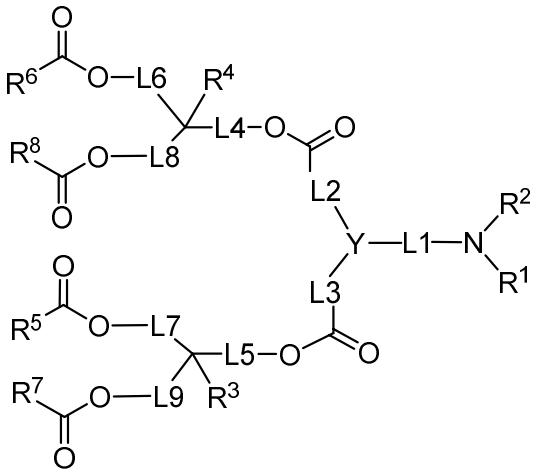
CLAIMS

1. A compound of Formula I, or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 and R^2 are each independently H or C_{1-6} alkyl; or

R^1 and R^2 are joined to form a saturated heterocyclic ring, wherein:

R^1 is a linear C_{1-4} alkylene; and

R^2 is $-(CH_2)_m(X)_n-$, wherein

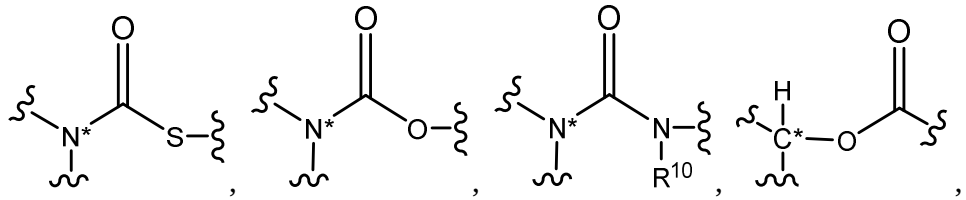
X is O, S, or NR^9, wherein R^9 is H or C_{1-6} alkyl;

m is 1, 2, 3 or 4, and

n is 0 or 1;

L1 is a linear C_{1-6} alkylene optionally substituted with one to three methyl groups;

Y is selected from the group consisting of:



, and ;

wherein:

each asterisk (*) indicates the atom attached to L2 and L3; and

R^{10} is H or C_{1-6} alkyl;

L2 and L3 are each independently a linear C_{1-8} alkylene;

L4, L5, L6, L7, L8 and L9 are each independently absent or $-CH_2-$, provided that:

at least two of L4, L6 and L8 are $-CH_2-$; and

at least two of L5, L7 and L9 are $-CH_2-$;

R^3 and R^4 are each independently H, methyl or ethyl; and

R^5, R^6, R^7 and R^8 are each independently selected from the group consisting of:

linear C_{1-20} alkyl, wherein each said linear C_{1-20} alkyl is optionally substituted with one or more substituents selected from the group consisting of:

C_{1-6} alkyl, C_{1-6} alkoxy and -F, wherein each said C_{1-6} alkyl substituent is optionally substituted with one or more groups selected from the group consisting of C_{1-3} alkoxy and -F;

C_{3-8} monocycloalkyl, wherein each said C_{3-8} monocycloalkyl is optionally substituted with one or more substituents selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy and -F;

C_{7-12} bicycloalkyl, wherein each said C_{7-12} bicycloalkyl is optionally substituted with one or more substituents selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy and -F; and

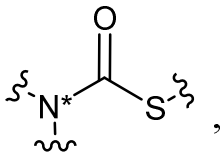
C_{6-10} aryl, wherein each said C_{6-10} aryl is a monocyclic or bicyclic aromatic hydrocarbon optionally substituted with one or more substituents selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy and -F;

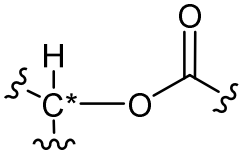
C_{3-8} monocycloalkyl, wherein each said C_{3-8} monocycloalkyl is optionally substituted with one or more substituents selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy and -F;

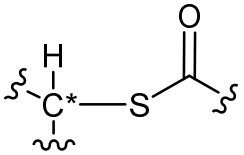
C_{7-12} bicycloalkyl, wherein each said C_{7-12} bicycloalkyl is optionally substituted with one or more substituents selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy and -F; and

C_{6-10} aryl, wherein each said C_{6-10} aryl is a monocyclic or bicyclic aromatic hydrocarbon optionally substituted with one or more substituents selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy and -F.

2. The compound of claim 1, wherein Y is selected from the group consisting of:



,


and


.

3. The compound of claim 1 or 2, wherein R^1 and R^2 are each independently C_{1-6} alkyl.

4. The compound of any one of claims 1 to 3, wherein R^5, R^6, R^7 and R^8 are each independently selected from the group consisting of:

linear C_{1-8} alkyl, wherein each said linear C_{1-8} alkyl is optionally substituted with one or more substituents selected from the group consisting of:

C_{1-3} alkyl, C_{1-3} alkoxy and -F, wherein each said C_{1-3} alkyl substituent is optionally substituted with one or more groups selected from the group consisting of C_{1-3} alkoxy and -F;

saturated C_{3-6} monocycloalkyl, wherein each said saturated C_{3-6} monocycloalkyl is optionally substituted with one or more substituents selected from the group consisting of C_{1-6} alkyl, C_{1-3} alkoxy and -F;

saturated C_{7-12} bicycloalkyl, wherein each said saturated C_{7-12} bicycloalkyl is optionally substituted with one or more substituents selected from the group consisting of C_{1-6} alkyl, C_{1-3} alkoxy and -F; and

C_{6-10} aryl, wherein each said C_{6-10} aryl is a monocyclic or bicyclic aromatic hydrocarbon optionally substituted with one or more substituents selected from the group consisting of C_{1-6} alkyl, C_{1-3} alkoxy and -F;

saturated C_{3-6} monocycloalkyl, wherein each said C_{3-6} monocycloalkyl is optionally substituted with one or more substituents selected from the group consisting of C_{1-6} alkyl, C_{1-3} alkoxy and -F;

saturated C_{7-12} bicycloalkyl, wherein each said saturated C_{7-12} bicycloalkyl is optionally substituted with one or more substituents selected from the group consisting of C_{1-6} alkyl, C_{1-3} alkoxy and -F; and

C_{6-10} aryl, wherein each said C_{6-10} aryl is a monocyclic or bicyclic aromatic hydrocarbon optionally substituted with one or more substituents selected from the group consisting of C_{1-6} alkyl, C_{1-3} alkoxy and -F.

5. The compound of claim 4, wherein R^5, R^6, R^7 and R^8 are each independently linear C_{1-8} alkyl, wherein each said linear C_{1-8} alkyl is optionally substituted with one or more substituents selected from the group consisting of C_{1-3} alkyl, C_{1-3} alkoxy and -F, wherein each said C_{1-3} alkyl substituent is optionally substituted with one or more groups selected from the group consisting of C_{1-3} alkoxy and -F.

6. The compound of claim 4, wherein R^5, R^6, R^7 and R^8 are each independently linear C_{1-8} alkyl optionally substituted with saturated C_{3-6} monocycloalkyl, wherein each said saturated C_{3-6} monocycloalkyl is optionally substituted with one or more substituents selected from the group consisting of C_{1-6} alkyl, C_{1-3} alkoxy and -F.

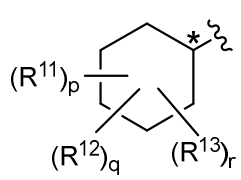
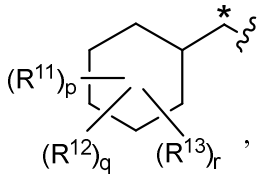
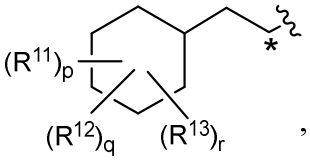
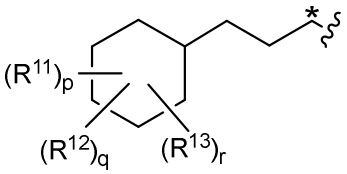
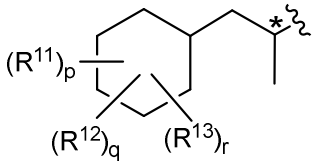
7. The compound of claim 6, wherein each said saturated C_{3-6} monocycloalkyl is optionally substituted with one or more C_{1-3} alkyl.

8. The compound of claim 4, wherein R^5, R^6, R^7 and R^8 are each independently linear C_{1-8} alkyl optionally substituted with saturated C_{7-12} bicycloalkyl or C_{6-10} aryl, wherein each said C_{6-10} aryl is a monocyclic or bicyclic aromatic hydrocarbon, and wherein each said saturated C_{7-12} bicycloalkyl or C_{6-10} aryl is optionally substituted with one or more substituents selected from the group consisting of C_{1-6} alkyl, C_{1-3} alkoxy and -F.

9. The compound of claim 4, wherein R^5, R^6, R^7 and R^8 are each independently saturated C_{3-6} monocycloalkyl or C_{7-12} bicycloalkyl, wherein each said C_{3-6} monocycloalkyl or C_{7-12}

bicycloalkyl is optionally substituted with one or more substituents selected from the group consisting of C_{1-6} alkyl, C_{1-3} alkoxy and -F.

10. The compound of claim 4, wherein R^5, R^6, R^7 and R^8 are each independently monocycloalkyl selected from the group consisting of:


,

,

,

and

;

wherein:

each asterisk (*) indicates the atom attached to the carbonyl carbon;

each R^{11} is independently C_{1-6} alkyl;

each R^{12} is independently C_{1-3} alkoxy;

each R^{13} is -F;

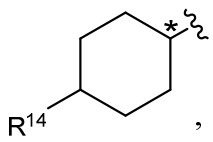
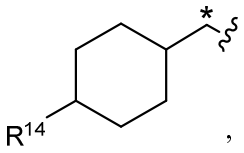
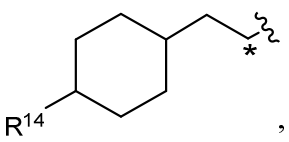
each p is independently 0 to 11;

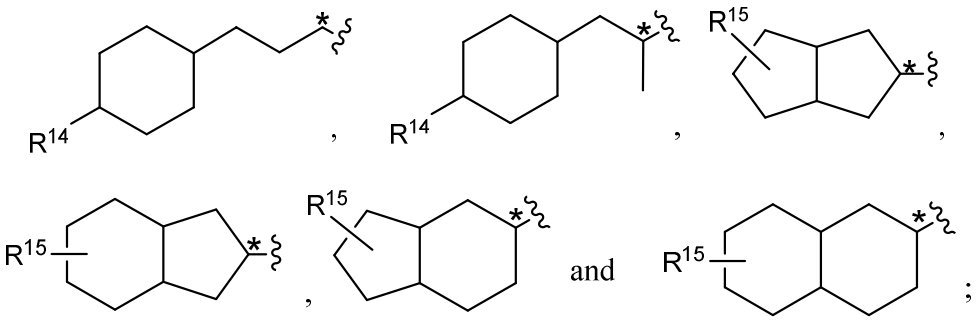
each q is independently 0 to 11; and

each r is independently 0 to 11;

wherein the sum of p, q and r is no greater than 11 .

11. The compound of claim 4, wherein R^5, R^6, R^7 and R^8 are each independently selected from the group consisting of:


,

,

,



wherein:

each asterisk (*) indicates the atom attached to the carbonyl carbon;

each R^{14} is independently H or C_{1-6} alkyl; and

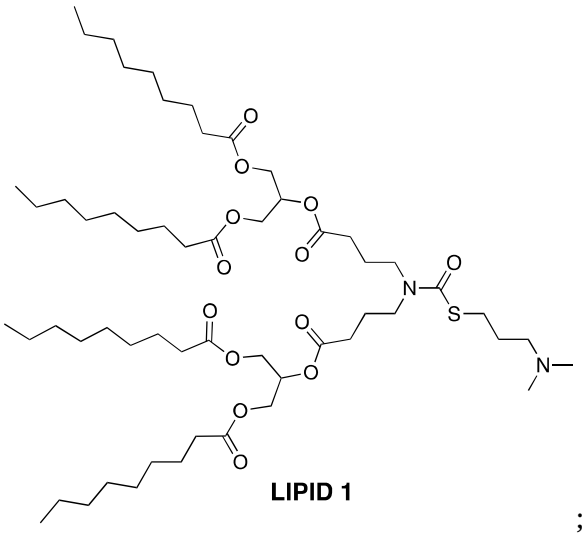
each R^{15} is independently H or C_{1-6} alkyl.

12. The compound of any one of claims 1 to 11, wherein L1 is linear unsubstituted alkylene.

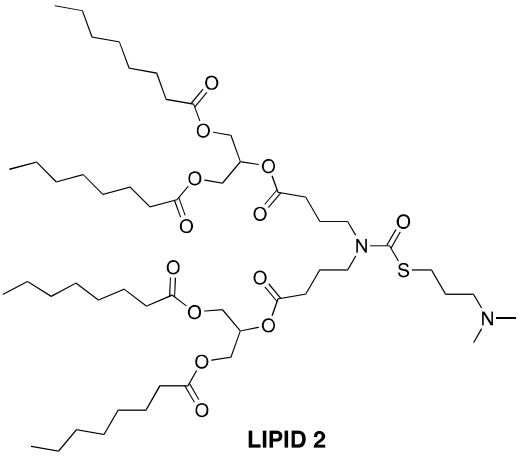
13. The compound of any one of claims 1 to 12, wherein L2 and L3 are each independently linear C_{1-5} alkylene.

14. The compound of any one of claims 1 to 13, wherein L6, L7, L8 and L9 are each $-CH_2-$; and L4 and L5 are absent.

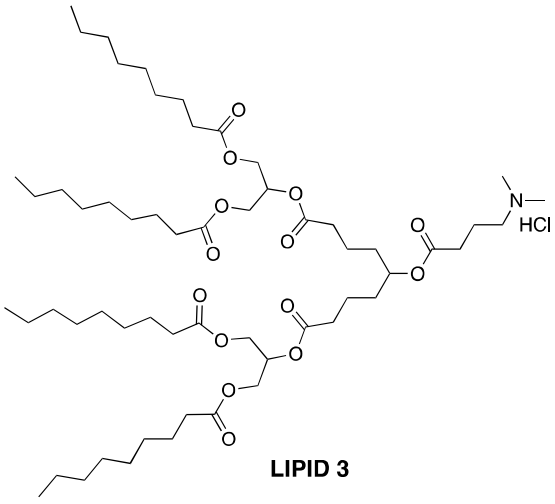
15. The compound of claim 1 selected from the group consisting of:



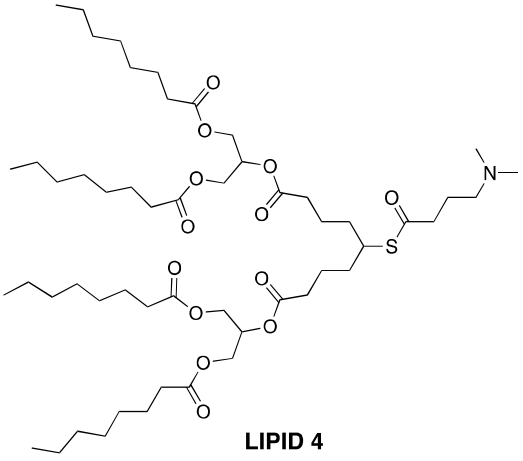
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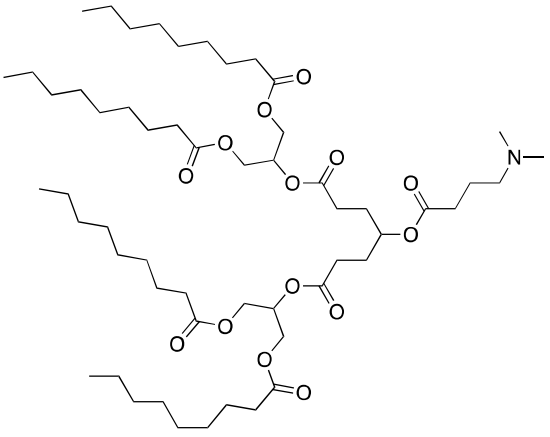
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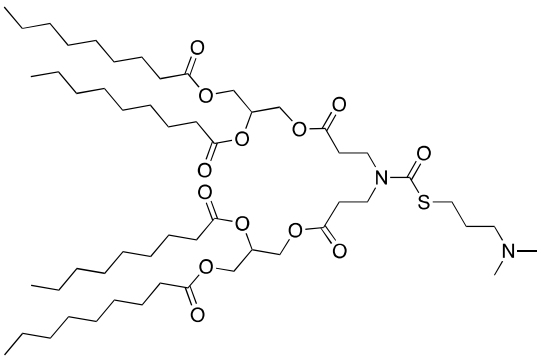
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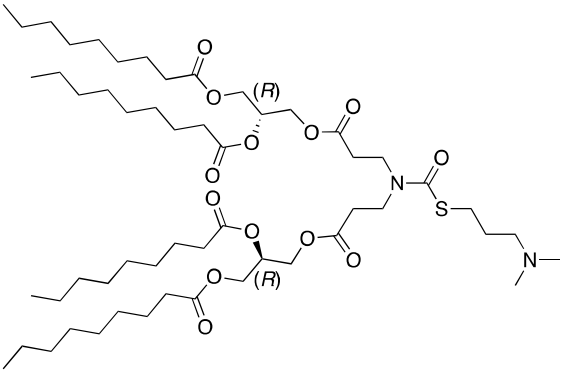
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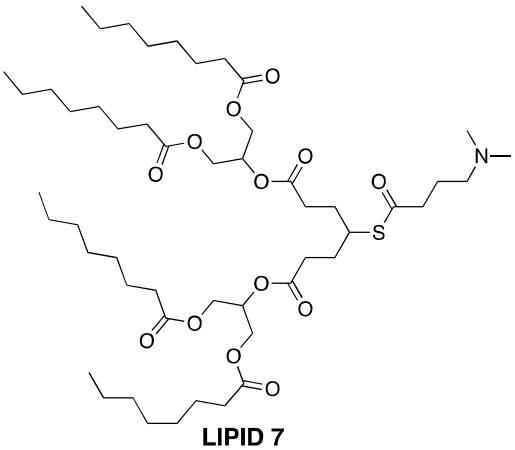
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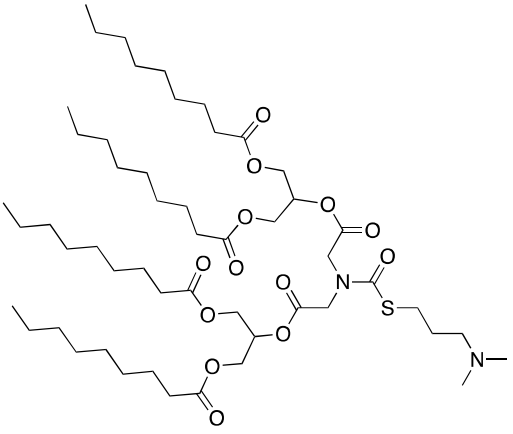
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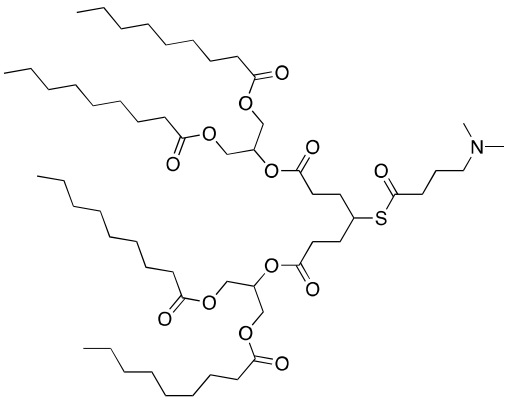
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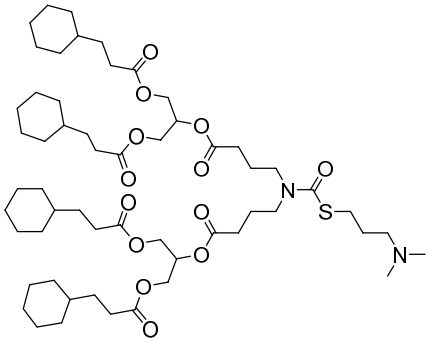
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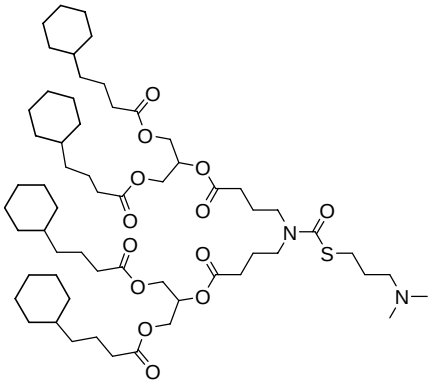
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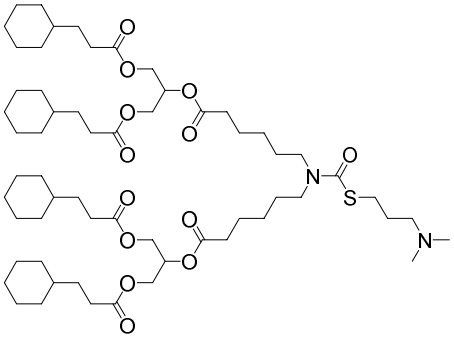
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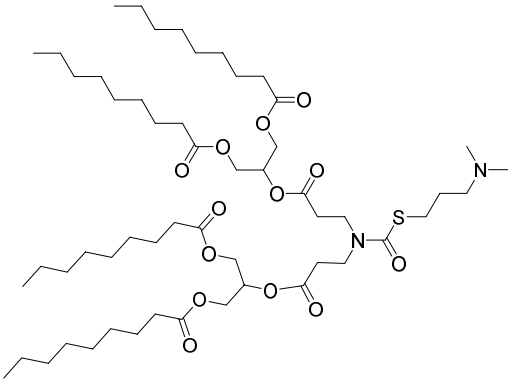
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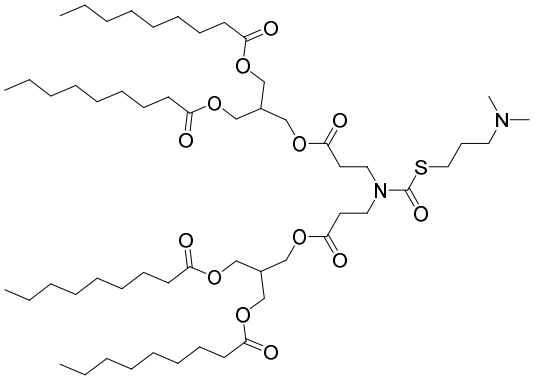
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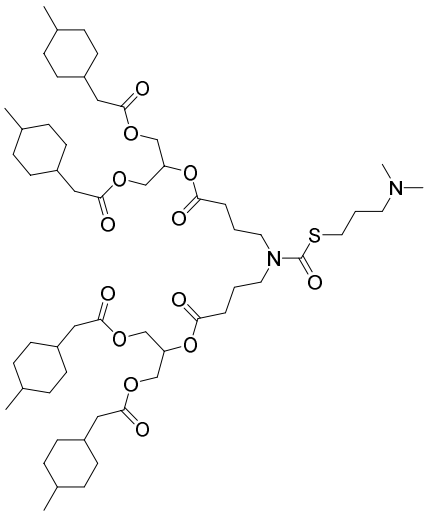
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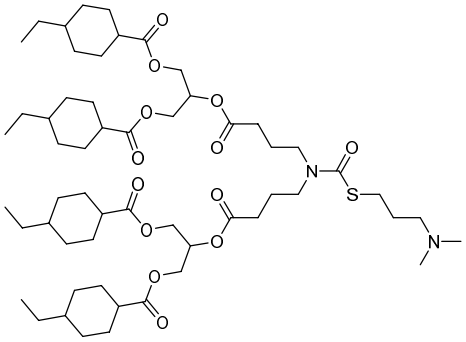
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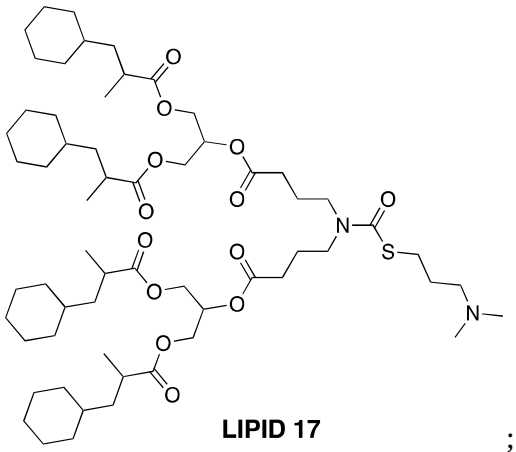
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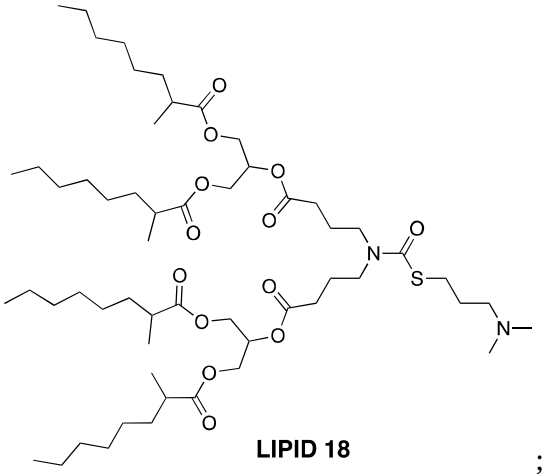
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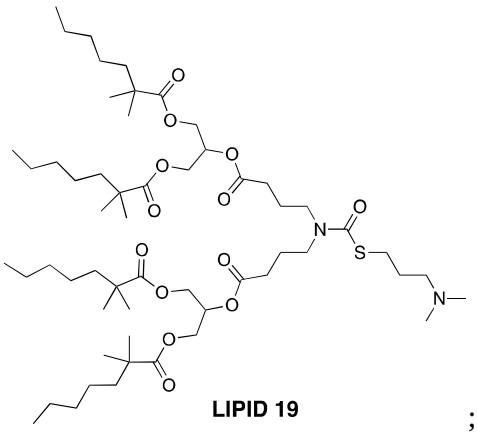
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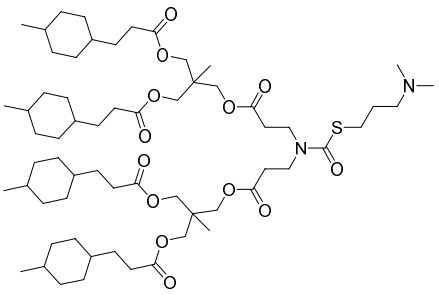
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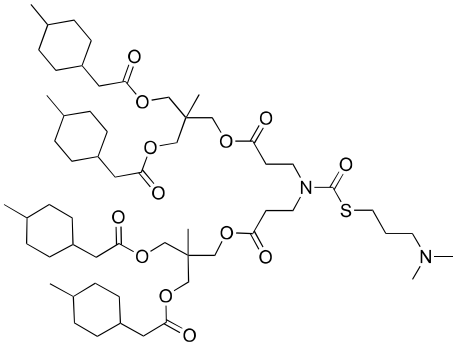
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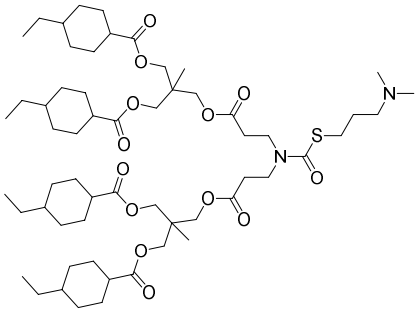
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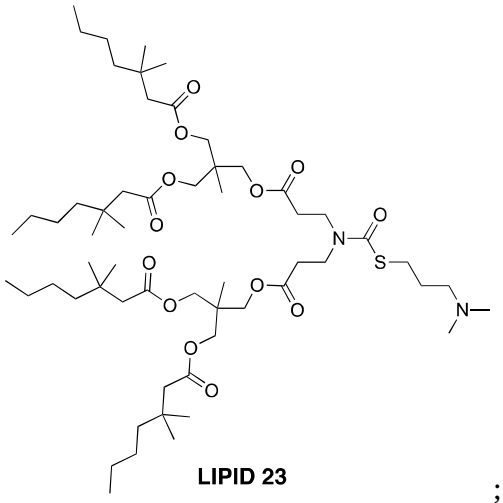
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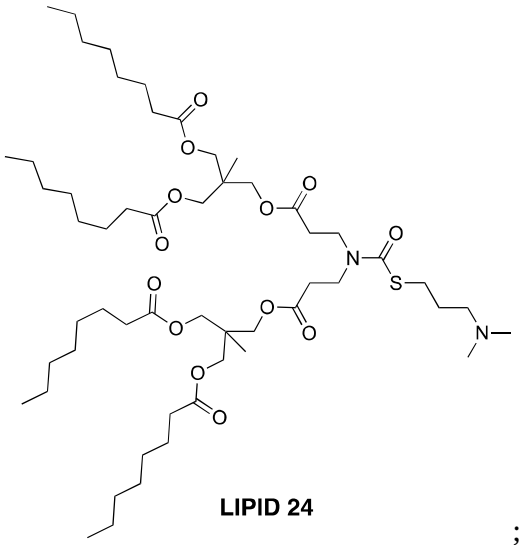
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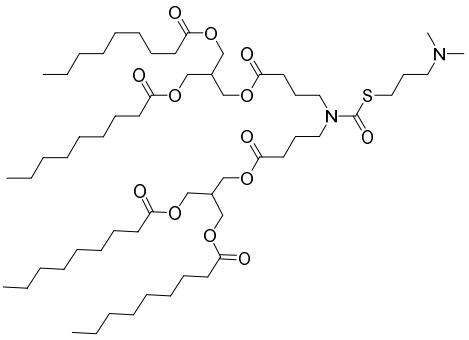
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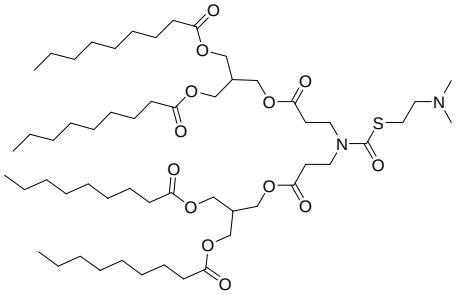
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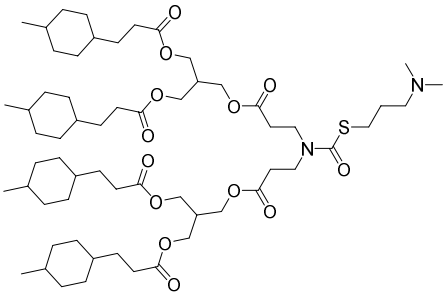
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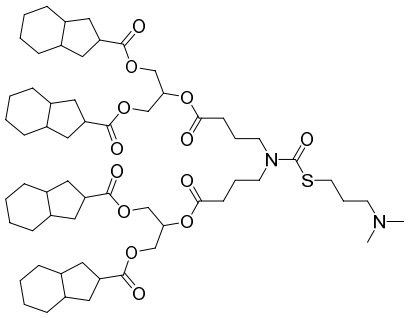
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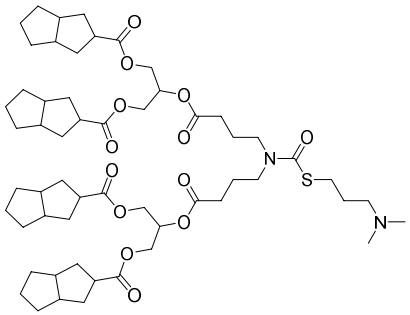
LIPID 26 ;



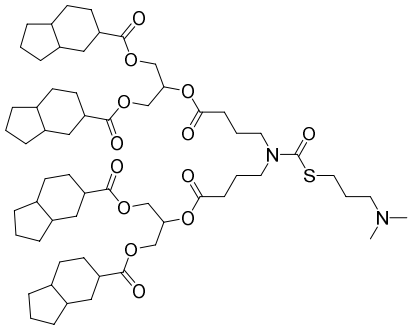
LIPID 27 ;



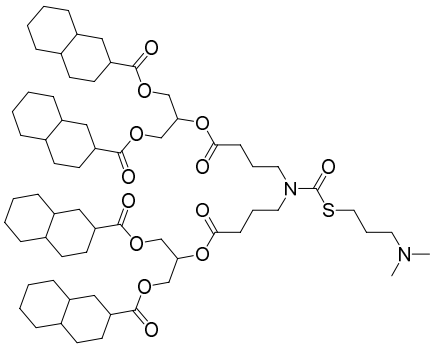
LIPID 28 ;



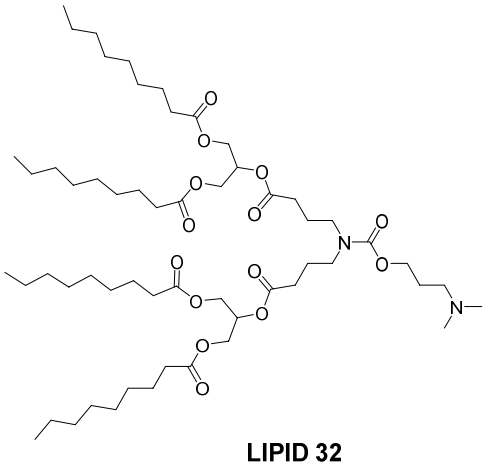
LIPID 29 ;



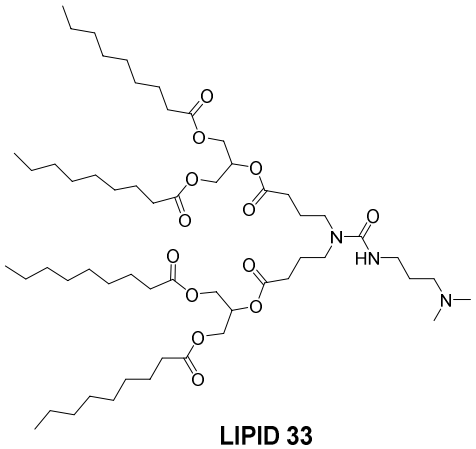
LIPID 30 ;



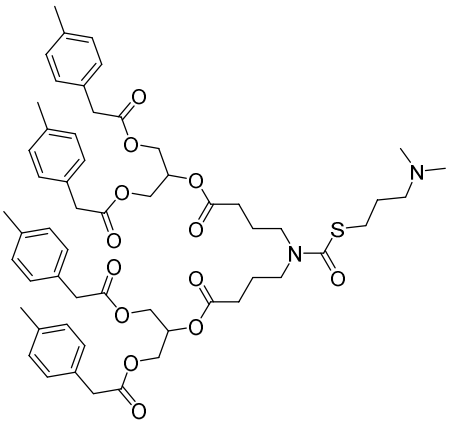
LIPID 31 ;



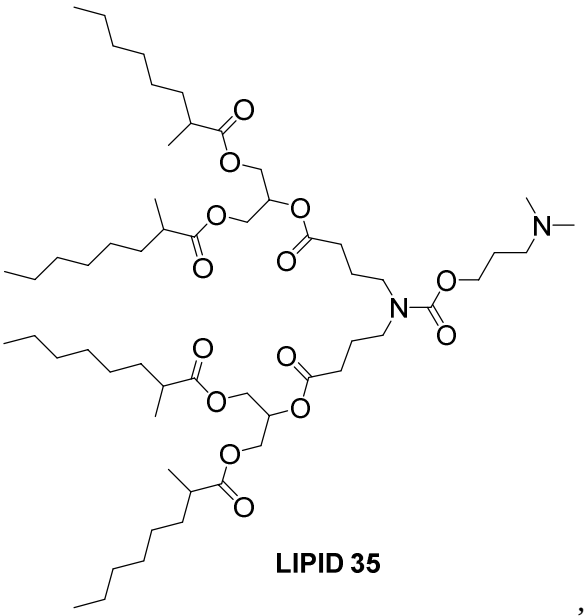
LIPID 32 ;



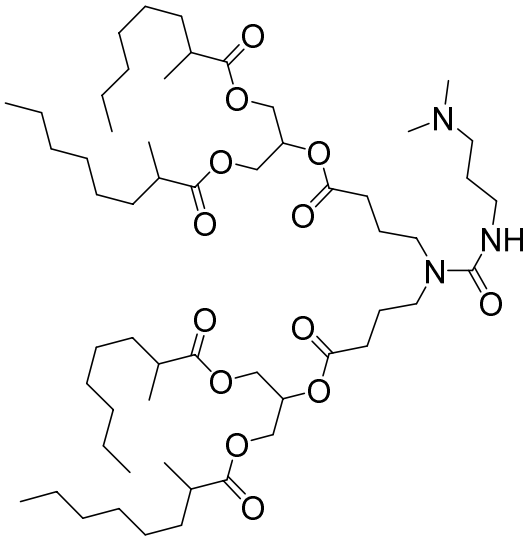
LIPID 33 ;



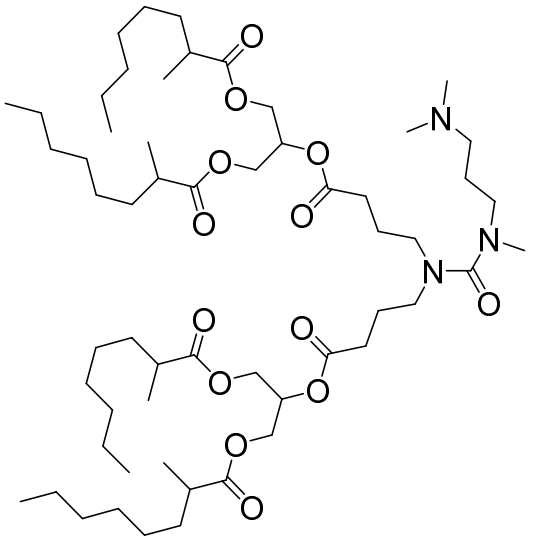
LIPID 34 ,



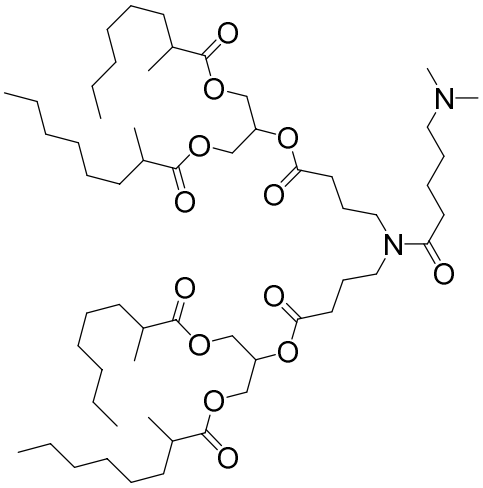
LIPID 35 ,



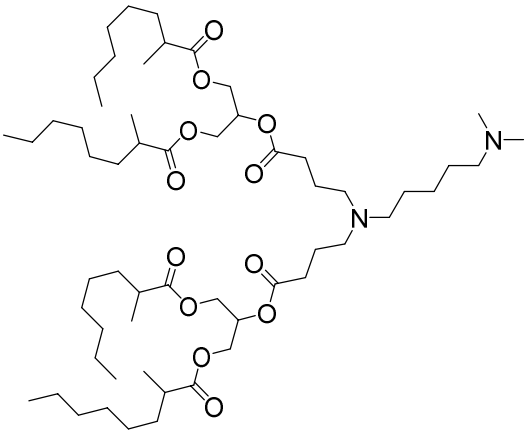
LIPID 36 ,



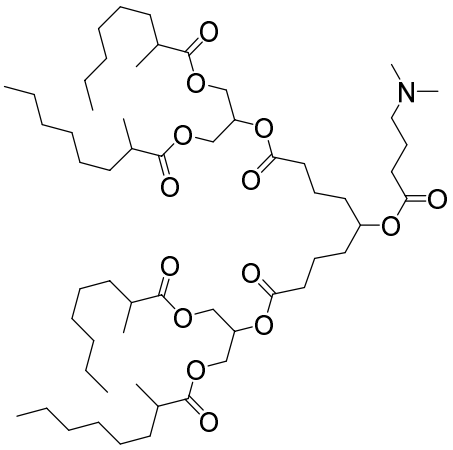
LIPID 37 ,



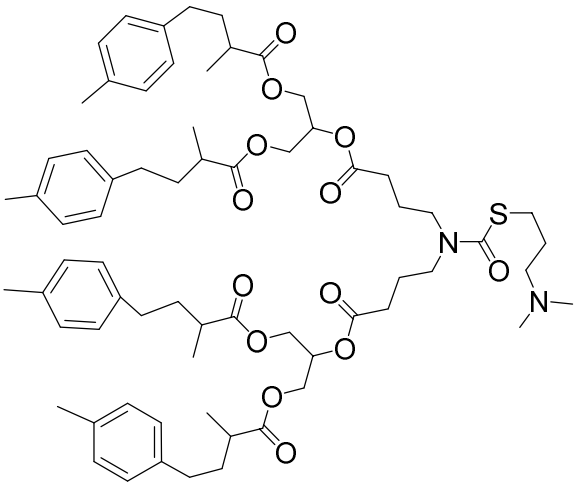
LIPID 38 ,



LIPID 39 ,



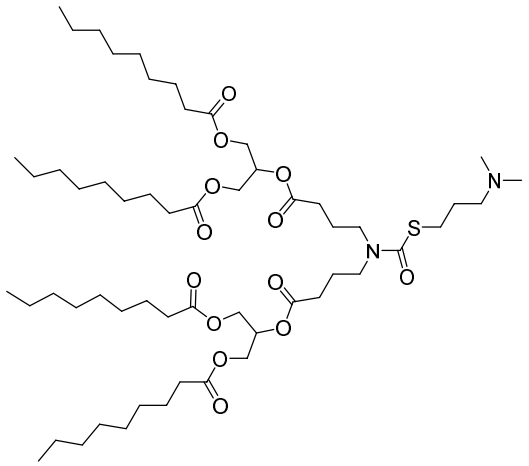
LIPID 40 , and



LIPID 41 ;

or pharmaceutically acceptable salts thereof.

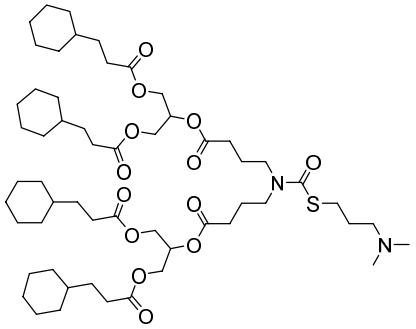
16. The compound of claim 15, wherein the compound is:



LIPID 1 ;

or a pharmaceutically acceptable salt thereof.

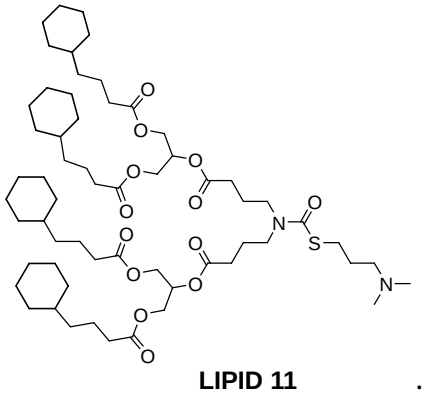
17. The compound of claim 15, wherein the compound is:



LIPID 10 ;

or a pharmaceutically acceptable salt thereof.

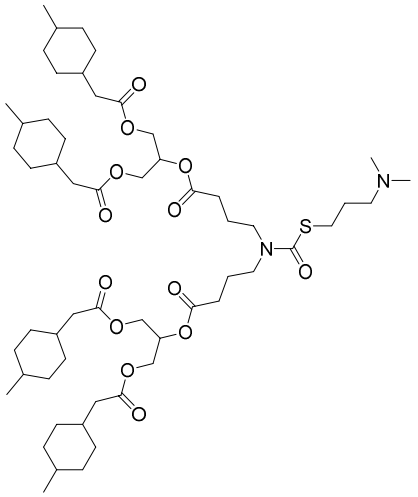
18. The compound of claim 15, wherein the compound is:



LIPID 11 ;

or a pharmaceutically acceptable salt thereof.

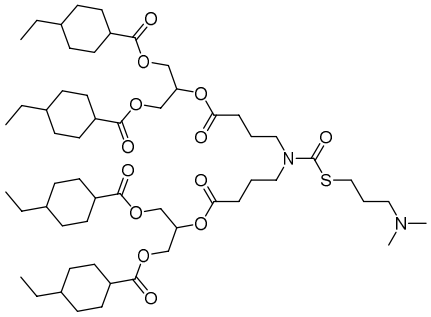
19. The compound of claim 15, wherein the compound is:



LIPID 15 ;

or a pharmaceutically acceptable salt thereof.

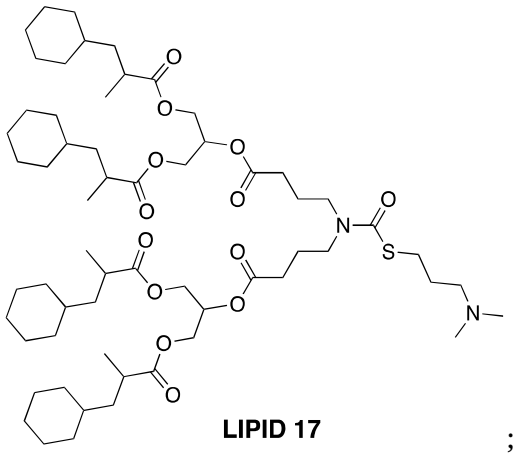
20. The compound of claim 15, wherein the compound is:



LIPID 16 ;

or a pharmaceutically acceptable salt thereof.

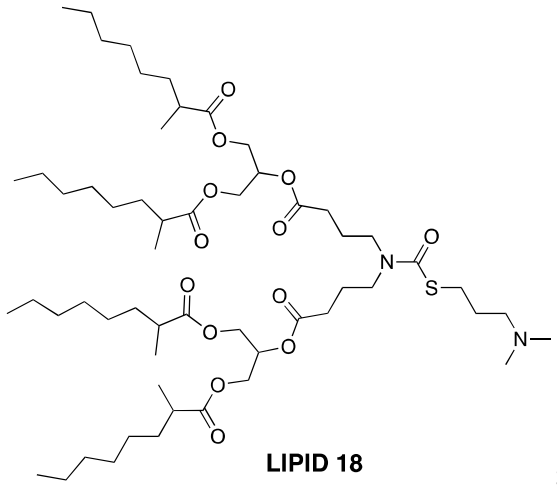
21. The compound of claim 15, wherein the compound is:



LIPID 17 ;

or a pharmaceutically acceptable salt thereof.

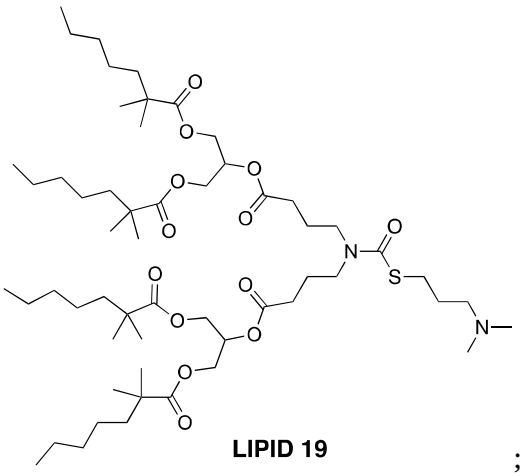
22. The compound of claim 15, wherein the compound is:



LIPID 18 ;

or a pharmaceutically acceptable salt thereof.

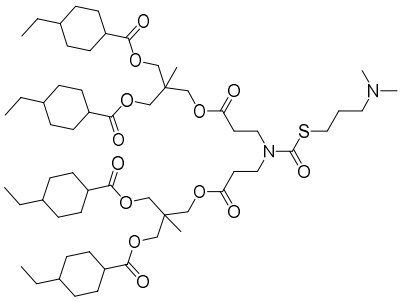
23. The compound of claim 15, wherein the compound is:



LIPID 19 ;

or a pharmaceutically acceptable salt thereof.

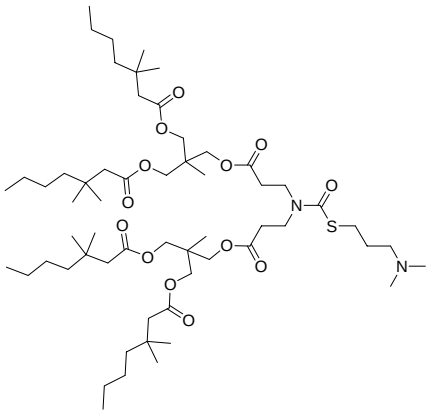
24. The compound of claim 15, wherein the compound is:



LIPID 22 ;

or a pharmaceutically acceptable salt thereof.

25. The compound of claim 15, wherein the compound is:



LIPID 23 ;

or a pharmaceutically acceptable salt thereof.

26. A lipid composition comprising a nucleic acid and a compound of any one of claims 1 to 25.

27. The lipid composition of claim 26, wherein the nucleic acid is selected from an siRNA, an mRNA, a self-replicating RNA, a DNA plasmid, and an antisense oligonucleotide, wherein the nucleic acid is a mRNA or a self-replicating RNA comprising a coding region that encodes a therapeutic protein of interest.

28. The lipid composition of claim 26 or 27, wherein the therapeutic protein of interest is an enzyme, and antibody, an antigen, a receptor, or a transporter.

29. The lipid composition of any one of claims 26 to 28, wherein the lipid composition comprises liposomes, lipoplexes, or lipid nanoparticles.

30. A lipid nanoparticle, comprising a plurality of ligands, wherein each ligand is independently a compound of any one of claims 1 to 25, wherein the plurality of ligands self-assembles to form the lipid nanoparticle comprising an interior and exterior.

31. A pharmaceutical composition comprising the compound of any one of claims 1 to 25, or the lipid nanoparticle of any one of claims 26 to 30, and a pharmaceutically acceptable excipient.

32. The pharmaceutical composition of claim 31, wherein the pharmaceutical is a lyophilized composition.

33. Use of the lipid nanoparticle of any one of claims 26 to 30 or the pharmaceutical composition of claim 31 or 32 in the manufacture of a medicament for treating a disease in a subject in need thereof.

34. Use of the lipid nanoparticle of any one of claims 26 to 30 or the pharmaceutical composition of claim 31 or 32 in the manufacture of a medicament for expressing a protein or polypeptide in a target cell.

35. Use of the lipid nanoparticle of any one of claims 26 to 30 or the pharmaceutical composition of claim 31 or 32 in the manufacture of a medicament for delivering a nucleic acid to a subject in needed thereof.