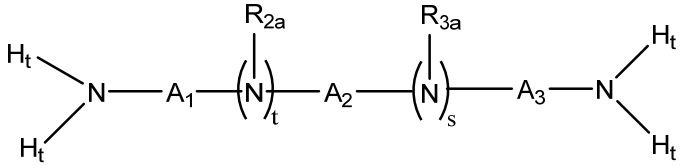
Claims

1. A lipid compound of formula (I),



(I)

wherein

R_{2a} and R_{3a} are each independently selected from the group consisting of hydrogen, a monovalent aliphatic group, a monovalent heteroaliphatic group, a monovalent aromatic group, a monovalent heteroaromatic group, and Ht;

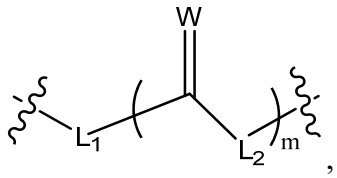
t and s are each independently 0 or 1, and when t or s is zero, it means that the part is directly a single bond, provided that t and s are not both 0;

A_1, A_2, and A_3 are each independently selected from the group consisting of a single bond, a divalent aliphatic group, a divalent heteroaliphatic group, a divalent aromatic group, and a divalent heteroaromatic group;

each Ht is independently at each occurrence $-R_1-X-R_2-Y-R_3-Z-R_4$,

wherein

each R_1 is independently at each occurrence selected from the group consisting of a divalent aliphatic group, a divalent heteroaliphatic group, a divalent aromatic group, and a divalent heteroaromatic group;

each X is independently at each occurrence ,

wherein

m is 1-6;

W is selected from the group consisting of O, S, and NR_c;

L_1 is directly connected to R_1 and is selected from the group consisting of a single bond, O, S, and NR_d;

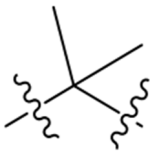
L_2 is selected from the group consisting of a bond, O, S, and NR_e;

wherein R_c, R_d, and R_e are each independently selected from the group consisting of hydrogen, hydroxy, an oxyaliphatic group, a monovalent aliphatic group, a monovalent heteroaliphatic group, a monovalent aromatic group, and a monovalent heteroaromatic group;

Y and Z are both S;

each R_2 is independently at each occurrence selected from the group consisting of a single bond, a divalent aliphatic group, a divalent heteroaliphatic group, a divalent aromatic

group, and a divalent heteroaromatic group;

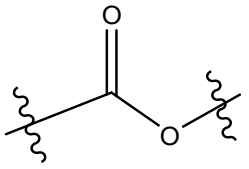
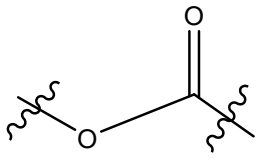
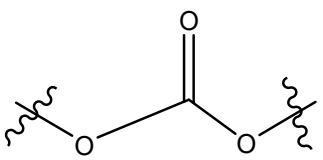
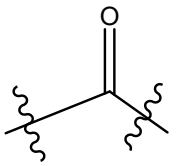
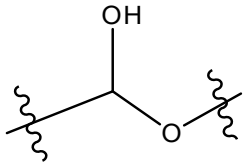
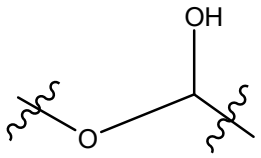
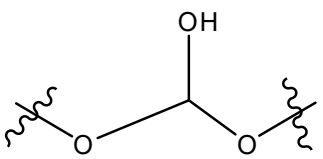
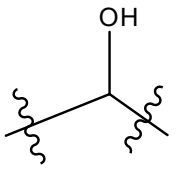
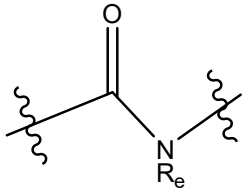
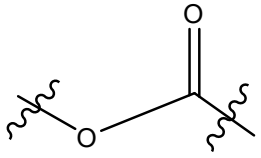
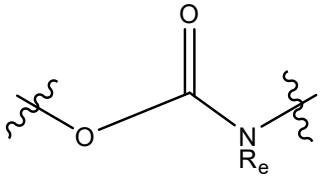
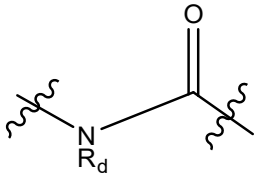
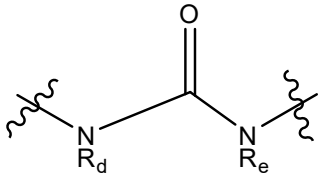
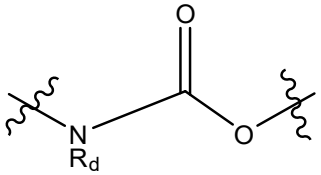
each R_3 is independently at each occurrence  ;

each R_4 is independently at each occurrence a hydrophobic group selected from the group consisting of $-(CH_2CH_2O)_y-C_{3-8}$ alkyl, $-(CH_2CH_2O)_y-C_{3-8}$ alkenyl or $-(CH_2CH_2O)_y-C_{3-8}$ alkynyl, wherein y is 0 or 1 or 2.

2. The lipid compound of claim 1, wherein t is 0 and s is 1; or t is 1 and s is 0.

3. The lipid compound of claim 1 or 2, wherein R_1 is selected from the group consisting of a C_{1-6} divalent aliphatic group and a C_{1-6} divalent heteroaliphatic group.

4. The lipid compound of claim 1, wherein L_1 is selected from the group consisting of a single bond, O, S, and NH.

5. The lipid compound of any one of claims 1-3, wherein X is  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  or  , wherein R_d and R_e are as defined for formula (I).

6. The lipid compound of claim 5, wherein R^d and R^e are each independently selected from the group consisting of H and a C_{1-4} monovalent aliphatic group.

7. The lipid compound of any one of claims 1-6, wherein each R_2 is independently at each

occurrence selected from the group consisting of a single bond and a C_{1-6} divalent aliphatic group.

8. The lipid compound of claim 7, wherein each R_2 is independently at each occurrence C_{1-4} divalent aliphatic group.

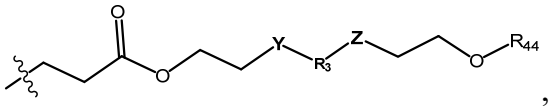
9. The lipid compound of any one of claims 1-8, wherein

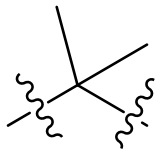
each R_4 is independently at each occurrence selected from the group consisting of C_{3-8} alkyl, C_{3-8} alkenyl, C_{3-8} alkynyl, -(CH_2CH_2O)-C_{3-8} alkyl, -(CH_2CH_2O)-C_{3-8} alkenyl, -(CH_2CH_2O)-C_{3-8} alkynyl, -$(CH_2CH_2O)_2$-C_{3-8} alkyl, -$(CH_2CH_2O)_2$-C_{3-8} alkenyl and -$(CH_2CH_2O)_2$-C_{3-8} alkynyl; or

each R_4 is independently at each occurrence selected from the group consisting of C_{4-8} alkyl, C_{4-8} alkenyl, C_{4-8} alkynyl, -(CH_2CH_2O)-C_{4-8} alkyl, -(CH_2CH_2O)-C_{4-8} alkenyl, -$(CH_2CH_2O)_2$-C_{4-8} alkynyl, -$(CH_2CH_2O)_2$-C_{4-8} alkyl, -$(CH_2CH_2O)_2$-C_{4-8} alkenyl and -$(CH_2CH_2O)_2$-C_{4-8} alkynyl.

10. The lipid compound of claim 9, wherein the alkyl in the C_{4-8} alkyl, -(CH_2CH_2O)-C_{4-8} alkyl or -$(CH_2CH_2O)_2$-C_{4-8} alkyl is a linear alkyl; the alkenyl in the C_{4-8} alkenyl, -(CH_2CH_2O)-C_{4-8} alkenyl or-$(CH_2CH_2O)_2$-C_{4-8} alkenyl is a linear alkenyl; and the alkynyl in the C_{4-8} alkynyl, -(CH_2CH_2O)-C_{4-8} alkynyl or -$(CH_2CH_2O)_2$-C_{4-8} alkynyl is a linear alkynyl.

11. The lipid compound of claim 9, wherein each R_4 is independently at each occurrence selected from the group consisting of -(CH_2CH_2O)-$(CH_2)_3CH_3$, -$(CH_2CH_2O)_2$-$(CH_2)_3CH_3$, -(CH_2CH_2O)-$(CH_2)_4CH_3$, -$(CH_2CH_2O)_2$-$(CH_2)_4CH_3$, -(CH_2CH_2O)-$(CH_2)_5CH_3$, -$(CH_2CH_2O)_2$-$(CH_2)_5CH_3$, -(CH_2CH_2O)-$(CH_2)_6CH_3$, -$(CH_2CH_2O)_2$-$(CH_2)_6CH_3$, -(CH_2CH_2O)-$(CH_2)_7CH_3$ and -$(CH_2CH_2O)_2$-$(CH_2)_7CH_3$.

12. The lipid compound of claim 1, wherein each Ht is independently at each occurrence 

, wherein Y and Z are both S; or Y is S and Z is O; or Y is O and Z is S; or Y and Z are both O; each R_3 is independently at each occurrence 
, and R_{44} is C_{4-8} alkyl, C_{4-8} alkenyl or C_{4-8} alkynyl.

13. The lipid compound of claim 12, wherein each R_{44} is independently at each occurrence selected from the group consisting of -$(CH_2)_3CH_3$, -$(CH_2)_4CH_3$, -$(CH_2)_5CH_3$, -$(CH_2)_6CH_3$ and -$(CH_2)_7CH_3$.

14. The lipid compound of claim 1, wherein

t is 1, s is 0, A_2 is a single bond, and A_1 and A_3 are each independently selected from the

group consisting of a divalent aliphatic group and a divalent heteroaliphatic group; or

t is 1, s is 0, A_2 is a single bond, and A_1 and A_3 are each independently a C_{1-6} divalent aliphatic group; or

t is 1, s is 0, A_2 is a single bond, A_1 and A_3 are each independently selected from the group consisting of $-CH_2CH_2-$ and $-CH_2CH_2CH_2-$, and

R_{2a} is selected from the group consisting of hydrogen and a monovalent aliphatic group.

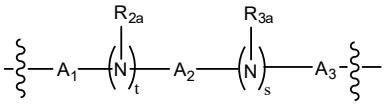
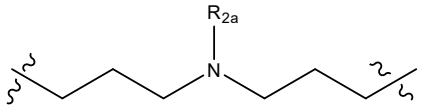
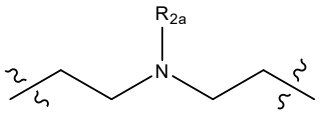
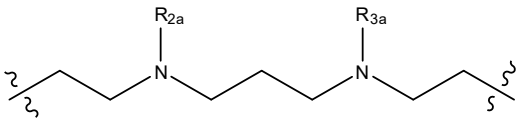
15. The lipid compound of claim 1, wherein

t is 1, s is 1, and A_1, A_2 and A_3 are each independently selected from the group consisting of a divalent aliphatic group and a divalent heteroaliphatic group; or

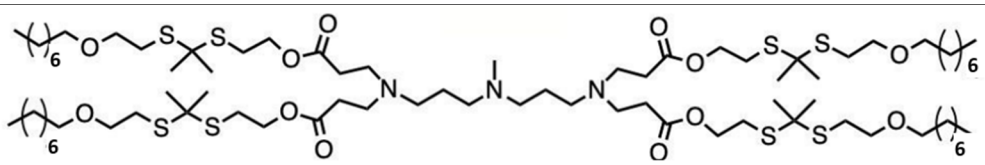
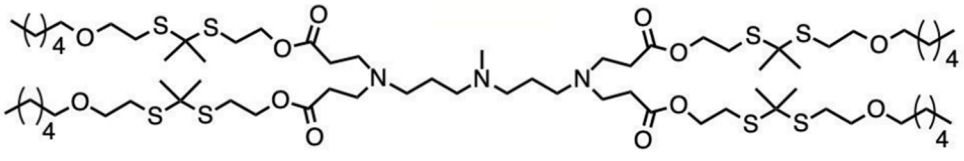
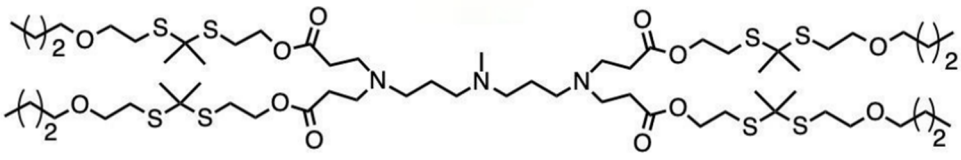
t is 1, s is 1, and A_1, A_2 and A_3 are each independently a C_{1-6} divalent aliphatic group; or

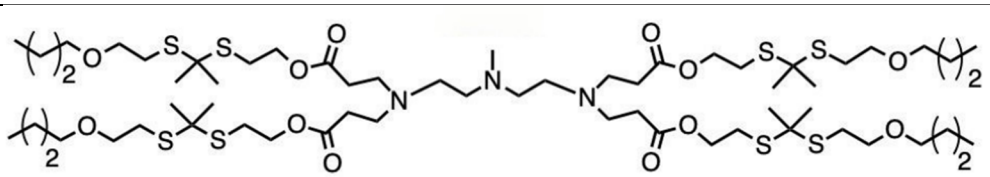
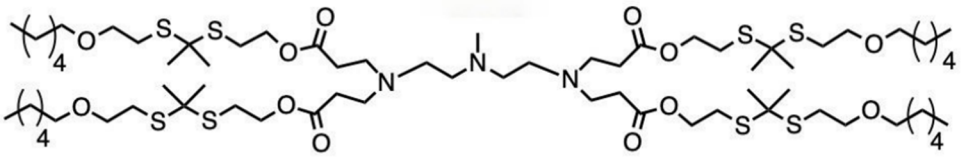
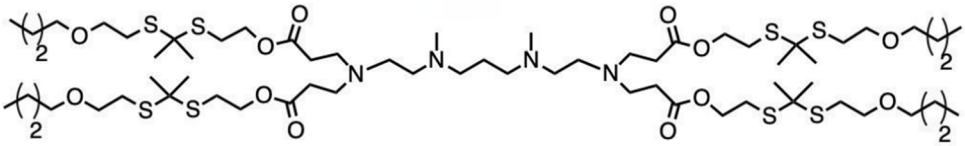
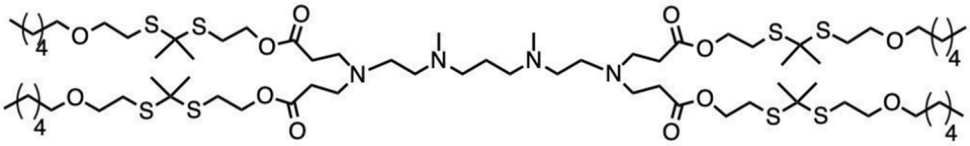
t is 1, s is 1, and A_1, A_2 and A_3 are each independently selected from the group consisting of $-CH_2CH_2-$ and $-CH_2CH_2CH_2-$, and

R_{2a} and R_{3a} are each independently selected from the group consisting of hydrogen and a monovalent aliphatic group.

16. The lipid compound of claim 1, wherein  is ,  or , wherein R_{2a} and R_{3a} are each independently selected from the group consisting of hydrogen and a monovalent aliphatic group.

17. A lipid compound selected from the group consisting of

YX17	
YX31	
YX27	

YX28	
YX35	
YX29	
YX33	

18. A pharmaceutical composition comprising a pharmaceutical carrier and a lipid nanoparticle, wherein the lipid nanoparticle comprises the lipid compound of any one of claims 1-17 and a pharmaceutically active molecule.

19. A method for regulating gene expression comprising delivering a nucleic acid to a cell, the method comprising: contacting the cell with the pharmaceutical composition of claim 18 under conditions sufficient to cause uptake of the nucleic acid into the cell.