, C_{5-7} cycloalkyl, C_8-C_{10} alkenyl, and C_{3-18} alkyl,~~

~~R^4 is C_{4-8} alkyl,~~

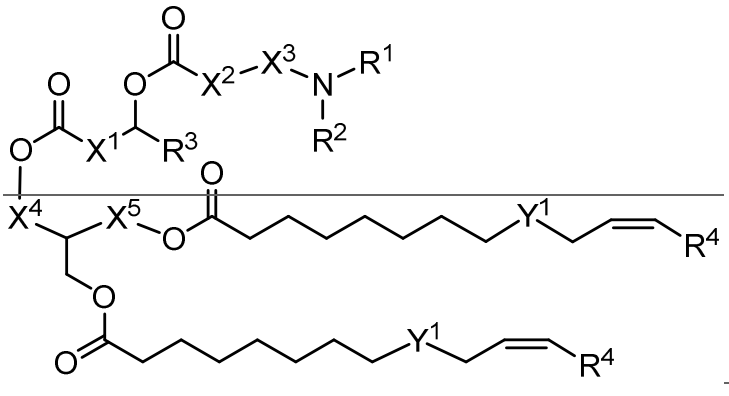
~~or a salt thereof,~~

~~with a proviso that when R^2 is Me, R^3 is linear C_{12} alkyl, X^1 is C_2 alkylene, X^2 is O, X^3 is C_3 alkylene, X^4 is a bond, X^5 is C_1 alkylene, Y^1 is *cis* –CH=CH–, and –Y^2–R^4 is *cis* –CH_2–CH=CH–(C_5-alkyl), then R^1 is C_{2-3} alkyl~~the formula



.

2. The compound of claim 1, wherein the compound is a compound of Formula I:



(I)

wherein, independently for each occurrence,

X^1 is C_{2-3} alkylene,

X^2 is selected from O, NH, NMe, and a bond,

X^3 is C_{2-4} alkylene,

X^4 is C_1 alkylene or a bond,

X^5 is C_1 alkylene or a bond,

R^1 is C_{1-2} alkyl,

R^2 is C_{1-2} alkyl, or

R^2 taken together with the nitrogen atom and either R^1 or a carbon atom of X^3 form a 5-membered or a 6-membered ring,

Y^1 is selected from -CH=CH-, -(C=O)O-, and -O(C=O)-,

R^3 is selected from H, C_{5-7} cycloalkyl, and C_{3-18} alkyl,

R^4 is C_{4-7} alkyl,

or a salt thereof,

with a proviso that when R^2 is Me, R^3 is linear C_{12} alkyl, X^1 is C_2 alkylene, X^2 is O, X^3 is C_3 alkylene, X^4 is a bond, X^5 is C_1 alkylene, Y^1 is *cis* CH=CH , and R^4 is C_5 alkyl, then R^1 is C_2 alkyl.

3. The compound of claim 1 or 2, wherein the compound is enantiomerically enriched or diastereomerically enriched.

4. The compound of any one of the preceding claims, wherein X^1 is C_2 alkylene.

5. The compound of claim 1, wherein X^1 is C_1 alkylene.

6. The compound of any one of claims 1-3, wherein X^1 is linear C_3 alkylene.

7. The compound of any one of claims 1-3, wherein X^1 is branched C_3 alkylene.

8. The compound of any one of the preceding claims, wherein X^2 is NH.

9. The compound of any one of claims 1-7, wherein X^2 is O.

10. The compound of any one of claims 1-7, wherein X^2 is NMe.

11. The compound of any one of claims 1-7, wherein X^2 is a bond.

12. The compound of any one of the preceding claims, wherein X^3 is C_{2-3} alkylene.

13. The compound of any one of claims 1-11, wherein X^3 is C_{3-4} alkylene.

14. The compound of any one of the preceding claims, wherein R^2 and a carbon atom of X^3 taken together form a 4-membered ring.

15. The compound of any one of claims 1-13, wherein R^2 and a carbon atom of X^3 taken together form a 5-membered ring.

16. The compound of any one of the claims 1-13, wherein R^2 and a carbon atom of X^3 taken together form a 6-membered ring.

17 The compound of any one of claims 1-15, wherein R^2 is C_1 alkyl.

18. The compound of any one of claims 1-16 wherein R^2 is C_2 alkyl.

19. The compound of any one of claims 1-13, wherein R^1 and R^2 together form a 4-membered ring.

20. The compound of any one of claims 1-13, wherein R^1 and R^2 together form a 5-membered ring.

21. The compound of any one of claims 1-13, wherein R^1 and R^2 together form a 6-membered ring.

22. The compound of any one of claims 1-18, wherein R^1 is C_1 alkyl.

23. The compound of any one of claims 1-18, wherein R^1 is C_2 alkyl.

24. The compound of any one of the preceding claims, wherein R^3 is linear C_{8-16} alkyl.

25. The compound of any one of the preceding claims, wherein R^3 is linear C_{7-12} alkyl.

26. The compound of any one of the preceding claims, wherein R^3 is linear C_{7-9} alkyl.

27. The compound of any one of claims 1-23, wherein R^3 is linear C_{3-6} alkyl.

28. The compound of any one of claims 1-23, wherein R^3 is branched C_{6-10} alkyl.

29. The compound of any one of claims 1-23, wherein R^3 is C_{5-7} cycloalkyl.

30. The compound of claim 29, wherein R^3 is C_6 cycloalkyl.

31. The compound of any one of claims 1-23, wherein R^3 is C_{8-10} alkenyl.

32. The compound of any one of claims 1-23, wherein R^3 is H.

33. The compound of any one of the preceding claims, wherein R^4 is linear C_{5-6} alkyl.

34. The compound of any one of the preceding claims, wherein X^4 is a bond.

35. The compound of any one of the preceding claims, wherein X^5 is a C_1 alkylene.

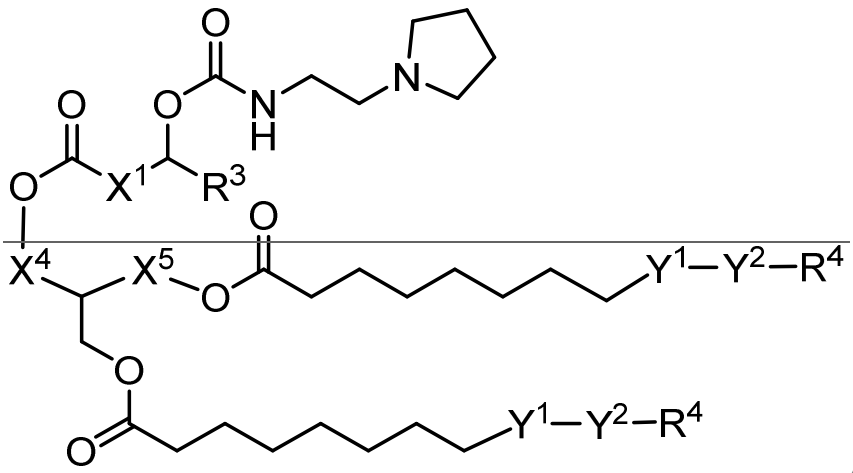
36. The compound of any one of the preceding claims, wherein the compound is a compound of Formula (IA); and Y^2–R^4 is –CH_2–CH=CH–R^4.

37. The compound of any one of claims 1–35, wherein the compound is a compound of Formula (IA); and Y^2 is linear C_3 alkylene.

38. The compound of any one of the preceding claims, wherein Y^1 is selected from a bond, –CH=CH–, and –O(C=O)–.

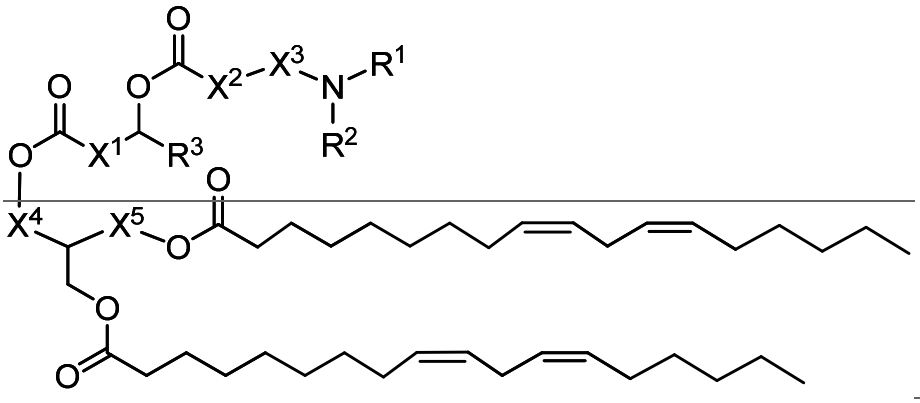
39. The compound of any one of the preceding claims, wherein Y^1 is selected from –CH=CH– and –O(C=O)–.

40. The compound of claim 1, wherein the compound is a compound of Formula II:



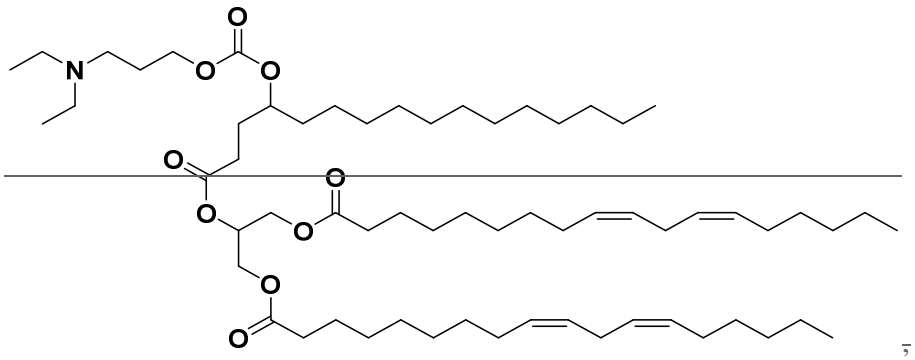
(II).

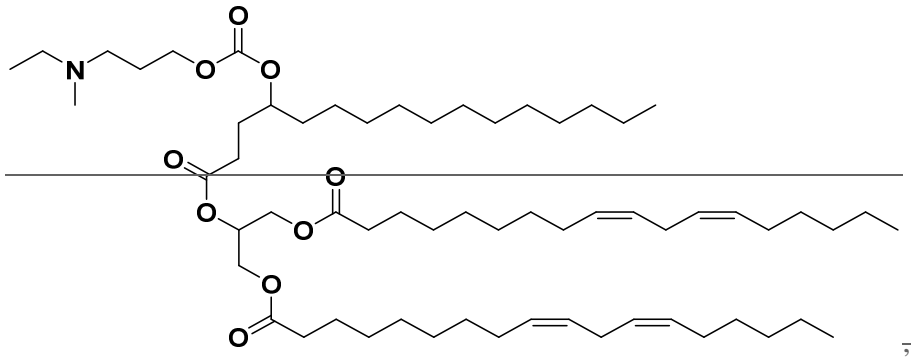
41. The compound of claim 1, wherein the compound is a compound of Formula III;

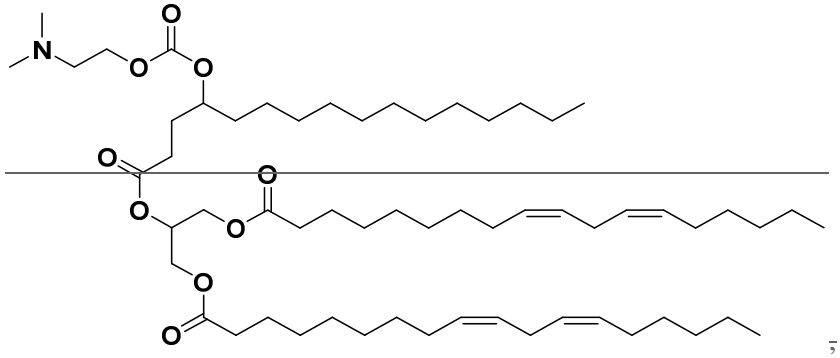


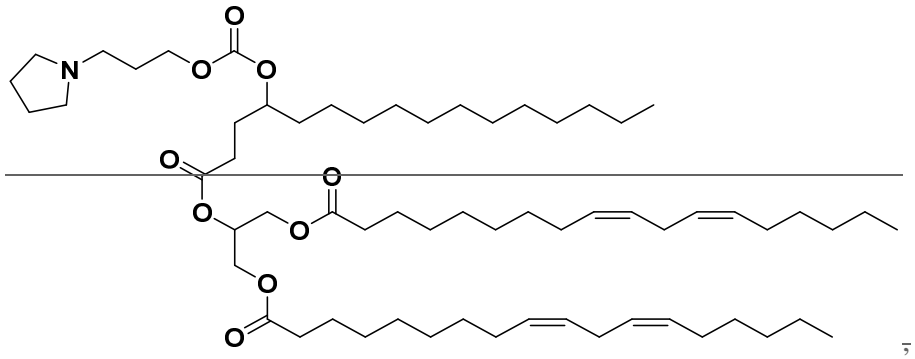
(III).

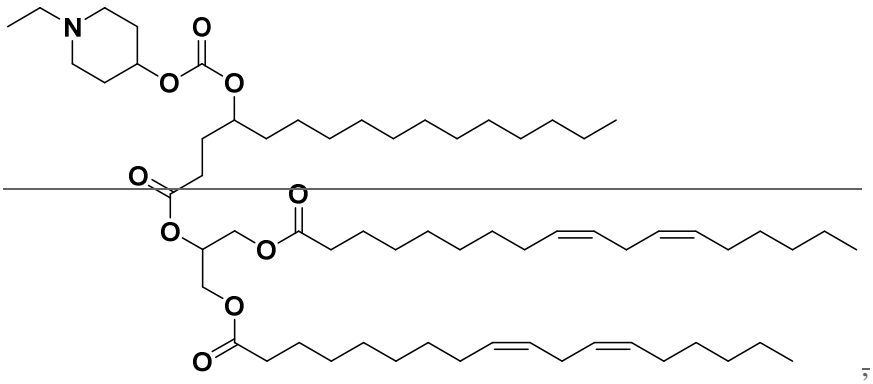
42. The compound of claim 1, wherein the compound is selected from:

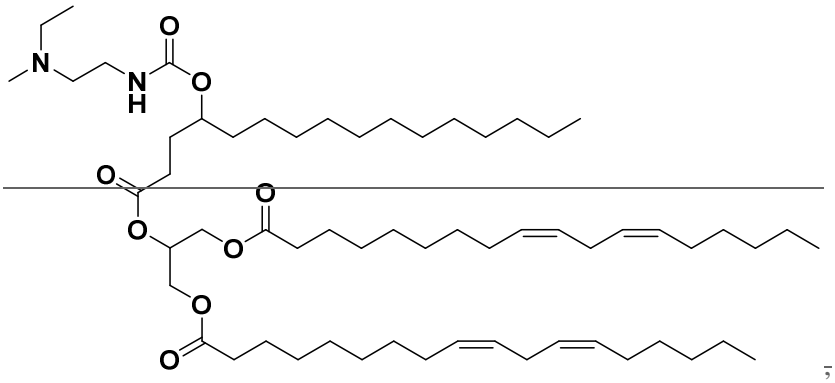

,

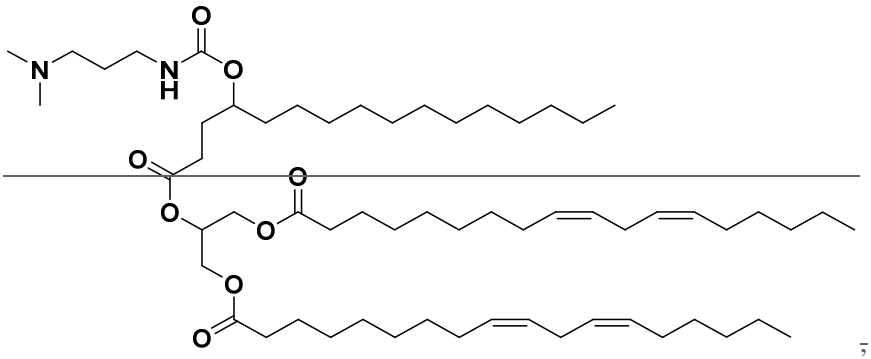

,

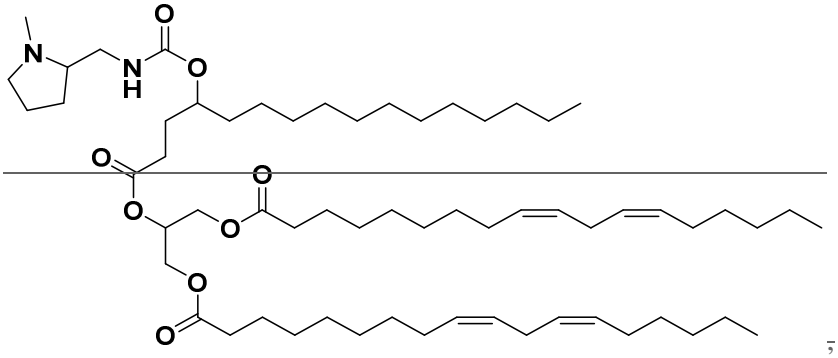

,

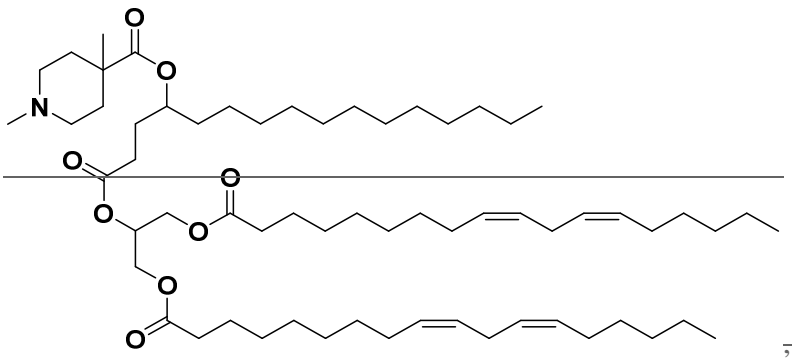

,

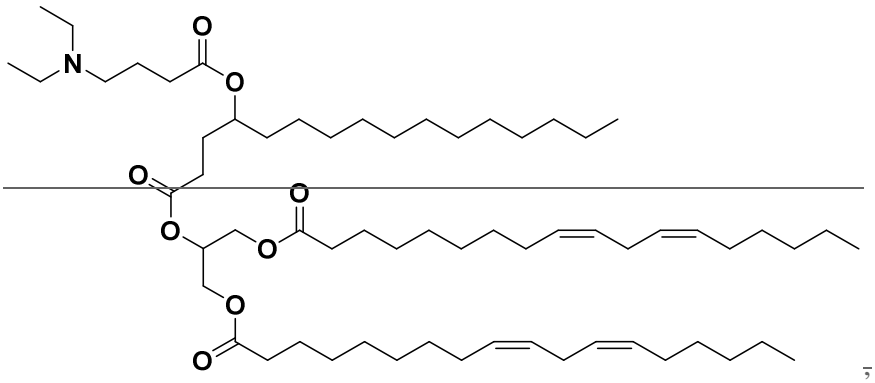


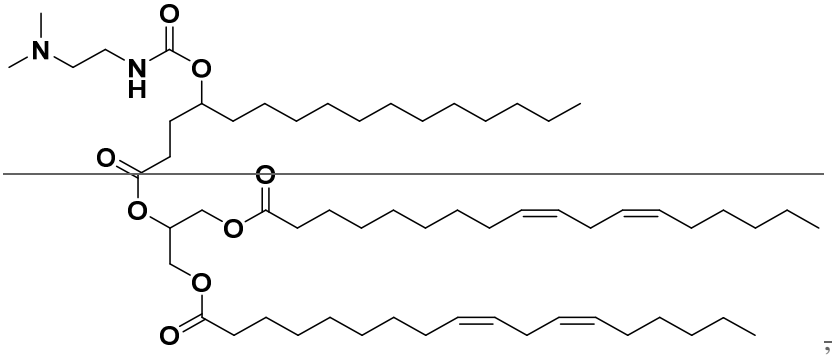


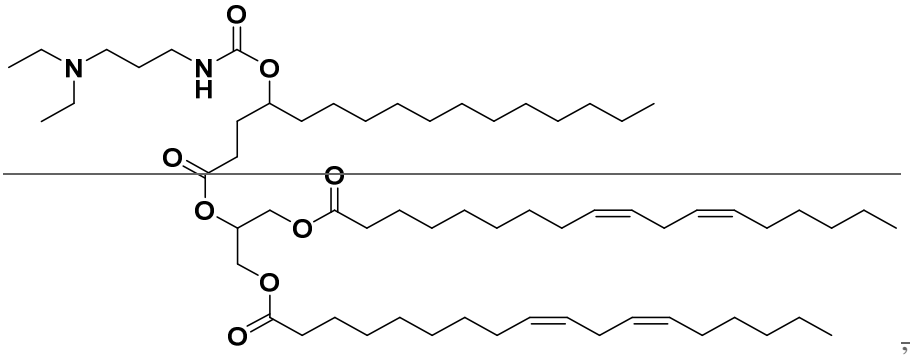


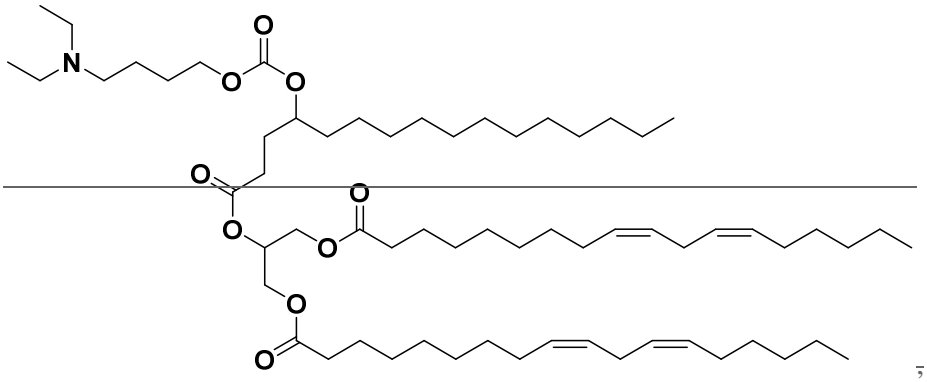


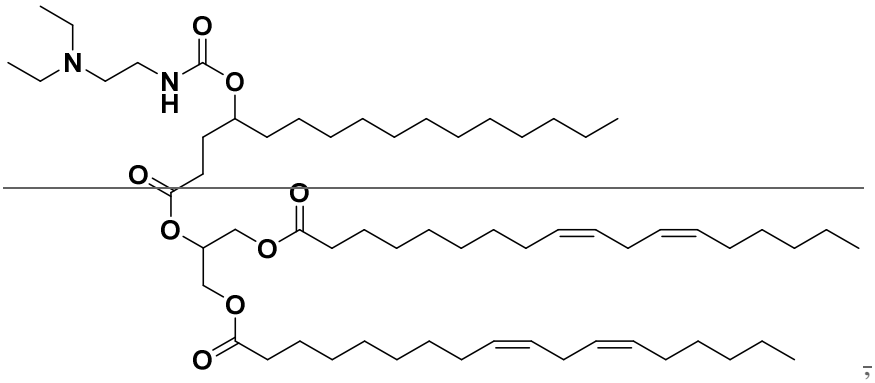


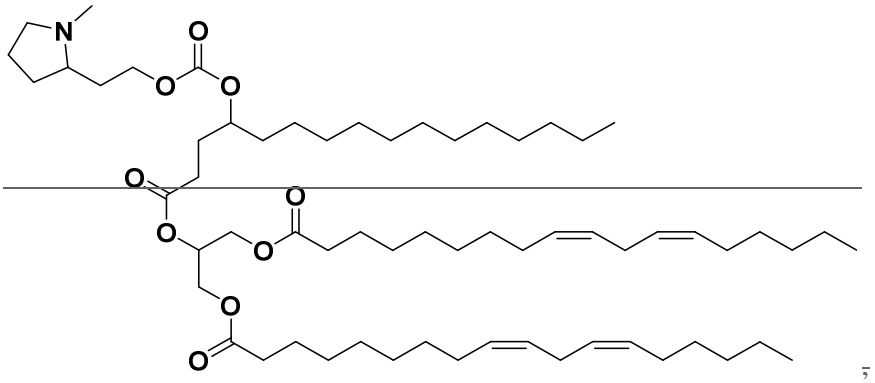


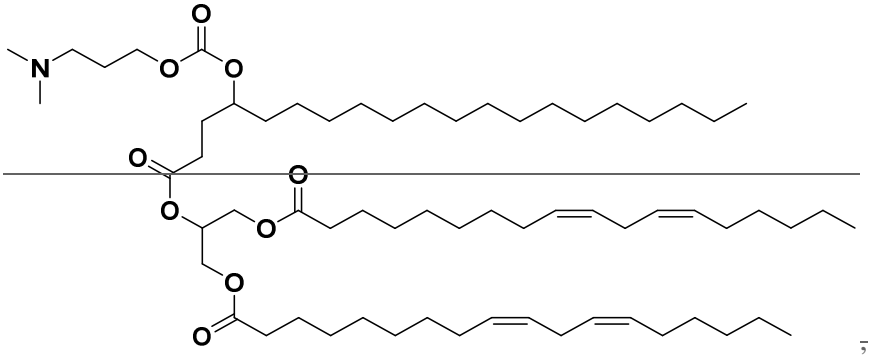


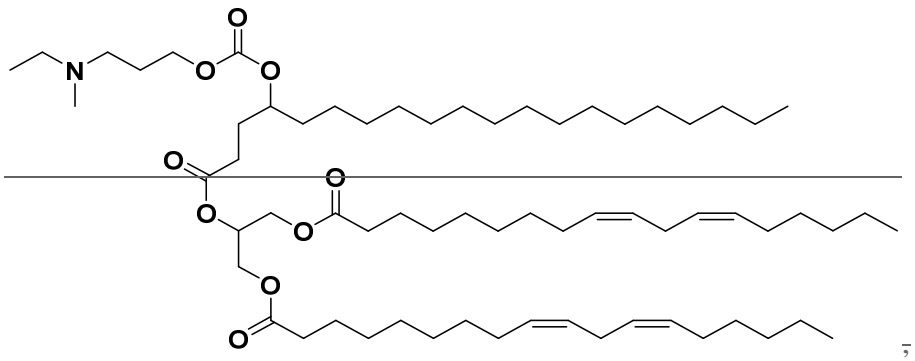


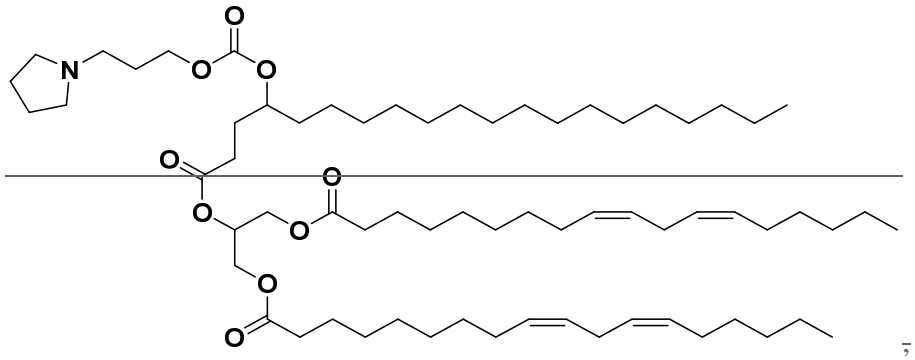


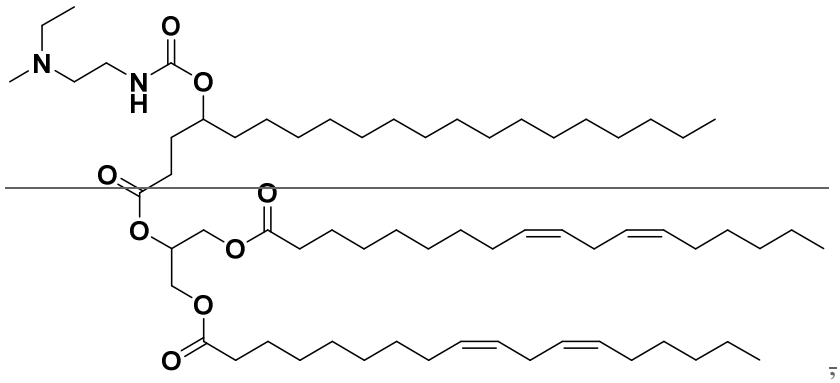


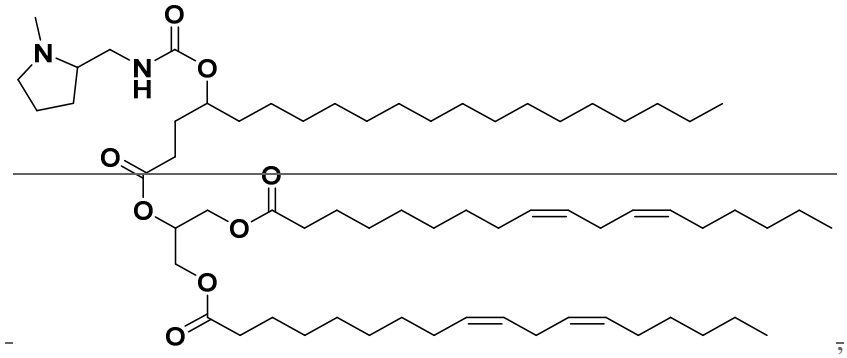


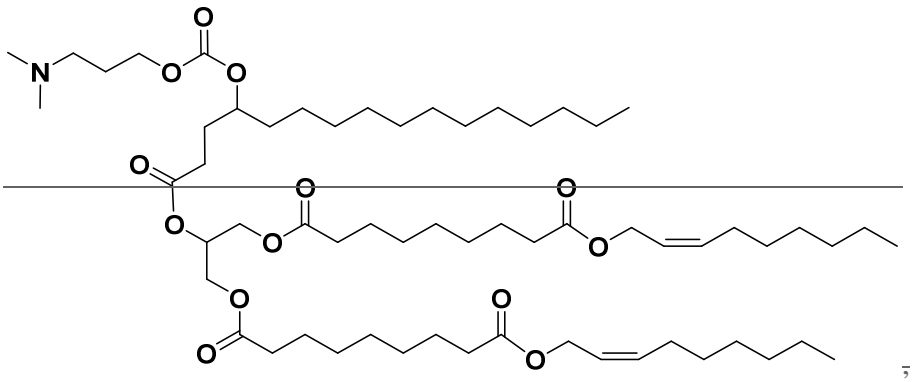


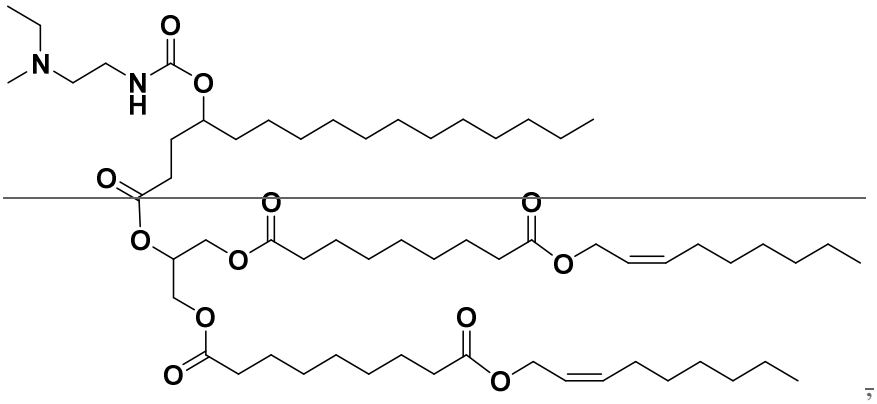


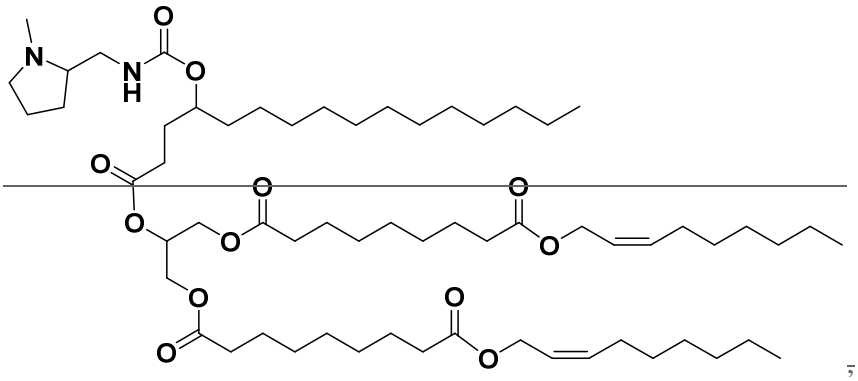


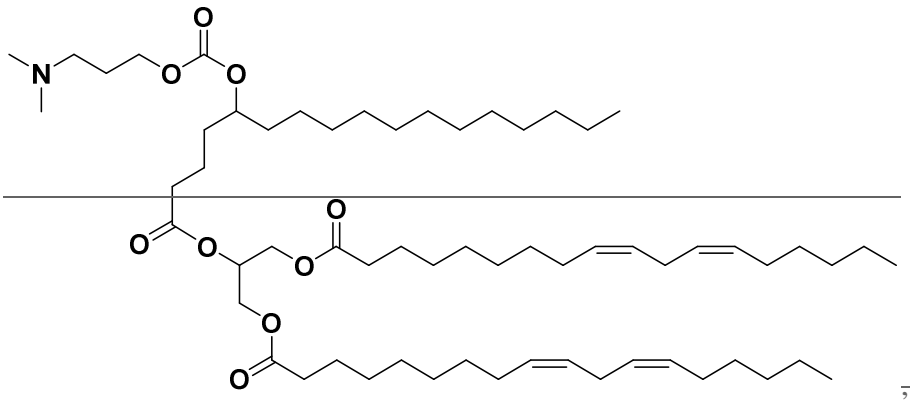


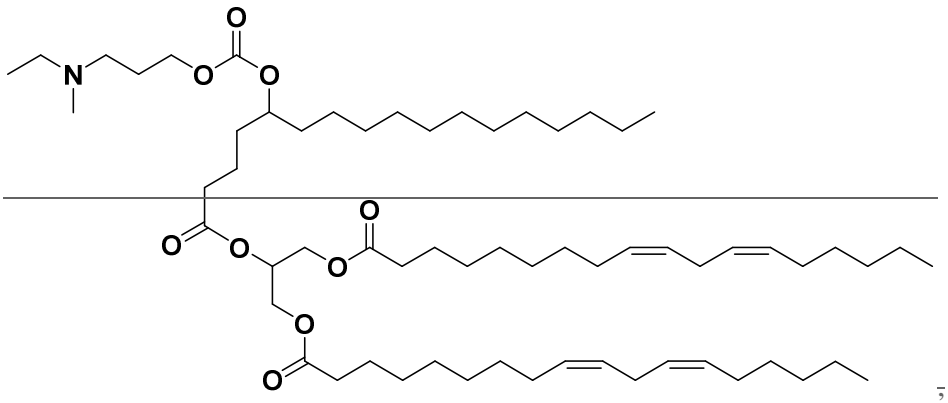


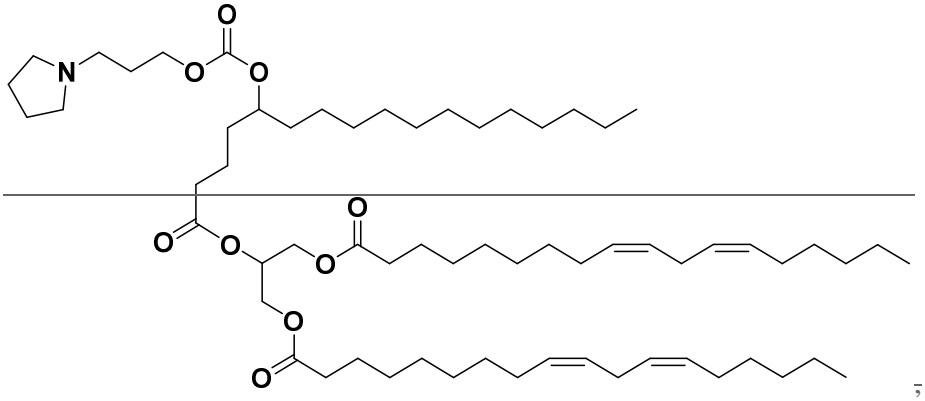


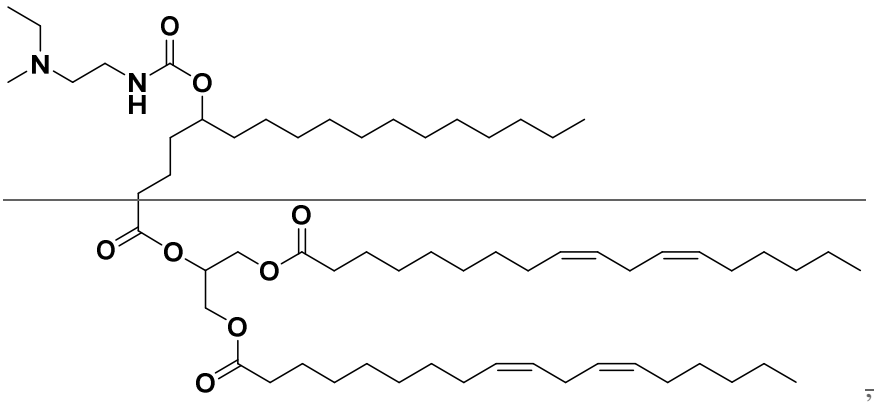


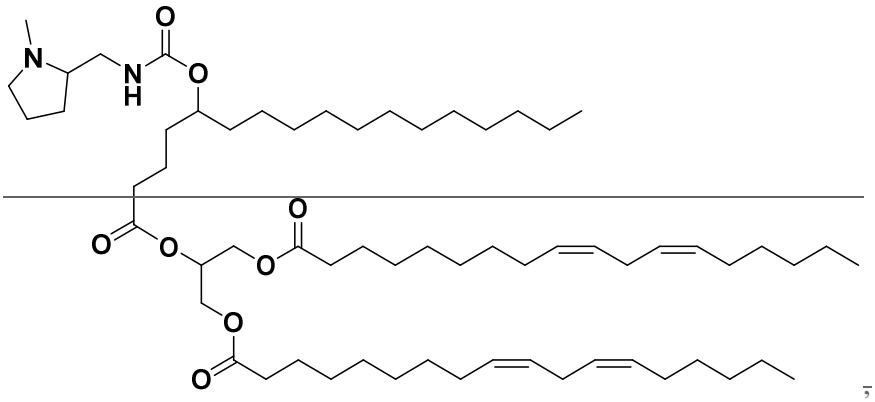


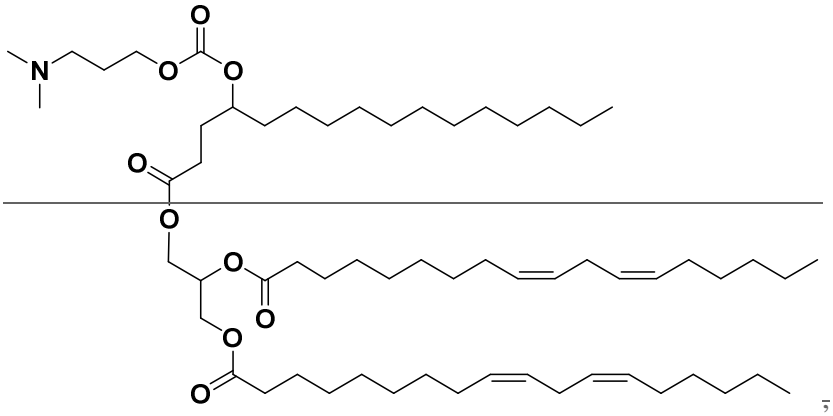


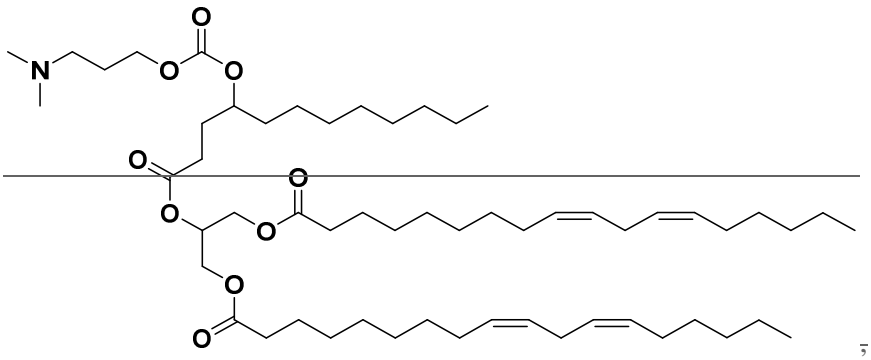


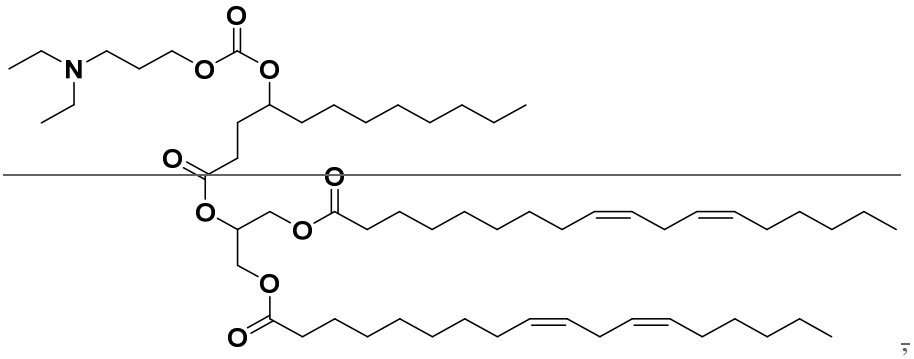


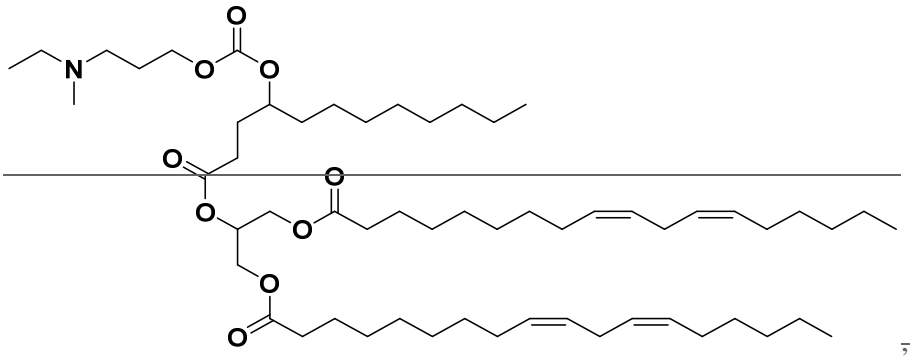


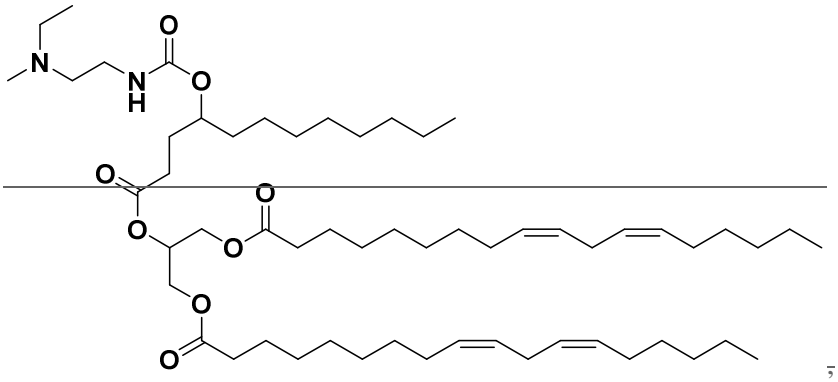


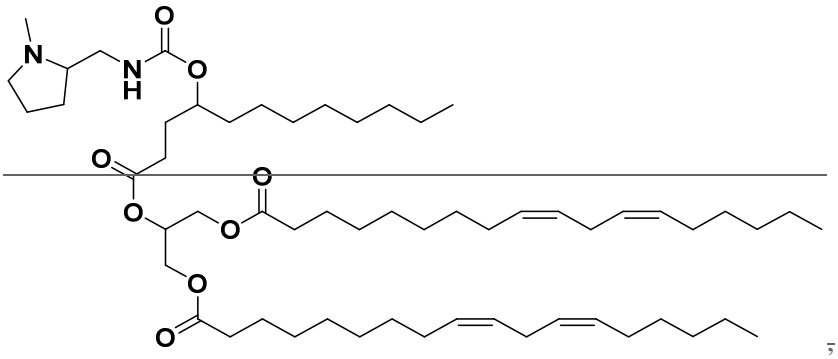


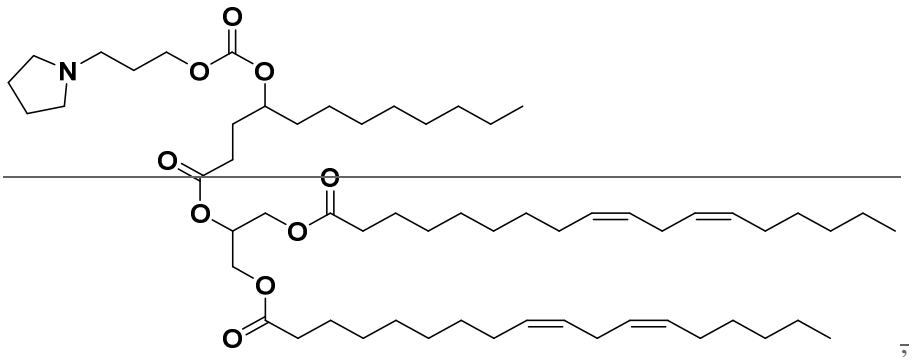


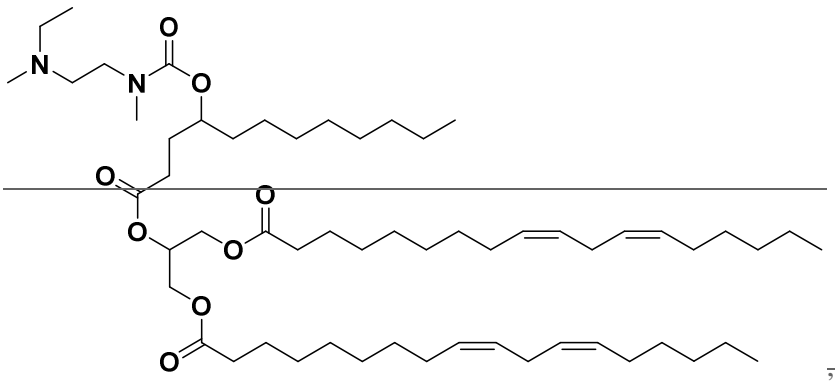


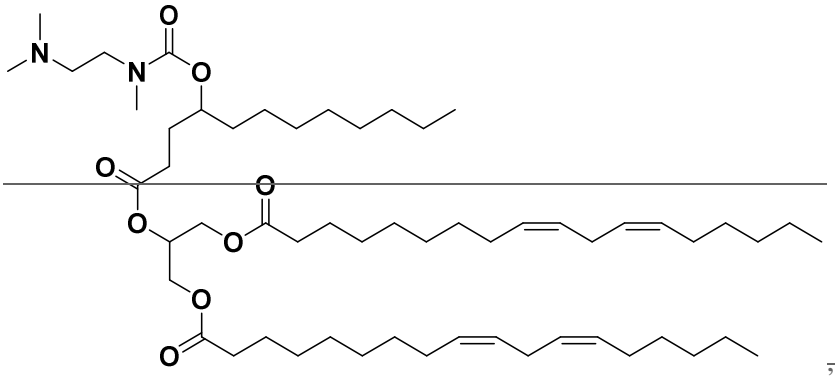


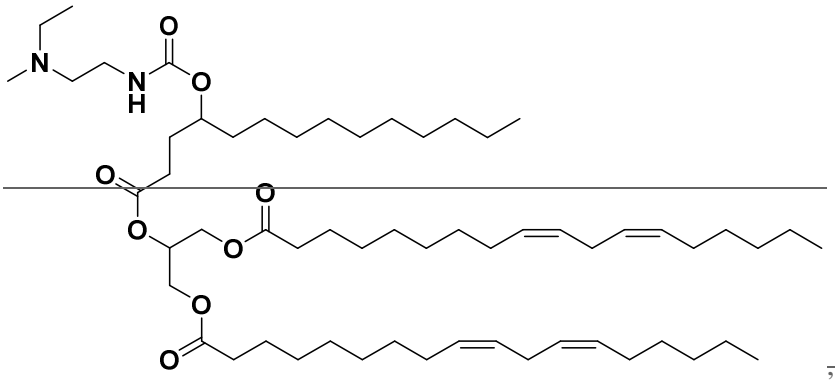


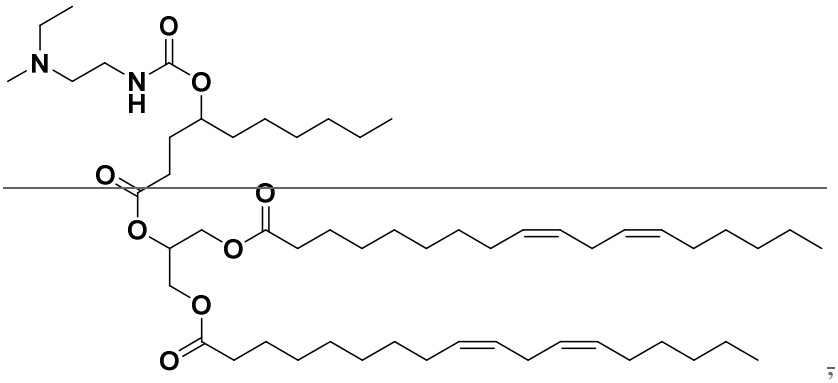


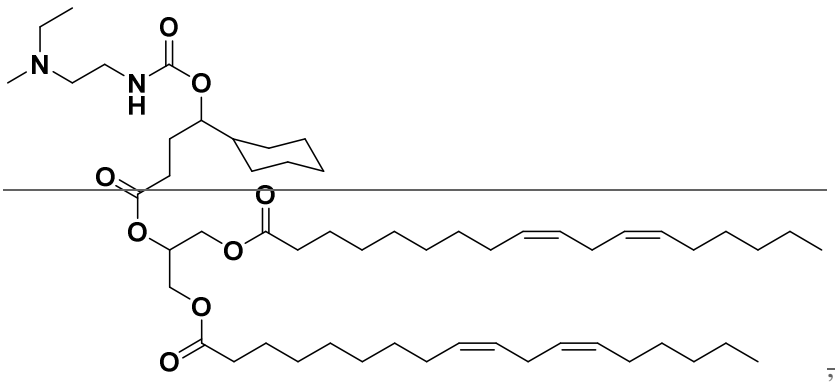


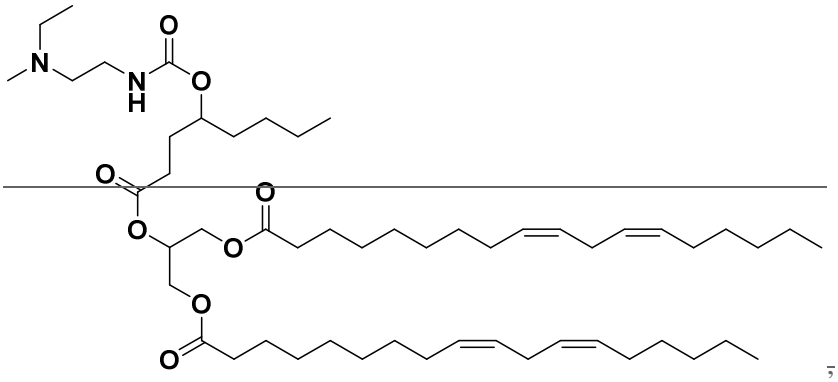


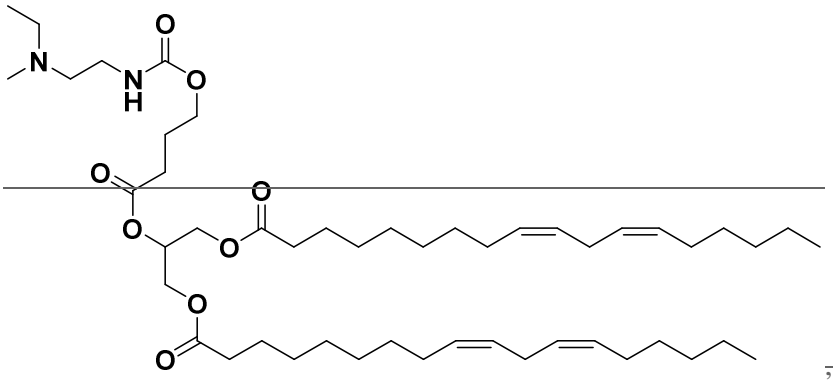


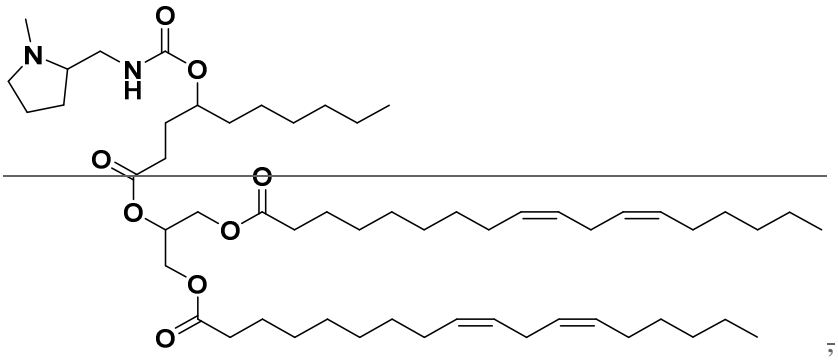


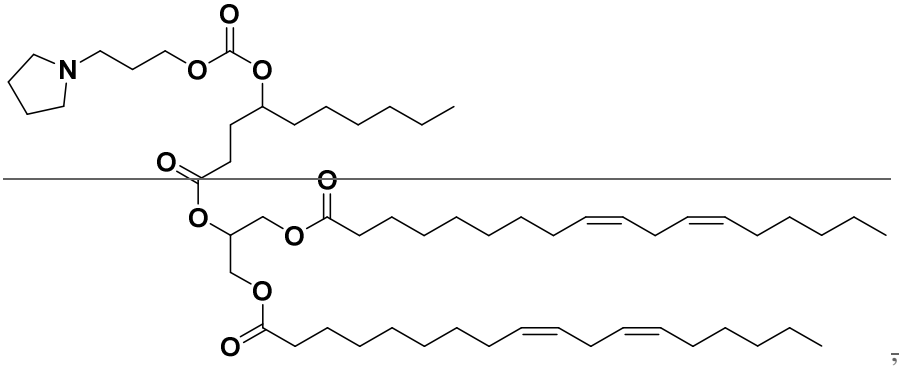


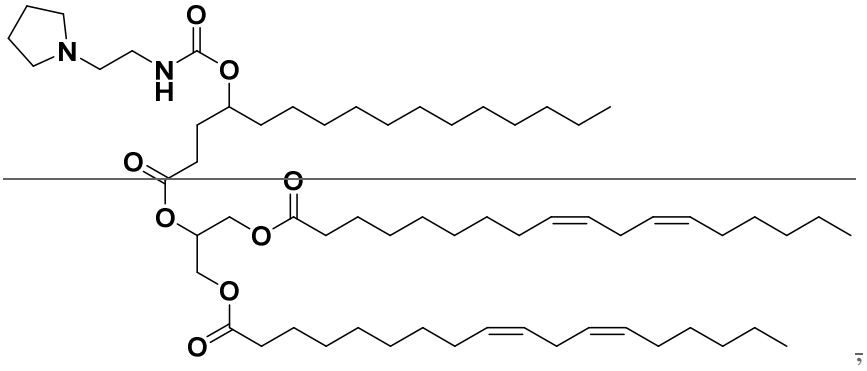


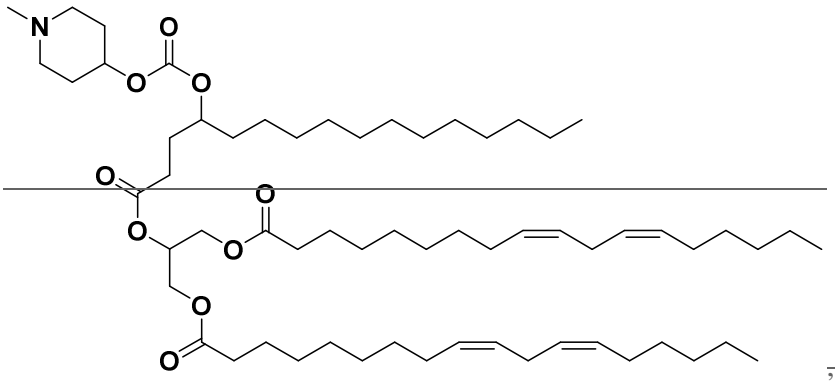


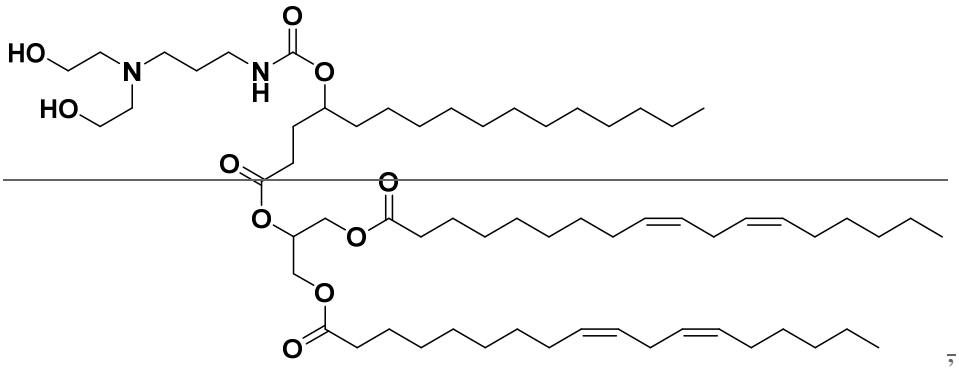


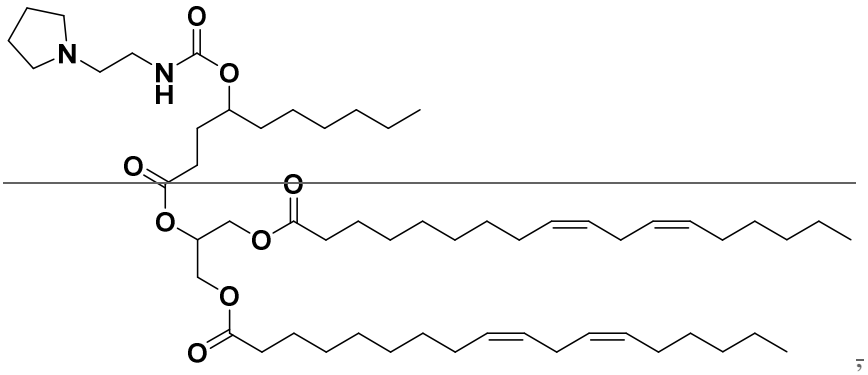


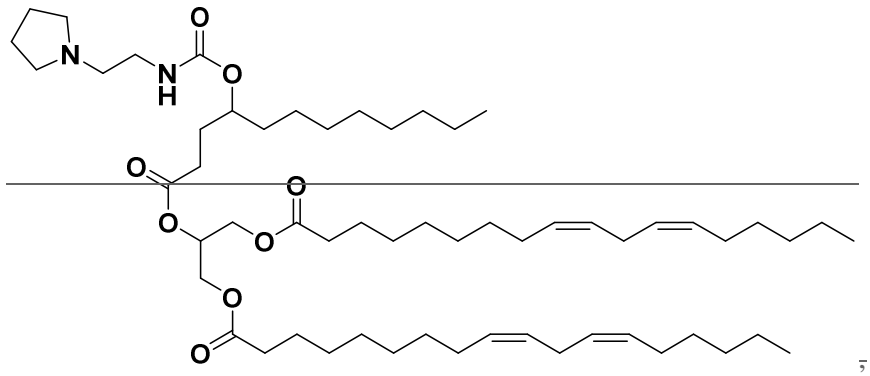


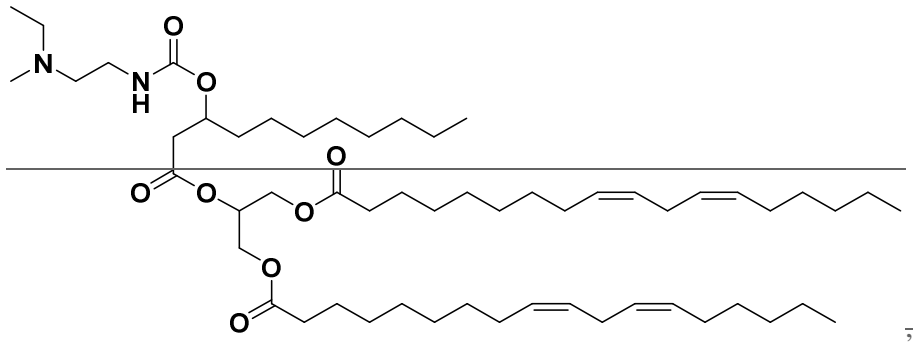


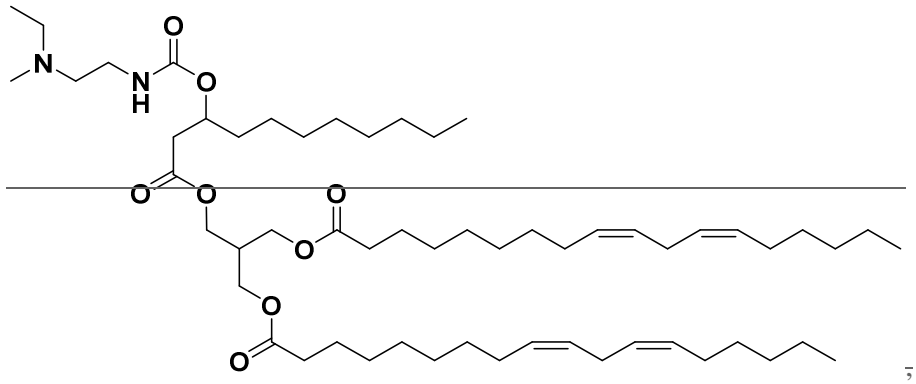


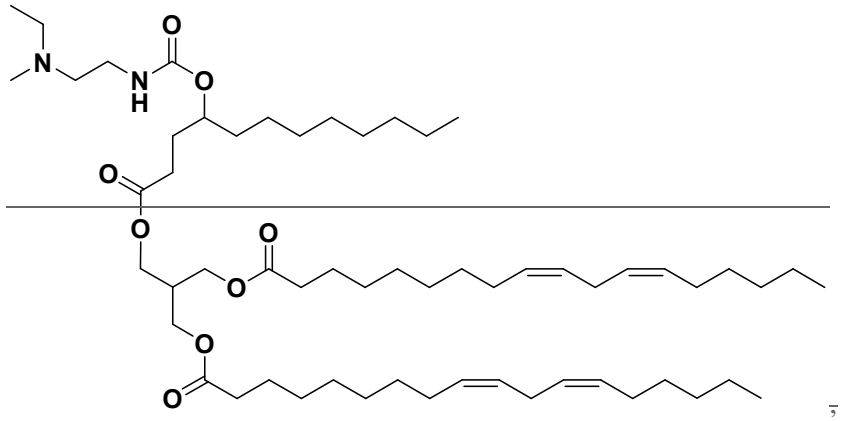


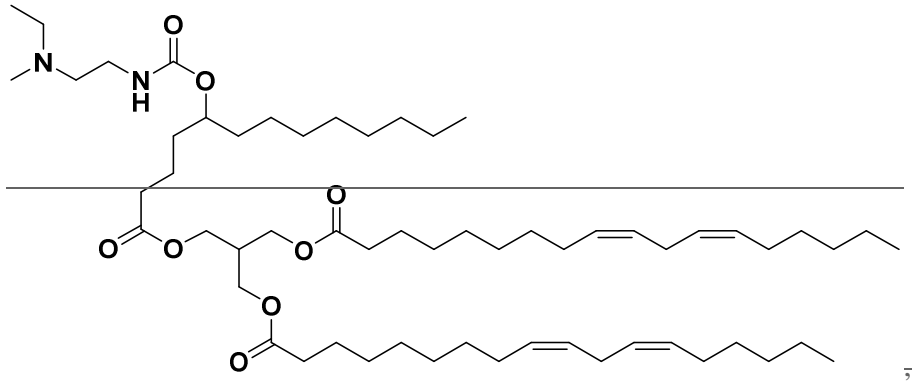


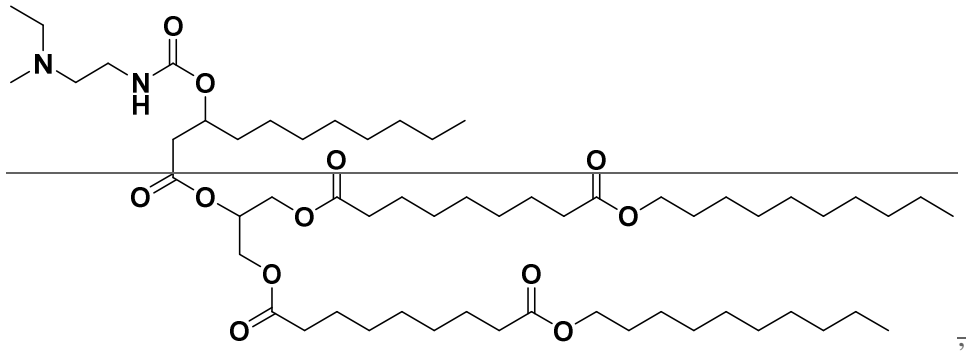


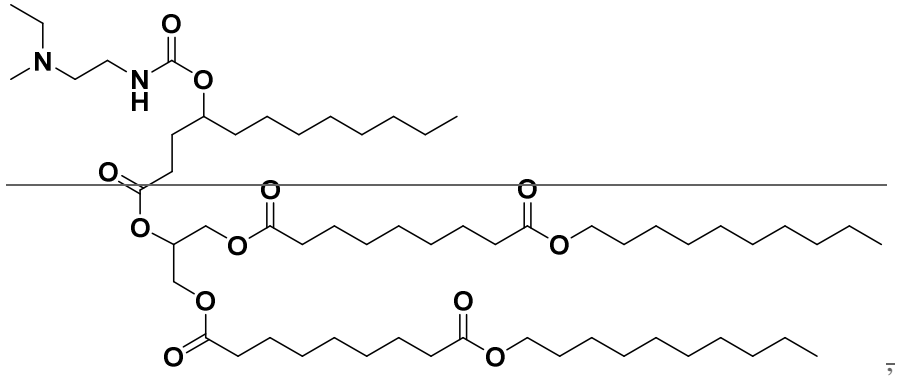


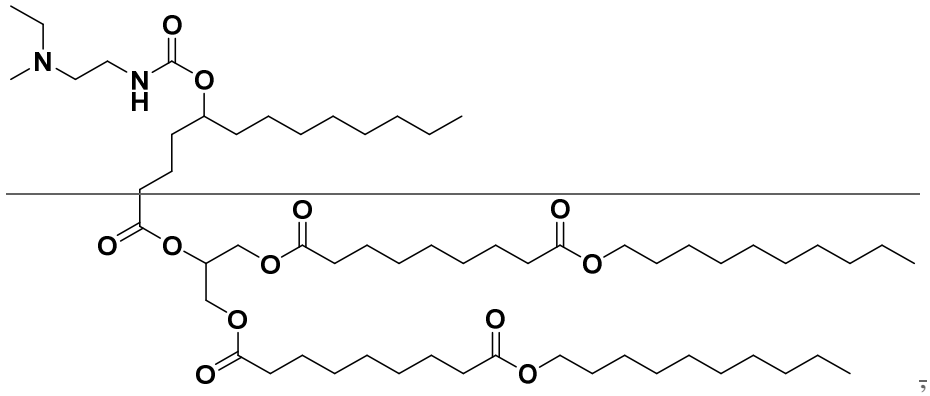


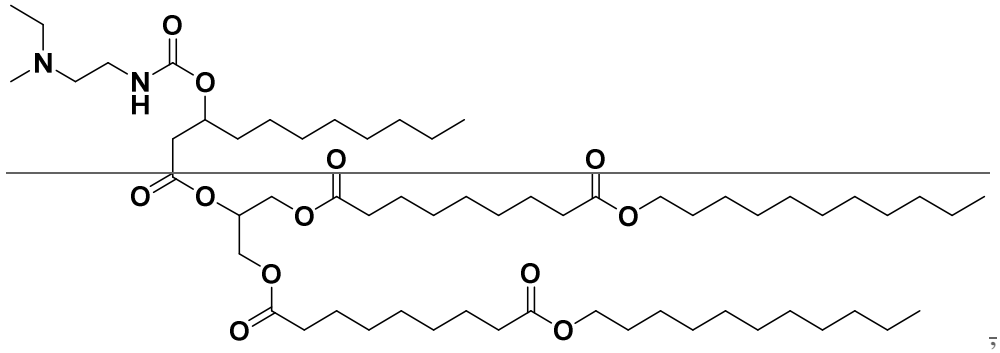


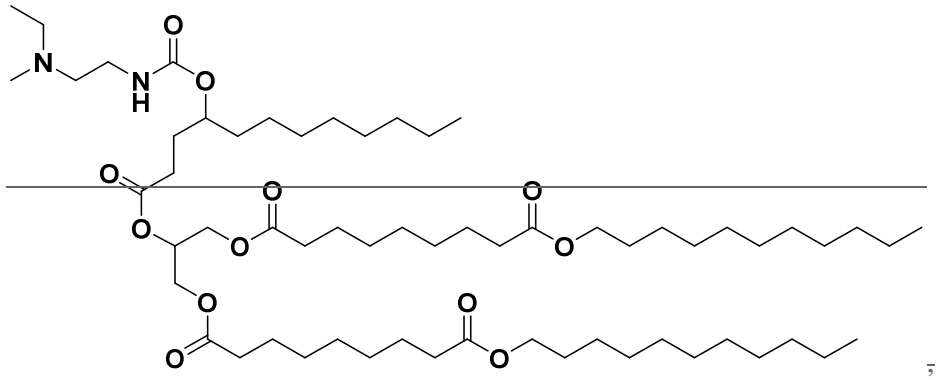


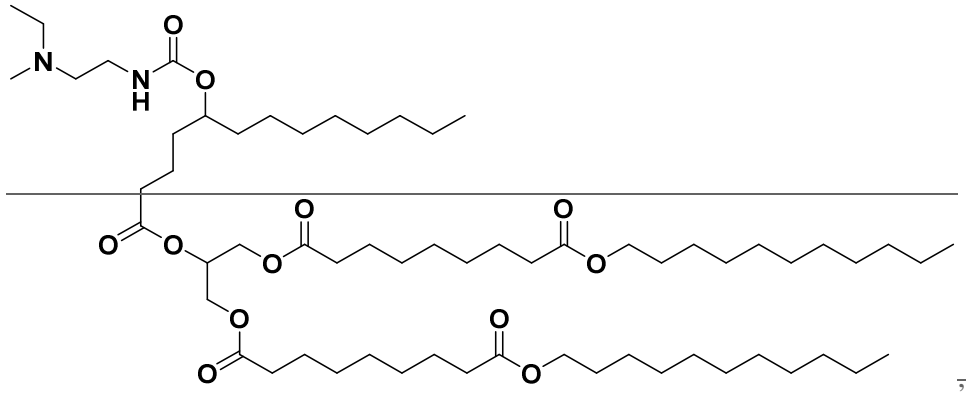


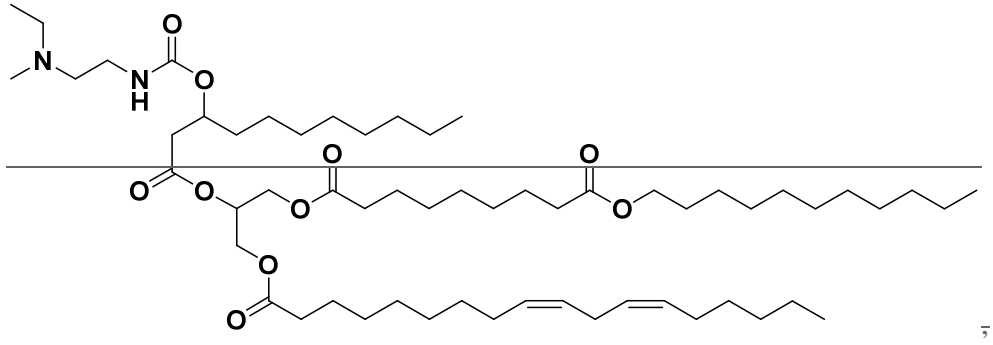


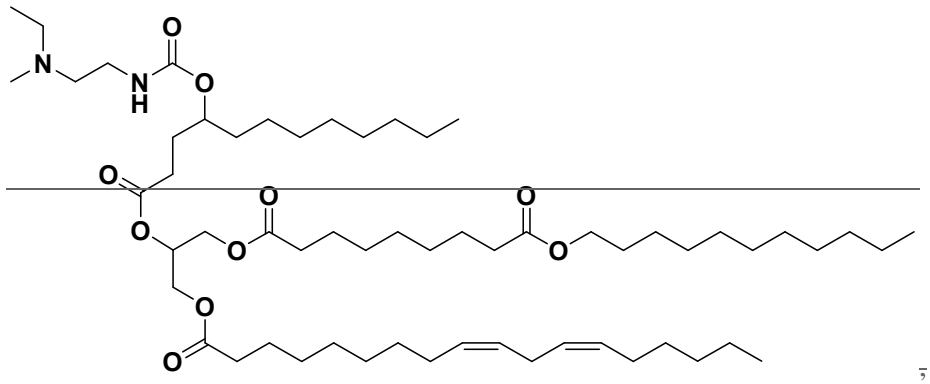


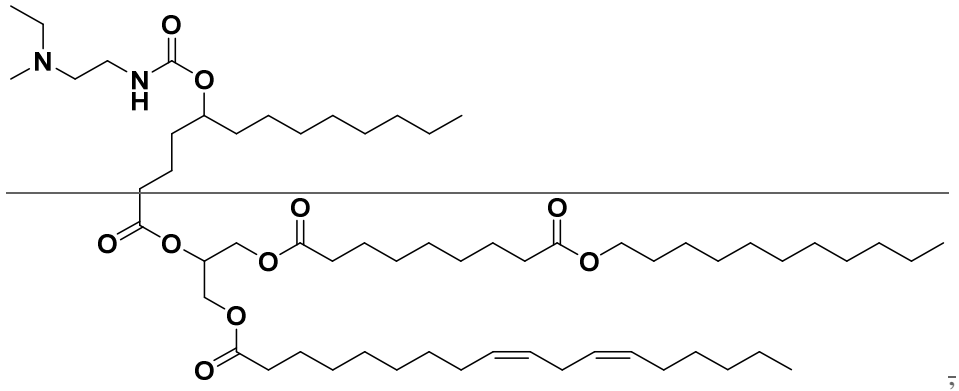


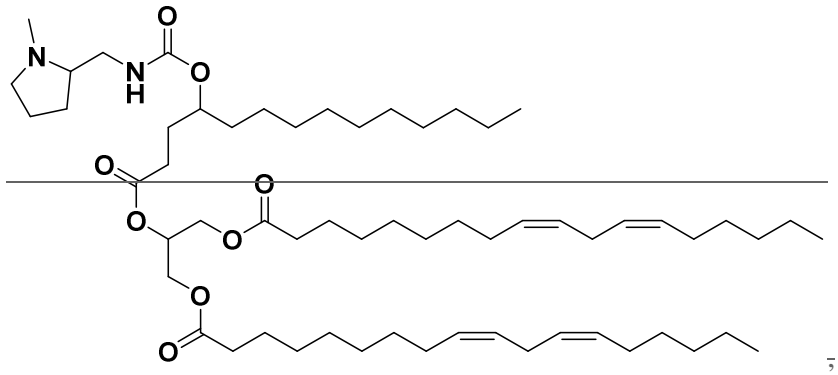


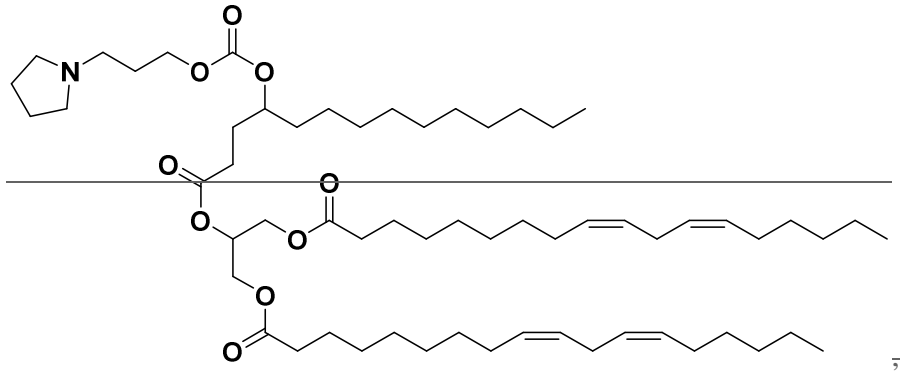


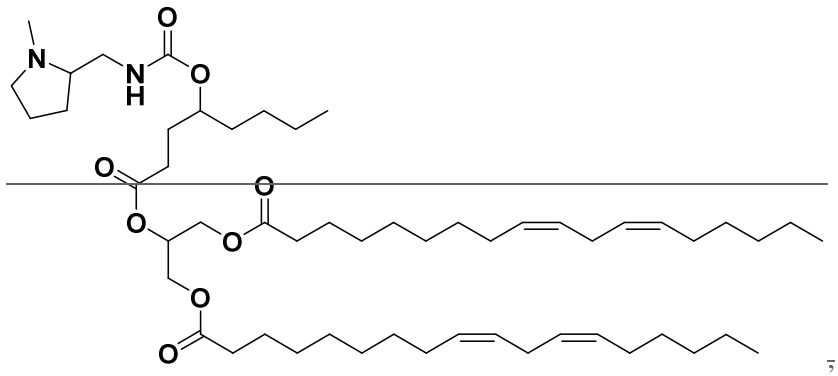


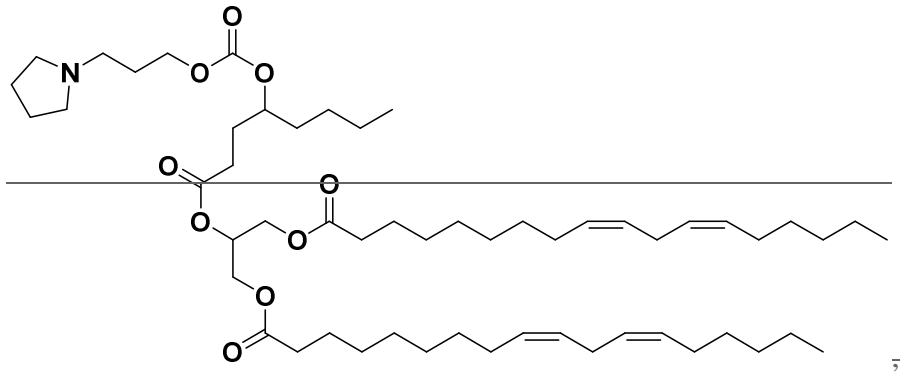


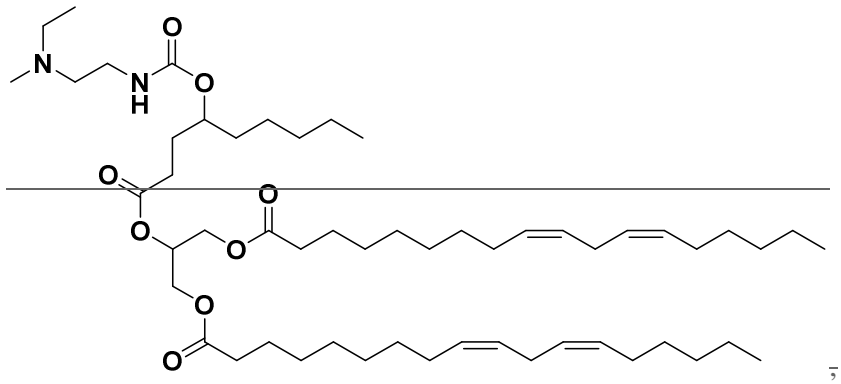


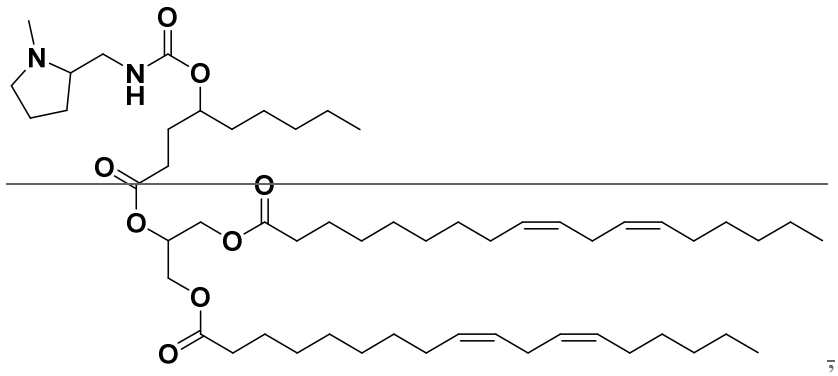


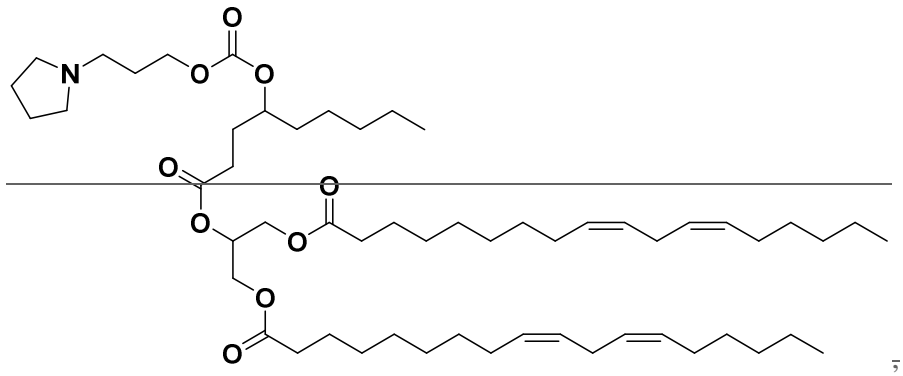


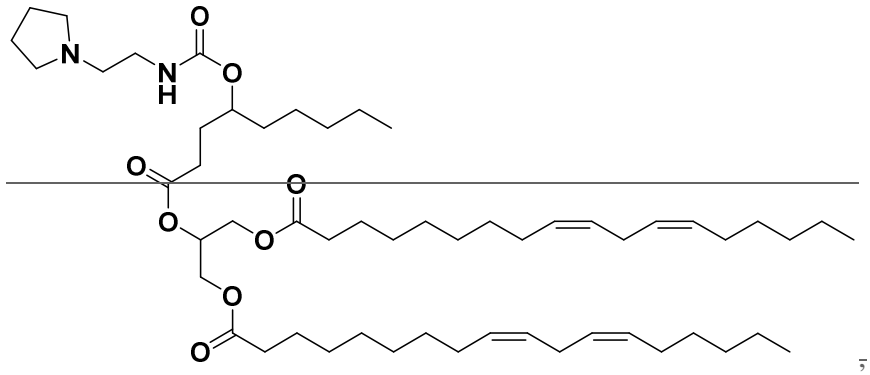


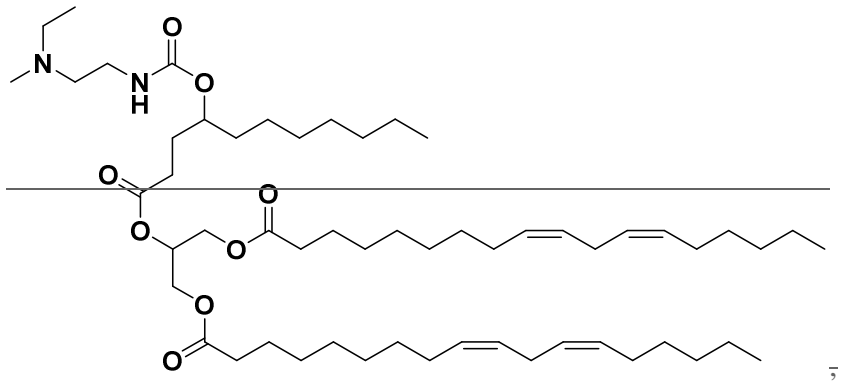


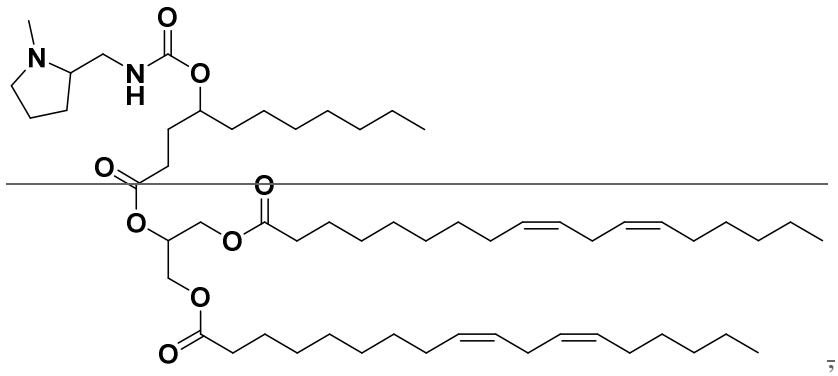


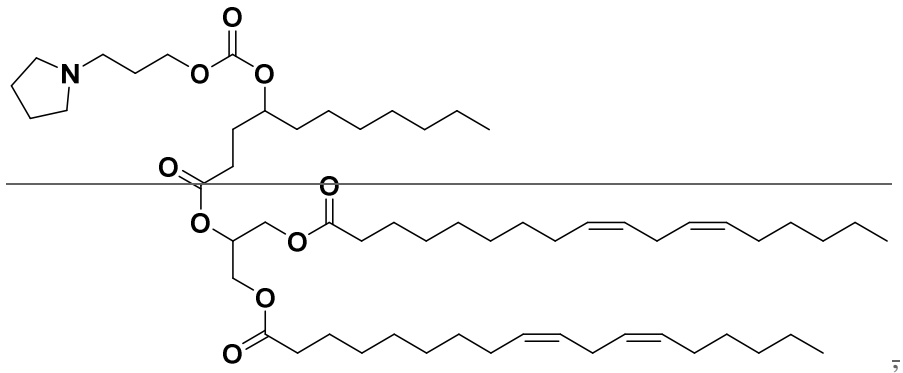


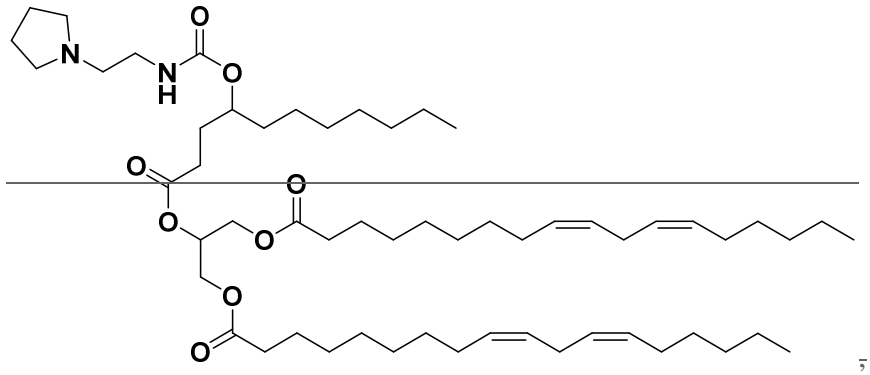


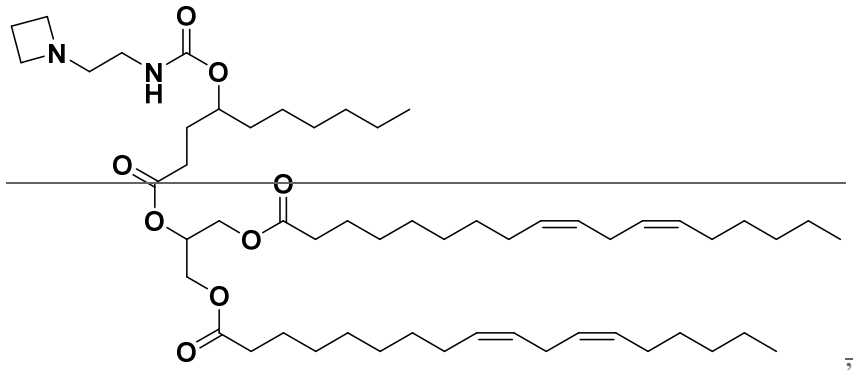


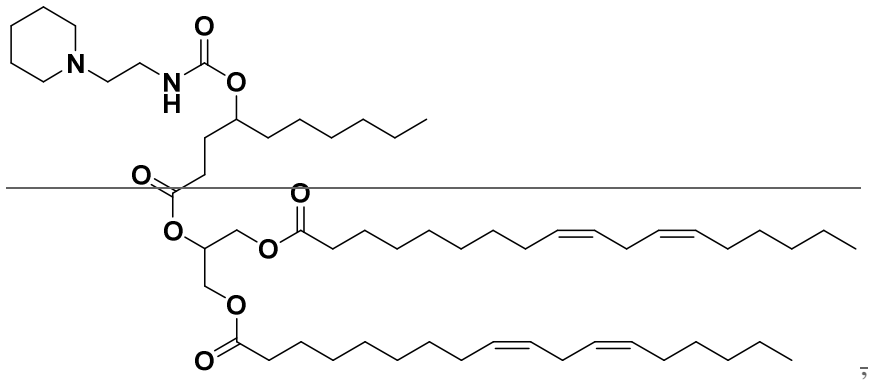


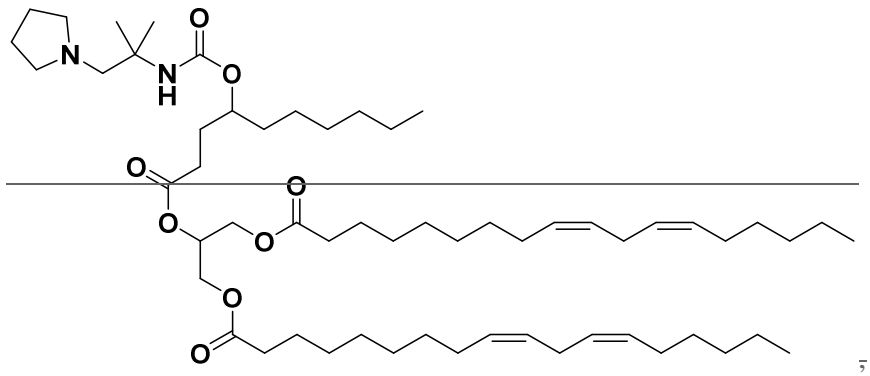


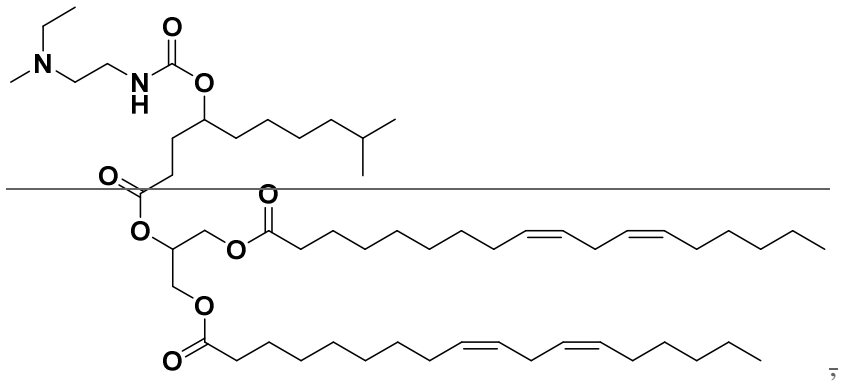


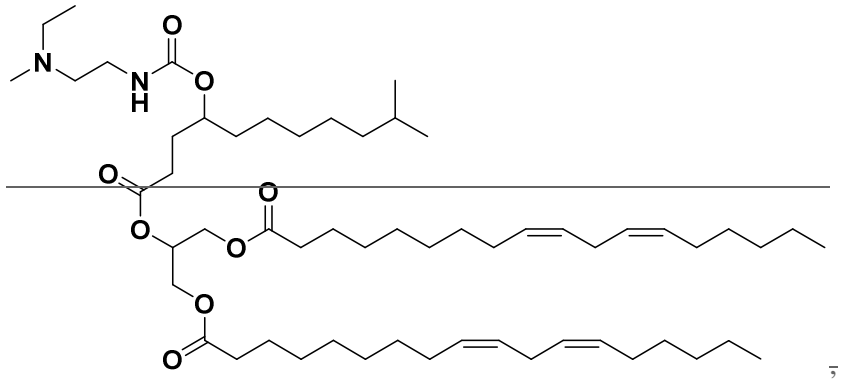


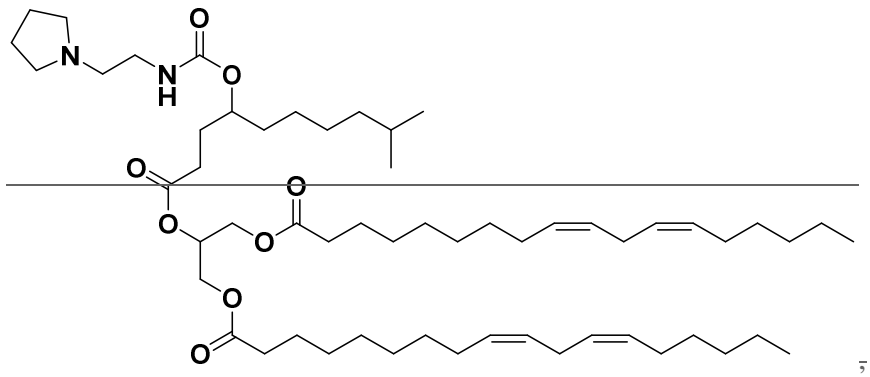


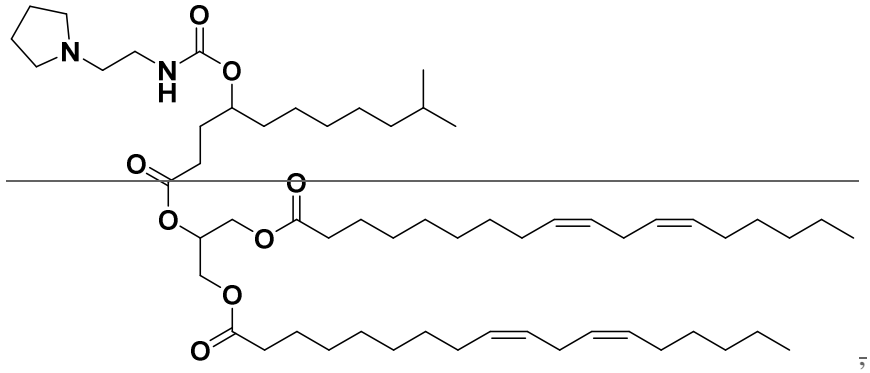


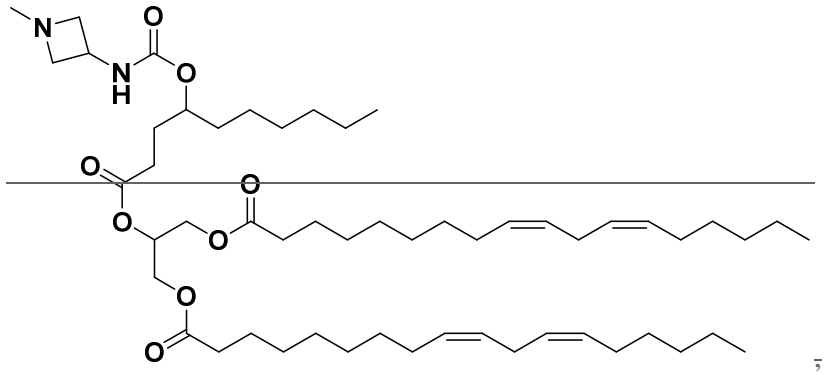


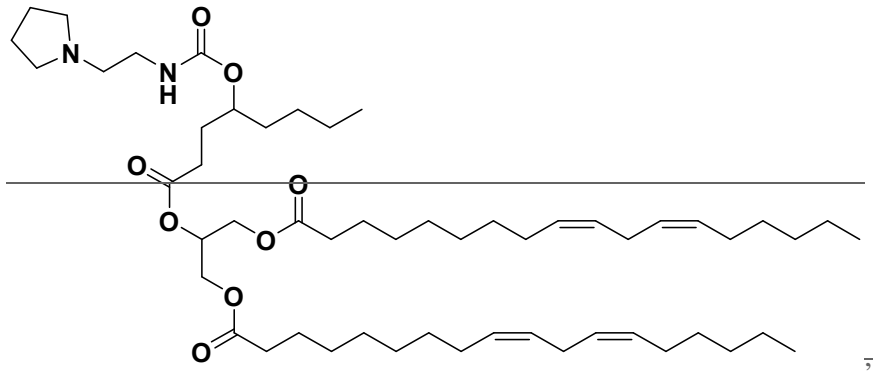


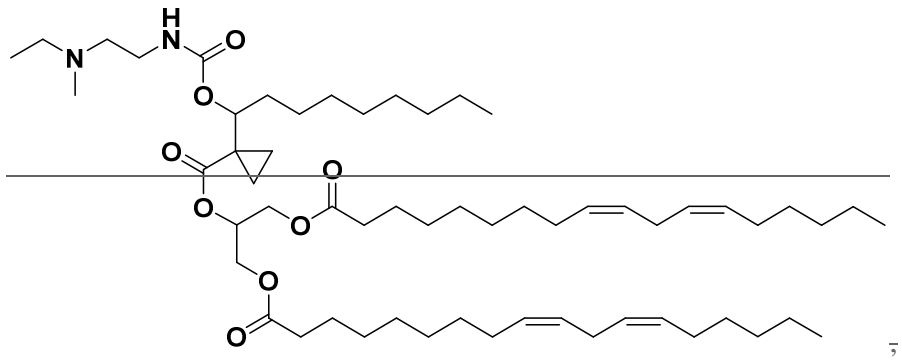


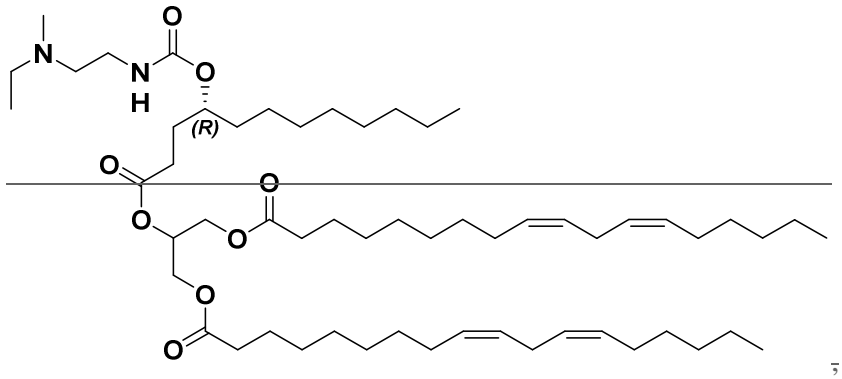


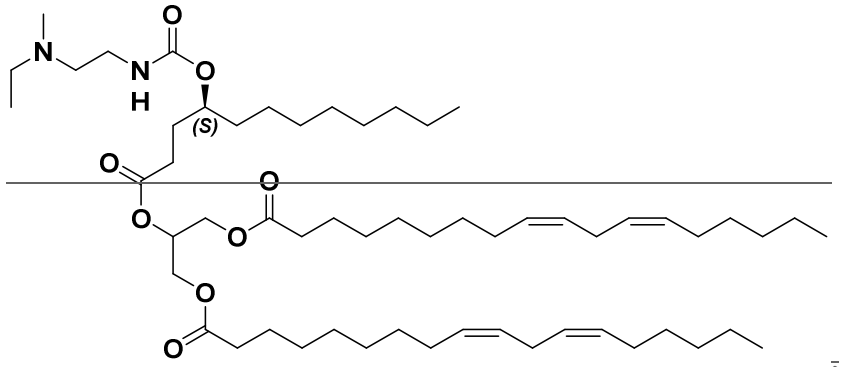


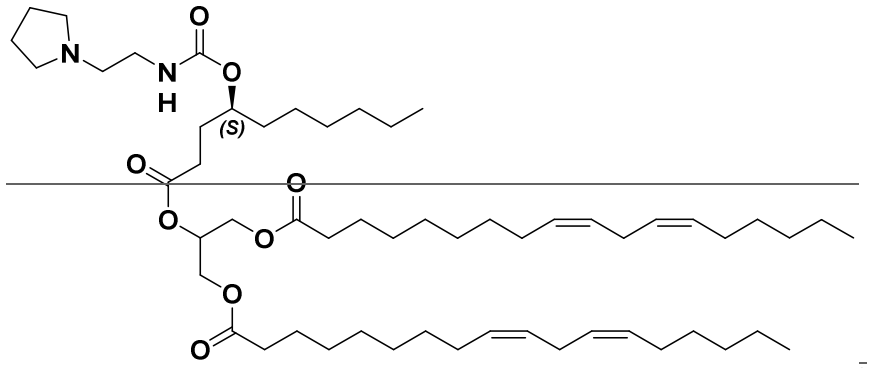


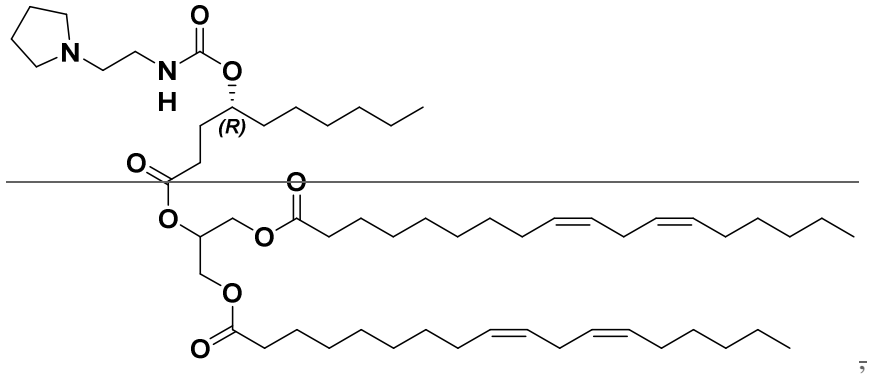


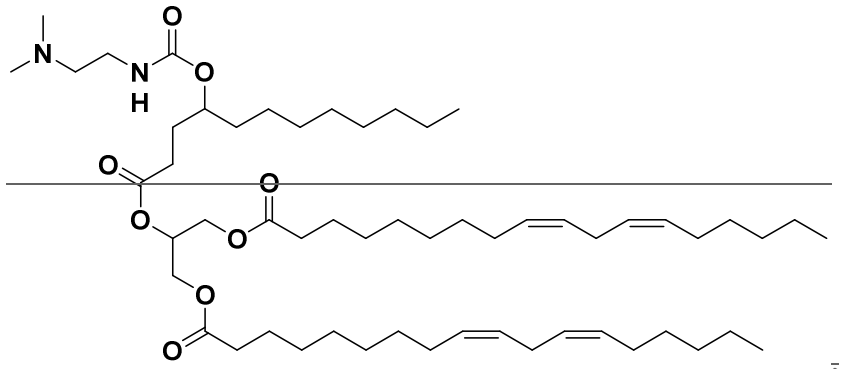


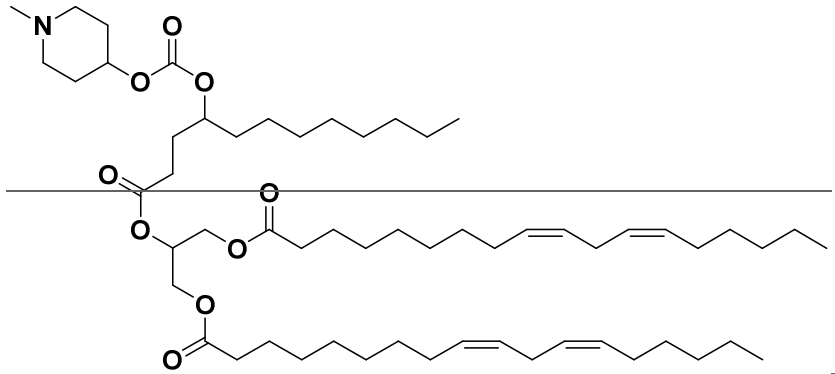


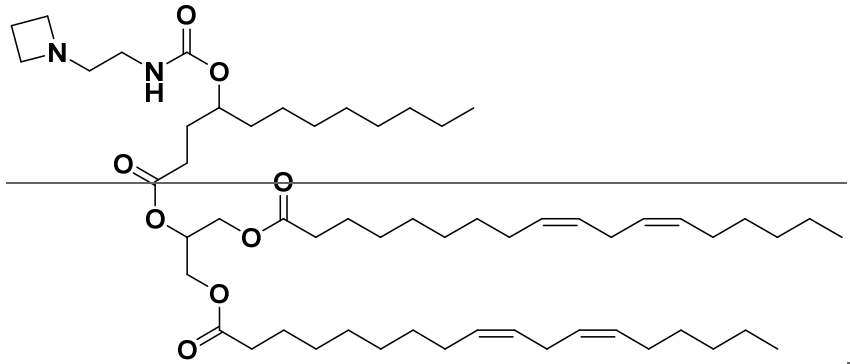


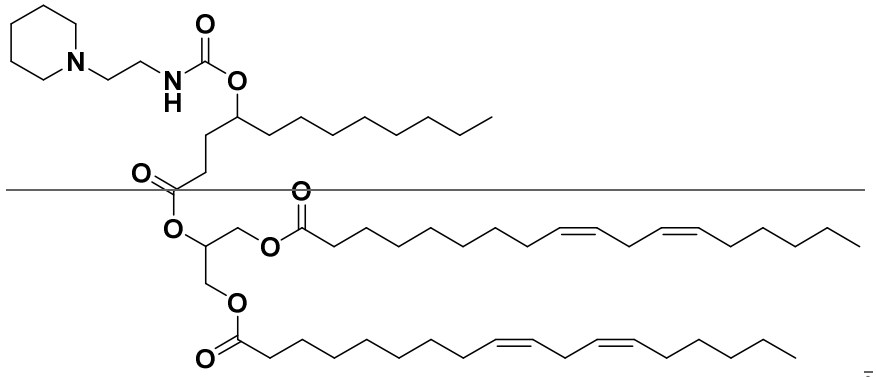


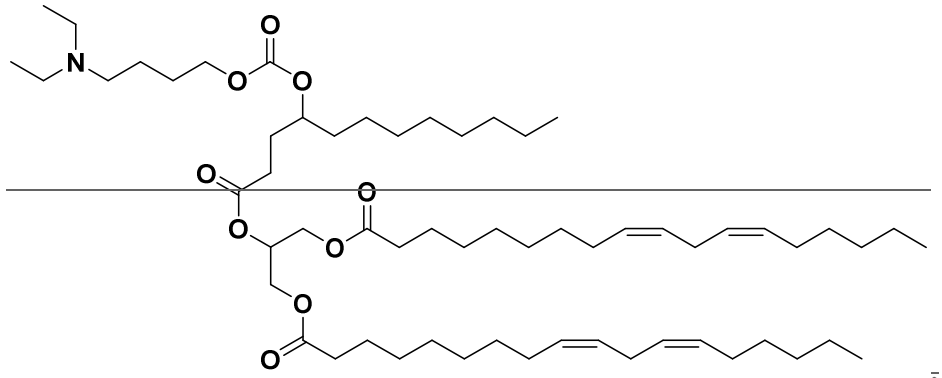


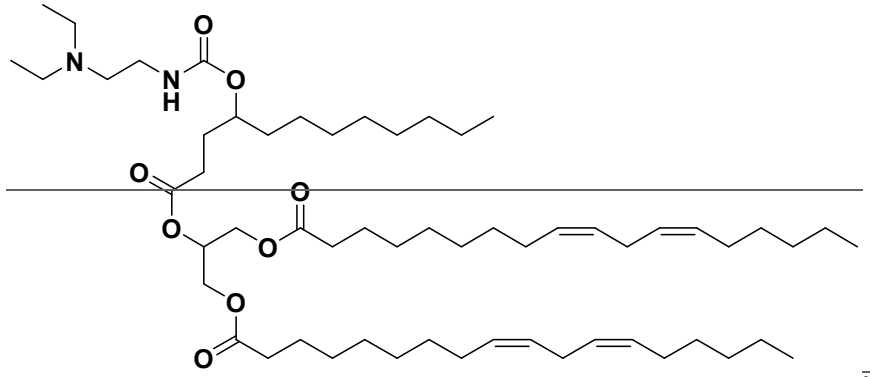


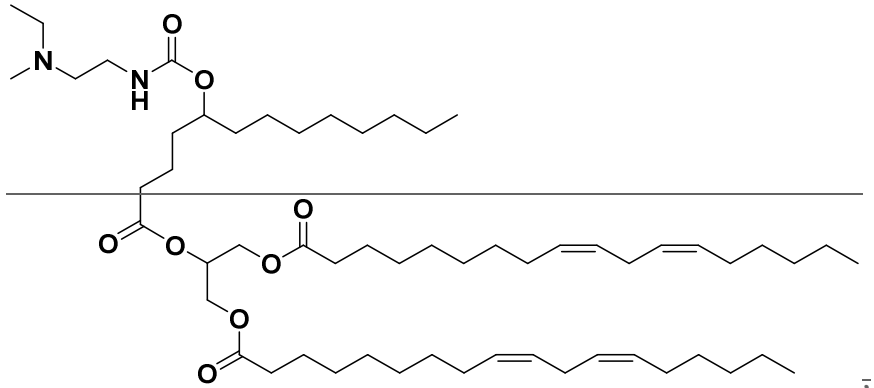


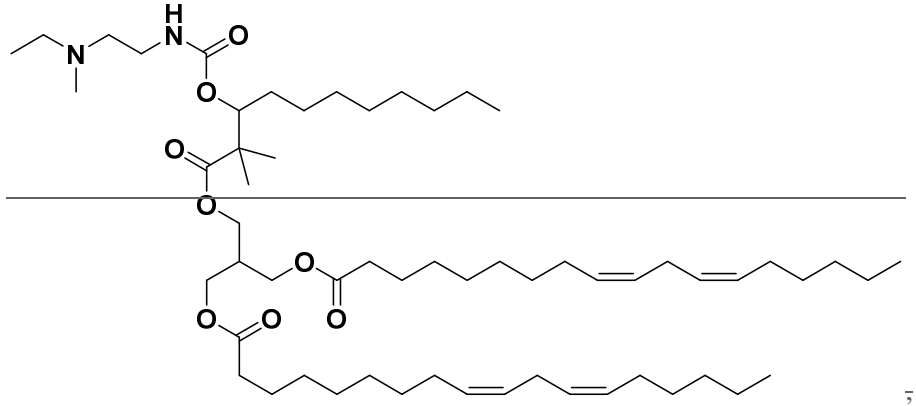


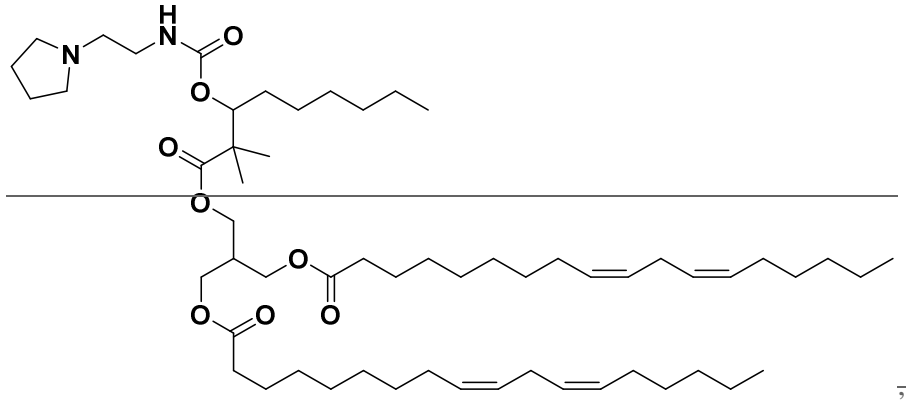


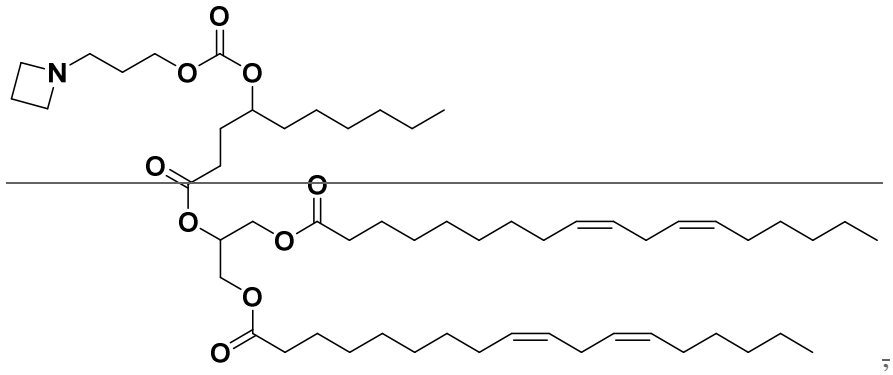


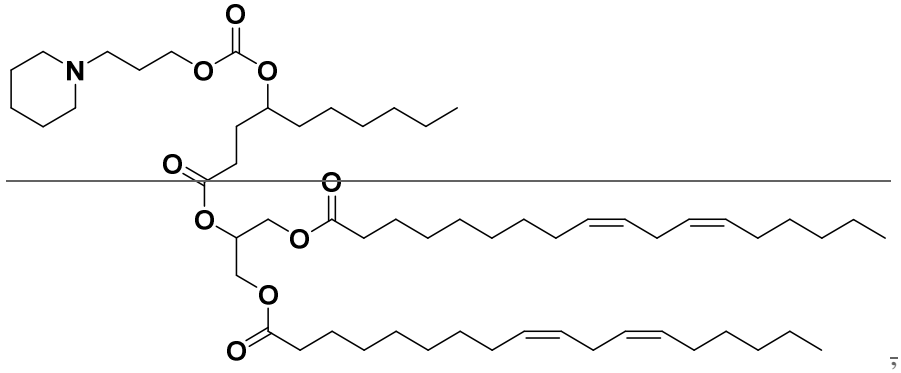


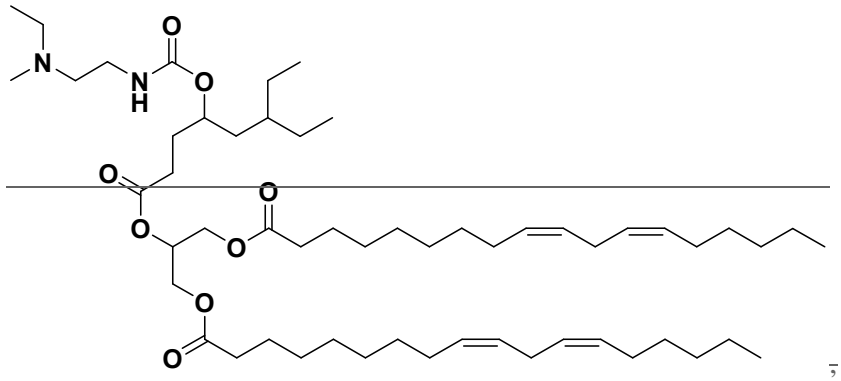


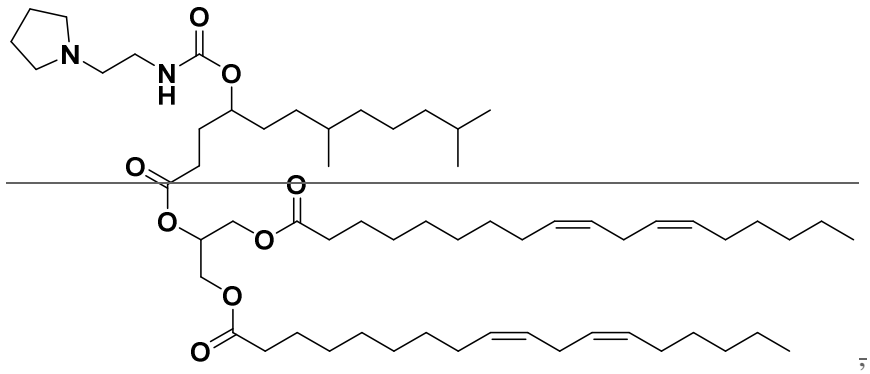


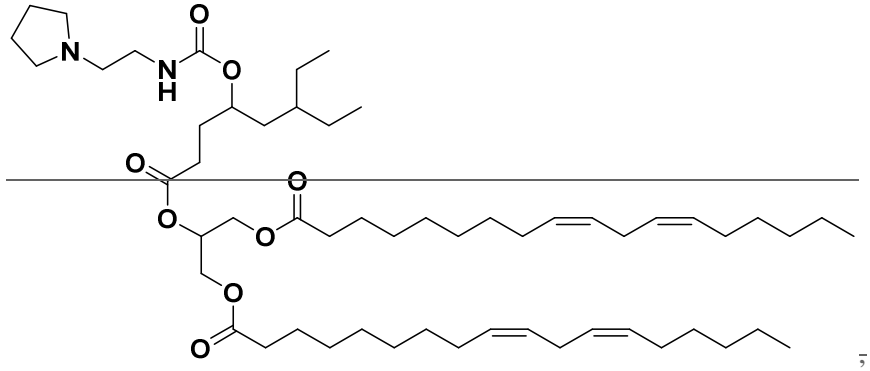


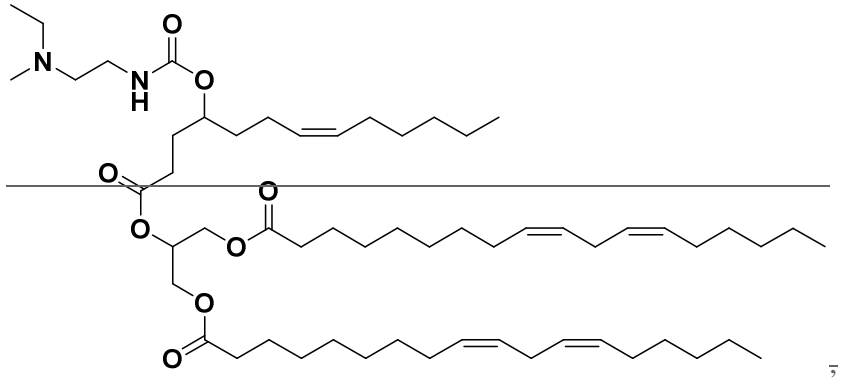


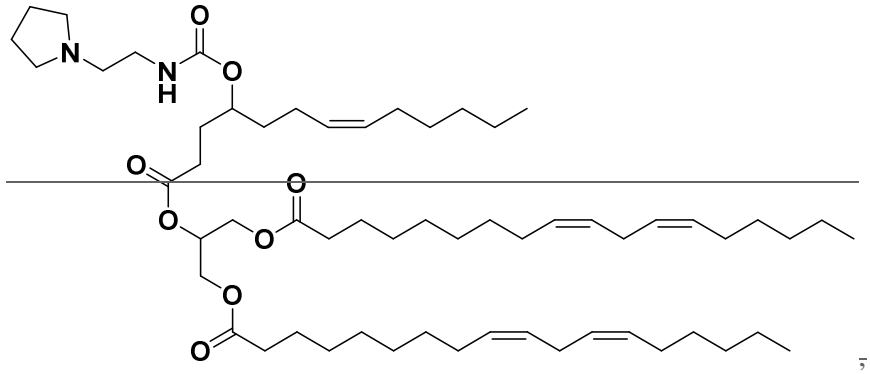


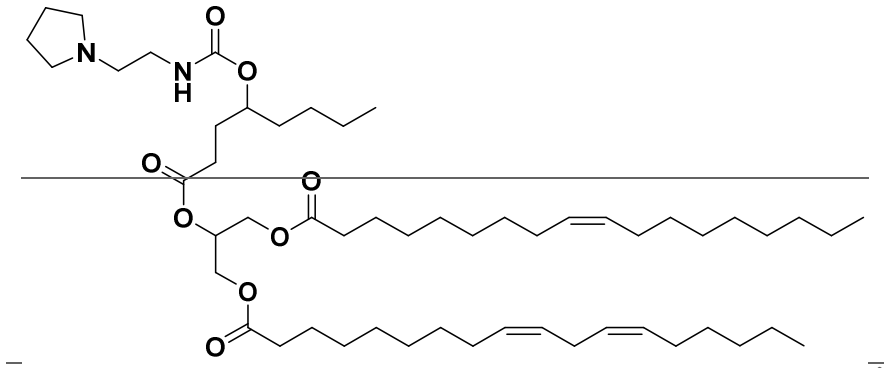




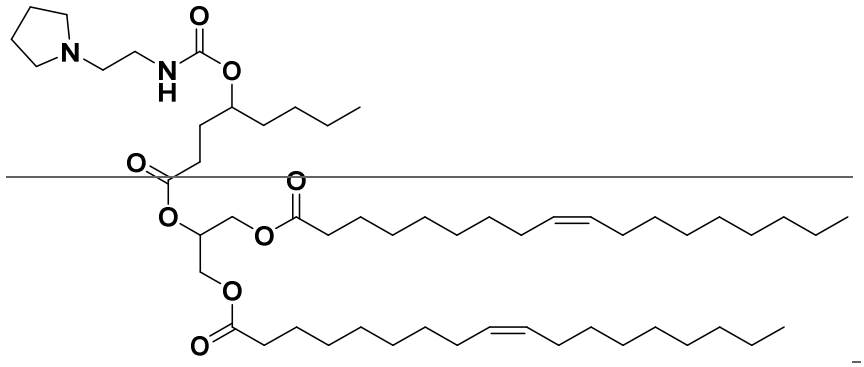




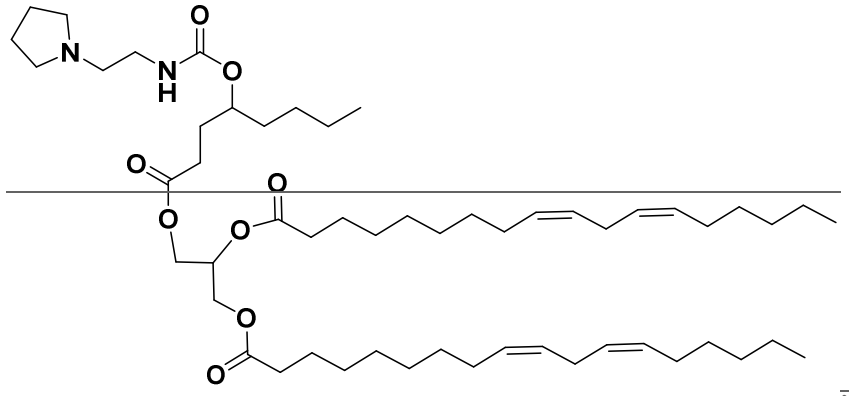




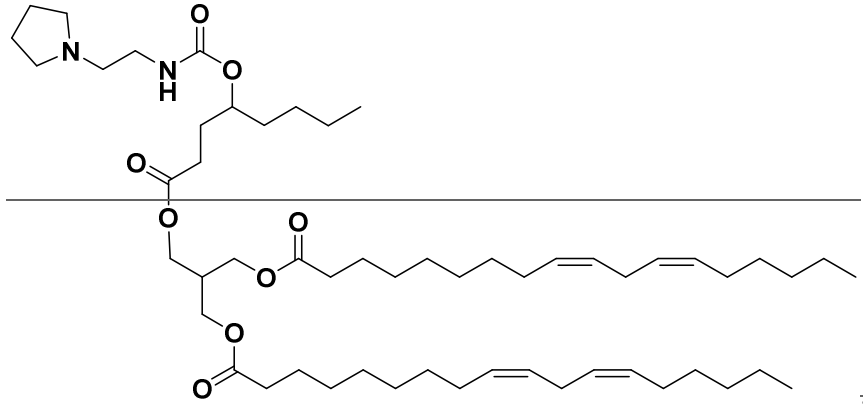
,



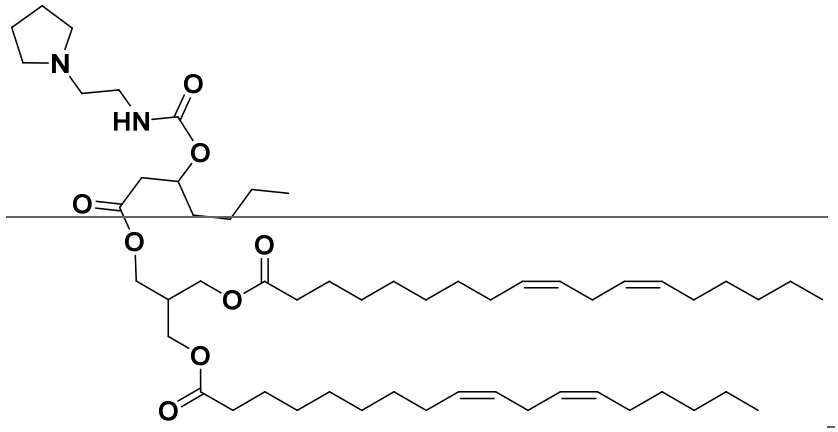
,



,



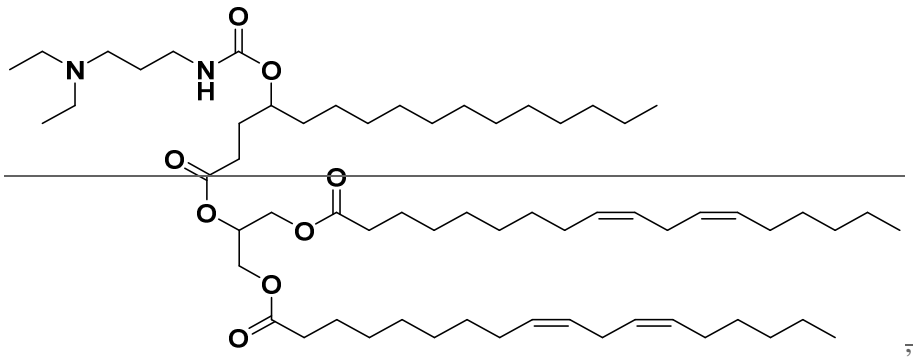
~~, and~~



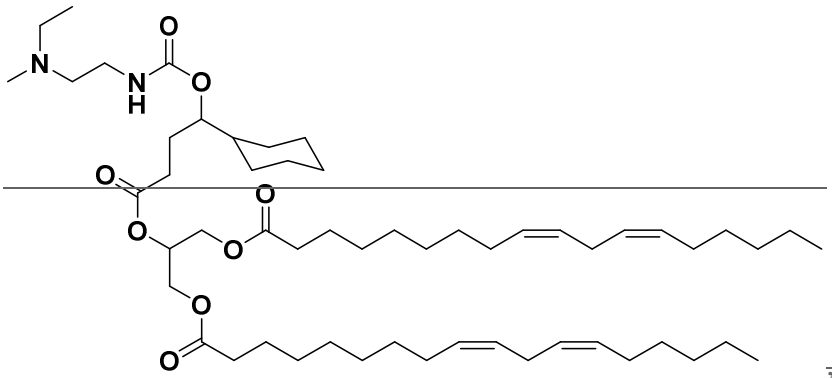
;

or a salt thereof.

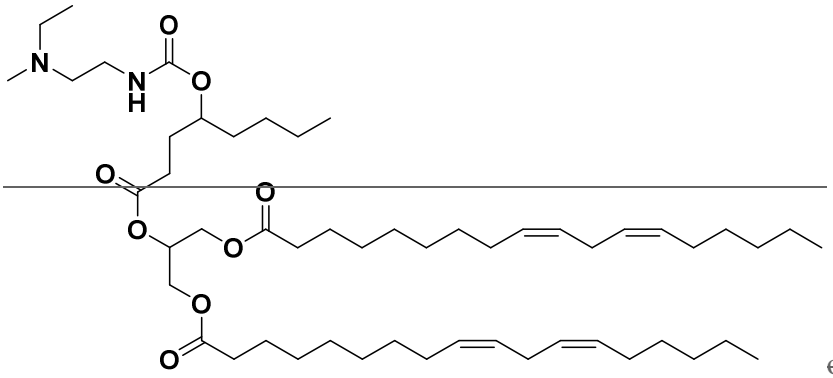
43. The compound of claim 1, wherein the compound is selected from:



;

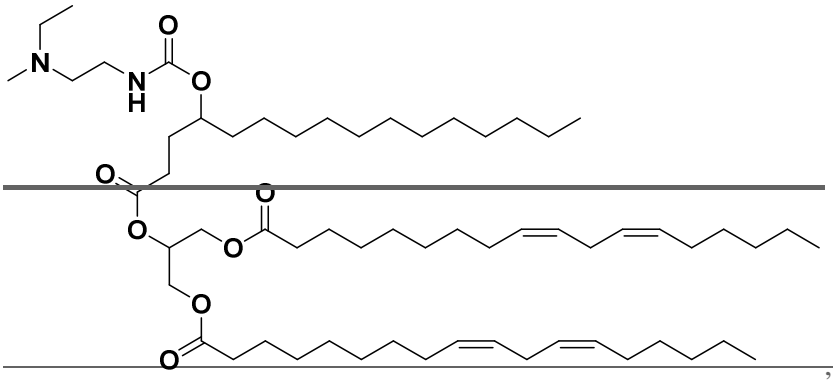


, and

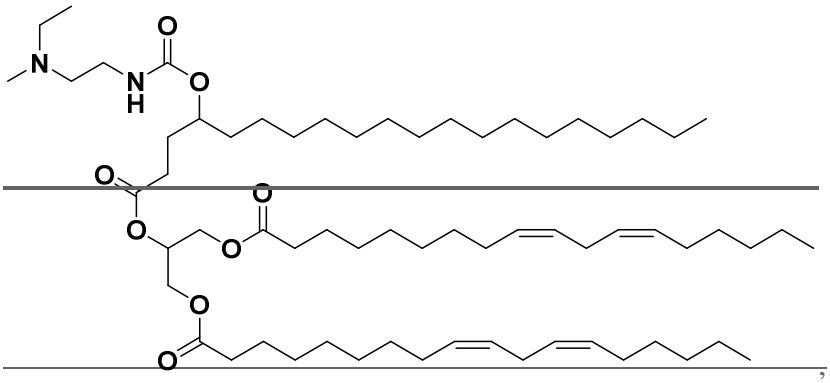


~~or a salt thereof.~~

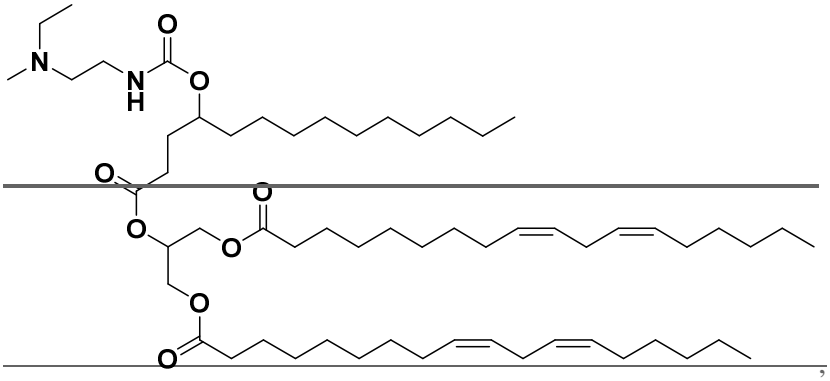
~~44. The compound of claim 1, wherein the compound is selected from~~



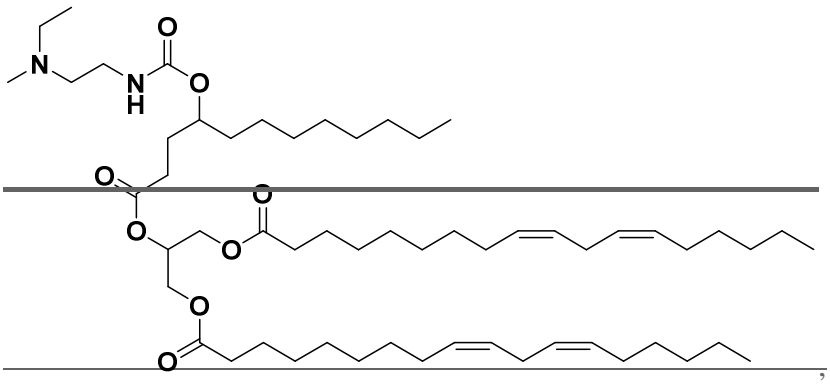
,

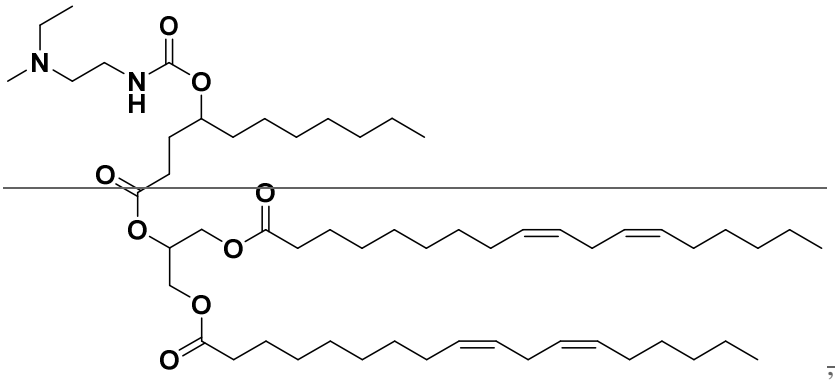


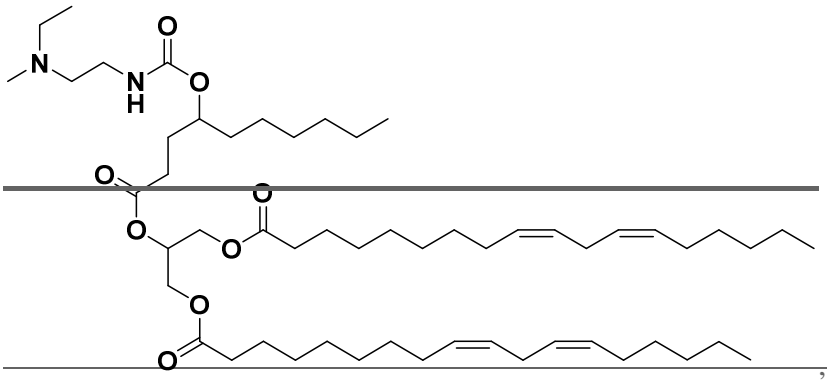
,

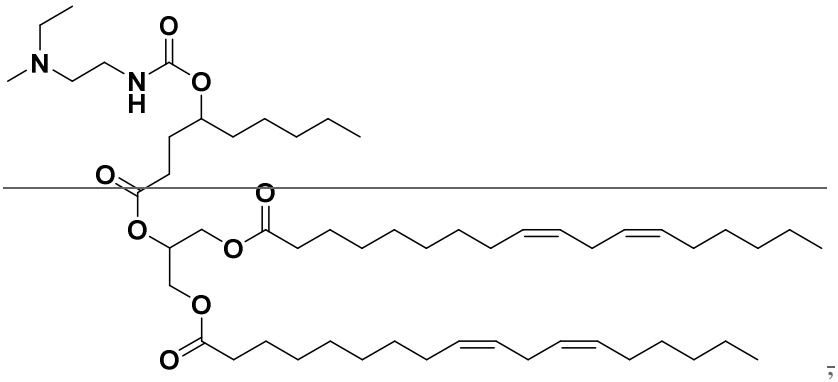


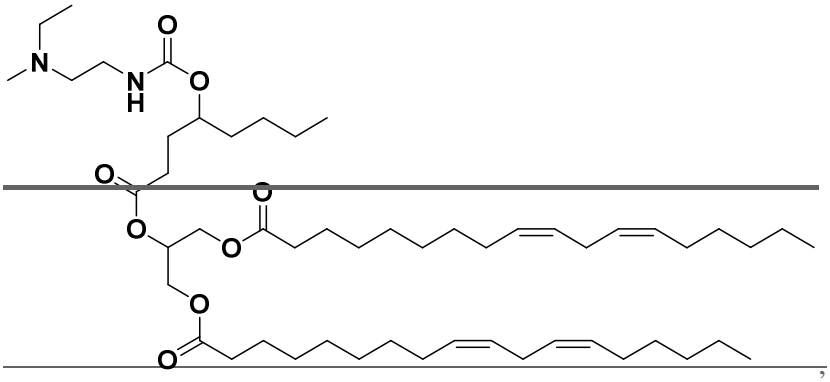
,



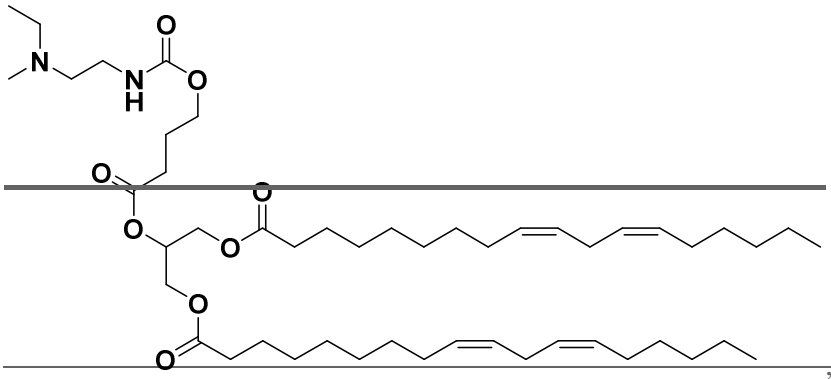




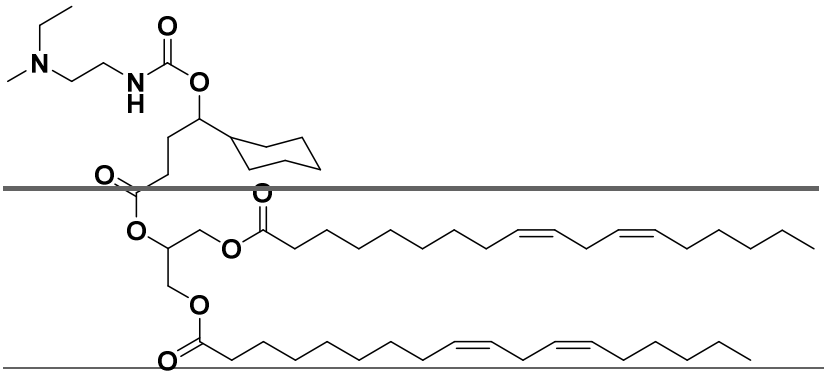




,

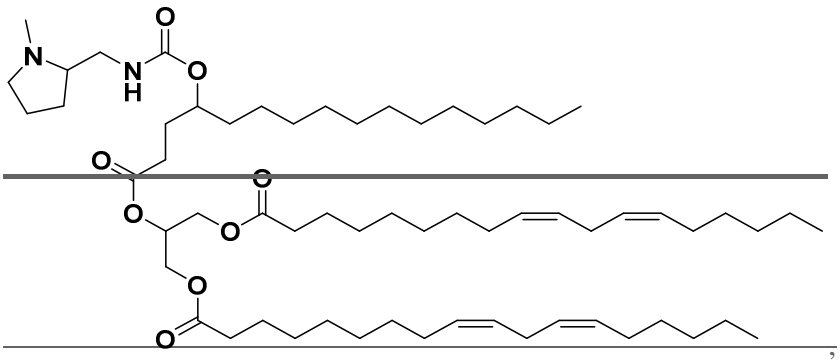


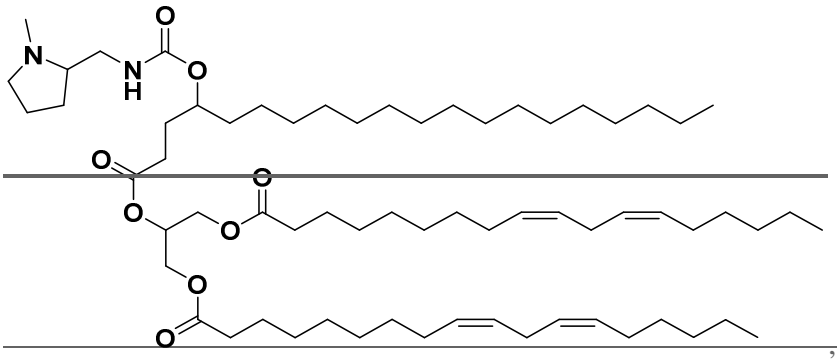
, and

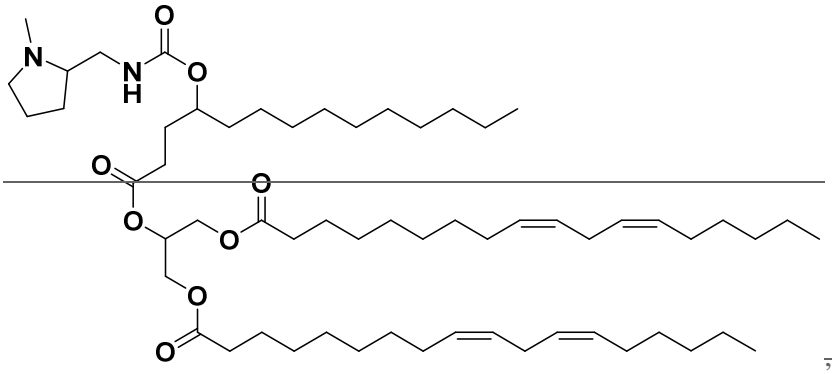


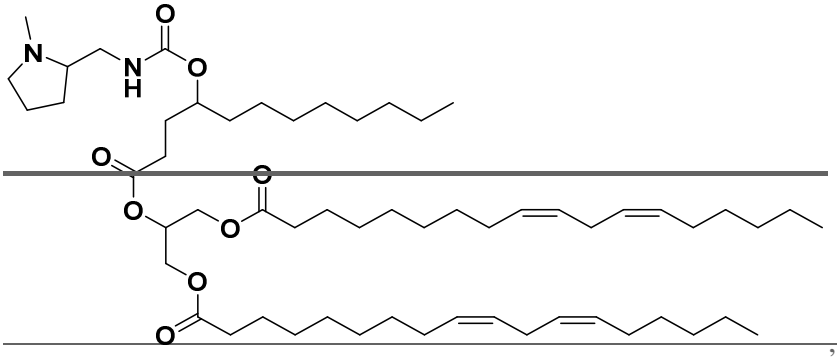
or a salt thereof.

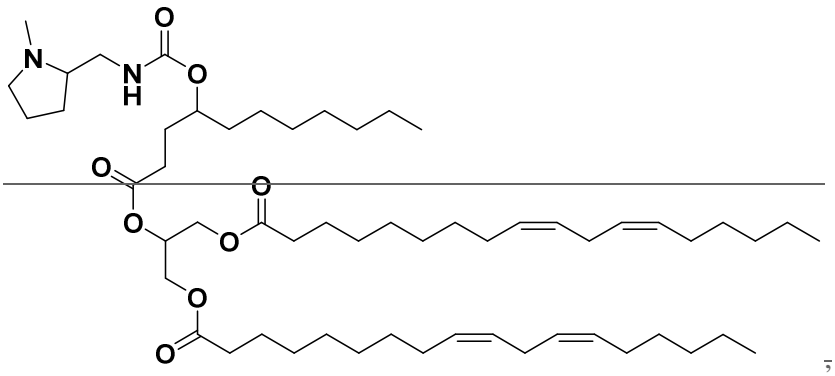
45. The compound of claim 1, wherein the compound is selected from



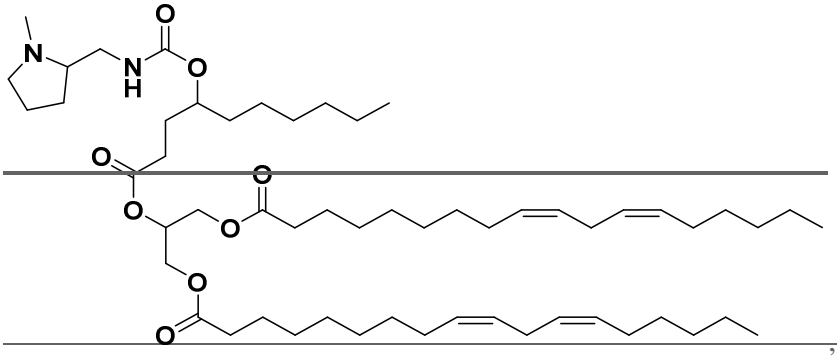




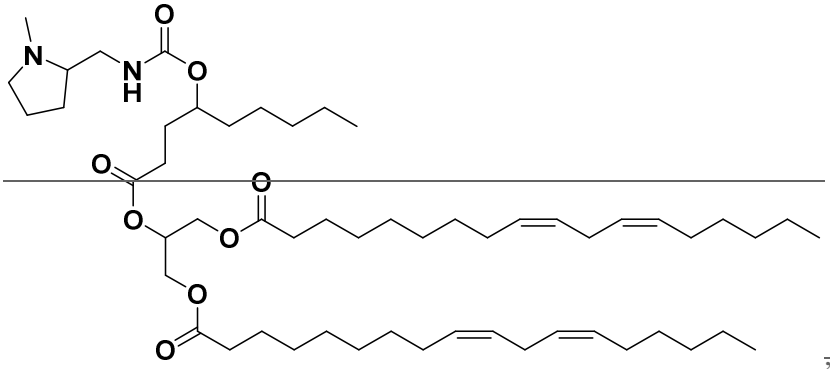




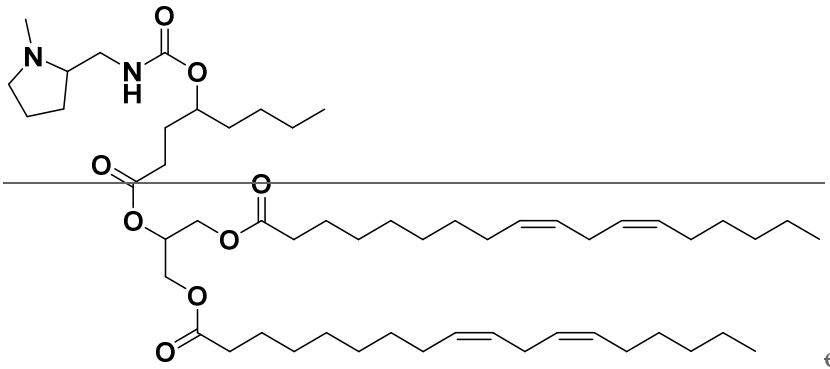
;



;

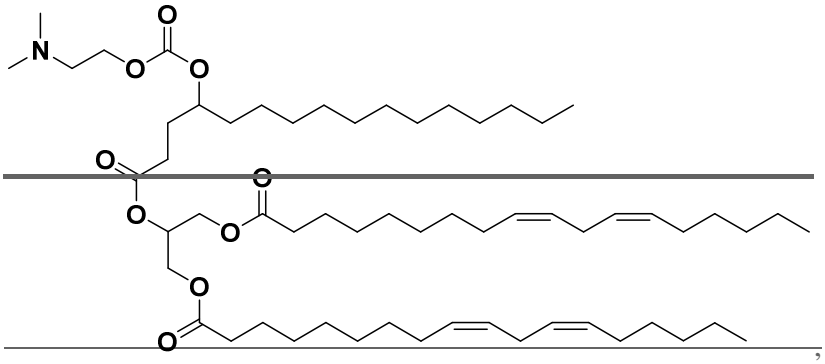


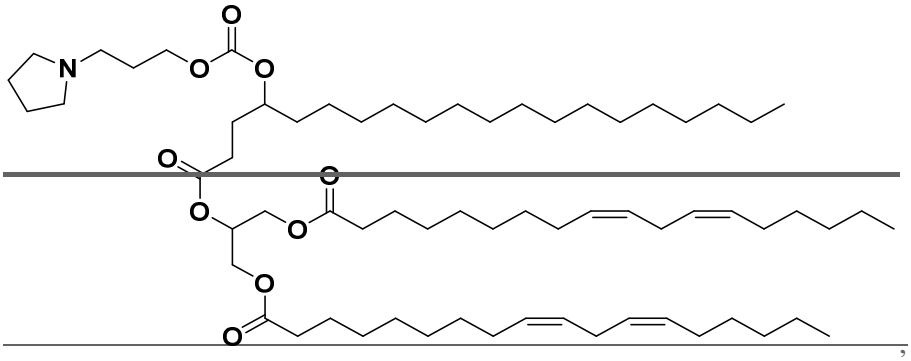
~~, and~~

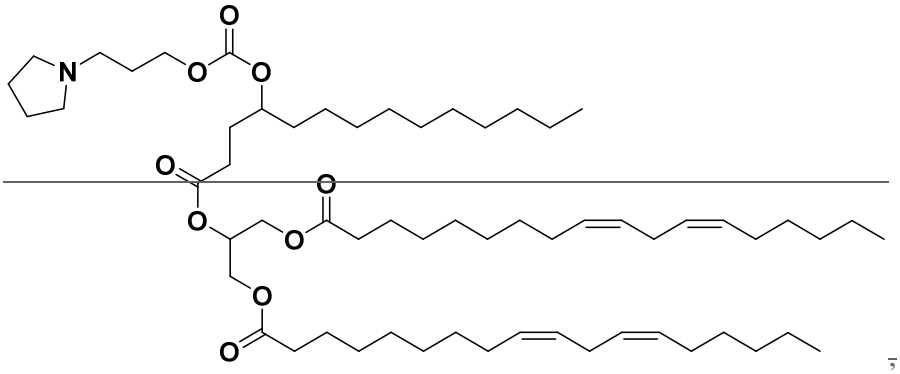


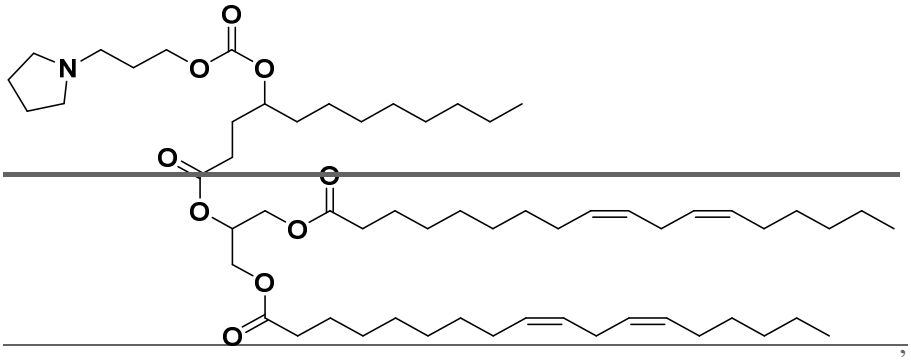
~~or a salt thereof.~~

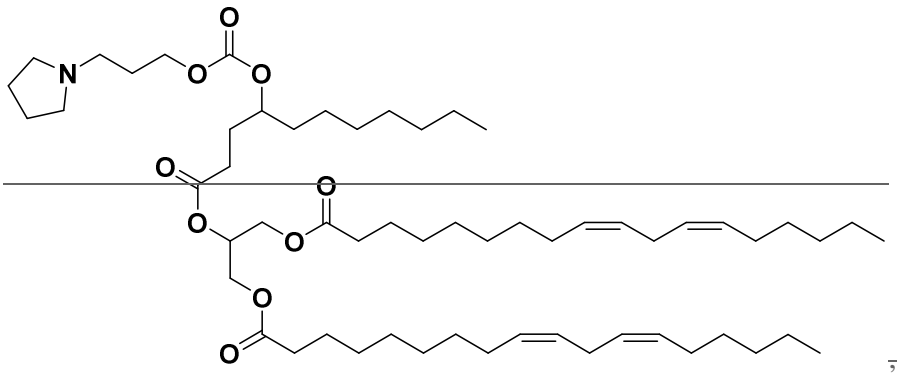
~~46. The compound of claim 1, wherein the compound is selected from~~

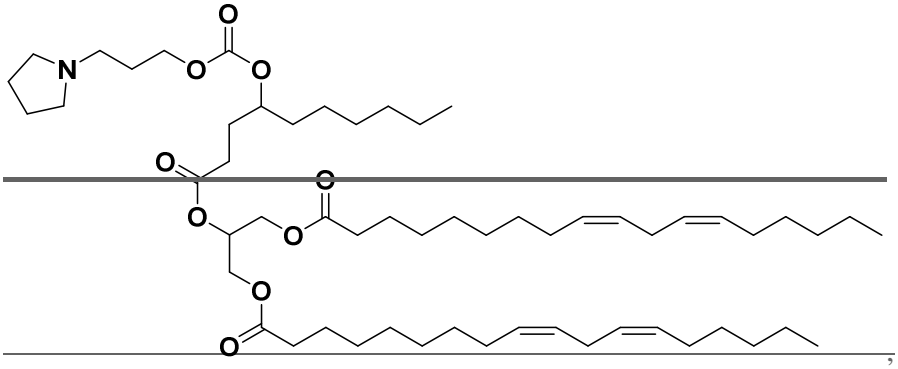


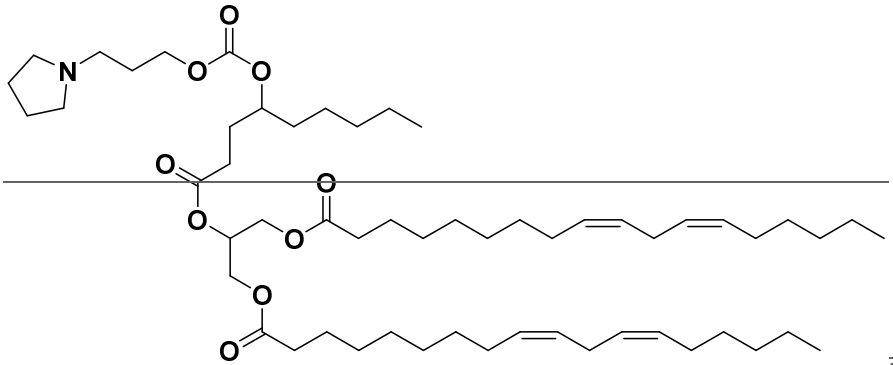


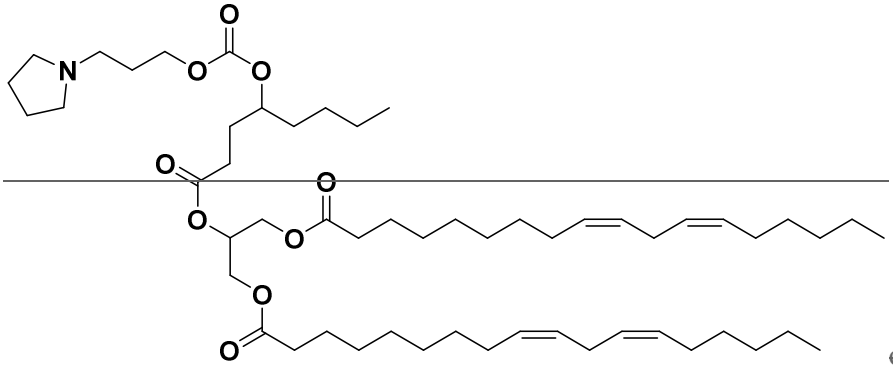





,


,


, and


or a salt thereof.

~~47. The compound of any one of claims 1-46, wherein the salt is a pharmaceutically acceptable salt.~~

~~48. The compound of any one of the preceding claims, wherein the pKa of the protonated form of the compound is from about 5.1 to about 8.0.~~

~~49. The compound of any one of the preceding claims, wherein the pKa of the protonated form of the compound is from about 5.6 to about 7.2.~~

~~50. The compound of any one of the preceding claims, wherein the pKa of the compound is from about 5.7 to about 6.5.~~

~~51. A composition comprising a compound of any one of the preceding claims in a lipid component.~~

~~52. The composition of claim 51, wherein the lipid component includes about 50% by weight of the compound of any one of claims 1-50.~~

~~53. The composition of claim 51 or 52, wherein the composition is an LNP composition.~~

~~54. The composition of any one of claims 51-53, wherein the lipid component comprises a helper lipid and a PEG lipid.~~

~~55. The composition of any one of claims 51-54, wherein the lipid component comprises a helper lipid, a PEG lipid, and a neutral lipid.~~

~~56. The composition of any one of claims 51-55, further comprising a cryoprotectant.~~

~~57. The composition of any one of claims 51-56, further comprising a buffer.~~

~~58. The composition of any one of claims 51-57, wherein the composition further comprises an aqueous component comprising a biologically active agent.~~

~~59. The composition of claim 58, wherein the biologically active agent comprises a polypeptide.~~

~~60. The composition of claim 58, wherein the biologically active agent comprises a nucleic acid.~~

~~61. The composition of claim 60, wherein the nucleic acid comprises RNA.~~

~~62. The composition of claim 60 or 61, wherein the composition has an N/P ratio of about 3-10.~~

~~63. The composition of claim 62, wherein the N/P ratio is about 6 ± 1.~~

~~64. The composition of claim 62, wherein the N/P ratio is about 6 ± 0.5.~~

~~65. The composition of claim 62, wherein the N/P ratio is about 6.~~

~~66. The composition of any one of claims 51-65, comprising an RNA component, wherein the RNA component comprises an mRNA.~~

~~67. The composition of claim 66, wherein the RNA component comprises a sequence encoding RNA-guided DNA binding agent, such as a Cas nuclease mRNA.~~

~~68. The composition of claim 66 or 67, wherein the RNA component comprises a Class 2 Cas nuclease mRNA.~~

~~69. The composition of any one of claims 66-68, wherein the RNA component comprises a Cas9 nuclease mRNA.~~

~~70. The composition of any one of claims 66-69, wherein the RNA component comprises a modified RNA.~~

~~71. The composition of any one of claims 66-70, wherein the RNA component comprises a gRNA nucleic acid.~~

~~72. The composition of claim 71, wherein the gRNA nucleic acid is a gRNA.~~

~~73. The composition of any one of claims 66-72, wherein the RNA component comprises a Class 2 Cas nuclease mRNA and a gRNA.~~

~~74. The composition of any one of claims 71-73, wherein the gRNA nucleic acid is or encodes a dual-guide RNA (dgRNA).~~

~~75. The composition of any one of claims 71-73, wherein the gRNA nucleic acid is or encodes a single-guide RNA (sgRNA).~~

~~76. The composition of any one of claims 71-75, wherein the gRNA is a modified gRNA.~~

~~77. The composition of claim 76, wherein the modified gRNA comprises a modification at one or more of the first five nucleotides at a 5' end.~~

~~78. The composition of claims 76 or 77, wherein the modified gRNA comprises a modification at one or more of the last five nucleotides at a 3' end.~~

~~79. The composition of any one of claims 58-78, further comprising at least one template nucleic acid.~~

~~80. A method of gene editing, comprising contacting a cell with a composition of any one of claims 51-79.~~

~~81. A method of cleaving a DNA, comprising contacting a cell with a composition of any one of claims 51-80.~~

~~82. The method of claim 81, wherein the contacting step results in a single stranded DNA nick.~~

~~83. The method of claim 81, wherein the contacting step results in a double-stranded DNA break.~~

~~84. The method of claim 81, wherein the composition comprises a Class 2 Cas mRNA and a gRNA nucleic acid.~~

~~85. The method of claim 80 or 84, further comprising introducing at least one template nucleic acid into the cell.~~

86. The method of claim 85, comprising contacting the cell with a composition comprising a template nucleic acid.

87. The method of any one of claims 80-86, wherein the method comprises administering the composition to an animal.

88. The method of any one of claims 80-86, wherein the method comprises administering the composition to a human.

89. The method of any one of claims 80-86, wherein the method comprises administering the composition to a cell.

90. The method of claim 89, wherein the cell is a eukaryotic cell.

91. The method of claim 80, wherein the method comprises administering mRNA formulated in a first LNP composition and a second LNP composition comprising one or more of an mRNA, a gRNA, a gRNA nucleic acid, and a template nucleic acid.

92. The method of claim 91, wherein the first and second LNP compositions are administered simultaneously.

93. The method of claim 91, wherein the first and second LNP compositions are administered sequentially.

94. The method of claim 91, wherein the method comprises administering the mRNA and the gRNA nucleic acid formulated in a single LNP composition.

95. The method of any one of claims 80-94, wherein the gene editing results in a gene knockout.

96. The method of any one of claims 80-94, wherein the gene editing results in a gene correction.