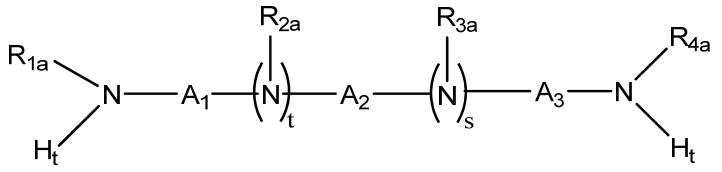
Claims

1. Use of a lipid compound of formula (I) as a drug delivery carrier for preparing a nucleic acid drug, wherein the drug delivery carrier delivers the nucleic acid drug to a target cell for the intracellular release of the nucleic acid drug in the target cell,

wherein the lipid compound of formula (I) is



(I)

wherein

R_{1a}, R_{2a}, R_{3a}, and R_{4a} are each independently hydrogen, a monovalent aliphatic group, a monovalent heteroaliphatic group, a monovalent aromatic group, a monovalent heteroaromatic group, or Ht;

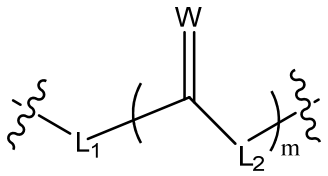
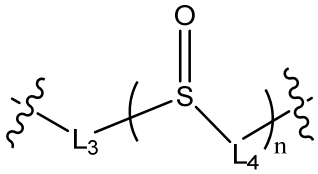
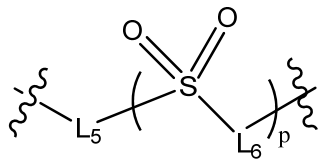
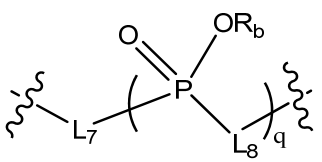
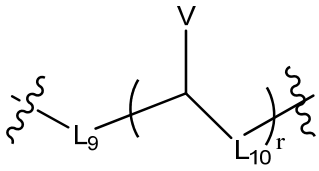
t and s are each independently 0 or 1, and when t or s is zero, it means that the part is directly a single bond;

A_1, A_2, and A_3 are each independently a single bond, a divalent aliphatic group, a divalent heteroaliphatic group, a divalent aromatic group, or a divalent heteroaromatic group, or a combination of two of the above;

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 a divalent aliphatic group, a divalent heteroaliphatic group, a divalent aromatic group, or a divalent heteroaromatic group;

each X is independently at each occurrence , , , , or ,

wherein

m, n, p, q, and r are each independently 1-6;

W is O, S, or NR_c;

L_1, L_3, L_5, L_7, and L_9 are directly connected to R_1 or R_2 and are each independently a single bond, O, S, or NR_d;

L_2, L_4, L_6, L_8, and L_{10} are each independently a bond, O, S, or NR_e;

V is an aliphatic group, OR_f, SR_g, or NR_hR_i,

wherein R_b, R_c, R_d, R_e, R_f, R_g, R_h, and R_i are each independently hydrogen, hydroxyl, an oxyaliphatic group, a monovalent aliphatic group, a monovalent heteroaliphatic group, a monovalent aromatic group, or a monovalent heteroaromatic group;

Y and Z are each independently at each occurrence S or O;

each R_2 is independently at each occurrence a single bond, a divalent aliphatic group, a divalent heteroaliphatic group, a divalent aromatic group, or a divalent heteroaromatic group;

each R_3 is independently at each occurrence a single bond, a divalent aliphatic group, a divalent heteroaliphatic group, a divalent aromatic group, or a divalent heteroaromatic group; and

each R_4 is independently at each occurrence a hydrophobic group;

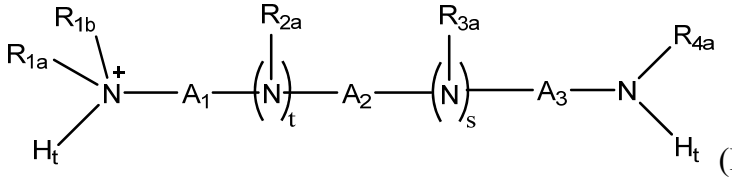
and N atoms in the backbone structure of formula (I) are optionally cationized;

provided that at least one of R_{1a} and R_{4a} is hydrogen, and

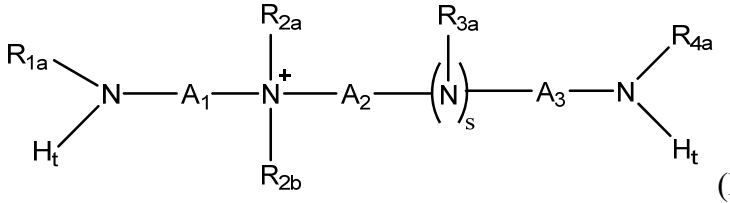
wherein the target cell is a cancer cell, a cell infected by a pathogen, or a cell mediating a disease;

wherein the nucleic acid is selected from an oligonucleotide, an aptamer, a single-stranded DNA, a double-stranded DNA, a plasmid DNA, a short isomer, an antisense molecule, a small interfering RNA (siRNA), an asymmetric interfering RNA (aiRNA), a microRNA (miRNA), a dsRNA (double-stranded RNA), an shRNA (small/short hairpin RNA), a transfer RNA (tRNA), a messenger RNA (mRNA), a small activating RNA, and a circRNA.

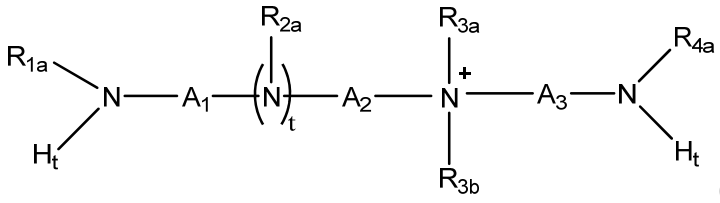
2. The use according to claim 1, wherein the lipid compound is in an ionizable form, thereby forming the following structures:

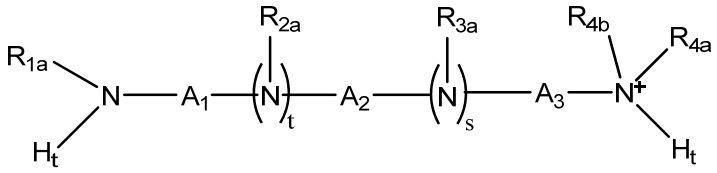


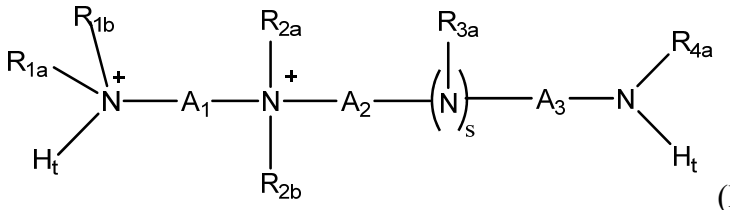
(I-1);

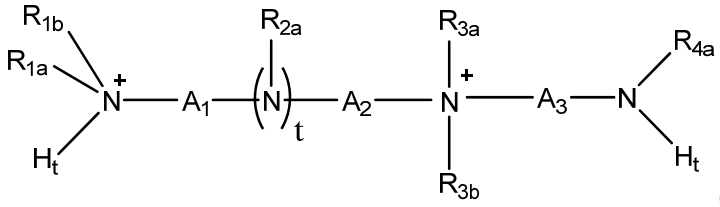


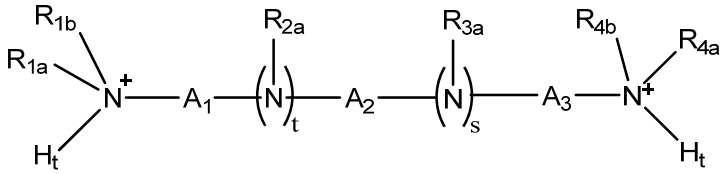
(I-2);


(I-3);


(I-4);

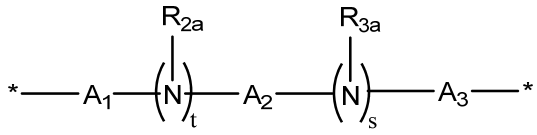

(I-5);


(I-6); and


(I-7);

and contains corresponding counter ions, wherein R_{1b}, R_{2b}, R_{3b}, and R_{4b} are each independently hydrogen, a monovalent aliphatic group, a monovalent heteroaliphatic group, a monovalent aromatic group, a monovalent heteroaromatic group, or Ht, and the remaining variables are as defined in formula (I).

3. The use according to claim 1, wherein t and s are both 0; R_{1a} is Ht and R_{4a} is hydrogen; or t and s are both 0; and R_{1a} is hydrogen and R_{4a} is Ht.

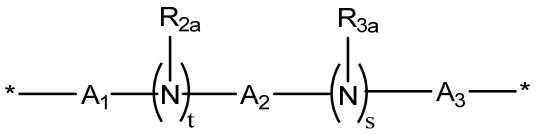
4. The use according to claim 1, wherein the fragment  is

- A_1-A_3, wherein A_1 and A_3 are each independently a C_1-C_6 divalent aliphatic group; or
- A_1-(NR_{2a})-A_3, wherein A_1 and A_3 are each independently a C_1-C_6 divalent aliphatic group, and R_{2a} is hydrogen, a monovalent aliphatic group, or a monovalent heteroaliphatic group; or

- A_1-(NR_{2a})-A_2-(NR_{2b})-A_3, wherein A_1, A_2, and A_3 are each independently a C_1-C_6 divalent aliphatic group; and R_{2a} and R_{2b} are each independently hydrogen, a monovalent aliphatic group, or a monovalent heteroaliphatic group; or
- A_1-A_2-A_3, wherein A_1 and A_3 are each independently a C_1-C_6 divalent aliphatic group; and A_2 is a divalent cyclic heteroaliphatic group;

wherein the asterisk * represents the connection of the terminal N atom in formula (I) or (I-1) to (I-7).

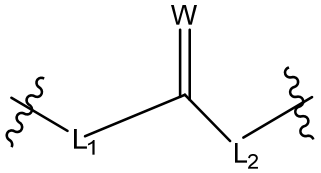
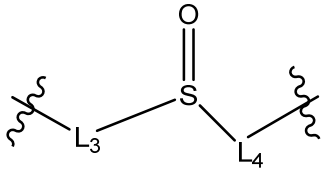
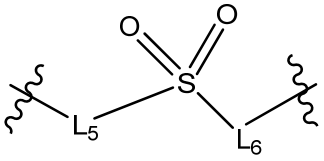
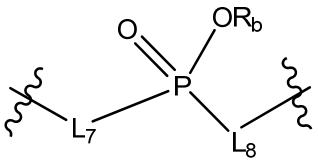
5. The use according to claim 1, wherein

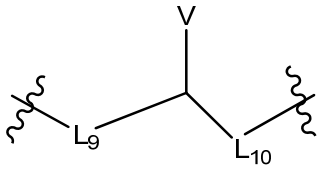
the fragment  is

- -(CH_2)$_{m1}$-, wherein m1 is an integer of 2-12; or
- -(CH_2)$_{m2}$-(NR_{2a})-(CH_2)$_{m3}$-, wherein m2 and m3 are each independently an integer of 1-6; R_{2a} is hydrogen, a monovalent C_{1-6} alkyl, amino C_{1-6} alkyl, di(C_{1-6} alkyl)aminoalkyl, mono(C_{1-6} alkyl)aminoalkyl, C_{1-6} alkoxy C_{1-6} alkyl, hydroxy C_{1-6} alkyl, C_{1-6} alkylthio C_{1-6} alkyl, or mercapto C_{1-6} alkyl; or
- -(CH_2)$_{m2}$-(NR_{2a})-(CH_2)$_{m4}$-(NR_{2b})-(CH_2)$_{m3}$, wherein m2, m3, and m4 are each independently an integer of 1-6; R_{2a} and R_{2b} are each independently hydrogen, a monovalent C_{1-6} alkyl, amino C_{1-6} alkyl, di(C_{1-6} alkyl)aminoalkyl, mono(C_{1-6} alkyl)aminoalkyl, C_{1-6} alkoxy C_{1-6} alkyl, hydroxy C_{1-6} alkyl, C_{1-6} alkylthio C_{1-6} alkyl, or mercapto C_{1-6} alkyl; or
- -(CH_2)$_{m2}$-A_2-(CH_2)$_{m3}$, wherein m2 and m3 are each independently an integer of 1-6; and A_2 is a divalent cyclic heteroaliphatic group;

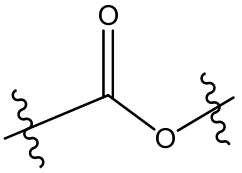
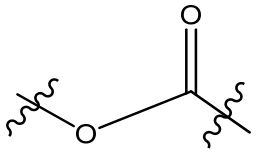
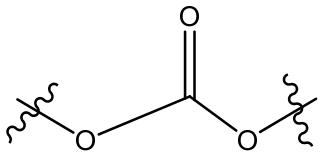
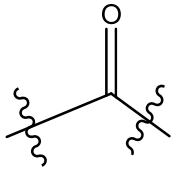
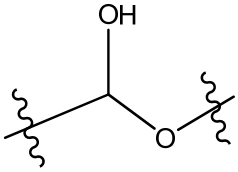
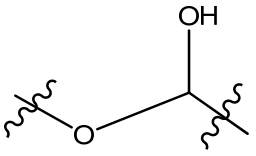
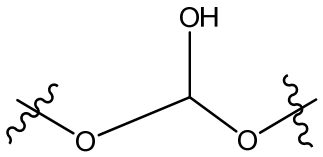
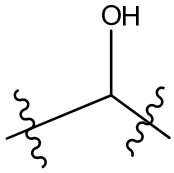
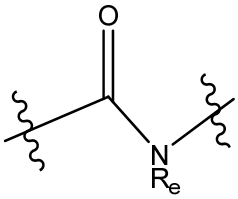
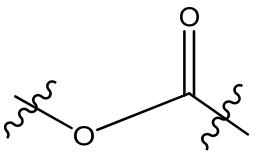
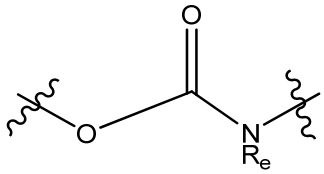
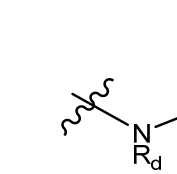
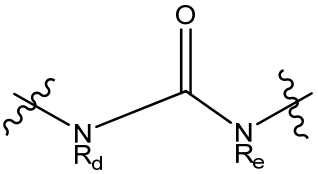
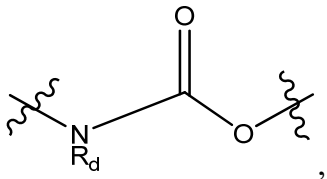
wherein the asterisk * represents the connection of the terminal N atom in formula (I) or (I-1) to (I-7).

6. The use according to claim 1, wherein R_1 is a C_{1-6} divalent aliphatic group or a C_{1-6} divalent heteroaliphatic group.

7. The use according to claim 1, wherein X is , , , , or



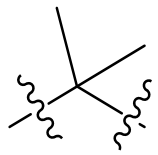
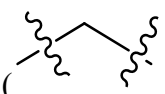
, wherein each variable is as defined in formula (I).

8. The use according to claim 1, wherein X is , , , , , , , , , , , , , , , ,  or , wherein R_d and R_e are as defined in formula (I).

9. The use according to claim 1, 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.

10. The use according to claim 1, wherein each R_2 is independently at each occurrence a single bond, or a C_{1-6} divalent aliphatic group, or a C_{1-6} divalent heteroaliphatic group.

11. The use according to claim 1, wherein each R_3 is independently at each occurrence a single bond or a C_{1-6} divalent aliphatic group.

12. The use according to claim 1, wherein each R_3 is independently at each occurrence a single bond, or , or methylene ().

13. The use according to claim 1, wherein each R_4 is independently at each occurrence a hydrophobic group selected from long-chain alkyl, alkenyl, aryl, alkylaryl, arylalkyl, arylalkenyl, a cyclic group, an alicyclic group, and a polycyclic group, and optionally having at least one

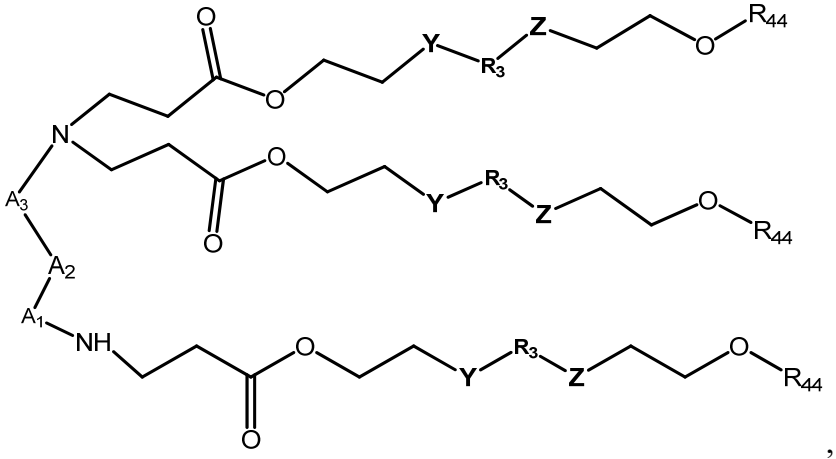
heteroatom selected from nitrogen, oxygen, and sulfur.

14. The use according to claim 1, wherein each R_4 is independently at each occurrence C_8-C_{30} alkyl, C_8-C_{30} alkenyl, or C_8-C_{30} alkynyl; or each R_4 is independently at each occurrence -$(CH_2CH_2O)_m$-C_8-C_{30} alkyl, -$(CH_2CH_2O)_y$-C_8-C_{30} alkenyl, or -$(CH_2CH_2O)_y$-C_8-C_{30} alkynyl, in which y is 0, or 1, or 2.

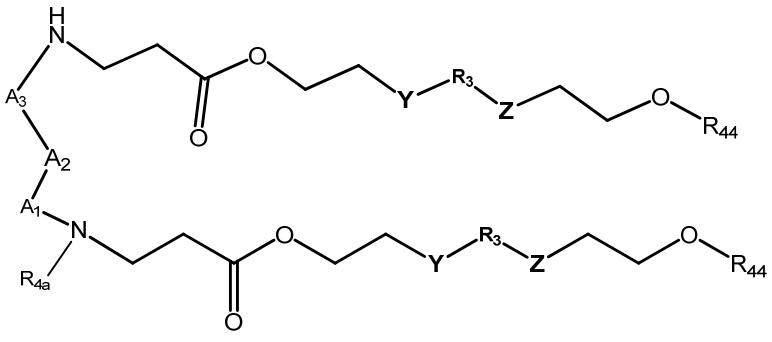
15. The use according to claim 1, wherein each R_4 is independently at each occurrence -CH_2CH_2O-C_8H_{17}, -CH_2CH_2O-$C_{10}H_{21}$, -CH_2CH_2O-$C_{12}H_{25}$, -CH_2CH_2O-$C_{14}H_{29}$, or -CH_2CH_2O-$C_{15}H_{31}$.

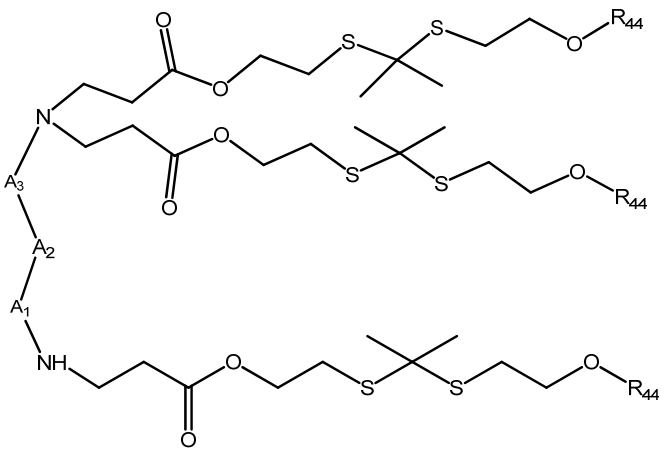
16. The use according to claim 1, wherein A_1 and A_3 are each independently a single bond or a divalent aliphatic group, and A_2 is a divalent aliphatic group or a divalent heteroaliphatic group.

17. The use according to claim 1, wherein the lipid compound of formula (I) is

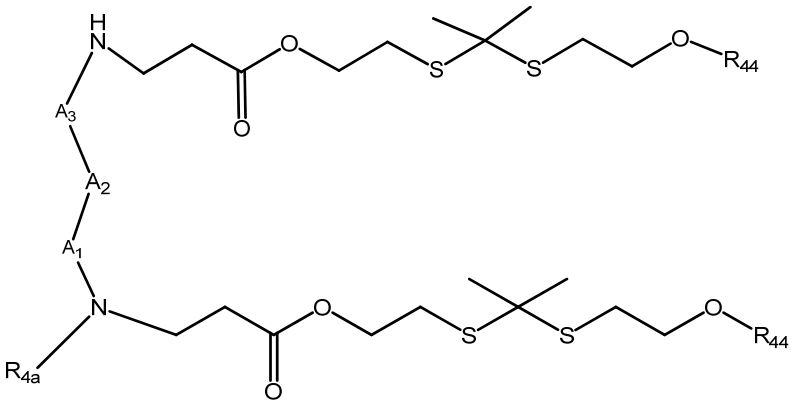


, or

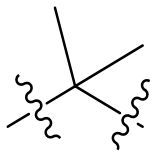
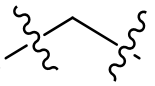




, or

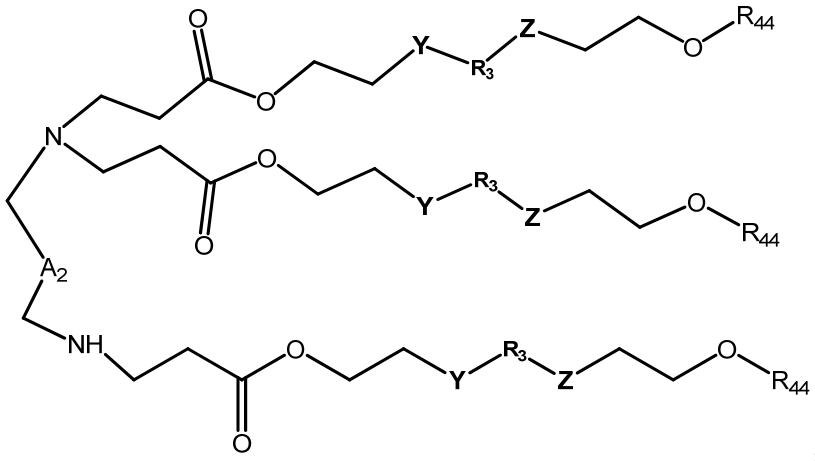


,

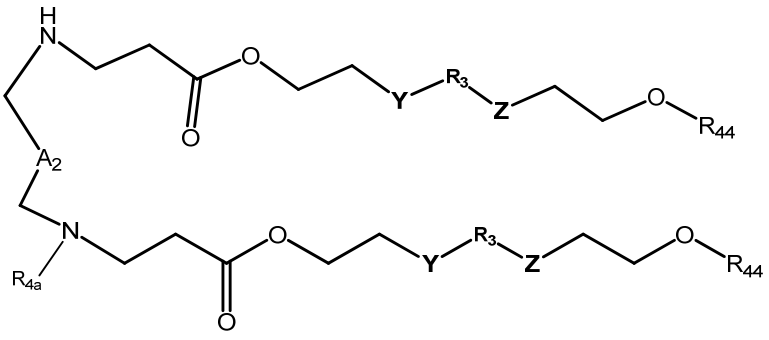
wherein A_1, A_2, A_3, and R_{4a} are as defined in formula (I), and -(CH_2CH_2O)-R_{44} is R_4 as defined in formula (I); Y and Z are both S; or Y is S and Z is O; or Y is O and Z is S; or Y and Z are both O; and each R_3 is independently at each occurrence a single bond, or , or methylene ().

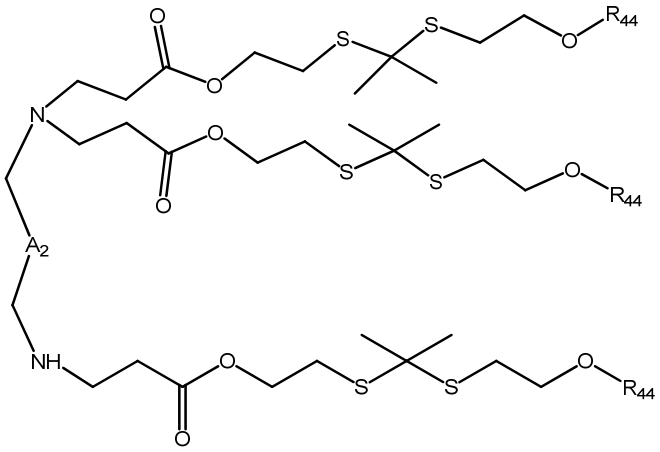
18. The use according to claim 17, wherein A_2 is a divalent cyclic heteroaliphatic group, and A_1 and A_3 are each independently C_{1-4} divalent alkyl.

19. The use according to claim 1, wherein the lipid compound of formula (I) is

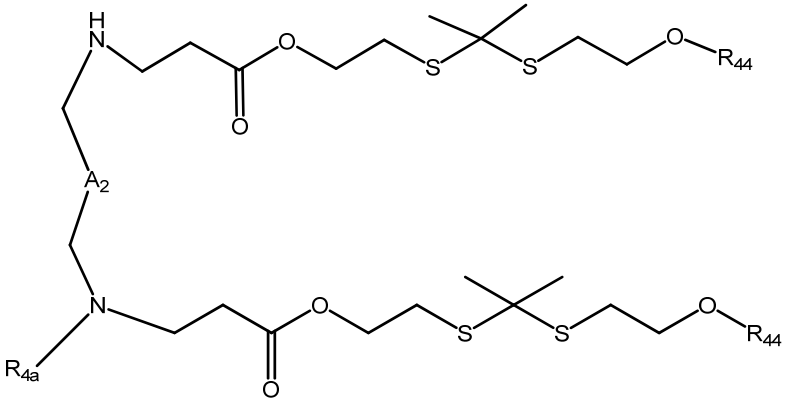


, or

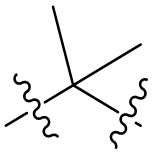
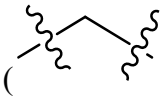




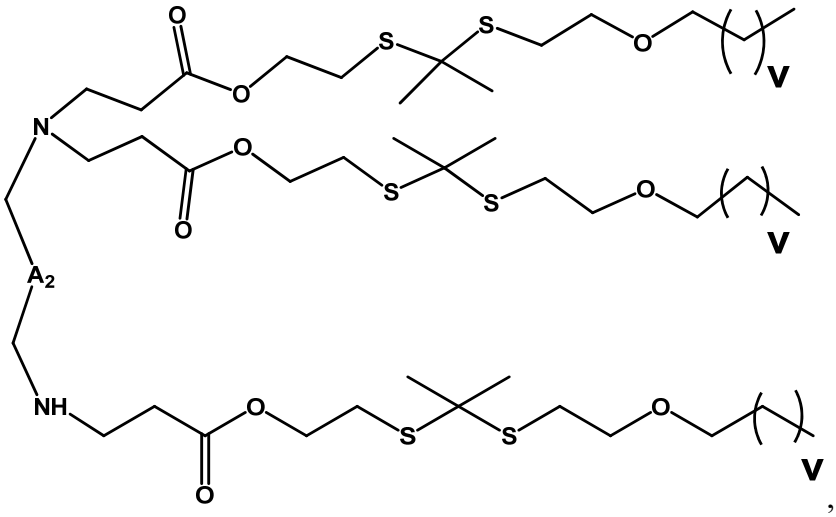
, or



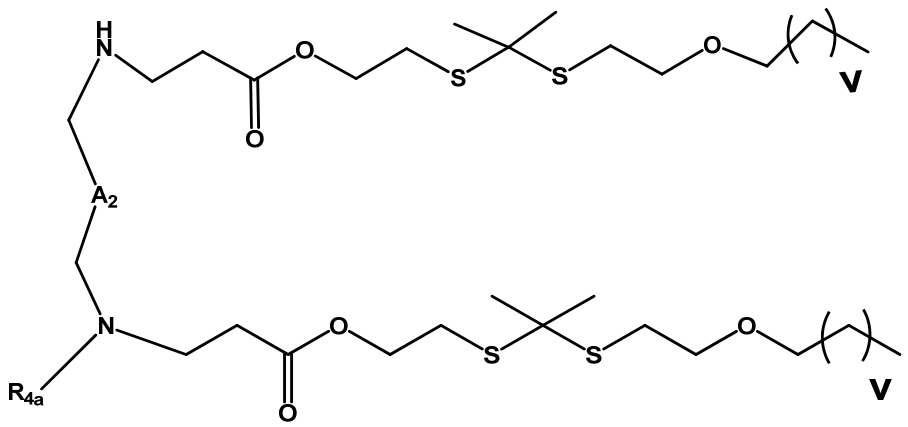
,

wherein A_2 and R_{4a} are as defined in formula (I), and -(CH_2CH_2O)-R_{44} is R_4 as defined in formula (I); 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; and each R_3 is independently at each occurrence a single bond, or , or methylene ().

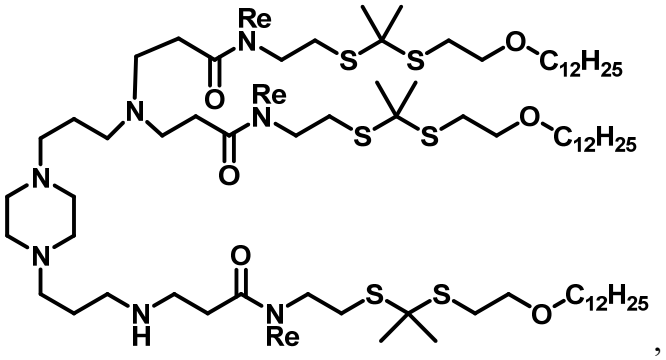
20. The use according to claim 1, wherein the lipid compound is



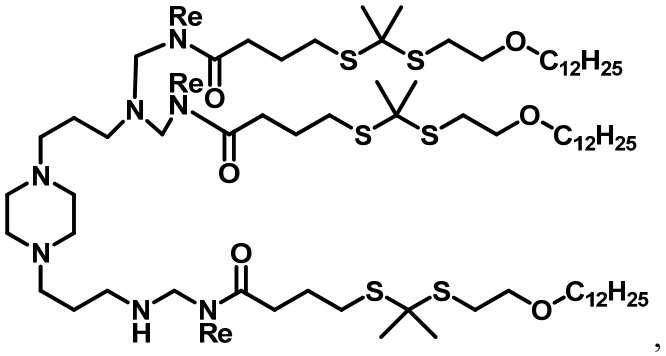
, or



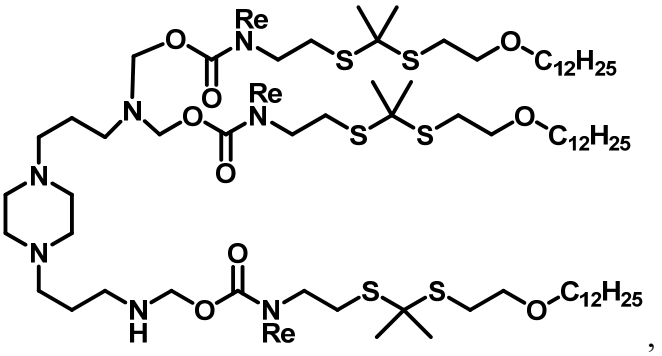
wherein v is 6-28; and A_2 and R_{4a} are as defined in formula (I); or



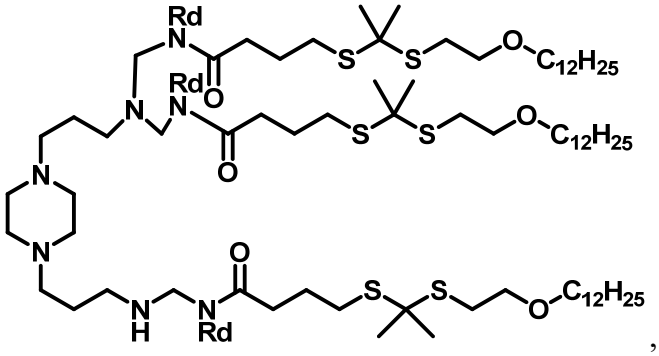
,

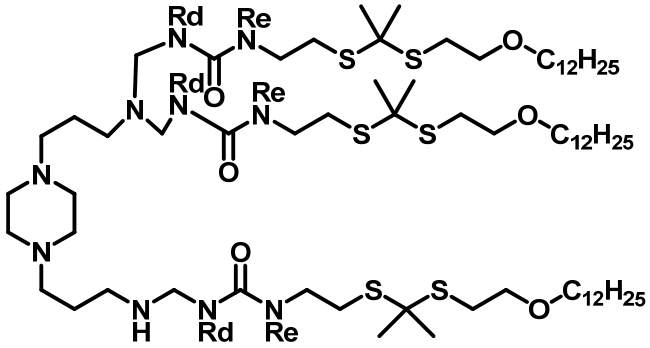


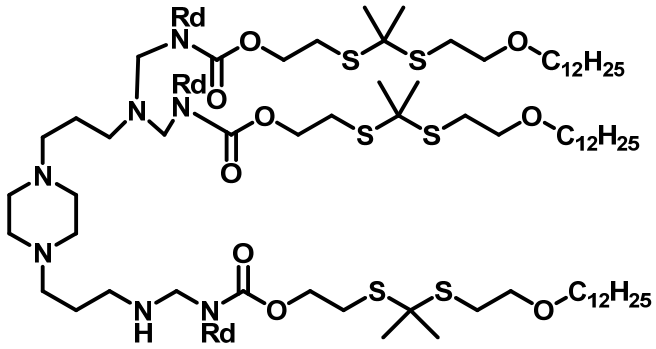
,



,

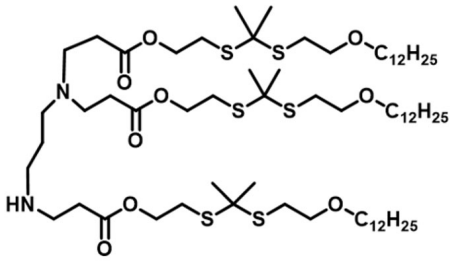

,

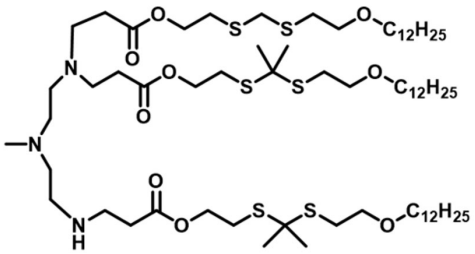

, or

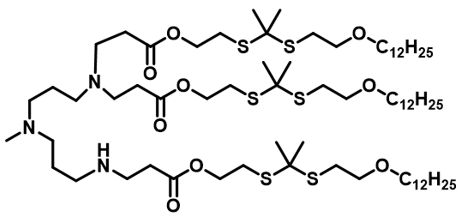


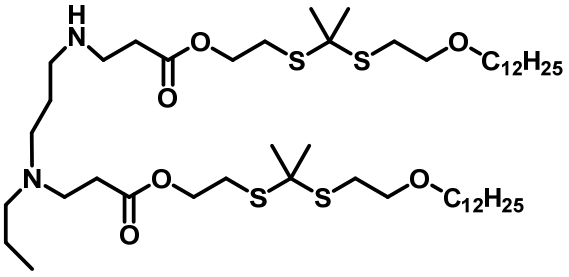
wherein R_d and R_e are as defined in formula (I).

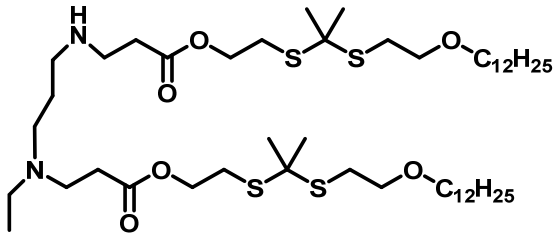
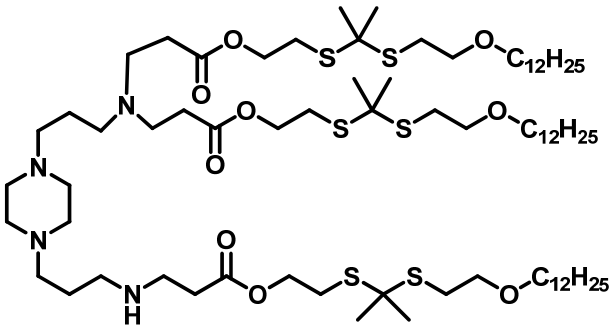
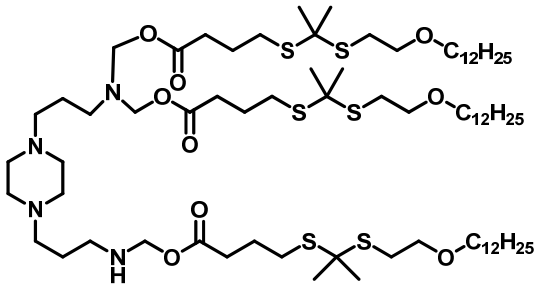
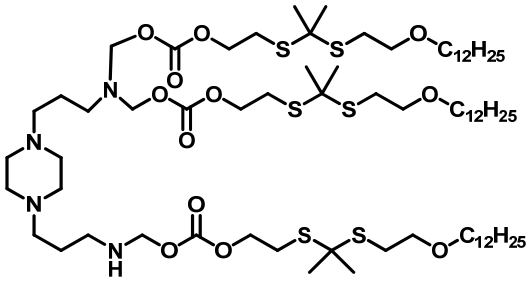
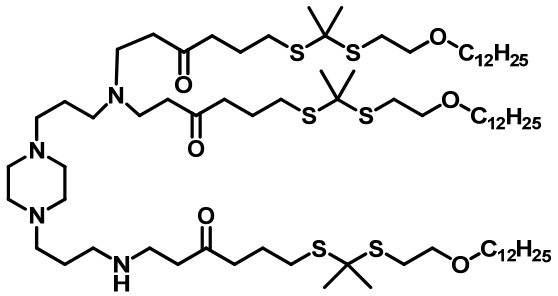
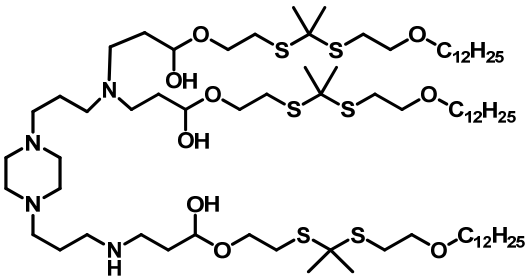
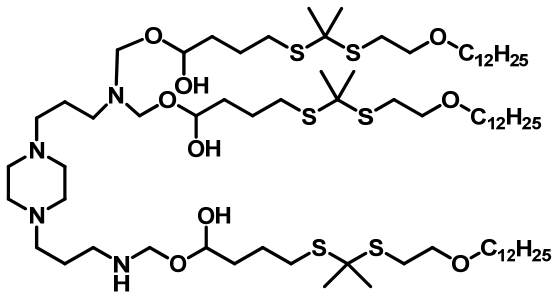
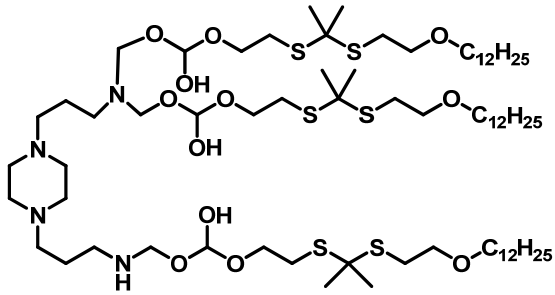
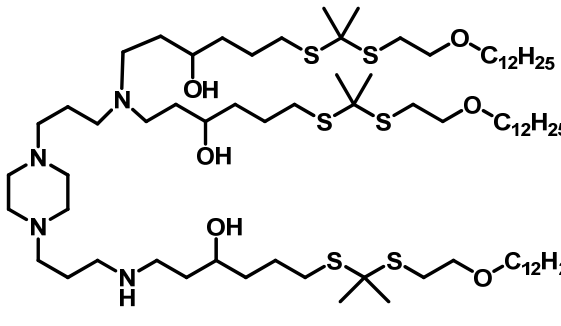
21. The use according to claim 1, wherein the lipid compound is


;


;

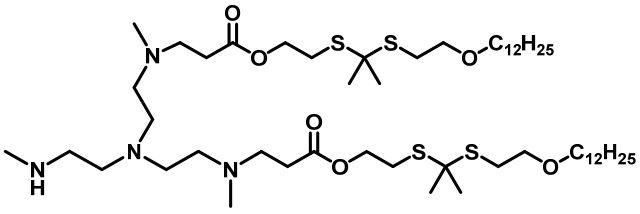
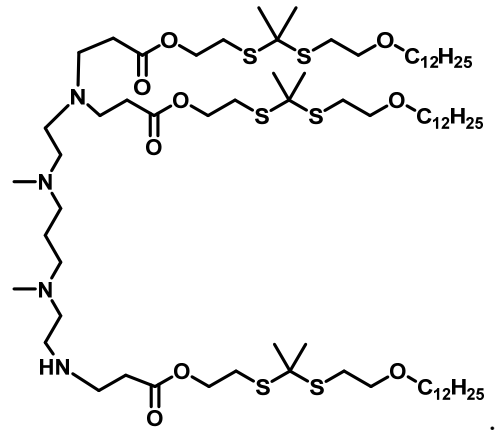

;


;


;

;

;

;

;

;

;

;

;

;

;


; or 
.