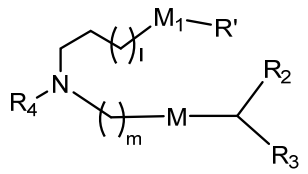
CLAIMS

1. A compound of Formula (IA):



(IA),

or its N-oxide, or a salt or isomer thereof, wherein

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

m is selected from 5, 6, 7, 8, and 9;

M_1 is a bond or M';

R_4 is $-(CH_2)_nQ$, in which Q is $-N(R)R_8$ and n is selected from 1, 2, 3, 4, and 5;

M and M' are independently selected from -C(O)O- and -OC(O)-;

R_8 is cyclobutenyl substituted with one or more of oxo, amino, heterocycloalkyl, and mono- or di-alkylamino, wherein mono- and di-alkylamino are substituted with one or more of C_{1-3} alkoxy and amino;

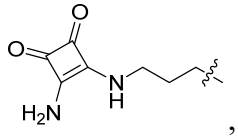
R_2 and R_3 are independently selected from the group consisting of H, C_{1-14} alkyl, and C_{2-14} alkenyl;

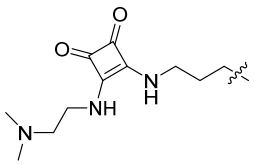
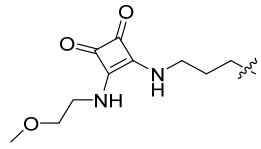
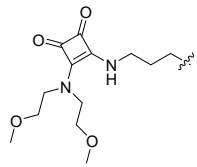
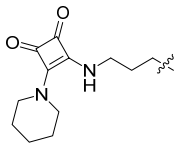
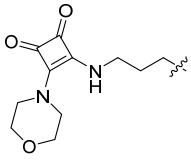
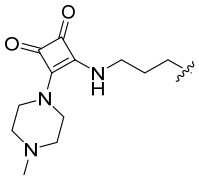
R is selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H; and

R' is selected from C_{1-18} alkyl and C_{2-18} alkenyl.

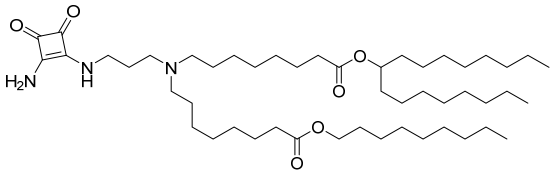
2. The compound of claim 1, wherein R_8 is cyclobutenyl substituted with one or more of oxo and mono- or di-alkylamino, wherein mono- and di-alkylamino are substituted with one or more of C_{1-3} alkoxy and amino.

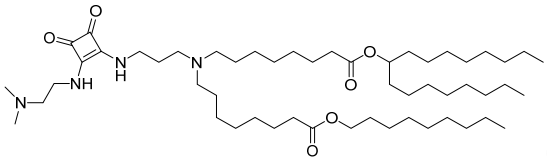
3. The compound of claim 1, wherein R_8 is cyclobutenyl substituted with one or more of oxo and heterocycloalkyl.

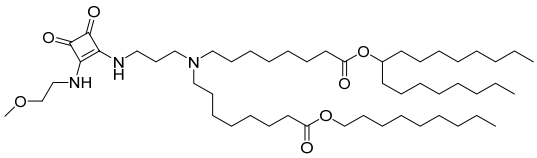
4. The compound of claim 1, wherein R_4 is selected from: ,

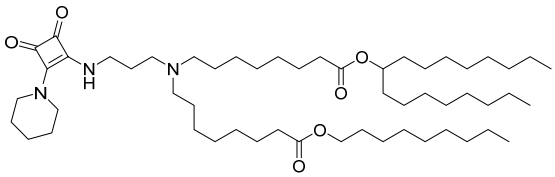
, , , , , and .

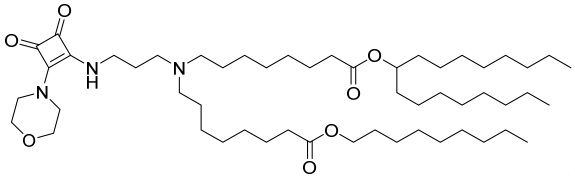
5. The compound of claim 1, wherein the compound is selected from:

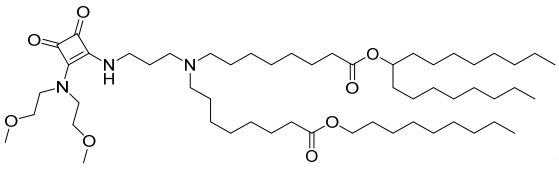
 (Compound 251),

 (Compound 280),

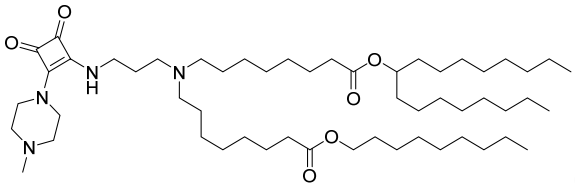
 (Compound 290),

 (Compound 291),

 (Compound 294),



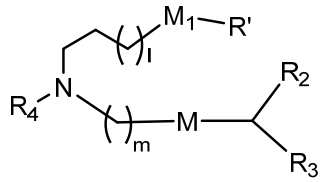
(Compound 295), and



(Compound 296),

or a salt or isomer thereof.

6. A compound of Formula (IA):



(IA),

or its N-oxide, or a salt or isomer thereof, wherein

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

m is selected from 5, 6, 7, 8, and 9;

M_1 is a bond or M';

R_4 is $-(CH_2)_nQ$, in which Q is $-N(R)R_8$ and n is selected from 1, 2, 3, 4, and 5;

R_8 is cyclobutenyl substituted with one or more of oxo and mono- or di-alkylamino;

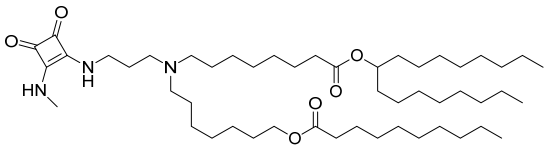
M and M' are independently selected from -C(O)O- and -OC(O); wherein at least one of M and M' is -OC(O);

R_2 and R_3 are independently selected from the group consisting of H, C_{1-14} alkyl, and C_{2-14} alkenyl;

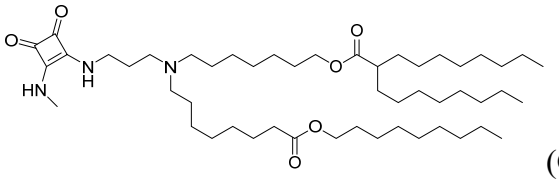
R selected from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H; and

R' is selected from C_{2-18} alkenyl and C_{1-18} alkyl.

7. The compound of claim 6, wherein the compound is selected from:



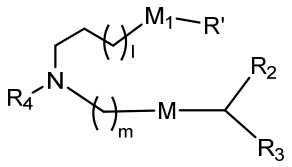
(Compound 309) and



(Compound 326),

or a salt or isomer thereof.

8. A compound of Formula (IA):



(IA),

or its N-oxide, or a salt or isomer thereof, wherein

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

m is selected from 5, 6, 7, 8, and 9;

M_1 is a bond or M';

R_4 is $-(CH_2)_nQ$, in which Q is $-N(R)R_8$ and n is selected from 1, 2, 3, 4, and 5;

R_8 is cyclobutenyl substituted with one or more of oxo and mono- or di-alkylamino;

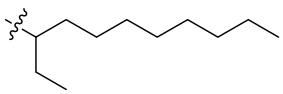
M and M' are independently selected from -C(O)O- and -OC(O)-;

R_2 and R_3 are independently selected from the group consisting of H, C_{1-14} alkyl, and C_{2-14} alkenyl;

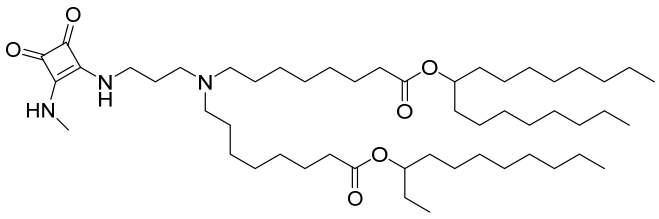
R is from the group consisting of C_{1-3} alkyl, C_{2-3} alkenyl, and H;

and

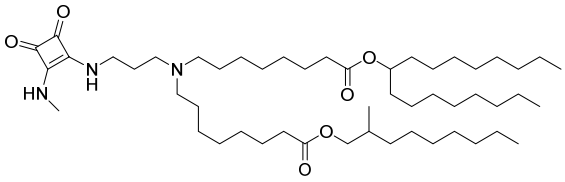
R' is branched C_{1-18} alkyl.

9. The compound of claim 8, wherein R' is .

10. The compound of claim 8, wherein the compound is:



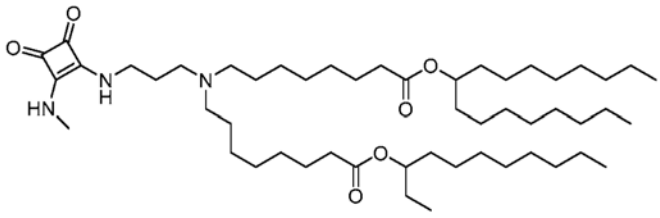
(Compound 301) or



(Compound 321),

or a salt or isomer thereof.

11. The compound of claim 10, wherein the compound is Compound 301:



(Compound 301),

or a salt or isomer thereof.

12. The compound of any one of claims 1-11, wherein the salt is a pharmaceutically acceptable salt.

13. A nanoparticle composition comprising a lipid component which comprises the compound of any one of claims 1-12.

14. The nanoparticle composition of claim 13, wherein the lipid component further comprises a phospholipid.

15. The nanoparticle composition of claim 14, 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.

16. The nanoparticle composition of claim 15, wherein the phospholipid is DSPC or DOPE.

17. The nanoparticle composition of claim 14, wherein the lipid component further comprises a structural lipid.

18. The nanoparticle composition of claim 17, wherein the structural lipid is selected from the group consisting of cholesterol, fecosterol, sitosterol, ergosterol, campesterol, stigmasterol, brassicasterol, tomatidine, ursolic acid, alpha-tocopherol, and mixtures thereof.

19. The nanoparticle composition of claim 18, wherein the structural lipid is cholesterol.

20. The nanoparticle composition of claim 17, wherein the lipid component further comprises a PEG lipid.

21. The nanoparticle composition of claim 20, 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.

22. The nanoparticle composition of claim 20, wherein the lipid component comprises 30 mol % to 60 mol % said Compound 301, 0 mol % to 30 mol % phospholipid, 18.5 mol % to 48.5 mol % structural lipid, and 0 mol % to 10 mol % PEG lipid.

23. The nanoparticle composition of claim 20, wherein the lipid component comprises 35 mol % to 55 mol % said Compound 301, 5 mol % to 25 mol % phospholipid, 30 mol % to 40 mol % structural lipid, and 0 mol % to 10 mol % PEG lipid.

24. The nanoparticle composition of claim 20, wherein the lipid component comprises 50 mol % said Compound 301, 10 mol % phospholipid, 38.5 mol % structural lipid, and 1.5 mol % PEG lipid.

25. The nanoparticle composition of any one of claims 13-24, further comprising a therapeutic and/or prophylactic agent.

26. The nanoparticle composition of claim 25, wherein the therapeutic and/or prophylactic agent is a nucleic acid.

27. The nanoparticle composition of claim 25, wherein the therapeutic and/or prophylactic agent is a ribonucleic acid (RNA).

28. The nanoparticle composition of claim 27, wherein the RNA is selected from the group consisting of a small interfering RNA (siRNA), an asymmetrical interfering RNA (aiRNA), a microRNA (miRNA), a Dicer-substrate RNA (dsRNA), a small hairpin RNA (shRNA), a messenger RNA (mRNA), and mixtures thereof.

29. The nanoparticle composition of claim 27, wherein the RNA is an mRNA.

30. The nanoparticle composition of claim 29, wherein the mRNA includes one or more of a stem loop, a chain terminating nucleoside, a polyA sequence, a polyadenylation signal, and/or a 5’ cap structure.

31. The nanoparticle composition of claim 29, wherein the encapsulation efficiency of the therapeutic and/or prophylactic agent is at least 80% or at least 90%.

32. The nanoparticle composition of claim 29, wherein the wt/wt ratio of the lipid component to the mRNA is from 10:1 to 60:1.

33. The nanoparticle composition of claim 29, wherein the wt/wt ratio of the lipid component to the mRNA is 20:1.

34. The nanoparticle composition of claim 29, wherein the N:P ratio is from 5:1 to 8:1.

35. A pharmaceutical composition comprising the nanoparticle composition of claim 29 and a pharmaceutically acceptable carrier.

36. An ex-vivo method of delivering a therapeutic and/or prophylactic agent to a mammalian cell, the method comprising administering to a subject the nanoparticle composition of any one of claims 25-34, said administering comprising contacting the cell with the nanoparticle composition, whereby the therapeutic and/or prophylactic agent is delivered to the cell.

37. A method of producing a polypeptide of interest in a mammalian cell, the method comprising contacting the cell with the nanoparticle composition of claim 29, 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.

38. The nanoparticle composition of any one of claims 25-34 for use in therapy.

39. Use of a therapeutically effective amount of the nanoparticle composition of any one of claims 25-34 in the preparation of a medicament for the treatment of a disease or disorder in a mammal in need thereof, wherein the disease or disorder is selected from the group consisting of

infectious diseases, cancer and proliferative diseases, genetic disesease, autoimmune diseases, diabetes, neurodegenerative diseases, cardio- and reno-vascular diseases, and metabolic diseases.