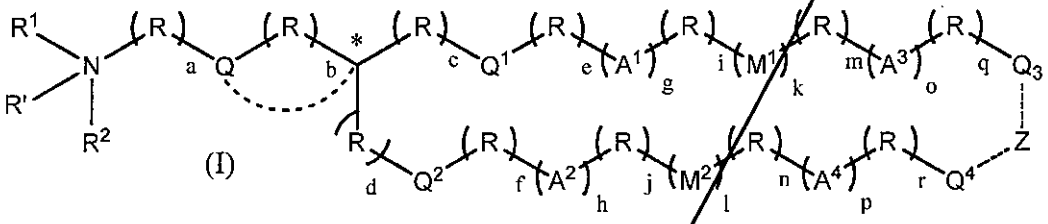
WHAT IS CLAIMED IS:

1. A compound of formula (I):



(I)

or a salt thereof,

wherein

R' is absent, hydrogen, or alkyl (e.g., C_1-C_4 alkyl);

with respect to R^1 and R^2,

(i) R^1 and R^2 are each, independently, optionally substituted alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, or heterocycle;

(ii) R^1 and R^2, together with the nitrogen atom to which they are attached, form an optionally substituted heterocylic ring; or

(iii) one of R^1 and R^2 is optionally substituted alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, or heterocycle, and the other forms a 4-10 member heterocyclic ring or heteroaryl with (a) the adjacent nitrogen atom and (b) the $(R)_a$ group adjacent to the nitrogen atom;

each occurrence of R is, independently, $-(CR^3R^4)-$;each occurrence of R^3 and R^4 are, independently H, OH, alkyl, alkoxy, $-NH_2$, alkylamino, or dialkylamino;

or R^3 and R^4, together with the carbon atom to which they are directly attached, form a cycloalkyl group, wherein no more than three R groups in each chain attached to the carbon C* are cycloalkyl (e.g., cyclopropyl);

the dashed line to Q is absent or a bond;

when the dashed line to Q is absent, then Q is absent or is -O-, -S-, -C(O)O-, -OC(O)-, -C(O)N(R^4)-, -N(R^5)C(O)-, -S-S-, -OC(O)O-, -O-N=C(R^5)-, -C(R^5)=N-O-, -OC(O)N(R^5)-, -N(R^5)C(O)N(R^5)-, -N(R^5)C(O)O-, -C(O)S-, -C(S)O- or -C(R^5)=N-O-C(O)-; or

when the dashed line to Q is a bond, then b is 0 and Q and the tertiary carbon adjacent to it (C*) form a substituted or unsubstituted, mono- or bi-cyclic heterocyclic group having from 5 to 10 ring atoms;

Q^1 and Q^2 are each, independently, absent, -O-, -S-, -OC(O)-, -C(O)O-, -SC(O)-, -C(O)S-, -OC(S)-, -C(S)O-, -S-S-, -C(O)(NR^5)-, -N(R^5)C(O)-, -C(S)(NR^5)-, -N(R^5)C(O)-, -N(R^5)C(O)N(R^5)-, or –OC(O)O-;

Q^3 and Q^4 are each, independently, H, -(C$R^5$$R^4$)-, aryl, or a cholesterol moiety;

each occurrence of A^1, A^2, A^3 and A^4 is, independently, -(C$R^5$$R^5$-C$R^5$=C$R^5$)-;

each occurrence of R^5 is, independently, H or alkyl;

M^1 and M^2 are each, independently, a biodegradable group;

Z is absent, alkylene or -O-P(O)(OH)-O-;

each ------ attached to Z is an optional bond, such that when Z is absent, Q^3 and Q^4 are not directly covalently bound together;

a is 1, 2, 3, 4, 5 or 6;

b is 0, 1, 2, or 3;

c, d, e, f, i, j, m, n, q and r are each, independently, 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

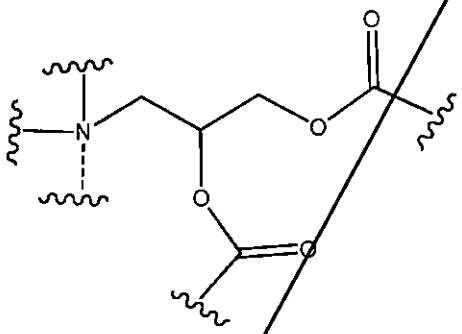
g and h are each, independently, 0, 1 or 2;

k and l are each, independently, 0 or 1, where at least one of k and l is 1; and

o and p are each, independently, 0, 1 or 2,

wherein

(i) the compound does not contain the following moiety:



wherein ---- is an optional bond; and

(ii) Q^3 and Q^4 are each, independently, separated from the tertiary carbon atom marked with an asterisk (*) by a chain of 8 or more atoms.

2. The compound of claim 1, wherein M^1 and M^2 are each, independently: -OC(O)-, -C(O)O-, -SC(O)-, -C(O)S-, -OC(S)-, -C(S)O-, -S-S-, $-C(R^5)=N-$, $-N=C(R^5)-$, $-C(R^5)=N-O-$, $-O-N=C(R^5)-$, $-C(O)(NR^5)-$, $-N(R^5)C(O)-$, $-C(S)(NR^5)-$, $-N(R^5)C(O)-$, $-N(R^5)C(O)N(R^5)-$, –OC(O)O-, $-OSi(R^5)_2O-$, $-C(O)(CR^3R^4)C(O)O-$, or $-OC(O)(CR^3R^4)C(O)-$.

3. The compound of claim 2, wherein M^1 and M^2 are each, independently: -C(O)-O-, -OC(O)-, $-C(R^5)=N-$, $-C(R^5)=N-O-$, -O-C(O)O-, $-C(O)N(R^5)-$, -C(O)S-, -C(S)O-, $-OSi(R^5)_2O-$, $-C(O)(CR^3R^4)C(O)O-$, or $-OC(O)(CR^3R^4)C(O)-$.

4. The compound of any of claims 2 and 3, wherein M^1 and M^2 are each –C(O)O-.

5. The compound of any of claims 1-4, wherein R^1 and R^2 are each alkyl.

6. The compound of claim 5, wherein R^1 and R^2 are each methyl.

7. The compound of any of claims 1-6, wherein Q is absent, -C(O)O-, -OC(O)-, -C(O)N(R^4)-, -N(R^5)C(O)-, -S-S-, -OC(O)O-, -C(R^5)=N-O-, -OC(O)N(R^5)-, -N(R^5)C(O)N(R^5)-, -N(R^5)C(O)O-, -C(O)S-, -C(S)O- or -C(R^5)=N-O-C(O)-.

8. The compound of of claims 1-7, wherein Q is absent.

9. The compound of any of claims 1-8, wherein each instance of R is, independently, -CH_2-, -$C(CH_3)_2$- or –CH(iPr)-

10. The compound of any of claims 1-9, wherein Q^1 and Q^2 are each, independently, absent or -O-.

11. The compound of any of claims 1-10, wherein a is 2, 3, or 4 and b is 0.

12. The compound of any of claims 1-11, wherein a carbon atom alpha or beta to a biodegradable group is substituted with one or two alkyl groups or a spirocyclic group.

13. The compound of claim 1, wherein one or more of the following applies:

(i) Q^1 and Q^2 are absent;

(ii) M^1 and M^2 are both –C(O)O-;

(iii) g and h are both 1;

(iv) g and h are both 0;

(v) c and e total 7;

(vi) d and f total 7;

(vii) c, e and i total 7;

(viii) d, f and j total 7;

(ix) i and j are each 7;

(x) k and l are both 1;

(xi) m and n are both 0;

(xii) m and q total 1 or m and q total 2;

(xiii) m and 1 total 6;

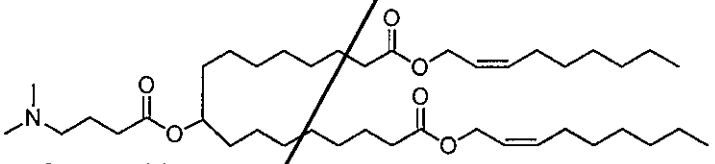
(xiv) r and n total 6;

(xv) p and o are both 0;

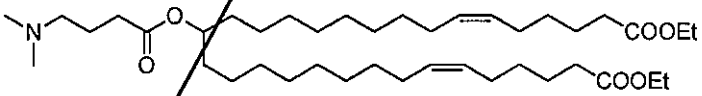
(xvi) n and r total 2 or n and r total 1; and

(xvii) Q^3 is H.

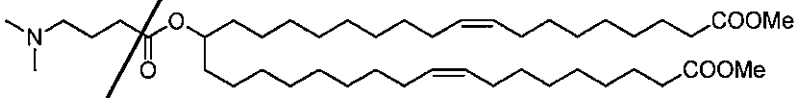
14. The compound of claim 1, selected from:



Compound 1



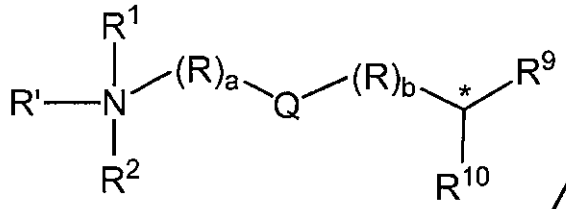
Compound 2 , and



Compound 3

or a salt thereof.

15. A compound of formula IA-1



(IA-1)

or a salt thereof,

wherein

R^1 and R^2 are each, independently, optionally substituted alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, or heterocycle; or

R^1 and R^2, together with the nitrogen atom to which they are attached, form an optionally substituted heterocylic ring;

each occurrence of R is, independently, $-(CR^3R^4)-$;

each occurrence of R^3 and R^4 are, independently H, OH, alkyl, alkoxy, $-NH_2$, alkylamino, or dialkylamino (in one preferred embodiment, each occurrence of R^3 and R^4 are, independently H or C_1-C_4 alkyl);

or R^3 and R^4, together with the carbon atom to which they are directly attached, form a cycloalkyl group, wherein no more than three R groups in each of R^9 and R^{10} are cycloalkyl;

Q is absent or is -O-, -NH-, -S-, -C(O)O-, -OC(O)-, $-C(O)N(R^4)-$, $-N(R^5)C(O)-$, -S-S-, -OC(O)O-, $-O-N=C(R^5)-$, $-C(R^5)=N-O-$, $-OC(O)N(R^5)-$, $-N(R^5)C(O)N(R^5)-$, $-N(R^5)C(O)O-$, -C(O)S-, -C(S)O- or $-C(R^5)=N-O-C(O)-$;

a is 1, 2, 3, 4, 5 or 6;

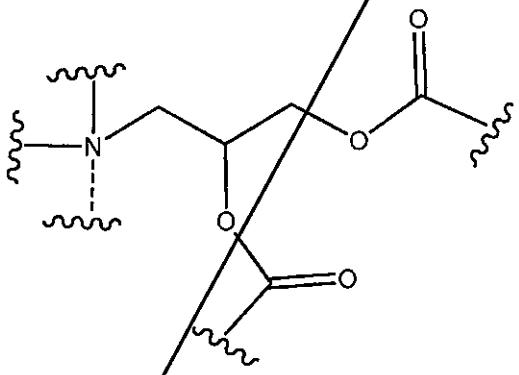
b is 0, 1, 2, or 3;

R' is absent, hydrogen, or alkyl (e.g., C_1-C_4 alkyl);

each of R^9 and R^{10} are independently C_{12}-C_{24} alkyl, C_{12}-C_{24} alkenyl, or C_{12}-C_{24} alkoxy having one or more biodegradable groups; each biodegradable group independently interrupts the C_{12}-C_{24} alkyl, alkenyl, or alkoxy group or is substituted at the terminus of the C_{12}-C_{24} alkyl, alkenyl, or alkoxy group;

wherein

(i) the compound does not contain the following moiety:

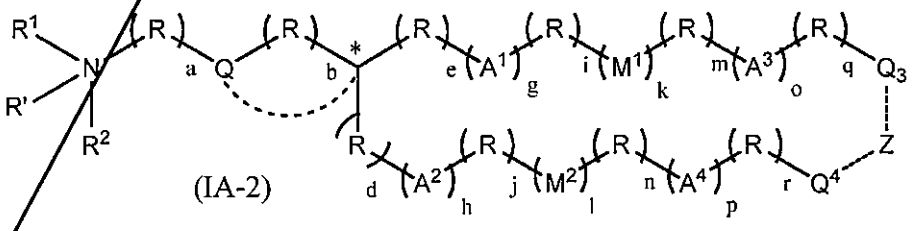


wherein ---- is an optional bond; and

(ii) the terminus of R^9 and R^{10} is separated from the tertiary carbon atom marked with an asterisk (*) by a chain of 8 or more atoms.

16. The compound of claim 15, wherein q is absent and the $R'R^1R^2N$-$(R)_a$-Q-$(R)_b$- group is $(CH_3)_2N$-$(CH_2)_3$-C(O)O-, $(CH_3)_2N$-$(CH_2)_2$-NH-C(O)O-, $(CH_3)_2N$-$(CH_2)_2$-OC(O)-NH-, or $(CH_3)_2N$-$(CH_2)_3$-$C(CH_3)$=N-O-.

17. A compound of formula IA-2



(IA-2)

or a salt thereof, wherein

R' is absent, hydrogen, or alkyl;

R^1 and R^2 are each, independently, optionally substituted C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_3-C_6 cycloalkyl, (C_3-C_6 cycloalkyl)C_1-C_4 alkyl, or a monocyclic heterocycle; or

R^1 and R^2, together with the nitrogen atom to which they are attached, form an optionally substituted 5- or 6-membered heterocylic ring;

each occurrence of R is, independently, $-(CR^3R^4)-$;

each occurrence of R^3 and R^4 are, independently H, OH, alkyl, alkoxy, $-NH_2$, alkylamino, or dialkylamino;

or R^3 and R^4, together with the carbon atom to which they are directly attached, form a C_3-C_6 cycloalkyl group, wherein no more than three R groups in each chain attached to the carbon C* are cycloalkyl;

the dashed line to Q is absent or a bond;

when the dashed line to Q is absent, then Q is absent or is -O-, -NH-, -S-, -C(O)O-, -OC(O)-, $-C(O)N(R^4)-$, $-N(R^5)C(O)-$, -S-S-, -OC(O)O-, $-O-N=C(R^5)-$, $-C(R^5)=N-O-$, $-OC(O)N(R^5)-$, $-N(R^5)C(O)N(R^5)-$, $-N(R^5)C(O)O-$, -C(O)S-, -C(S)O- or $-C(R^5)=N-O-C(O)-$; or

when the dashed line to Q is a bond, then b is 0 and Q and the tertiary carbon adjacent to it (C*) form a substituted or unsubstituted, mono- or bi-cyclic heterocyclic group having from 5 to 10 ring atoms;

Q^3 and Q^4 are each, independently, H, $-(CR^3R^4)-$, aryl, or a cholesterol moiety;

each occurrence of A^1, A^2, A^3 and A^4 is, independently, $-(CR^5R^5-CR^5=CR^5)-$;

each occurrence of R^5 is, independently, H or alkyl;

M^1 and M^2 are each, independently, -C(O)-O-, -OC(O)-, $-C(R^5)=N-$, $-C(R^5)=N-O-$, -O-C(O)O-, $-C(O)N(R^5)-$, -C(O)S-, -C(S)O-, $-OSi(R^5)_2O-$, $-C(O)(CR^3R^4)C(O)O-$, or $-OC(O)(CR^3R^4)C(O)-$;

Z is absent, alkylene or -O-P(O)(OH)-O-;

each ------ attached to Z is an optional bond, such that when Z is absent, Q^3 and Q^4 are not directly covalently bound together;

a is 1, 2, 3, 4, 5 or 6;

b is 0, 1, 2, or 3;

d, e, i, j, m, n, q and r are each, independently, 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

g and h are each, independently, 0, 1 or 2;

the sum of d + 3h is at least 4, and the sum of e + 3g is at least 4;

k and l are each, independently, 0 or 1, where at least one of k and l is 1; and

o and p are each, independently, 0, 1 or 2,

wherein Q^3 and Q^4 are each, independently, separated from the tertiary carbon atom marked with an asterisk (*) by a chain of 8 or more atoms.

18. The compound of claim 17, wherein R' is absent or alkyl.

19. The compound of claim 17 or 18, wherein R^1 and R^2 are each, independently, C_1-C_4 alkyl.

20. The compound of any one of claims 17-19, wherein each occurrence of R is, independently, $-CH_2-$ or $-CH(CH_3)-$.

21. The compound of any one of claims 17-20, wherein Q^3 and Q^4 are each, independently, H, aryl, or a cholesterol moiety.

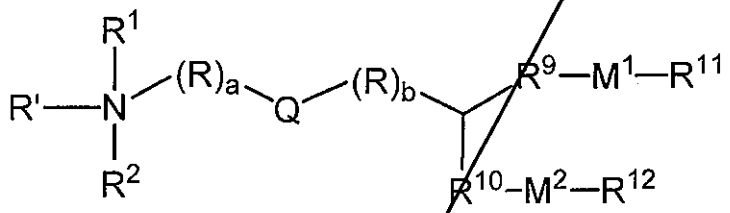
22. The compound of any one of claims 17-21, wherein M^1 and M^2 are each -C(O)-O-

.

23. The compound of any one of claims 17-22, wherein the sum of e+3g+i+m+3o+q is from about 8 to about 20.

24. The compound of any one of claims 17-22, wherein the sum of d+3h+j+n+3p+r is from about 8 to about 20.

25. A compound of formula IB



(IB)

wherein

R^1 and R^2 are each, independently, optionally substituted alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, or heterocycle; or

R^1 and R^2, together with the nitrogen atom to which they are attached, form an optionally substituted heterocylic ring;

each occurrence of R is, independently, $-(CR^3R^4)-$;

each occurrence of R^3 and R^4 are, independently H, OH, alkyl, alkoxy, $-NH_2$, alkylamino, or dialkylamino (in one preferred embodiment, each occurrence of R^3 and R^4 are, independently H or C_1-C_4 alkyl);

or R^3 and R^4, together with the carbon atom to which they are directly attached, form a cycloalkyl group, wherein no more than three R groups in each chain attached to the carbon C* are cycloalkyl (e.g., cyclopropyl);

Q is absent or is -O-, -NH-, -S-, -C(O)O-, -OC(O)-, $-C(O)N(R^4)-$, $-N(R^5)C(O)-$, -S-S-, $-OC(O)O-$, $-O-N=C(R^5)-$, $-C(R^5)=N-O-$, $-OC(O)N(R^5)-$, $-N(R^5)C(O)N(R^5)-$, $-N(R^5)C(O)O-$, -C(O)S-, -C(S)O- or $-C(R^5)=N-O-C(O)-$;

a is 1, 2, 3, 4, 5 or 6;

b is 0, 1, 2, or 3;

R' is absent, hydrogen, or alkyl (e.g., C_1-C_4 alkyl);

M^1 and M^2 are each, independently, a biodegradable group;

each of R^9 and R^{10} are independently alkylene, or alkenylene; and

each of R^{11} and R^{12} are independently alkyl or alkenyl, optionally terminated by $COOR^{13}$ where each R^{13} is independently alkyl;

with the proviso that:

R^9, M^1, and R^{11} are together at least 8 carbons atoms in length; and

R^{10}, M^2, and R^{12} are together at least 8 carbons atoms in length.

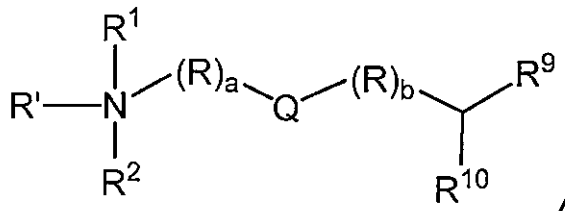
26. The compound of claim 25, wherein R^9 and R^{10} are each independently C_4-C_{12} alkylene or C_4-C_{12} alkenylene, M^1 and M^2 are -C(O)O-, and R^{11} and R^{12} are C_4-C_{12} alkylene or C_4-C_{12} alkenylene.

27. The compound of claim 25 or 26, wherein R^9, M^1, and R^{11} are together at 12 to 24 carbons atoms in length.

28. The compound of claim 25 or 26, wherein, R^{10}, M^2, and R^{12} are together at 12 to 24 carbons atoms in length.

29. The compound of any one of claims 25-28, wherein the $R'R^1R^2N$-$(R)_a$-Q-$(R)_b$- group is $(CH_3)_2N$-$(CH_2)_3$-C(O)O-, $(CH_3)_2N$-$(CH_2)_2$-NH-C(O)O-, $(CH_3)_2N$-$(CH_2)_2$-OC(O)-NH-, or $(CH_3)_2N$-$(CH_2)_3$-$C(CH_3)$=N-O-.

30. A compound of formula IC



(IC)

wherein

R^1 and R^2 are each, independently, optionally substituted alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, or heterocycle; or

R^1 and R^2, together with the nitrogen atom to which they are attached, form an optionally substituted heterocylic ring;

each occurrence of R is, independently, $-(CR^3R^4)-$;

each occurrence of R^3 and R^4 are, independently H, OH, alkyl, alkoxy, $-NH_2$, alkylamino, or dialkylamino (in one preferred embodiment, each occurrence of R^3 and R^4 are, independently H or C_1-C_4 alkyl);

or R^3 and R^4, together with the carbon atom to which they are directly attached, form a cycloalkyl group, wherein no more than three R groups in each chain attached to the carbon C* are cycloalkyl (e.g., cyclopropyl);

Q is absent or is -O-, -NH-, -S-, -C(O)O-, -OC(O)-, $-C(O)N(R^4)-$, $-N(R^5)C(O)-$, -S-S-, -OC(O)O-, $-O-N=C(R^5)-$, $-C(R^5)=N-O-$, $-OC(O)N(R^5)-$, $-N(R^5)C(O)N(R^5)-$, $-N(R^5)C(O)O-$, -C(O)S-, -C(S)O- or $-C(R^5)=N-O-C(O)-$;

a is 1, 2, 3, 4, 5 or 6;

b is 0, 1, 2, or 3;

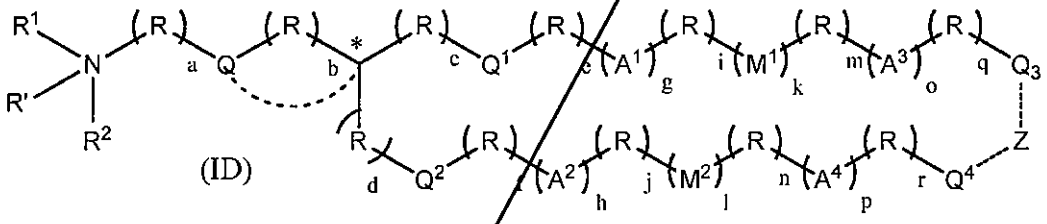
R' is absent, hydrogen, or alkyl (e.g., C_1-C_4 alkyl);

each of R^9 and R^{10} are independently C_{12}-C_{24} alkyl or alkenyl substituted at its terminus with a biodegradable group.

31. The compound of claim 30, wherein each of the biodegradable groups is $-COOR^{13}$ wherein each R^{13} is, independently, alkyl.

32. The compound of claim 30 or 31, wherein the $R'R^1R^2N$-$(R)_a$-Q-$(R)_b$- group is $(CH_3)_2N$-$(CH_2)_3$-C(O)O-, $(CH_3)_2N$-$(CH_2)_2$-NH-C(O)O-, $(CH_3)_2N$-$(CH_2)_2$-OC(O)-NH-, or $(CH_3)_2N$-$(CH_2)_3$-$C(CH_3)$=N-O-.

33. A compound of formula ID



(ID)

or a salt thereof,

wherein

R' is absent, hydrogen, or alkyl;

R^1 and R^2 are each, independently, optionally substituted alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, or heterocycle; or

R^1 and R^2, together with the nitrogen atom to which they are attached, form an optionally substituted heterocylic ring;

each occurrence of R is, independently, $-(CR^3R^4)-$;

each occurrence of R^3 and R^4 are, independently H, OH, alkyl, alkoxy, $-NH_2$, alkylamino, or dialkylamino (in one preferred embodiment, each occurrence of R^3 and R^4 are, independently H or alkyl);

or R^3 and R^4, together with the carbon atom to which they are directly attached, form a cycloalkyl group, wherein no more than three R groups in each chain attached to the carbon C* are cycloalkyl (e.g., cyclopropyl);

the dashed line to Q is absent or a bond;

when the dashed line to Q is absent, then Q is absent or is -O-, -NH-, -S-, -C(O)O-, -OC(O)-, -C(O)N(R^4)-, -N(R^5)C(O)-, -S-S-, -OC(O)O-, -O-N=C(R^5)-, -C(R^5)=N-O-, -OC(O)N(R^5)-, -N(R^5)C(O)N(R^5)-, -N(R^5)C(O)O-, -C(O)S-, -C(S)O- or -C(R^5)=N-O-C(O)-; or

when the dashed line to Q is a bond, then b is 0 and Q and the tertiary carbon adjacent to it (C*) form a substituted or unsubstituted, mono- or bi-cyclic heterocyclic group having from 5 to 10 ring atoms (e.g., the heteroatoms in the heterocyclic group are selected from O and S, preferably O);

Q^1 and Q^2 are each, independently, absent, -O-, -S-, -OC(O)-, -C(O)O-, -SC(O)-, -C(O)S-, -OC(S)-, -C(S)O-, -S-S-, -C(O)(NR^5)-, -N(R^5)C(O)-, -C(S)(NR^5)-, -N(R^5)C(O)-, -N(R^5)C(O)N(R^5)-, or –OC(O)O-;

Q^3 and Q^4 are each, independently, H, -(CR^3R^4)-, aryl, -OH, or a cholesterol moiety;

each occurrence of A^1, A^2, A^3 and A^4 is, independently, -(CR^5R^5-CR^5=CR^5)-;

each occurrence of R^5 is, independently, H or alkyl;

M^1 and M^2 are each, independently, a biodegradable group (e.g., -OC(O)-, -C(O)O-, -SC(O)-, -C(O)S-, -OC(S)-, -C(S)O-, -S-S-, -C(R^5)=N-, -N=C(R^5)-, -C(R^5)=N-O-, -O-N=C(R^5)-, -C(O)(NR^5)-, -N(R^5)C(O)-, -C(S)(NR^5)-, -N(R^5)C(O)-, -N(R^5)C(O)N(R^5)-, –OC(O)O-, -OSi(R^5)$_2$O-, -C(O)(CR^3R^4)C(O)O-, or -OC(O)(CR^3R^4)C(O)-);

Z is absent, alkylene or -O-P(O)(OH)-O-;

each ------ attached to Z is an optional bond, such that when Z is absent, Q^3 and Q^4 are not directly covalently bound together;

a is 1, 2, 3, 4, 5 or 6;

b is 0, 1, 2, or 3;

c, d, e, f, i, j, m, n, q and r are each, independently, 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

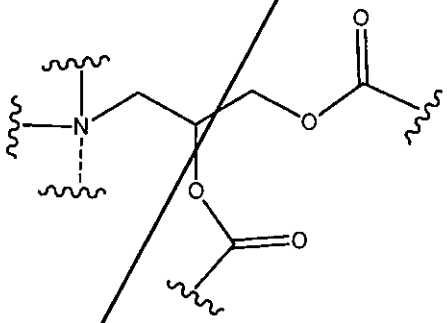
g and h are each, independently, 0, 1 or 2;

k and l are each, independently, 0 or 1;

o and p are each, independently, 0, 1 or 2,

wherein

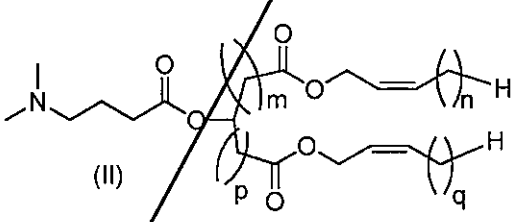
(j) the compound does not contain the following moiety:



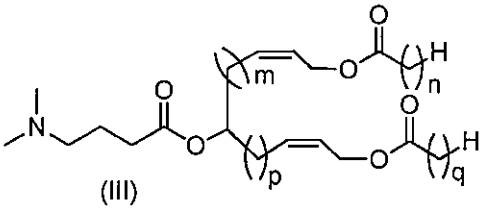
wherein ---- is an optional bond; and

Q^3 and Q^4 are each, independently, separated from the tertiary carbon atom marked with an asterisk (*) by a chain of 8 or more atoms.

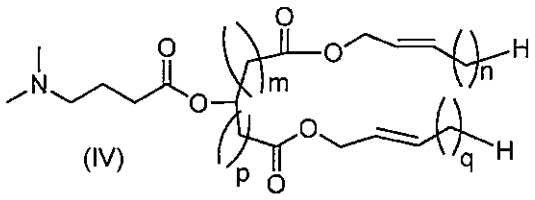
34. A compound selected from a compound of formulas II-XXIII:



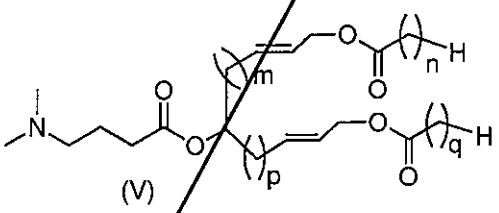
(II)



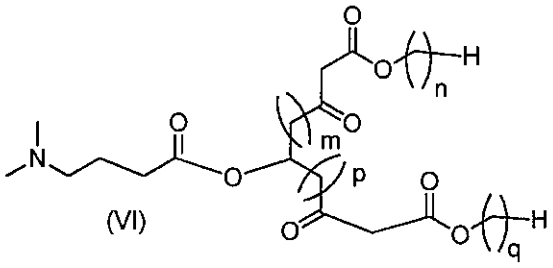
(III)



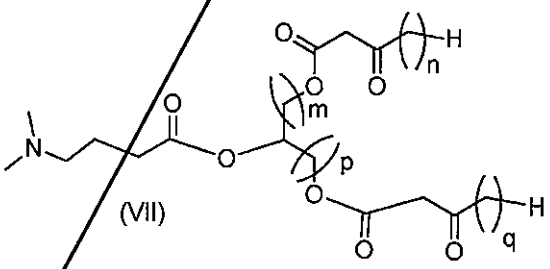
(IV)



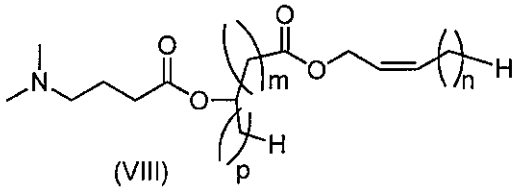
(V)



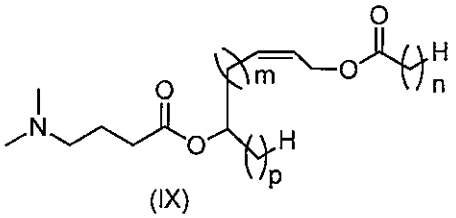
(VI)



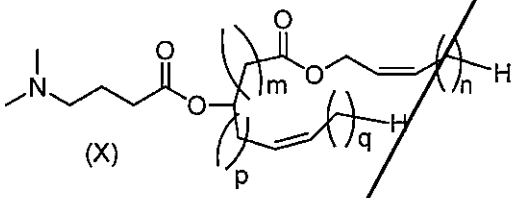
(VII)



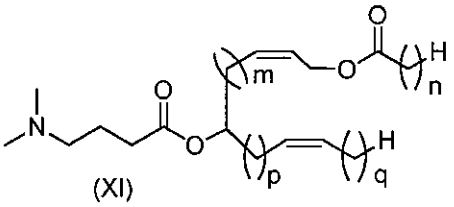
(VIII)



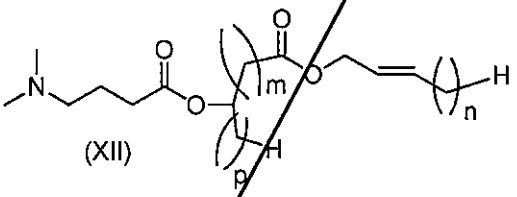
(IX)



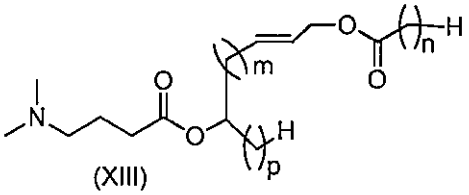
(X)



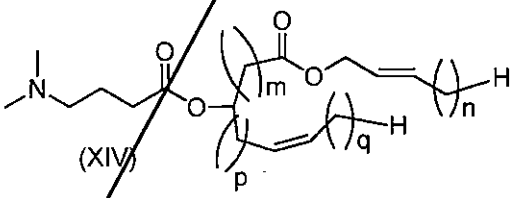
(XI)



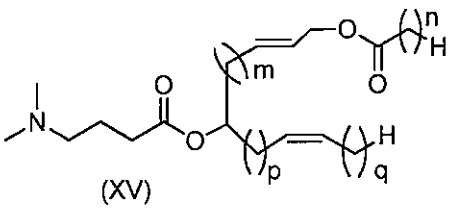
(XII)



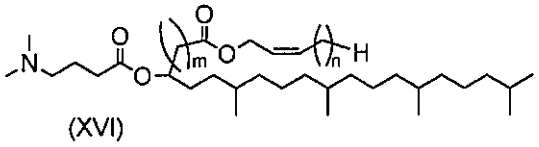
(XIII)



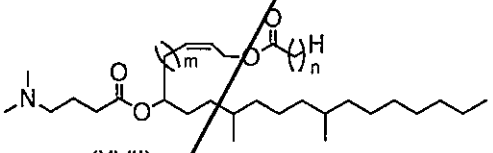
(XIV)



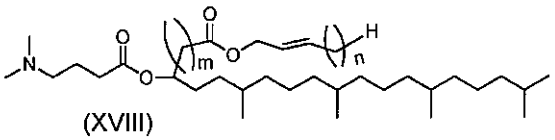
(XV)



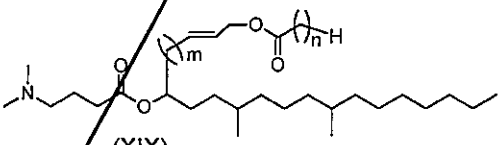
(XVI)



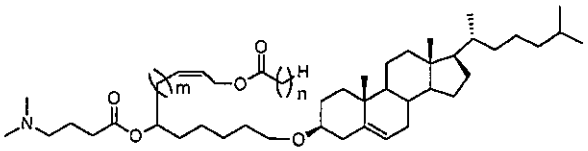
(XVII)



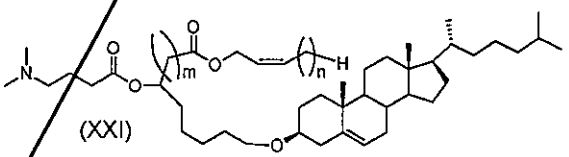
(XVIII)



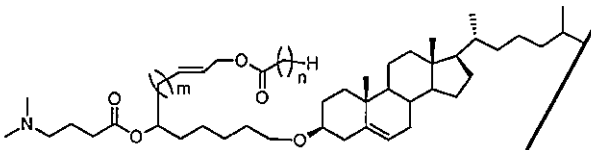
(XIX)



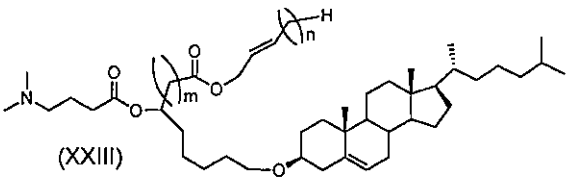
(XX)



(XXI)



(XXII)



(XXIII)

and salts thereof,

wherein

m, n, o and p are each, individually, 1-25, with the proviso that:

(i) in Formulas (II), (IV), (VI) and (VII), m and p are both 4 or greater;

(ii) in Formulas (VIII), (X), (XII), (XIV), (XVI), (XVIII), (XXI) and (XXIII), m is 4 or greater; and

(iii) in Formulas (VIII), (IX), (XII) and (XIII), p is 8 or greater.

35. A compound having:

(i) a central carbon atom,

(ii) an nitrogen containing head group bound to the central atom, and

(iii) two hydrophobic tails directly bound to the central carbon atom, each hydrophobic tail comprising a C_8 or greater aliphatic group attached to the central carbon atom, where the aliphatic group (a) is interrupted by a biodegradable group such that there is a chain of at least four carbon atoms between the biodegradable group and the central carbon atom, or (b) includes a biodegradable group at the terminal end of the hydrophobic tail.

36. The compound of claim 35, wherein the biodegradable group is selected from -OC(O)-, -C(O)O-, -SC(O)-, -C(O)S-, -OC(S)-, -C(S)O-, -S-S-, $-C(R^5)=N-$, $-N=C(R^5)-$, $-C(R^5)=N-O-$, $-O-N=C(R^5)-$, $-C(O)(NR^5)-$, $-N(R^5)C(O)-$, $-C(S)(NR^5)-$, $-N(R^5)C(O)-$, $-N(R^5)C(O)N(R^5)-$, –OC(O)O-, $-OSi(R^5)_2O-$, $-C(O)(CR^3R^4)C(O)O-$, and $-OC(O)(CR^3R^4)C(O)-$.

37. The compound of any of claims 35 and 36, wherein the aliphatic group in one or both of the hydrophobic tails of the cationic lipid includes at least one carbon-carbon double bond.

38. The compound of any of the preceding claims, wherein the compound is in the form of a pharmaceutically acceptable salt.

39. The compound of any of the preceding claims, wherein the compound is in the form of a cationic lipid.

40. A lipid particle comprising a neutral lipid, a lipid capable of reducing aggregation, and a cationic lipid of claim 39.

41. The lipid particle of claim 20, wherein the neutral lipid is selected from DSPC, DPPC, POPC, DOPE, or SM; the lipid capable of reducing aggregation is a PEG lipid; and the lipid particle further comprises a sterol.

42. The lipid particle of any one of claims 40 and 41, wherein the cationic lipid is present in a mole percentage of about 20% and about 60%; the neutral lipid is present in a mole percentage of about 5% to about 25%; the sterol is present in a mole percentage of about 25% to

about 55%; and the PEG lipid is PEG-DMA, PEG-DMG, or a combination thereof, and is present in a mole percentage of about 0.5% to about 15%.

43. The lipid particle of any of claims 40-42, further comprising an active agent.

44. The lipid particle of claim 43, wherein the active agent is a nucleic acid selected from a plasmid, an immunostimulatory oligonucleotide, an siRNA, an antisense oligonucleotide, a microRNA, an antagomir, an aptamer, and a ribozyme.

45. The lipid particle of any one of claims 40-44, wherein the lipid particle has an *in vivo* half life ($t_{1/2}$) of less than about 3 hours.

46. The lipid particle of any one of claims 40-44, wherein the lipid particle has an *in vivo* half life ($t_{1/2}$) of less than about 10 % of that for a lipid particle containing the same cationic lipid without a biodegrable group.

47. A pharmaceutical composition comprising a lipid particle of any one of claims 40-46 and a pharmaceutically acceptable carrier.

48. A method of modulating the expression of a target gene in a cell, comprising providing to the cell a lipid particle of any one of claims 40-46.

49. The method of claim 48, wherein the active agent is a nucleic acid selected from a plasmid, an immunostimulatory oligonucleotide, an siRNA, an antisense oligonucleotide, a microRNA, an antagomir, an aptamer, and a ribozyme.

50. A method of treating a disease or disorder characterized by the overexpression of a polypeptide in a subject, comprising providing to the subject the pharmaceutical composition of claim 47, wherein the active agent is a nucleic acid selected from the group consisting of an siRNA, a microRNA, and an antisense oligonucleotide, and wherein the siRNA, microRNA, or antisense oligonucleotide includes a polynucleotide that specifically binds to a polynucleotide that encodes the polypeptide, or a complement thereof.

51. A method of treating a disease or disorder characterized by underexpression of a polypeptide in a subject, comprising providing to the subject the pharmaceutical composition of

claim 47, wherein the active agent is a plasmid that encodes the polypeptide or a functional variant or fragment thereof.

52. A method of inducing an immune response in a subject, comprising providing to the subject the pharmaceutical composition of claim47, wherein the active agent is an immunostimulatory oligonucleotide.

53. The method of claim 52, wherein the target gene is selected from the group consisting of Factor VII, Eg5, PCSK9, TPX2, apoB, SAA, TTR, RSV, PDGF beta gene, Erb-B gene, Src gene, CRK gene, GRB2 gene, RAS gene, MEKK gene, JNK gene, RAF gene, Erk1/2 gene, PCNA(p21) gene, MYB gene, JUN gene, FOS gene, BCL-2 gene, Cyclin D gene, VEGF gene, EGFR gene, Cyclin A gene, Cyclin E gene, WNT-1 gene, beta-catenin gene, c-MET gene, PKC gene, NFKB gene, STAT3 gene, survivin gene, Her2/Neu gene, SORT1 gene, XBP1 gene, topoisomerase I gene, topoisomerase II alpha gene, p73 gene, p21(WAF1/CIP1) gene, p27(KIP1) gene, PPM1D gene, RAS gene, caveolin I gene, MIB I gene, MTAI gene, M68 gene, tumor suppressor genes, and p53 tumor suppressor gene.

54. The method of claim 53, wherein the target gene contains one or more mutations.

55. A method of delivering a nucleic acid molecule comprising administering a nucleic lipid particle comprising the nucleic acid molecule and a cationic lipid, the cationic lipid having

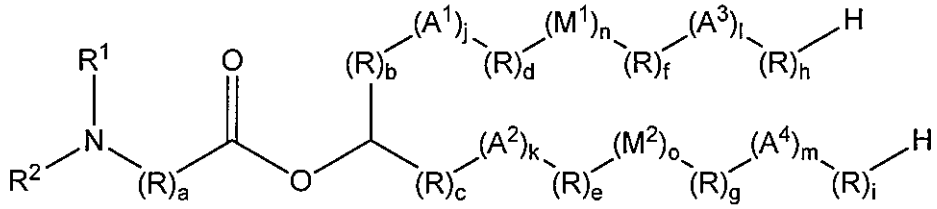
(i) a central carbon atom,

(ii) a nitrogen containing head group directly bound to the central atom, and

(iii) two hydrophobic tails directly bound to the central carbon atom, each hydrophobic tail comprising a C_{14} or greater aliphatic group attached to the central atom, where the aliphatic group is (a) interrupted by a biodegradable group such that there is a chain of at least four carbon atoms between the biodegradable group and the central carbon atom, or (b) includes a biodegradable group at the terminal end of the hydrophobic tail, such that the cationic lipid remains intact until delivery of the nucleic acid molecule after which cleavage of the hydrophobic tail occurs *in vivo*.

WHAT IS CLAIMED IS:

1. A compound of formula (I):



or a salt thereof,

wherein

with respect to R^1 and R^2,

(i) R^1 and R^2 are each, independently, alkyl, alkenyl, or alkynyl; or

(ii) R^1 and R^2, together with the nitrogen atom to which they are attached, form an optionally substituted heterocylic ring;

each occurrence of R is, independently, $-(CR^3R^4)-$;

each occurrence of R^3 and R^4 are, independently H, or alkyl;

each occurrence of A^1, A^2, A^3 and A^4 is, independently, $-(CR^5R^5-CR^5=CR^5)-$;

each occurrence of R^5 is, independently, H or alkyl;

M^1 and M^2 are each, independently, selected from the group consisting of –C(O)O-, -OC(O)-, -OC(O)O-, -C(O)NH-, -C(O)S-, -C(S)O-, $-CR^5=NO-$, $-CR^5=N-$, and $-O-Si(R^6R^6)O-$, wherein R^6 is H or C_1-C_6 alkyl ;

a is an integer between 1 and 6 inclusive ;

b and c are, independently, an integer between 1 and 10 inclusive ;

d, e, f, g, h, and i are each, independently, an integer between 0 and 10 inclusive ;

j, k, l, and m are each, independently, an integer between 0 and 2 inclusive;

n and o are each, independently, 0 or 1, wherein at least one of n and o is 1 , and

wherein the terminal –H of each chain and the tertiary carbon are separated by a chain of at least 8 atoms.

2. The compound of claim 1, wherein M^1 and M^2 are each, independently: -OC(O)-, -C(O)O-, -OC(O)O- or –C(O)NH- .

3. The compound of claim 2, wherein M^1 and M^2 are each, independently: -C(O)O- or -OC(O)- .

4. The compound of claim 2, wherein M^1 and M^2 are each –C(O)O-.

5. The compound of claim 1, wherein R^1 and R^2 are each alkyl.

6. The compound of claim 5, wherein R^1 and R^2 are each methyl.

7. The compound of claim 1, wherein each instance of R is, independently, $-CH_2-$, $-C(CH_3)_2-$ or –CH(iPr)-.

8. The compound of claim 1, wherein a is 2, 3, or 4.

9. The compound of claim 1, wherein a carbon atom alpha or beta to a biodegradable group is substituted with one or two alkyl groups .

10. The compound of claim 1, wherein one or more of the following applies:

(i) M^1 and M^2 are both –C(O)O-;

(ii) j and k are both 1;

(iii) j and k are both 0;

(iv) b is 7;

(v) c is 7;

(vi) b and d total 7;

(vii) c and e total 7;

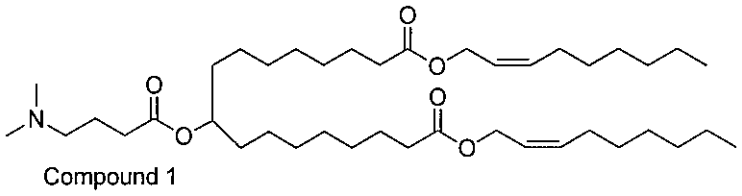
(viii) d and e are each 7;

(ix) n and o are both 1;

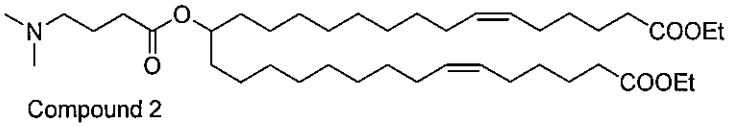
(x) f and g are both 0;

(xi)) f and h total 1 or 2;

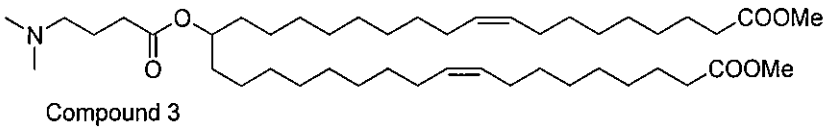
11. The compound of claim 1, selected from:



Compound 1 ,



Compound 2 , and



Compound 3 .

or a salt thereof.

12. The compound of claim 1 , wherein the R^1R^2N-$(R)_a$- group is $(CH_3)_2N$-$(CH_2)_3$- .

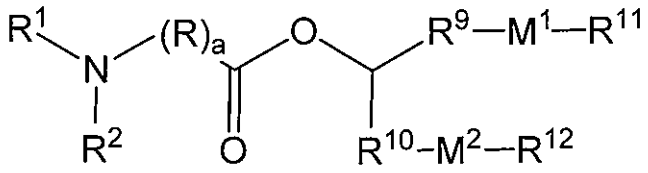
13. The compound of claim 1 , wherein R^1 and R^2 are each, independently, C_1-C_4 alkyl.

14. The compound of claim 1 , wherein each occurrence of R is, independently, -CH_2- or –$CH(CH_3)$-.

15. The compound of claim 1, wherein the sum of b+3j+d+f+3l+h is from about 8 to about 20.

16. The compound of claim 1, wherein the sum of f+3k+e+g+3m+i is from about 8 to about 20.

17. A compound of formula IB



(IB)

wherein

R^1 and R^2 are each, independently, alkyl, alkenyl, or alkynyl; or

R^1 and R^2, together with the nitrogen atom to which they are attached, form an optionally substituted heterocylic ring;

each occurrence of R is, independently, $-(CR^3R^4)-$;

each occurrence of R^3 and R^4 are, independently H or alkyl;

a is 1, 2, 3, 4, 5 or 6;

M^1 and M^2 are each, independently, selected from the group consisting of –C(O)O-, -OC(O)-, -OC(O)O-, -C(O)NH-, -C(O)S-, -C(S)O-, $-CR^5$=NO-, $-CR^5$=N-, and -O-Si(R^6R^6)O-, wherein each occurrence of R^5 is, independently, H or alkyl, and R^6 is H or C_1-C_6 alkyl ;

each of R^9 and R^{10} are independently alkylene or alkenylene; and

each of R^{11} and R^{12} are independently alkyl or alkenyl;

with the proviso that:

R^9, M^1, and R^{11} are together at least 8 carbons atoms in length; and

R^{10}, M^2, and R^{12} are together at least 8 carbons atoms in length.

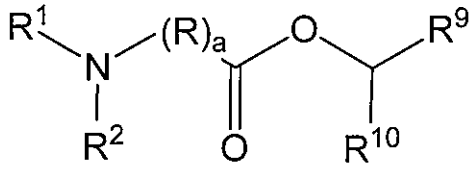
18. The compound of claim 17, wherein R^9 and R^{10} are each independently C_4-C_{12} alkylene or C_4-C_{12} alkenylene, M^1 and M^2 are -C(O)O-, and R^{11} and R^{12} are C_4-C_{12} alkylene or C_4-C_{12} alkenylene.

19. The compound of claim 17, wherein R^9, M^1, and R^{11} are together at 12 to 24 carbons atoms in length.

20. The compound of claim 17, wherein, R^{10}, M^2, and R^{12} are together at 12 to 24 carbons atoms in length.

21. The compound of claim 17, wherein the R^1R^2N-$(R)_a$- group is $(CH_3)_2N$-$(CH_2)_3$- .

22. A compound of formula IC



(IC)

wherein

R^1 and R^2 are each, independently, optionally substituted alkyl, alkenyl, or alkynyl; or

R^1 and R^2, together with the nitrogen atom to which they are attached, form an optionally substituted heterocylic ring;

each occurrence of R is, independently, $-(CR^3R^4)$-;

each occurrence of R^3 and R^4 are, independently H or alkyl;

a is 1, 2, 3, 4, 5 or 6;

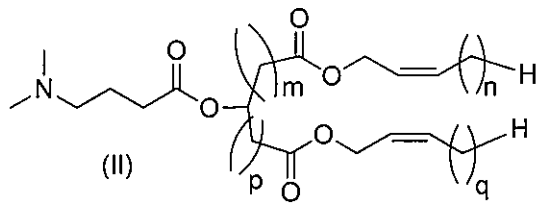
each of R^9 and R^{10} are independently C_{12}-C_{24} alkyl or alkenyl substituted at its terminus with a group M selected from the group consisting of –C(O)O-, -OC(O)-, -OC(O)O-, -C(O)NH-

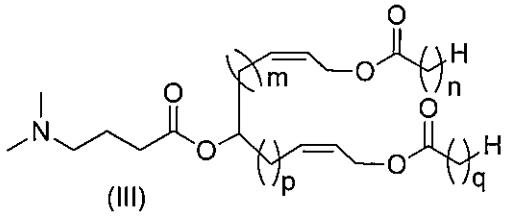
, -C(O)S-, -C(S)O-, -CR^5=NO-, -CR^5=N-, and -O-Si(R^6R^6)O-, wherein each occurrence of R^5 is, independently, H or alkyl, and R^6 is H or C_1-C_6 alkyl.

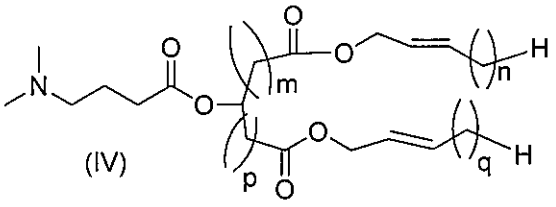
23. The compound of claim 22, wherein each group M is -$COOR^{13}$ wherein each R^{13} is, independently, alkyl.

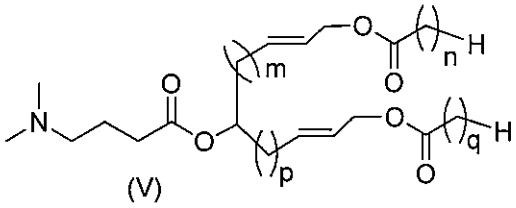
24. The compound of claim 22, wherein the R^1R^2N-$(R)_a$- group is $(CH_3)_2N$-$(CH_2)_3$- .

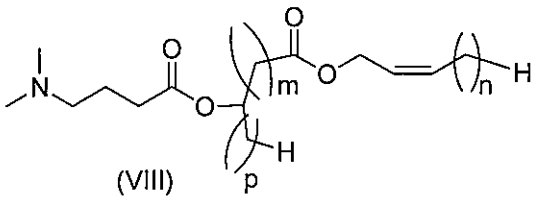
25. A compound selected from a compound of formulas II-XXIII:

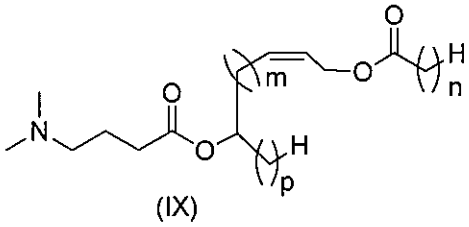


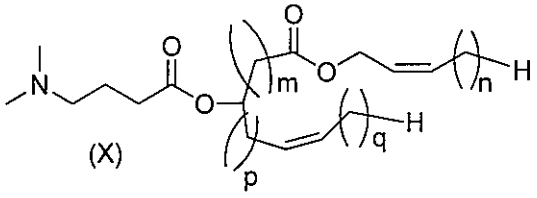


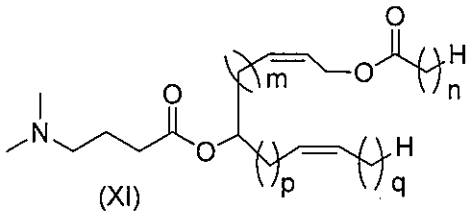


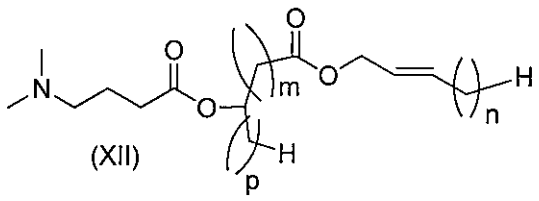




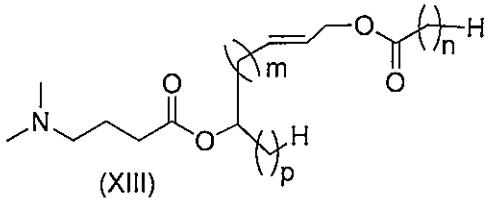




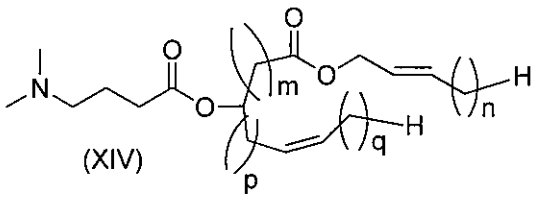




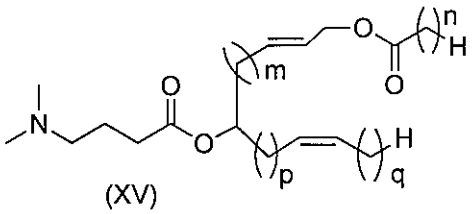
(XII)



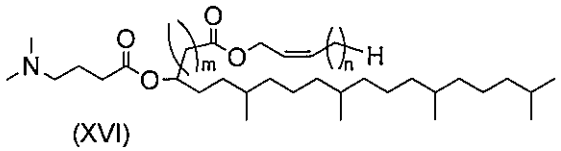
(XIII)



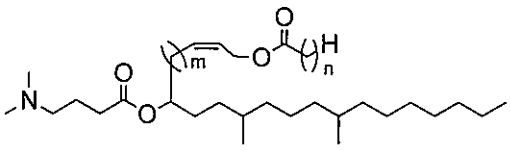
(XIV)



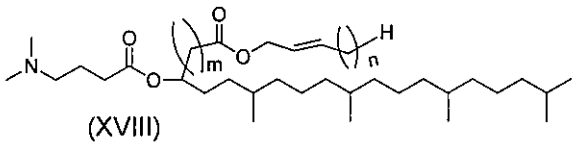
(XV)



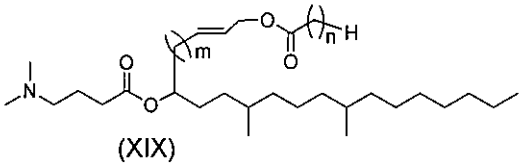
(XVI)



(XVII)



(XVIII)



(XIX)

and salts thereof,

wherein

m, n, o and p are each, individually, 1-25, with the proviso that:

(i) in Formulas (II), (IV), (VI) and (VII), m and p are both 4 or greater;

(ii) in Formulas (VIII), (X), (XII), (XIV), (XVI), (XVIII), (XXI) and (XXIII), m is 4 or greater; and

(iii) in Formulas (VIII), (IX), (XII) and (XIII), p is 8 or greater.

26. The compound of claim 1, wherein the compound is in the form of a pharmaceutically acceptable salt.

27. The compound of claim 1, wherein the compound is in the form of a cationic lipid.

28. A lipid particle comprising a neutral lipid, a lipid capable of reducing aggregation, and a cationic lipid of claim 27.

29. The lipid particle of claim 28 , wherein the neutral lipid is selected from DSPC, DPPC, POPC, DOPE, or SM; the lipid capable of reducing aggregation is a PEG lipid; and the lipid particle further comprises a sterol.

30. The lipid particle of claim 28, wherein the cationic lipid is present in a mole percentage of about 20% and about 60%; the neutral lipid is present in a mole percentage of about 5% to about 25%; the sterol is present in a mole percentage of about 25% to about 55%; and the PEG lipid is PEG-DMA, PEG-DMG, or a combination thereof, and is present in a mole percentage of about 0.5% to about 15%.

31. The lipid particle of claim 28, further comprising an active agent.

32. The lipid particle of claim 31, wherein the active agent is a nucleic acid selected from a plasmid, an immunostimulatory oligonucleotide, an siRNA, an antisense oligonucleotide, a microRNA, an antagomir, an aptamer, and a ribozyme.

33. The lipid particle of claim 28, wherein the lipid particle has an *in vivo* half life ($t_{1/2}$) of less than about 3 hours.

34. The lipid particle of claim 28, wherein the lipid particle has an *in vivo* half life ($t_{1/2}$) of less than about 10 % of that for a lipid particle containing the same cationic lipid without a biodegrable group.

35. A pharmaceutical composition comprising a lipid particle of claim 28 and a pharmaceutically acceptable carrier.

36. A method of modulating the expression of a target gene in a cell, comprising providing to the cell a lipid particle of claim 28.

37. The method of claim 36, wherein the active agent is a nucleic acid selected from a plasmid, an immunostimulatory oligonucleotide, an siRNA, an antisense oligonucleotide, a microRNA, an antagomir, an aptamer, and a ribozyme.

38. A method of inducing an immune response in a subject, comprising providing to the subject the pharmaceutical composition of claim 35, wherein the active agent is an immunostimulatory oligonucleotide.

39. The method of claim 38, wherein the target gene is selected from the group consisting of Factor VII, Eg5, PCSK9, TPX2, apoB, SAA, TTR, RSV, PDGF beta gene, Erb-B gene, Src gene, CRK gene, GRB2 gene, RAS gene, MEKK gene, JNK gene, RAF gene, Erk1/2 gene, PCNA(p21) gene, MYB gene, JUN gene, FOS gene, BCL-2 gene, Cyclin D gene, VEGF gene, EGFR gene, Cyclin A gene, Cyclin E gene, WNT-1 gene, beta-catenin gene, c-MET gene, PKC gene, NFKB gene, STAT3 gene, survivin gene, Her2/Neu gene, SORT1 gene, XBP1 gene, topoisomerase I gene, topoisomerase II alpha gene, p73 gene, p21(WAF1/CIP1) gene, p27(KIP1) gene, PPM1D gene, RAS gene, caveolin I gene, MIB I gene, MTAI gene, M68 gene, tumor suppressor genes, and p53 tumor suppressor gene.

40. The method of claim 39, wherein the target gene contains one or more mutations.

41. A method of delivering a nucleic acid molecule comprising administering a lipid particle of claim 32 to a subject.