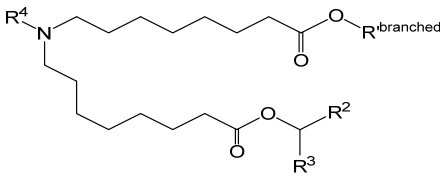
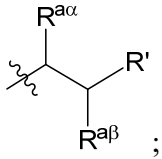
CLAIMS

1. A compound of Formula (A-1):



(A-1) or its N-oxide,

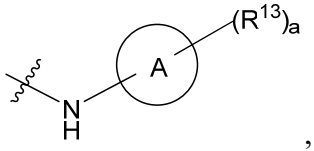
or a salt thereof, wherein:

$R^{branched}$ is  ; wherein  denotes a point of attachment;

wherein $R^{a\alpha}$ and $R^{a\beta}$ are each independently selected from the group consisting of H and C_{1-2} alkyl, wherein at least one of $R^{a\alpha}$ and $R^{a\beta}$ is a C_1 or C_2 alkyl;

R' is selected from the group consisting of C_{1-18} alkyl and C_{2-18} alkenyl;

R^2 and R^3 are each independently selected from the group consisting of C_{1-14} alkyl and C_{2-14} alkenyl;

R^4 is $-(CH_2)_nQ$, wherein n is independently selected from 1, 2, 3, 4, and 5, where Q is selected from $NRS(O)_2R^{SX}$ and  , wherein A is a 3-14 membered heterocycle containing one or more heteroatoms selected from N, O and S; and a is 1, 2, 3, or 4; wherein  denotes a point of attachment;

R is selected from H and C_{1-3} alkyl;

R^{SX} is selected from a C_{3-8} carbocycle, a 3-14 membered heterocycle containing one or more heteroatoms selected from N, O and S, C_{1-6} alkyl, C_{2-6} alkenyl, (C_{1-3} alkoxy)C_{1-3} alkyl, $(CH_2)_{p1}O(CH_2)_{p2}R^{SX1}$, and $(CH_2)_{p1}R^{SX1}$, wherein the carbocycle and heterocycle are optionally substituted with one or more groups selected from oxo, C_{1-6} alkyl, and (C_{1-3} alkoxy)C_{1-3} alkyl;

R^{SX1} is selected from $C(O)NR^{14}R^{14'}$, a C_{3-8} carbocycle, and a 3-14 membered heterocycle containing one or more heteroatoms selected from N, O and S, wherein the carbocycle and heterocycle are each optionally substituted with one or more groups selected from oxo, halo, C_{1-3} alkyl, (C_{1-3} alkoxy)C_{1-3} alkyl, C_{1-6} alkylamino, di-(C_{1-6} alkyl) amino, and NH_2;

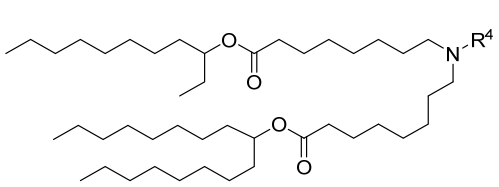
each R^{13} is selected from the group consisting of OH, oxo, halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{1-6} alkylamino, di-(C_{1-6} alkyl) amino, NH_2, $C(O)NH_2$, CN, and NO_2;

R^{14} and $R^{14'}$ are each independently selected from the group consisting of H and C_{1-6} alkyl;

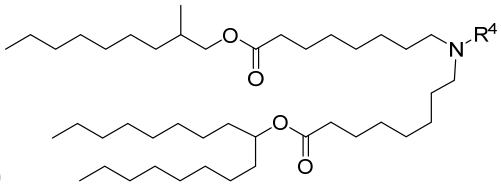
p_1 is selected from 1, 2, 3, 4, and 5; and

p_2 is selected from 1, 2, 3, 4, and 5.

2. The compound of claim 1, having one of the following structures:



(A-1a)



(A-1b).

3. The compound of any one of the preceding claims, wherein n is 3.

4. The compound of any one of the preceding claims, wherein Q is $NRS(O)_2R^{SX}$.

5. The compound of any one of the preceding claims, wherein R is H.

6. The compound of any one of the preceding claims, wherein R^{SX} is selected from a C_{3-6} carbocycle and a C_{1-3} alkyl.

7. The compound of any one of the preceding claims, wherein R^{SX} is ethyl.

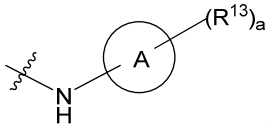
8. The compound of any one of the preceding claims, wherein R^{SX} is cyclopropyl.

9. The compound of any one of the preceding claims, wherein R^{SX} is $(CH_2)_{p1}R^{SX1}$.

10. The compound of any one of the preceding claims, wherein p_1 is 1 and R^{SX1} is a 6-membered heterocycloalkyl, a 5-membered heteroaryl, or phenyl.

11. The compound of any one of the preceding claims, wherein R^{SX1} is a 5-membered heteroaryl.

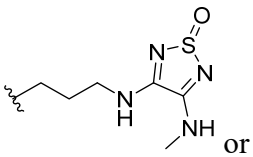
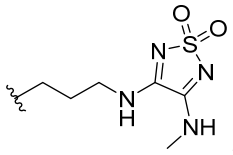
12. The compound of any one of the preceding claims, wherein R^{SX1} is oxazlole or isoxazole.

13. The compound of any one of the preceding claims, wherein Q is .

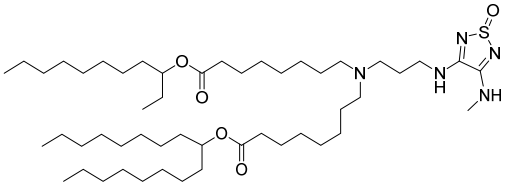
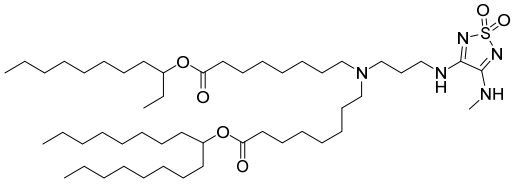
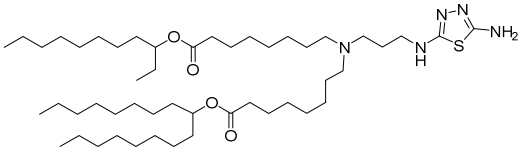
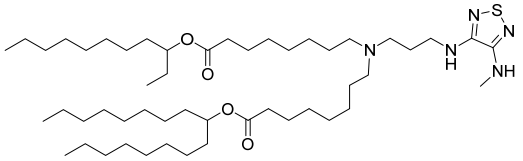
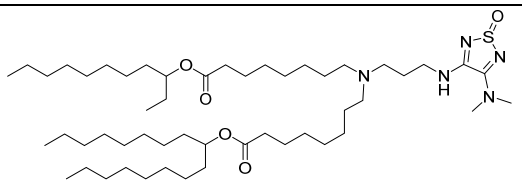
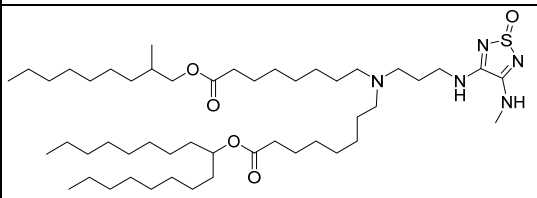
14. The compound of any one of the preceding claims, wherein A is a 5-membered heteroaryl.

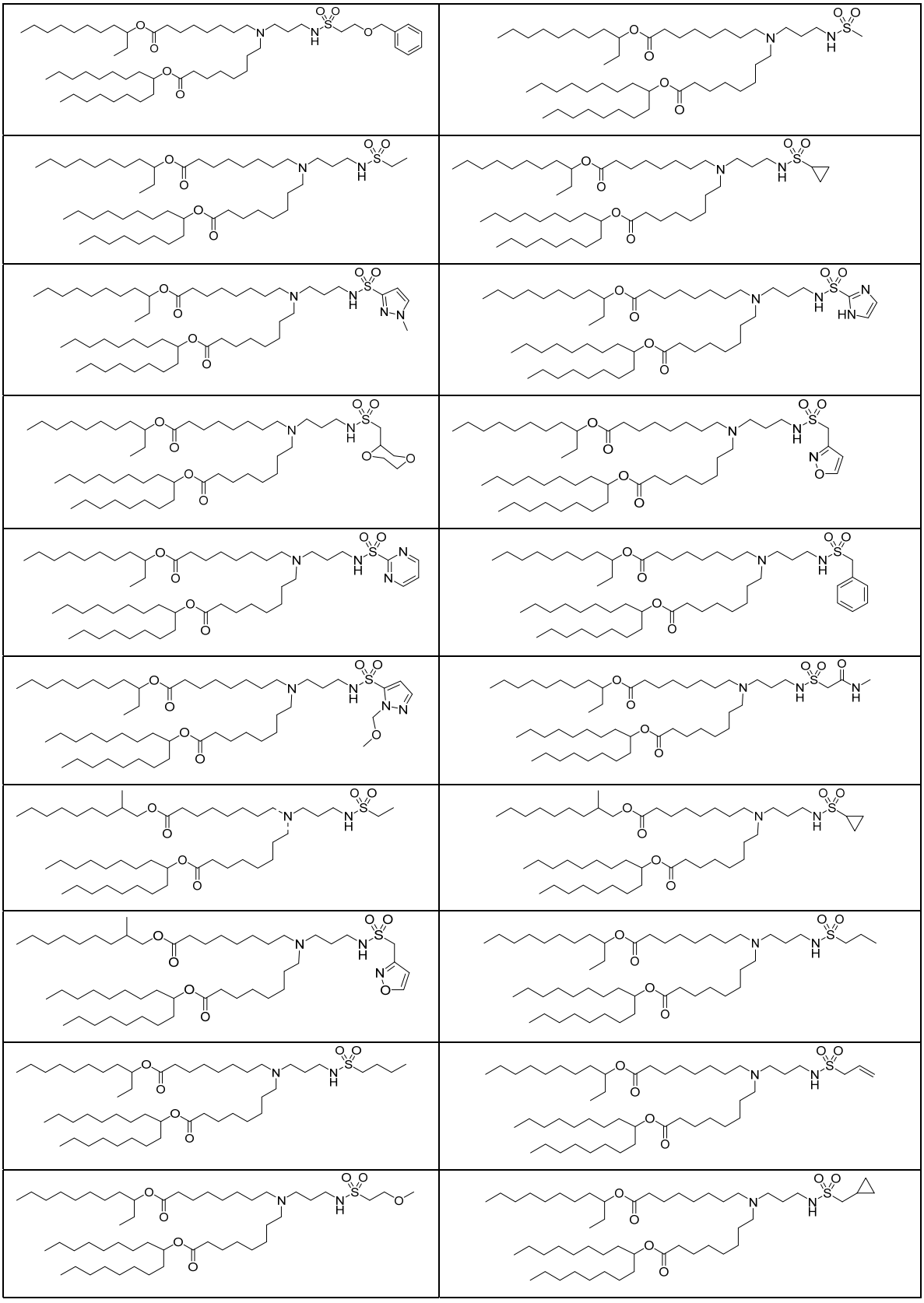
15. The compound of any one of the preceding claims, wherein A is a thiadiazole.

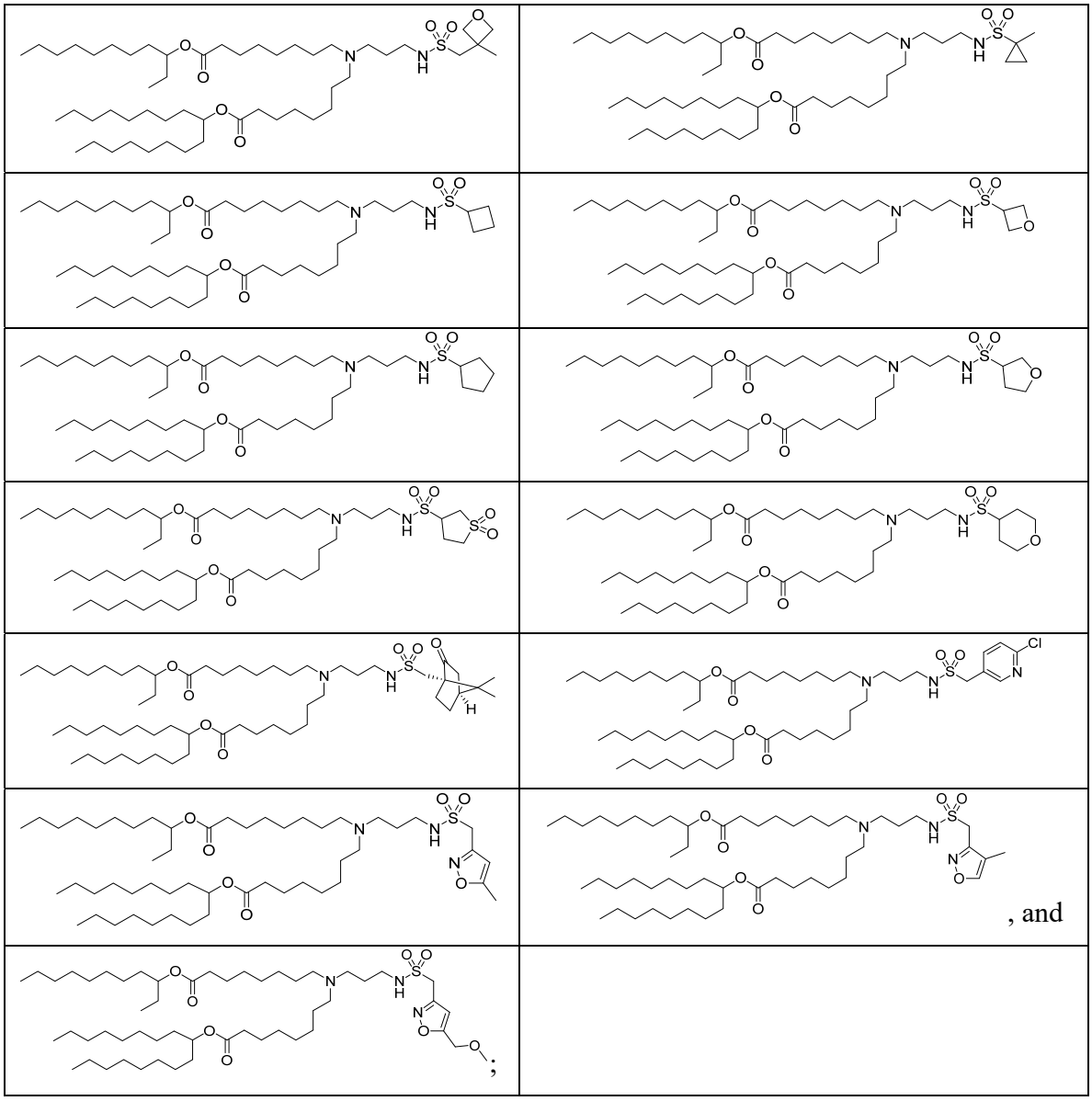
16. The compound of any one of the preceding claims, wherein each R^{13} is selected from the group consisting of oxo, C_{1-6} alkylamino, di-(C_{1-6} alkyl) amino, and NH_2.

17. The compound of any one of the preceding claims, wherein R^4 is  or .

18. A compound selected from the group consisting of:

Structure	Structure
	
	
	




, and
;

or a pharmaceutically acceptable salt thereof.

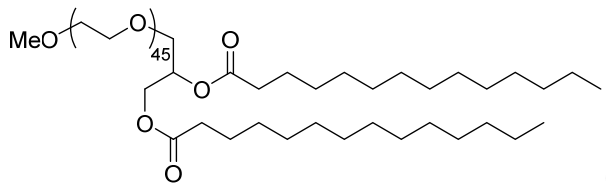
19. An empty lipid nanoparticle (empty LNP) comprising a compound of any one of the preceding claims, a phospholipid, a structural lipid, and a PEG lipid.

20. The empty LNP of claim 19:

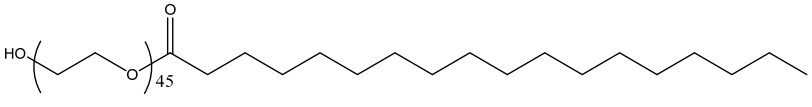
a) comprising about 40 mol % to about 60 mol % said compound, about 0 mol % to about 20 mol % phospholipid, about 30 mol % to about 50 mol % structural lipid, and about 0 mol % to about 5 mol % PEG lipid;

b) wherein the phospholipid is selected from the group consisting of:

1,2-dilinoleoyl-sn-glycero-3-phosphocholine (DLPC),
1,2-dimyristoyl-sn-glycero-phosphocholine (DMPC), 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC), 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC),
1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC),
1,2-diundecanoyl-sn-glycero-phosphocholine (DUPC),
1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC),
1,2-di-O-octadecenyl-*sn*-glycero-3-phosphocholine (18:0 Diether PC),
1-oleoyl-2-cholesterylhemisuccinoyl-*sn*-glycero-3-phosphocholine (OChemsPC),
1-hexadecyl-sn-glycero-3-phosphocholine (C16 Lyso PC),
1,2-dilinolenoyl-sn-glycero-3-phosphocholine, 1,2-diarachidonoyl-sn-glycero-3-phosphocholine,
1,2-didocosahexaenoyl-sn-glycero-3-phosphocholine,1,2-dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE), 1,2-diphytanoyl-sn-glycero-3-phosphoethanolamine (ME 16.0 PE),
1,2-distearoyl-sn-glycero-3-phosphoethanolamine,
1,2-dilinoleoyl-sn-glycero-3-phosphoethanolamine,
1,2-dilinolenoyl-sn-glycero-3-phosphoethanolamine,
1,2-diarachidonoyl-sn-glycero-3-phosphoethanolamine,
1,2-didocosahexaenoyl-sn-glycero-3-phosphoethanolamine,
1,2-dioleoyl-sn-glycero-3-phospho-rac-(1-glycerol) sodium salt (DOPG), sphingomyelin, and mixtures thereof;
c) wherein the structural lipid is selected from the group consisting of cholesterol, fecosterol, sitosterol, ergosterol, campesterol, stigmasterol, brassicasterol, and mixtures thereof;
d) wherein the PEG lipid is selected from the group consisting of a PEG-modified phosphatidylethanolamine, a PEG-modified phosphatidic acid, a PEG-modified ceramide, a PEG-modified dialkylamine, a PEG-modified diacylglycerol, a PEG-modified dialkylglycerol, and mixtures thereof; and/or
e) wherein the PEG lipid is selected from PEG_{2k}-DMG and PEG-1:



(PEG_{2k}-DMG),



(PEG-1),

and mixtures thereof.

21. A loaded lipid nanoparticle (loaded LNP), which comprises the empty LNP of claim 19 or 20 and one or more therapeutic and/or prophylactic agents.

22. The loaded LNP of claim 21, wherein the one or more therapeutic and/or prophylactic agents is a nucleic acid.

23. The loaded LNP of claim 22, wherein the nucleic acid is an RNA, and wherein the RNA is selected from the group consisting of a short interfering RNA (siRNA), an asymmetrical interfering RNA (aiRNA), an RNA interference (RNAi) molecule, a microRNA (miRNA), an antagomir, an antisense RNA, a ribozyme, a Dicer-substrate RNA (dsRNA), a small hairpin RNA (shRNA), a messenger RNA (mRNA), and mixtures thereof.

24. The loaded LNP of claim 23, wherein the RNA is an mRNA.

25. A pharmaceutical composition comprising the loaded LNP of any one of claims 21 to 24 and a pharmaceutically acceptable carrier.

26. Use of the loaded LNP of any one of claims 21 to 24, or the pharmaceutical composition of claim 25, in the manufacture of a medicament for delivering a therapeutic and/or prophylactic agent to a cell within a subject, wherein the loaded LNP or the pharmaceutical composition is to be administered to the subject.

27. Use of the loaded LNP of any one of claims 21 to 24, or the pharmaceutical composition of claim 25, in the manufacture of a medicament for specifically delivering a therapeutic and/or prophylactic agent to an organ of a subject, wherein the loaded LNP or the pharmaceutical composition is to be administered to the subject.

28. Use of the loaded LNP of any one of claims 21 to 24, or the pharmaceutical composition of claim 25, in the manufacture of a medicament for producing a polypeptide of interest in a cell

within a subject, wherein the loaded LNP or the pharmaceutical composition is to be administered to the subject.

29. Use of the loaded LNP of any one of claims 21 to 24, or the pharmaceutical composition of claim 25, in the manufacture of a medicament for treating a disease or disorder in a subject in need thereof, wherein the loaded LNP or the pharmaceutical composition is to be administered to the subject.