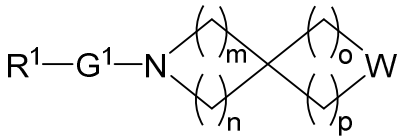
CLAIMS

1. A compound of Formula (I)



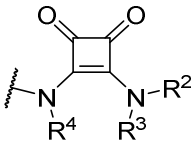
Formula (I)

or a pharmaceutically acceptable salt, N-oxide, tautomer, or stereoisomer thereof, wherein

m, n, o, and p are each independently 1 - 3;

G^1 is C_{1-12}alkylene or C_{2-12}alkenylene;

R^1 is $-N(R^2)R^3$, $-OR^4$, CN, $-N(R^4)$(heteroaryl), $-O(CH_2)_qOH$, $-(OCH_2CH_2)_rOH$, $-OC(=O)R^5$, $-N(R^4)C(=O)R^5$, $-N(R^4)S(O)_2R^5$, $-N(R^4)C(=O)N(R^2)R^3$, $-OC(=O)N(R^2)R^3$, $-N(R^4)C(=O)OR^5$, $-N(R^4)C(=S)N(R^2)R^3$, $-N(R^4)C(=NR^6)N(R^2)R^3$, or



R^2 and R^3 are each independently H, C_{1-6}alkyl, C_{3-8}cycloalkyl, or aryl; or R^2 and R^3 together with the nitrogen atom to which they are attached form a heterocyclic ring;

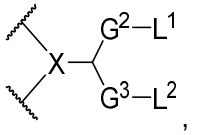
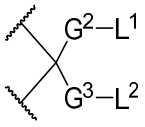
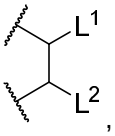
R^4 is H, C_{1-6}alkyl or C_{3-8}cycloalkyl;

R^5 is C_{1-6}alkyl or C_{3-8}cycloalkyl optionally substituted by C_{1-6}alkyl;

R^6 is H, CN, NO_2, C_{1-6}alkyl, OR^5, $S(O)_2R^5$, or $S(O)_2N(R^2)R^3$;

q is 2 – 6;

r is 1 – 6;

W is , , or ,

X is N or CH;

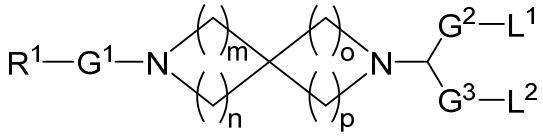
G^2 and G^3 are each independently C_{1-12}alkylene or C_{2-12}alkenylene;

L^1 and L^2 are each independently $-C(=O)OR^7$, $-OC(=O)R^7$, $-OC(=O)(CH_2)_rC(=O)OR^7$, $-OC(=O)(CH_2)_rOC(=O)R^7$, $-OC(=O)N(R^4)R_7$, $-N(R^4)C(=O)OR_7$, $-N(R^4)C(=O)N(R^4)R^7$, $-OC(=O)OR^7$, or $-S\text{-}SR^7$; and

R^7 is C_{6-24}alkyl, C_{6-24}alkenyl, or C_{6-24}alkynyl where each is optionally substituted by F, C_{1-6}alkoxy, C_{3-8}cycloalkyl, or C_{3-8}cycloalkenyl, wherein the R^7 of L^1 and L^2 may be the same or different.

2. The compound of claim 1:

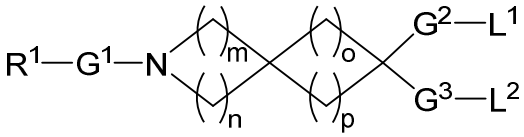
a) having Formula (Ia)



Formula (Ia)

or a pharmaceutically acceptable salt, N-oxide, tautomer or stereoisomer thereof, wherein m, n, o, and p are each independently 1 or 2;

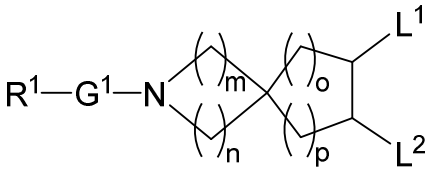
b) having Formula (Ib)



Formula (Ib)

or a pharmaceutically acceptable salt, N-oxide, tautomer or stereoisomer thereof, wherein m, n, o, and p are each independently 1 or 2; or

c) having Formula (Ic)



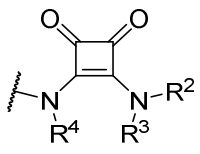
Formula (Ic)

or a pharmaceutically acceptable salt, N-oxide, tautomer or stereoisomer thereof, wherein m and n are each independently 1 or 2; and

o and p are each 1.

3. The compound of claim 1 or claim 2, wherein

G^1 is C_{1-12}alkylene;

R^1 is -OH or ;

R^2 and R^3 are each independently H, C_{1-6}alkyl, or C_{3-8}cycloalkyl; or R^2 and R^3 together with the nitrogen atom to which they are attached form a heterocyclic ring;

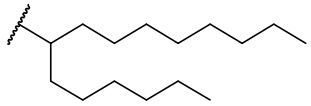
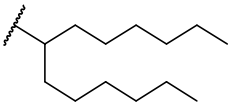
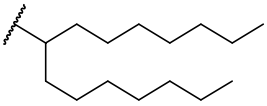
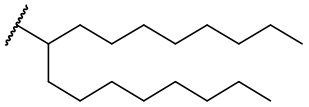
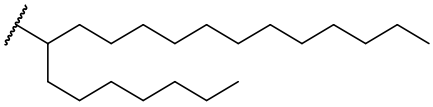
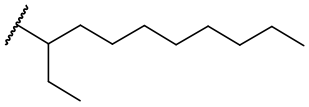
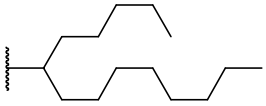
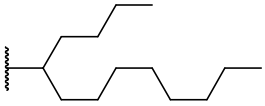
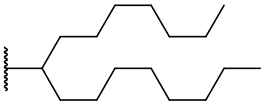
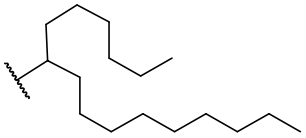
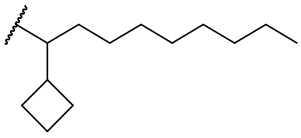
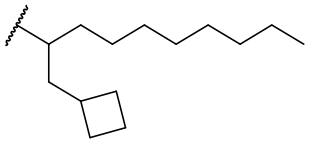
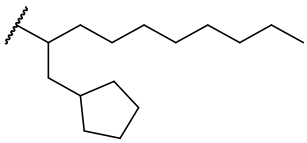
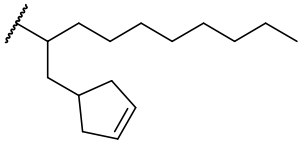
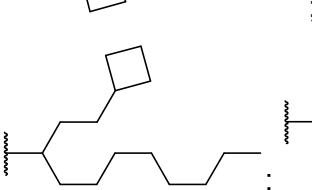
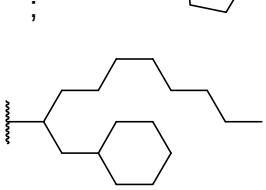
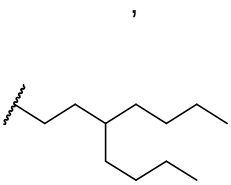
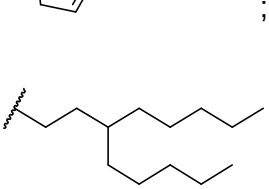
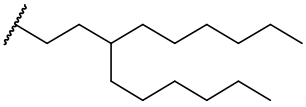
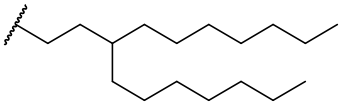
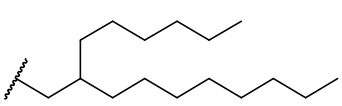
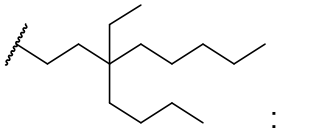
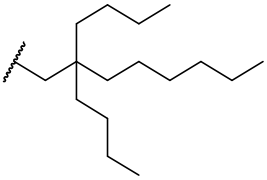
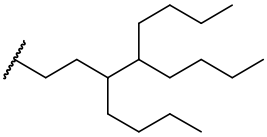
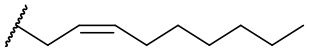
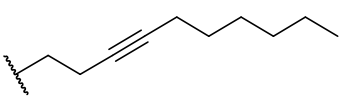
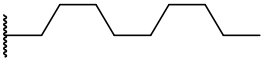
R^4 is H, C_{1-6}alkyl or C_{3-8}cycloalkyl;

G^2 and G^3 are each independently C_{1-12}alkylene;

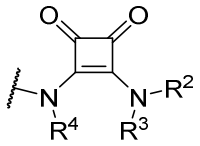
L^1 and L^2 are each -OC(=O)R^7; and

R^7 is C_{6-24}alkyl, C_{6-24}alkenyl, or C_{6-24}alkynyl wherein each is optionally substituted by F, C_{1-6}alkoxy, C_{3-8}cycloalkyl, or C_{3-8}cycloalkenyl, wherein the R^7 of L^1 and L^2 may be the same or different.

4. The compound of any one of claims 1-3, wherein R^7, or both, has the following structure:


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; or

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5. The compound of any one of claims 1-4, wherein R^1 is OH or



.

6. The compound of any one of claims 1-5, wherein G^1 is C_2-C_5 alkylene or C_3-C_5 alkylene.

7. The compound of claim 1:

a) selected from the group consisting of:

(3-(4-hydroxybutyl)-3-azaspiro[5.5]undecane-9,9-diyl)bis(methylene) bis(2-heptylnonanoate);

2-(3-(4-hydroxybutyl)-3-azaspiro[5.5]undecan-9-yl)propane-1,3-diyl bis(2-heptylnonanoate);

2-(9-(4-hydroxybutyl)-3,9-diazaspiro[5.5]undecan-3-yl)propane-1,3-diyl bis(2-heptylnonanoate);

2-(9-(4-hydroxybutyl)-3,9-diazaspiro[5.5]undecan-3-yl)propane-1,3-diyl bis(2-cyclobutyldecanoate);

2-(9-(5-hydroxypentyl)-3,9-diazaspiro[5.5]undecan-3-yl)propane-1,3-diyl bis(2-hexyldecanoate);

2-(2-(4-hydroxybutyl)-2,8-diazaspiro[4.5]decan-8-yl)propane-1,3-diyl bis(2-hexyldecanoate);

3-((2-hexyldecanoyl)oxy)-2-(9-(4-hydroxybutyl)-3,9-diazaspiro[5.5]undecan-3-yl)propyl palmitate;

2-(9-(3-((2-(methylamino)-3,4-dioxocyclobut-1-en-1-yl)amino)propyl)-3,9-diazaspiro[5.5]undecan-3-yl)propane-1,3-diyl bis(2-heptylnonanoate);

2-(9-(3-(1-methylcyclopropane-1-carboxamido)propyl)-3,9-diazaspiro[5.5]undecan-3-yl)propane-1,3-diyl bis(2-hexyldecanoate);

2-(9-(3-hydroxypropyl)-3,9-diazaspiro[5.5]undecan-3-yl)propane-1,3-diyl bis(2-heptylnonanoate);

2-(9-(3-(ethylsulfonamido)propyl)-3,9-diazaspiro[5.5]undecan-3-yl)propane-1,3-diyl bis(2-hexyldecanoate);

2-(7-(4-hydroxybutyl)-2,7-diazaspiro[4.4]nonan-2-yl)propane-1,3-diyl bis(2-heptylnonanoate);

2-(7-(4-hydroxybutyl)-2,7-diazaspiro[3.5]nonan-2-yl)propane-1,3-diyl bis(2-heptylnonanoate);

2-(8-(4-hydroxybutyl)-2,8-diazaspiro[4.5]decan-2-yl)propane-1,3-diyl bis(2-heptylnonanoate);

3-(9-(4-hydroxybutyl)-3,9-diazaspiro[5.5]undecan-3-yl)pentane-1,5-diyl bis(2-hexyldecanoate);

2-(7-(5-hydroxypentyl)-2,7-diazaspiro[4.4]nonan-2-yl)propane-1,3-diyl bis(2-hexyldecanoate);

2-(2-(5-hydroxypentyl)-2,8-diazaspiro[4.5]decan-8-yl)propane-1,3-diyl bis(2-hexyldecanoate);

2-(7-(5-hydroxypentyl)-2,7-diazaspiro[3.5]nonan-2-yl)propane-1,3-diyl bis(2-heptylnonanoate);

2-(9-(4-hydroxybutyl)-3,9-diazaspiro[5.5]undecan-3-yl)pentane-1,5-diyl bis(2-hexyldecanoate);

2-(2-(4-hydroxybutyl)-2,7-diazaspiro[3.5]nonan-7-yl)propane-1,3-diyl bis(2-heptylnonanoate);

2-(9-(5-hydroxypentan-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)propane-1,3-diyl bis(2-hexyldecanoate);

2-(2-(4-hydroxybutyl)-2,8-diazaspiro[4.5]decan-8-yl)propane-1,3-diyl bis(2-heptylnonanoate);

2-(9-(4-hydroxybutyl)-3,9-diazaspiro[5.5]undecan-3-yl)propane-1,3-diyl bis(2-hexyldecanoate);

2-(9-(4-hydroxybutyl)-3,9-diazaspiro[5.5]undecan-3-yl)propane-1,3-diyl bis(2-octyldecanoate);

2-(9-(5-hydroxypentyl)-3,9-diazaspiro[5.5]undecan-3-yl)propane-1,3-diyl bis(2-heptylnonanoate);

2-(9-(4-hydroxybutyl)-3,9-diazaspiro[5.5]undecan-3-yl)propane-1,3-diyl bis(2-heptyldecanoate);

2-(9-(4-hydroxybutyl)-3,9-diazaspiro[5.5]undecan-3-yl)propane-1,3-diyl bis(2-butyldecanoate);

2-(9-(4-hydroxybutyl)-3,9-diazaspiro[5.5]undecan-3-yl)propane-1,3-diyl bis(3-hexylundecanoate);

2-(9-(4-hydroxybutyl)-3,9-diazaspiro[5.5]undecan-3-yl)propane-1,3-diyl bis(2-pentyldecanoate);

2-(9-(4-hydroxybutyl)-3,9-diazaspiro[5.5]undecan-3-yl)propane-1,3-diyl bis(2-(cyclobutylmethyl)decanoate);

2-(9-(4-hydroxybutyl)-3,9-diazaspiro[5.5]undecan-3-yl)propane-1,3-diyl bis(2-heptyltetradecanoate);

2-(9-(4-hydroxybutyl)-3,9-diazaspiro[5.5]undecan-3-yl)propane-1,3-diyl bis(2-(cyclopentylmethyl)decanoate);

2-(7-(4-hydroxybutyl)-2,7-diazaspiro[4.4]nonan-2-yl)propane-1,3-diyl bis(2-hexyldecanoate);

2-(7-(4-hydroxybutyl)-2,7-diazaspiro[3.5]nonan-2-yl)propane-1,3-diyl bis(2-hexyldecanoate);

2-(9-(4-hydroxybutyl)-3,9-diazaspiro[5.5]undecan-3-yl)propane-1,3-diyl bis(2-(cyclopent-3-en-1-ylmethyl)decanoate);

2-(9-(4-hydroxybutyl)-3,9-diazaspiro[5.5]undecan-3-yl)propane-1,3-diyl bis(2-(2-cyclobutylethyl)decanoate);

2-(9-(4-hydroxybutyl)-3,9-diazaspiro[5.5]undecan-3-yl)propane-1,3-diyl bis(2-(cyclohexylmethyl)decanoate);

2-(9-(4-hydroxybutyl)-3,9-diazaspiro[5.5]undecan-3-yl)propane-1,3-diyl bis(4,5-dibutylnonanoate);

2-(9-(4-hydroxybutyl)-3,9-diazaspiro[5.5]undecan-3-yl)propane-1,3-diyl bis(3,3-dibutylnonanoate);

2-(9-(4-hydroxybutyl)-3,9-diazaspiro[5.5]undecan-3-yl)propane-1,3-diyl bis(4-heptylundecanoate);

2-(7-(5-hydroxypentyl)-2,7-diazaspiro[4.4]nonan-2-yl)propane-1,3-diyl bis(2-heptylnonanoate);

3-(decanoyloxy)-2-(9-(4-hydroxybutyl)-3,9-diazaspiro[5.5]undecan-3-yl)propyl 2-hexyldecanoate;

3-((2-hexyldecanoyl)oxy)-2-(9-(4-hydroxybutyl)-3,9-diazaspiro[5.5]undecan-3-yl)propyl (Z)-dodec-5-enoate;

3-((2-(cyclobutylmethyl)decanoyl)oxy)-2-(9-(4-hydroxybutyl)-3,9-diazaspiro[5.5]undecan-3-yl)propyl 2-hexyldecanoate;

3-((2-hexyldecanoyl)oxy)-2-(9-(4-hydroxybutyl)-3,9-diazaspiro[5.5]undecan-3-yl)propyl 2-butylundecanoate;

3-((4,5-dibutylnonanoyl)oxy)-2-(9-(4-hydroxybutyl)-3,9-diazaspiro[5.5]undecan-3-yl)propyl palmitate;

3-(9-(4-hydroxybutyl)-3,9-diazaspiro[5.5]undecan-3-yl)pentane-1,5-diyl bis(2-heptylnonanoate);

2-(2-(5-hydroxypentyl)-2,8-diazaspiro[4.5]decan-8-yl)propane-1,3-diyl bis(2-heptylnonanoate);

2-(7-(5-hydroxypentyl)-2,7-diazaspiro[3.5]nonan-2-yl)propane-1,3-diyl bis(2-hexyldecanoate);

2-(2-(4-hydroxybutyl)-2,7-diazaspiro[3.5]nonan-7-yl)propane-1,3-diyl bis(2-hexyldecanoate);

rac-(2R,3R)-8-(4-hydroxybutyl)-8-azaspiro[4.5]decane-2,3-diyl bis(2-heptylnonanoate);

rac-(2R,3R)-8-(2-hydroxyethyl)-8-azaspiro[4.5]decane-2,3-diyl bis(2-heptylnonanoate);

rac-(7R,8R)-2-(3-hydroxypropyl)-2-azaspiro[4.4]nonane-7,8-diyl bis(2-heptylnonanoate);

rac-(2R,3R)-8-(3-hydroxypropyl)-8-azaspiro[4.5]decane-2,3-diyl bis(2-heptylnonanoate);

rac-(2R,3R)-8-(3-((2-(methylamino)-3,4-dioxocyclobut-1-en-1-yl)amino)propyl)-8-azaspiro[4.5]decane-2,3-diyl bis(2-heptylnonanoate);

rac-(2R,3R)-8-(5-hydroxypentyl)-8-azaspiro[4.5]decane-2,3-diyl bis(2-heptylnonanoate);

(2R,3R)-8-(4-hydroxybutyl)-8-azaspiro[4.5]decane-2,3-diyl bis(2-heptylnonanoate);

(2S,3S)-8-(4-hydroxybutyl)-8-azaspiro[4.5]decane-2,3-diyl bis(2-heptylnonanoate);

rac-(2R,3R)-8-(4-hydroxybutyl)-8-azaspiro[4.5]decane-2,3-diyl bis(2-octyldecanoate);

rac-(2R,3R)-8-(4-hydroxybutyl)-8-azaspiro[4.5]decane-2,3-diyl bis(2-heptyltetradecanoate);

rac-(2R,3R)-8-(4-hydroxybutyl)-8-azaspiro[4.5]decane-2,3-diyl bis(2-hexyldecanoate);

rac-O,O'-((2R,3R)-8-(4-hydroxybutyl)-8-azaspiro[4.5]decane-2,3-diyl) di(pentadecan-8-yl) disuccinate;

rac-O'^{1},O^{1}-((2R,3R)-8-(4-hydroxybutyl)-8-azaspiro[4.5]decane-2,3-diyl) 7,7'-di(pentadecan-8-yl) di(heptanedioate);

rac-(((2R,3R)-8-(4-hydroxybutyl)-8-azaspiro[4.5]decane-2,3-diyl)bis(oxy))bis(6-oxohexane-6,1-diyl) bis(2-heptylnonanoate);

rac-(2R,3R)-8-(4-hydroxybutyl)-8-azaspiro[4.5]decane-2,3-diyl bis(2-pentyldecanoate);

rac-(2R,3R)-8-(4-hydroxybutyl)-8-azaspiro[4.5]decane-2,3-diyl bis(2-heptyldecanoate);

rac-(2R,3R)-8-(4-hydroxybutyl)-8-azaspiro[4.5]decane-2,3-diyl bis(2-hexylundecanoate);

rac-(2R,3R)-8-(4-hydroxybutyl)-8-azaspiro[4.5]decane-2,3-diyl bis(2-hexylnonanoate);

rac-(2R,3R)-8-(4-hydroxybutyl)-8-azaspiro[4.5]decane-2,3-diyl bis(2-butyldecanoate);

rac-(2R,3R)-3-((2-ethylnonanoyl)oxy)-8-(4-hydroxybutyl)-8-azaspiro[4.5]decan-2-yl 2-hexyldecanoate; and

bis(3-pentyloctyl) 3-(9-(4-hydroxybutyl)-3,9-diazaspiro[5.5]undecan-3-yl)pentanedioate;

or a pharmaceutically acceptable salt thereof; or

b) selected from the group consisting of:

2-(9-(4-hydroxybutyl)-3,9-diazaspiro[5.5]undecan-3-yl)propane-1,3-diyl bis(2-heptylnonanoate);

2-(7-(4-hydroxybutyl)-2,7-diazaspiro[3.5]nonan-2-yl)propane-1,3-diyl bis(2-heptylnonanoate);

2-(2-(4-hydroxybutyl)-2,8-diazaspiro[4.5]decan-8-yl)propane-1,3-diyl bis(2-heptylnonanoate);

2-(9-(4-hydroxybutyl)-3,9-diazaspiro[5.5]undecan-3-yl)propane-1,3-diyl bis(2-hexyldecanoate);

2-(9-(5-hydroxypentyl)-3,9-diazaspiro[5.5]undecan-3-yl)propane-1,3-diyl bis(2-heptylnonanoate);

rac-(2R,3R)-8-(4-hydroxybutyl)-8-azaspiro[4.5]decane-2,3-diyl bis(2-heptylnonanoate);

rac-(2R,3R)-8-(4-hydroxybutyl)-8-azaspiro[4.5]decane-2,3-diyl bis(2-hexyldecanoate);

2-(2-(4-hydroxybutyl)-2,8-diazaspiro[4.5]decan-8-yl)propane-1,3-diyl bis(2-hexyldecanoate);

2-(9-(3-hydroxypropyl)-3,9-diazaspiro[5.5]undecan-3-yl)propane-1,3-diyl bis(2-heptylnonanoate);

2-(9-(4-hydroxybutyl)-3,9-diazaspiro[5.5]undecan-3-yl)propane-1,3-diyl bis(3-hexylundecanoate);

2-(7-(4-hydroxybutyl)-2,7-diazaspiro[4.4]nonan-2-yl)propane-1,3-diyl bis(2-hexyldecanoate);

2-(7-(5-hydroxypentyl)-2,7-diazaspiro[3.5]nonan-2-yl)propane-1,3-diyl bis(2-hexyldecanoate);

2-(2-(4-hydroxybutyl)-2,7-diazaspiro[3.5]nonan-7-yl)propane-1,3-diyl bis(2-hexyldecanoate); and

rac-(2R,3R)-8-(5-hydroxypentyl)-8-azaspiro[4.5]decane-2,3-diyl bis(2-heptylnonanoate); or a pharmaceutically acceptable salt thereof.

8. A pharmaceutical composition comprising a nucleic acid, at least one pharmaceutically acceptable excipient, and the compound according to any one of claims 1-7, or a pharmaceutically acceptable salt thereof.

9. The pharmaceutical composition of claim 8, wherein the pharmaceutically acceptable excipient is selected from the group consisting of neutral lipids, steroids and polymer conjugated lipids.

10. The pharmaceutical composition of claim 9, wherein:

a) the pharmaceutical composition comprises 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC), 1,2-Dipalmitoyl-sn-glycero-3-phosphocholine (DPPC), 1,2-Dimyristoyl-sn-glycero-3-phosphocholine (DMPC), 1-Palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC), 1,2-

dioleoyl-sn-glycero-3-phosphocholine (DOPC), phophatidylethanolamines such as 1,2-Dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE), sphingomyelins (SM), or a combination thereof

b) the steroid is cholesterol; and/or

c) the polymer conjugated lipid is a pegylated lipid, optionally wherein the pegylated lipid is PEG-DAG, PEG-PE, PEG-S-DAG, PEG-cer, PEG-DMG, 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159) or a PEG dialkyoxypropylcarbamate.

11. The pharmaceutical composition of claim 8, wherein the nucleic acid is RNA, optionally wherein the RNA is messenger RNA, modRNA or saRNA.

12. A method of making the pharmaceutical composition of any one of claims 8-11, the method comprising combining the nucleic acid, at least one pharmaceutically acceptable excipient, and the compound according to any one of claims 1-7.

13. A compound according to any one of claims 1 to 7, for use as a medicament.