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POBOLJŠANE LIPIDNE NANOČESTICE ZA ISPORUKU NUKLEINSKIH KISELINA

HR P20241255 T1

PATENTNI ZAHTJEVI

1. Lipidne nanočestice (LNP-ovi) za uporabu u postupku liječenja ili prevencije bolesti kod primata kojima je to potrebno, pri čemu postupak sadrži davanje LNP-ova primatu, pri čemu svaki od LNP-ova sadrži:

- i) nukleinsku kiselinu, ili njenu farmaceutski prihvatljivu sol, inkapsuliranu unutar LNP;
- ii) kationski lipid;
- iii) neutralni lipid;
- iv) steroid; i
- v) polimerno-konjugirani lipid,

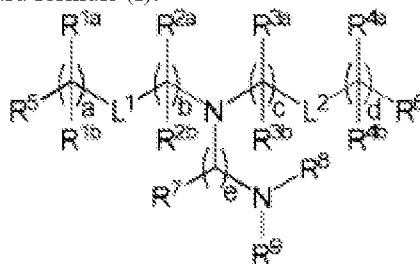
pri čemu se srednji promjer čestica LNP-ova kreće od 40 nm do 68 nm kako je određeno kvazi-elastičnim svjetlom raspršivanja.

2. LNP-ovi za uporabu prema zahtjevu 1, naznačen time što je srednji promjer čestice u rasponu od 50 nm do 68 nm, od 55 nm do 65 nm, od 50 nm do 60 nm ili od 60 nm do 68 nm.

3. LNP-ovi za uporabu prema zahtjevu 1, naznačen time što je srednji promjer čestice oko 47 nm, oko 48 nm, oko 49 nm, oko 50 nm, oko 51 nm, oko 52 nm, oko 53 nm, oko 54 nm, oko 55 nm, oko 56 nm, oko 57 nm, oko 58 nm, oko 59 nm, oko 60 nm, oko 61 nm, oko 62 nm, oko 63 nm, oko 64 nm ili oko 65 nm.

4. LNP-ovi za uporabu prema bilo kojem od zahtjeva 1-3, naznačen time što:

- i) kationski lipid ima strukturu formule (I):



(I)

ili njegova farmaceutski prihvatljiva sol, tautomer ili stereoisomer, naznačen time što:

jedan od L¹ ili L² je -O(C=O)-, -(C=O)O-, -C(=O)-, -O-, -S(O)_x-, -S-S-, -C(=O)S-, SC(=O)-, -NR^aC(=O)-, -C(=O)NR^a-, NR^aC(=O)NR^a-, -OC(=O)NR^a- ili -NR^aC(=O)O-, i drugi od L¹ ili L² je -O(C=O)-, -(C=O)O-, -C(=O)-, -O-, -S(O)_x-, -S-S-, -C(=O)S-, SC(=O)-, -NR^aC(=O)-, -C(=O)NR^a-, NR^aC(=O)NR^a-, -OC(=O)NR^a- ili -NR^aC(=O)O- ili izravna veza;

R^a je H ili C₁-C₁₂ alkil;

R^{1a} i R^{1b} su, pri svakom pojavljivanju, neovisno ili (a) H ili C₁-C₁₂ alkil, ili (b) R^{1a} je H ili C₁-C₁₂ alkil, i R^{1b} zajedno s atomom ugljika na koji je vezan uzet je zajedno sa susjednim R^{1b} i atom ugljika na koji je vezan tvore dvostruku vezu ugljik-ugljik;

R^{2a} i R^{2b} su, pri svakom pojavljivanju, neovisno ili (a) H ili C₁-C₁₂ alkil, ili (b) R^{2a} je H ili C₁-C₁₂ alkil, i R^{2b} zajedno s atomom ugljika na koji je vezan uzet je zajedno sa susjednim R^{2b} i atom ugljika na koji je vezan tvore dvostruku vezu ugljik-ugljik;

R^{3a} i R^{3b} su, pri svakom pojavljivanju, neovisno ili (a) H ili C₁-C₁₂ alkil, ili (b) R^{3a} je H ili C₁-C₁₂ alkil, i R^{3b} zajedno s atomom ugljika na koji je vezan uzet je zajedno sa susjednim R^{3b} i atom ugljika na koji je vezan tvore dvostruku vezu ugljik-ugljik;

R^{4a} i R^{4b} su, pri svakom pojavljivanju, neovisno ili (a) H ili C₁-C₁₂ alkil, ili (b) R^{4a} je H ili C₁-C₁₂ alkil, i R^{4b} zajedno s atomom ugljika na koji je vezan uzet je zajedno sa susjednim R^{4b} i atom ugljika na koji je vezan tvore dvostruku vezu ugljik-ugljik;

R⁵ i R⁶ su svaki neovisno metil ili cikloalkil;

R⁷ je, pri svakom pojavljivanju, neovisno H ili C₁-C₁₂ alkil;

R⁸ i R⁹ su svaki neovisno nesupstituirani C₁-C₁₂ alkil; ili R⁸ i R⁹, zajedno s atomom dušika na koji su vezani, tvore 5, 6 ili 7-člani heterociklički prsten koji sadrži jedan atom dušika;

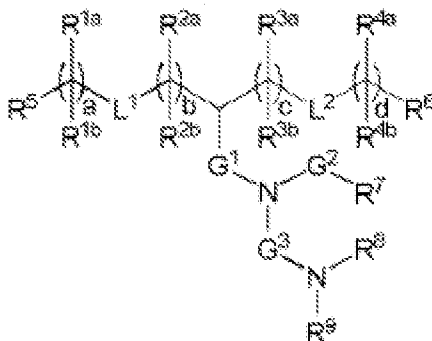
a i d su svaki neovisno cijeli broj od 0 do 24;

b i c su svaki neovisno cijeli broj od 1 do 24;

e je 1 ili 2; i

x je 0, 1 ili 2; ili

- ii) kationski lipid ima strukturu formule (II):



(II)

ili njegova farmaceutski prihvatljiva sol, tautomer ili stereoisomer, naznačen time što:

jedan od L^1 ili L^2 je $-O(C=O)-$, $-(C=O)O-$, $-C(=O)-$, $-O-$, $-S(O)_x-$, $-S-S-$, $-C(=O)S-$, $SC(=O)-$, $-NR^aC(=O)-$, $-C(=O)NR^a$, $NR^aC(=O)NR^a$, $-OC(=O)NR^a$ ili $-NR^aC(=O)O-$, i drugi od L^1 ili L^2 je $-O(C=O)-$, $-(C=O)O-$, $-C(=O)-$, $-O-$, $-S(O)_x-$, $-S-S-$, $-C(=O)S-$, $SC(=O)-$, $-NR^aC(=O)-$, $-C(=O)NR^a$, $NR^aC(=O)NR^a$, $-OC(=O)NR^a$ ili $-NR^aC(=O)O-$ ili izravna veza;

G^1 je C_1-C_2 alkilen, $-(C=O)-$, $-O(C=O)-$, $-SC(=O)-$, $-NR^aC(=O)-$ ili izravna veza;

G^2 je $-C(=O)-$, $-(C=O)O-$, $-C(=O)S-$, $-C(=O)NR^a$ ili izravna veza;

G^3 je C_1-C_6 alkilen;

R^a je H ili C_1-C_{12} alkil;

R^{1a} i R^{1b} su, pri svakom pojavljivanju, neovisno ili (a) H ili C_1-C_{12} alkil, ili (b) R^{1a} je H ili C_1-C_{12} alkil, i R^{1b} zajedno s atomom ugljika na koji je vezan uzet je zajedno sa susjednim R^{1b} i atom ugljika na koji je vezan tvore dvostruku vezu ugljik-ugljik;

R^{2a} i R^{2b} su, pri svakom pojavljivanju, neovisno ili (a) H ili C_1-C_{12} alkil, ili (b) R^{2a} je H ili C_1-C_{12} alkil, i R^{2b} zajedno s atomom ugljika na koji je vezan uzet je zajedno sa susjednim R^{2b} i atom ugljika na koji je vezan tvore dvostruku vezu ugljik-ugljik;

R^{3a} i R^{3b} su, pri svakom pojavljivanju, neovisno ili (a) H ili C_1-C_{12} alkil, ili (b) R^{3a} je H ili C_1-C_{12} alkil, i R^{3b} zajedno s atomom ugljika na koji je vezan uzet je zajedno sa susjednim R^{3b} i atom ugljika na koji je vezan tvore dvostruku vezu ugljik-ugljik;

R^{4a} i R^{4b} su, pri svakom pojavljivanju, neovisno ili (a) H ili C_1-C_{12} alkil, ili (b) R^{4a} je H ili C_1-C_{12} alkil, i R^{4b} zajedno s atomom ugljika na koji je vezan uzet je zajedno sa susjednim R^{4b} i atom ugljika na koji je vezan tvore dvostruku vezu ugljik-ugljik;

R^5 i R^6 su svaki neovisno H ili metil;

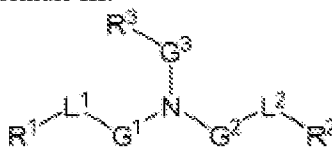
R^7 je C_4-C_{20} alkil;

R^8 i R^9 su svaki neovisno C_1-C_{12} alkil; ili R^8 i R^9 , zajedno s atomom dušika na koji su vezani, tvore 5, 6 ili 7-člani heterociklički prsten;

a, b, c i d su svaki neovisno cijeli broj od 1 do 24; i

x je 0, 1 ili 2; ili

iii) kationski lipid ima strukturu formule III:



(III)

ili njegova farmaceutski prihvatljiva sol ili stereoisomer, gdje:

jedan od L^1 ili L^2 je $-O(C=O)-$, $-(C=O)O-$, $-C(=O)-$, $-O-$, $-S(O)_x-$, $-S-S-$, $-C(=O)S-$, $SC(=O)-$, $-NR^aC(=O)-$, $-C(=O)NR^a$, $NR^aC(=O)NR^a$, $-OC(=O)NR^a$ ili $-NR^aC(=O)O-$, i drugi od L^1 ili L^2 je $-O(C=O)-$, $-(C=O)O-$, $-C(=O)-$, $-O-$, $-S(O)_x-$, $-S-S-$, $-C(=O)S-$, $SC(=O)-$, $-NR^aC(=O)-$, $-C(=O)NR^a$, $NR^aC(=O)NR^a$, $-OC(=O)NR^a$ ili $-NR^aC(=O)O-$ ili izravna veza;

G^1 i G^2 su svaki neovisno nesupstituirani C_1-C_{12} alkilen ili C_1-C_{12} alkenilen;

G^3 je C_1-C_{24} alkilen, C_1-C_{24} alkenilen, C_3-C_8 cikloalkilen, C_3-C_8 cikloalkenilen;

R^a je H ili C_1-C_{12} alkil;

R^1 i R^2 su svaki neovisno C_6-C_{24} alkil ili C_6-C_{24} alkenil;

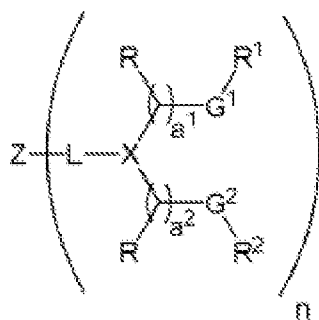
R^3 je H, OR^5 , CN, $-C(=O)OR^4$, $-OC(=O)R^4$ ili $-NR^5C(=O)R^4$;

R^4 je C_1-C_{12} alkil;

R^5 je H ili C_1-C_6 alkil; i

x je 0, 1 ili 2; ili

iv) kationski lipid ima sljedeću formulu (IV):



(IV)

ili njegova farmaceutski prihvatljiva sol ili stereoisomer, naznačen time što:

jedan od G^1 ili G^2 je, pri svakom pojavljivanju, $-O(C=O)-$, $-(C=O)O-$, $-C(=O)-$, $-O-$, $-S(O)_y-$, $-S-S-$, $-C(=O)S-$, $SC(=O)-$, $-N(R^a)C(=O)-$, $-C(=O)N(R^a)-$, $-N(R^a)C(=O)N(R^a)-$, $-OC(=O)N(R^a)-$ ili $-N(R^a)C(=O)O-$, i drugi od G^1 ili G^2 je, pri svakom pojavljivanju, $-O(C=O)-$, $-(C=O)O-$, $-C(=O)-$, $-O-$, $-S(O)_y-$, $-S-S-$, $-C(=O)S-$, $SC(=O)-$, $-N(R^a)C(=O)-$, $-C(=O)N(R^a)-$, $-N(R^a)C(=O)N(R^a)-$, $-OC(=O)N(R^a)-$ ili $-N(R^a)C(=O)O-$ ili izravna veza;

L je, pri svakom pojavljivanju, $\sim O(C=O)-$, pri čemu \sim predstavlja kovalentnu vezu s X;

X je CR^a ;

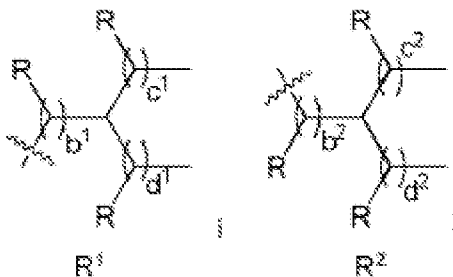
Z je alkil, cikloalkil ili monovalentna skupina koja sadrži najmanje jednu polarnu funkcionalnu skupinu kada je n 1; ili

Z je alkilen, cikloalkilen ili polivalentna skupina koja sadrži najmanje jednu polarnu funkcionalnu skupinu kada je n veći od 1;

R^a je, pri svakom pojavljivanju, neovisno H, C_1 - C_{12} alkil, C_1 - C_{12} hidroksilalkil, C_1 - C_{12} aminoalkil, C_1 - C_{12} alkilaminilalkil, C_1 - C_{12} alkoksialkil, C_1 - C_{12} alkoksikarbonil, C_1 - C_{12} alkilkarboniloksi, C_1 - C_{12} alkilkarboniloksialkil ili C_1 - C_{12} alkilkarbonil;

R je, pri svakom pojavljivanju, neovisno ili: (a) H ili C_1 - C_{12} alkil; ili (b) R zajedno s atomom ugljika na koji je vezan uzet je zajedno sa susjednim R i atomom ugljika na koji je vezan da tvori dvostruku vezu ugljik-ugljik;

R^1 i R^2 imaju, pri svakom pojavljivanju, sljedeću strukturu, respektivno:



a^1 i a^2 su, pri svakom pojavljivanju, neovisno cijeli broj od 3 do 12;

b^1 i b^2 su, pri svakom pojavljivanju, neovisno 0 ili 1;

c^1 i c^2 su, pri svakom pojavljivanju, neovisno cijeli broj od 5 do 10;

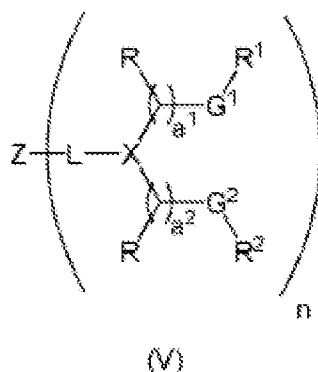
d^1 i d^2 su, pri svakom pojavljivanju, neovisno cijeli broj od 5 do 10;

y je, pri svakom pojavljivanju, neovisno cijeli broj od 0 do 2; i

n je cijeli broj od 1 do 6,

pri čemu je svaki alkil, alkilen, hidroksilalkil, aminoalkil, alkilaminilalkil, alkoksialkil, alkoksikarbonil, alkilkarboniloksi, alkilkarboniloksialkil i alkilkarbonil izborno supstituiran s jednim ili više supstituenata; ili

v) kationski lipid ima sljedeću formulu (V):



ili njegova farmaceutski prihvatljiva sol ili stereoizomer, pri čemu:

jedan od G^1 ili G^2 je, pri svakom pojavljivanju, $-O(C=O)-$, $-(C=O)O-$, $-C(=O)-$, $-O-$, $-S(O)_y-$, $-S-S-$, $-C(=O)S-$, $SC(=O)-$, $-N(R^a)C(=O)-$, $-C(=O)N(R^a)-$, $-N(R^a)C(=O)N(R^a)-$, $-OC(=O)N(R^a)-$ ili $-N(R^a)C(=O)O-$, i drugi od G^1 ili G^2 je, pri svakom pojavljivanju, $-O(C=O)-$, $-(C=O)O-$, $-C(=O)-$, $-O-$, $-S(O)_y-$, $-S-S-$, $-C(=O)S-$, $SC(=O)-$, $-N(R^a)C(=O)-$, $-C(=O)N(R^a)-$, $-N(R^a)C(=O)N(R^a)-$, $-OC(=O)N(R^a)-$ ili $-N(R^a)C(=O)O-$ ili izravna veza;

L je, pri svakom pojavljivanju, $\sim O(C=O)-$, gdje \sim predstavlja kovalentnu vezu s X;

X je CR^a ;

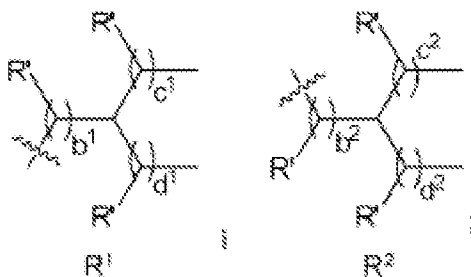
Z je alkil, cikloalkil ili monovalentna skupina koja sadrži najmanje jednu polarnu funkcionalnu skupinu kada je n 1; ili

Z je alken, cikloalkilen ili polivalentna skupina koja sadrži najmanje jednu polarnu funkcionalnu skupinu kada je n veći od 1;

R^a je, pri svakom pojavljivanju, neovisno H, C_1-C_{12} alkil, C_1-C_{12} hidroksilalkil, C_1-C_{12} aminoalkil, C_1-C_{12} alkilaminilalkil, C_1-C_{12} alkoksialkil, C_1-C_{12} alkoksikarbonil, C_1-C_{12} alkilkarboniloksi, C_1-C_{12} alkilkarboniloksialkil ili C_1-C_{12} alkilkarbonil;

R je, pri svakom pojavljivanju, neovisno ili: (a) H ili C_1-C_{12} alkil; ili (b) R zajedno s atomom ugljika na koji je vezan uzet je zajedno sa susjednim R i atomom ugljika na koji je vezan da tvori dvostruku vezu ugljik-ugljik;

R^1 i R^2 imaju, pri svakom pojavljivanju, sljedeću strukturu, respektivno:



R^1 je, pri svakom pojavljivanju, neovisno H ili C_1-C_{12} alkil;

a^1 i a^2 su, pri svakom pojavljivanju, neovisno cijeli broj od 3 do 12;

b^1 i b^2 su, pri svakom pojavljivanju, neovisno 0 ili 1;

c^1 i c^2 su, pri svakom pojavljivanju, neovisno cijeli broj od 2 do 12;

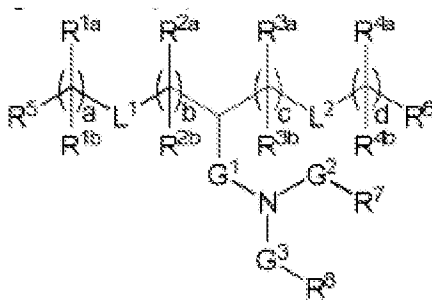
d^1 i d^2 su, pri svakom pojavljivanju, neovisno cijeli broj od 2 do 12;

y je, pri svakom pojavljivanju, neovisno cijeli broj od 0 do 2; i

n je cijeli broj od 1 do 6,

pri čemu su a^1 , a^2 , c^1 , c^2 , d^1 i d^2 odabrani tako da je zbroj $a^1+c^1+d^1$ cijeli broj od 18 do 30, i zbroj $a^1+c^1+d^1$ je cijeli broj od 18 do 30, i gdje je svaki alkil, alken, hidroksilalkil, aminoalkil, alkilaminilalkil, alkoksialkil, alkoksikarbonil, alkilkarboniloksi, alkilkarboniloksialkil i alkilkarbonil izborno supstituiran s jednim ili više supstituenata; ili

vi) kationski lipid ima sljedeću formulu (VI):



(VI)

ili njegova farmaceutski prihvatljiva sol, tautomer ili stereoizomer, pri čemu:

L¹ i L² su svaki neovisno -O(C=O)-, -(C=O)O-, -C(=O)-, -O-, -S(O)_x, -S-S-, -C(=O)S-, -SC(=O)-, -NR^aC(=O)-, -C(=O)NR^a, -NR^aC(=O)NR^a, -OC(=O)NR^a, -NR^aC(=O)O- ili izravna veza;

G¹ je C₁-C₂ alkilen, -(C=O)-, -O(C=O)-, -SC(=O)-, -NR^aC(=O)- ili izravna veza;

G² je -C(=O)-, -(C=O)O-, -C(=O)S-, -C(=O)NR^a- ili izravna veza;

G³ je C₁-C₆ alkilen;

R^a je H ili C₁-C₁₂ alkil;

R^{1a} i R^{1b} su, pri svakom pojavljivanju, neovisno ili (a) H ili C₁-C₁₂ alkil, ili (b) R^{1a} je H ili C₁-C₁₂ alkil, i R^{1b} zajedno s atomom ugljika na koji je vezan uzet je zajedno sa susjednim R^{1b} i atom ugljika na koji je vezan tvore dvostruku vezu ugljik-ugljik;

R^{2a} i R^{2b} su, pri svakom pojavljivanju, neovisno ili (a) H ili C₁-C₁₂ alkil, ili (b) R^{2a} je H ili C₁-C₁₂ alkil, i R^{2b} zajedno s atomom ugljika na koji je vezan uzet je zajedno sa susjednim R^{2b} i atom ugljika na koji je vezan tvore dvostruku vezu ugljik-ugljik;

R^{3a} i R^{3b} su, pri svakom pojavljivanju, neovisno ili (a) H ili C₁-C₁₂ alkil, ili (b) R^{3a} je H ili C₁-C₁₂ alkil, i R^{3b} zajedno s atomom ugljika na koji je vezan uzet je zajedno sa susjednim R^{3b} i atom ugljika na koji je vezan tvore dvostruku vezu ugljik-ugljik;

R^{4a} i R^{4b} su, pri svakom pojavljivanju, neovisno ili (a) H ili C₁-C₁₂ alkil, ili (b) R^{4a} je H ili C₁-C₁₂ alkil, i R^{4b} zajedno s atomom ugljika na koji je vezan uzet je zajedno sa susjednim R^{4b} i atom ugljika na koji je vezan tvore dvostruku vezu ugljik-ugljik;

R⁵ i R⁶ su svaki neovisno H ili metil;

R⁷ je H ili C₁-C₂₀ alkil;

R⁸ je OH, -N(R⁹)(C=O)R¹⁰, -(C=O)NR⁹R¹⁰, -NR⁹R¹⁰, -(C=O)OR¹¹ ili -O(C=O)R¹¹, pod uvjetom da je G³ C₄-C₆ alkilen kada je R⁸ -NR⁹R¹⁰,

R⁹ i R¹⁰ su svaki neovisno H ili C₁-C₁₂ alkil;

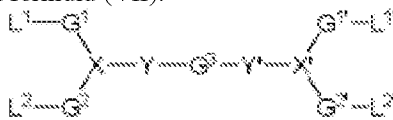
R¹¹ je aralkil;

a, b, c i d su svaki neovisno cijeli broj od 1 do 24; i

x je 0, 1 ili 2,

pri čemu je svaki alkil, alkilen i aralkil izborno supstituiran; ili

vii) kationski lipid ima sljedeću formulu (VII):



(VII)

ili njegova farmaceutski prihvatljiva sol ili stereoizomer, pri čemu:

X i X' su svaki neovisno N ili CR;

Y i Y' su svaki neovisno odsutni, -O(C=O)-, -(C=O)O- ili NR, pod uvjetom da:

- Y je odsutan kada X je N;
- Y' je odsutan kada X' je N;
- Y je -O(C=O)-, -(C=O)O- ili NR kada X je CR; i
- Y' je -O(C=O)-, -(C=O)O- ili NR kada X' je CR,

L¹ i L^{1'} su svaki neovisno -O(C=O)R¹, -(C=O)OR¹, -C(=O)R¹, -OR¹, -S(O)_zR¹, -S-SR¹, -C(=O)SR¹, -SC(=O)R¹, -NR^aC(=O)R¹, -C(=O)NR^bR^c, -NR^aC(=O)NR^bR^c, -OC(=O)NR^bR^c ili -NR^aC(=O)OR¹;

L² i L^{2'} su svaki neovisno -O(C=O)R², -(C=O)OR², -C(=O)R², -OR², -S(O)_zR², -S-SR², -C(=O)SR², -SC(=O)R², -NR^dC(=O)R², -C(=O)NR^eR^f, -NR^dC(=O)NR^eR^f, -OC(=O)NR^eR^f; -NR^dC(=O)OR² ili izravna veza na R²;

G¹, G^{1'}, G² i G^{2'} su svaki neovisno C₂-C₁₂ alkilen ili C₂-C₁₂ alkenilen;

G³ je C₂-C₂₄ heteroalkilen ili C₂-C₂₄ heteroalkenilen;

R^a, R^b, R^d i R^e su, pri svakom pojavljivanju, neovisno H, C₂-C₁₂ alkil ili C₂-C₁₂ alkenil;

R^c i R^f su, pri svakom pojavljivanju, neovisno C₁-C₁₂ alkil ili C₂-C₁₂ alkenil;

G^2 je $-\text{CH}_2-$ ili $-(\text{C}=\text{O})-$;

R je, pri svakom pojavljivanju, neovisno H ili OH;

R^1 i R^2 su svaki neovisno izborno supstituirani razgranati, zasićeni ili nezasićeni C_{12} - C_{36} alkil;

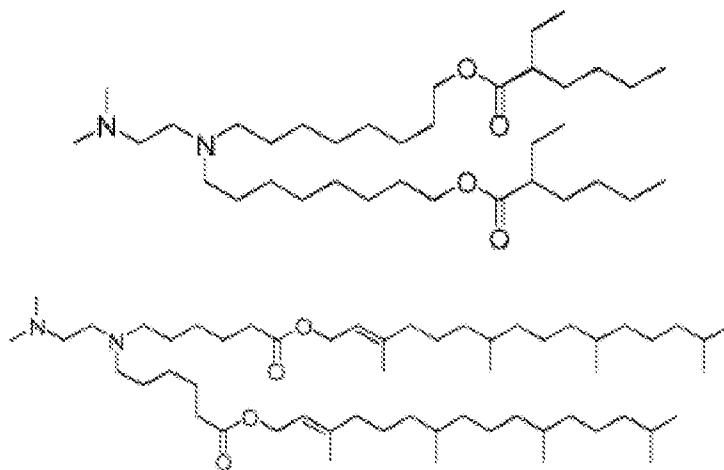
R^3 i R^4 su svaki neovisno H ili izborno supstituirani ravni ili razgranati, zasićeni ili nezasićeni C_1 - C_6 alkil;

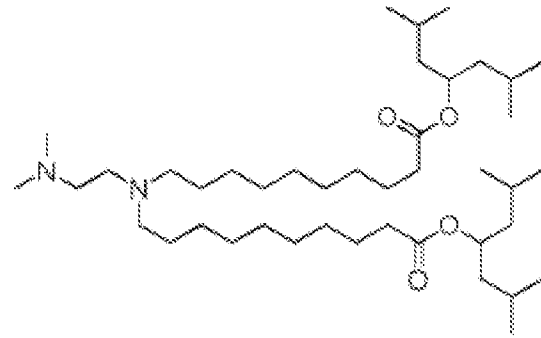
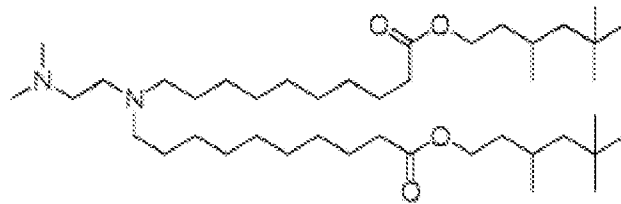
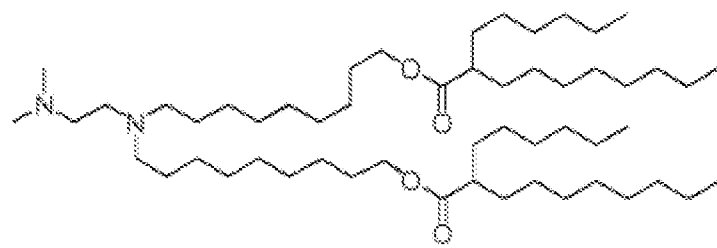
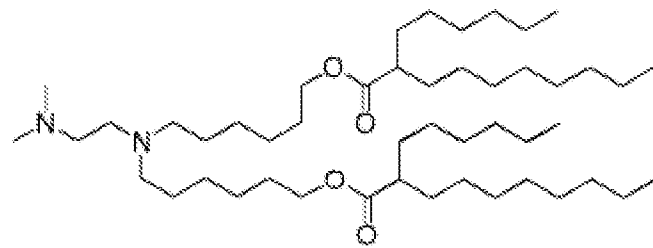
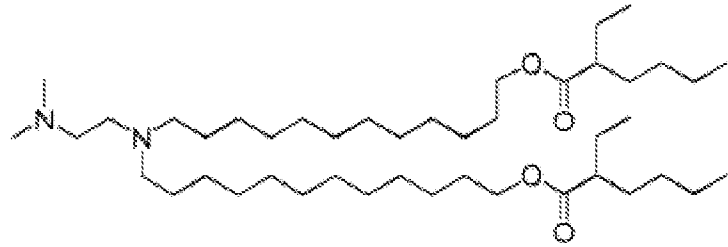
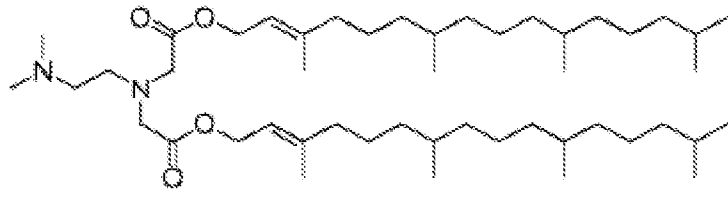
R^5 je izborno supstituirani ravni ili razgranati, zasićeni ili nezasićeni C_1 - C_6 alkil; i

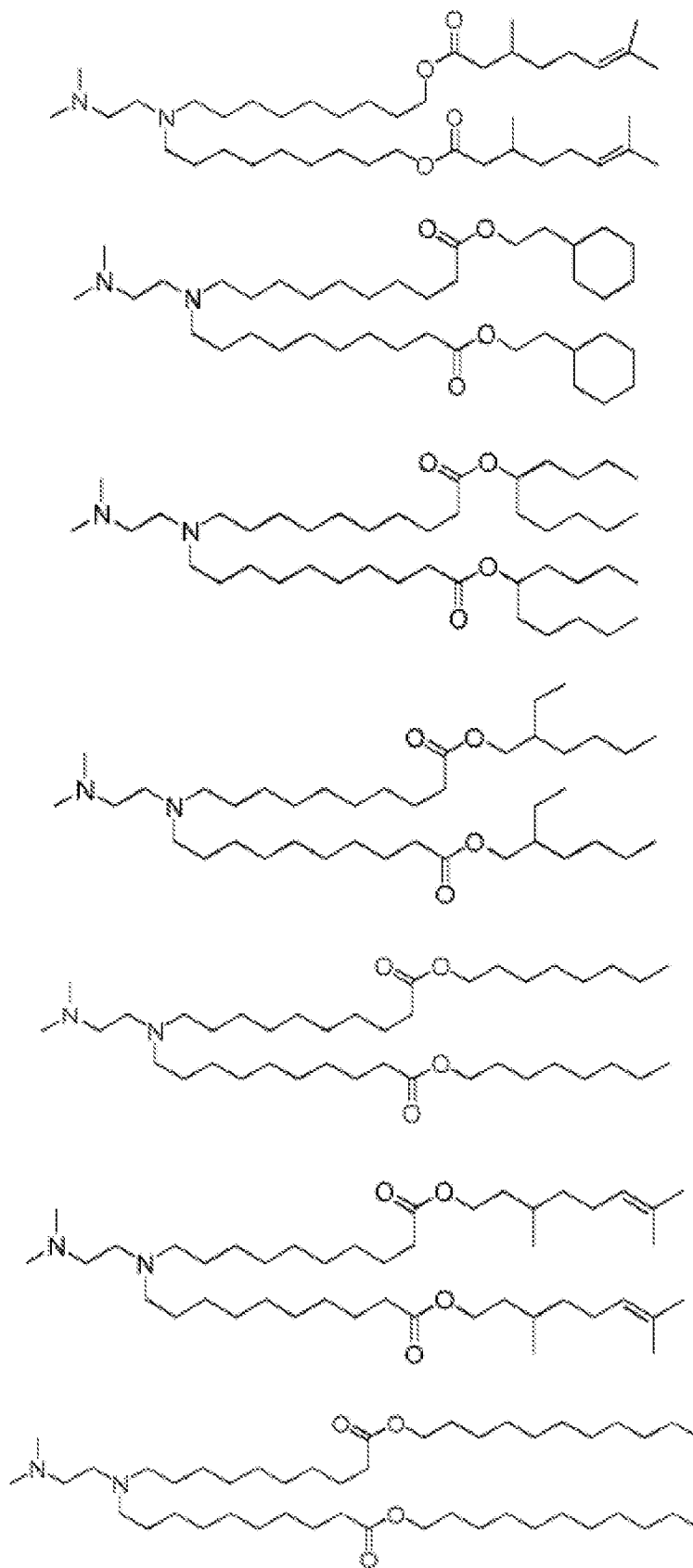
n je cijeli broj od 2 do 6.

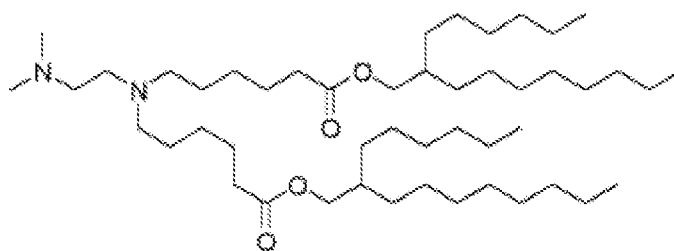
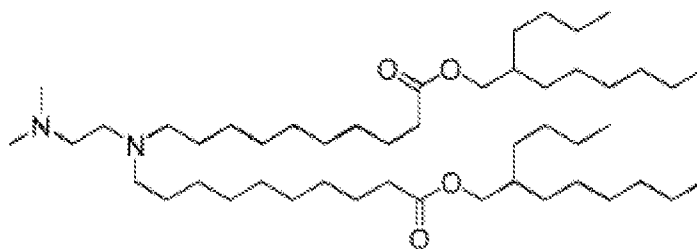
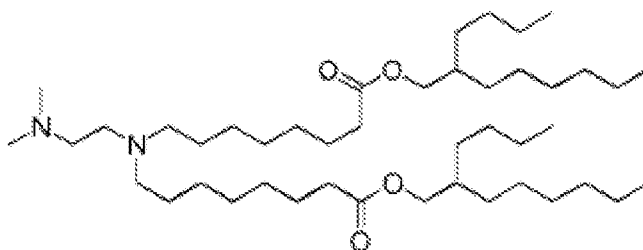
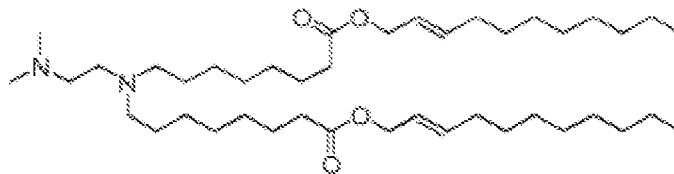
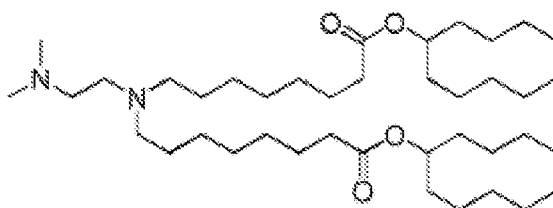
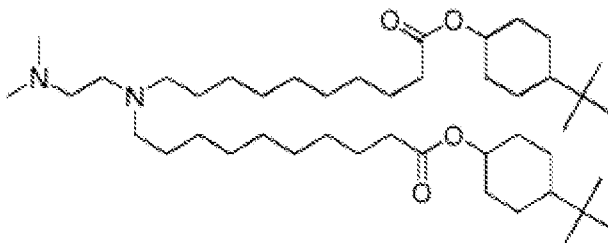
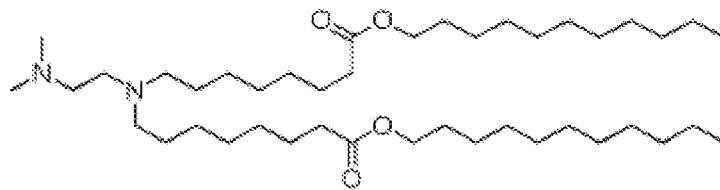
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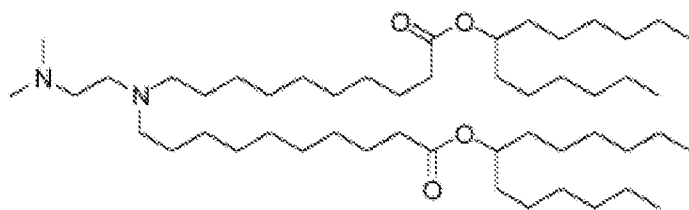
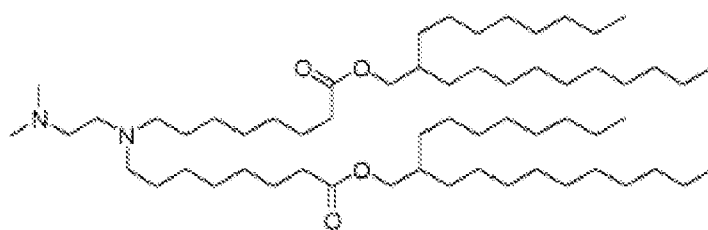
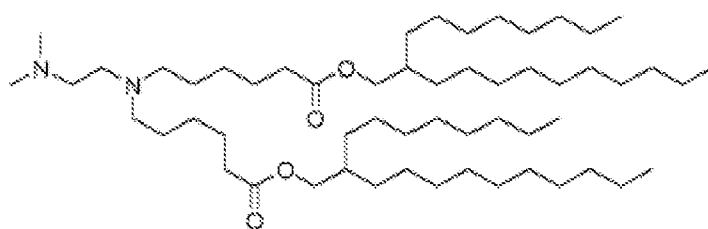
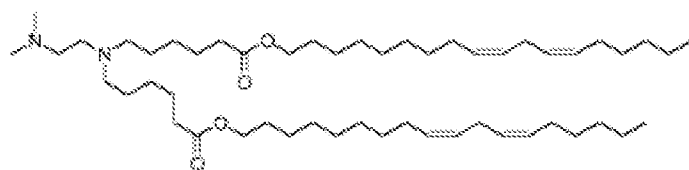
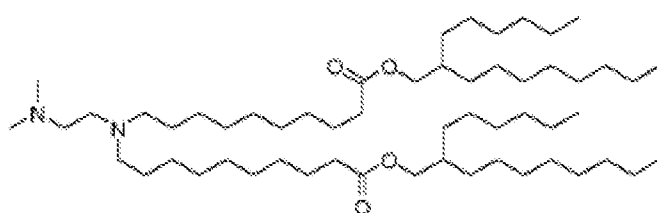
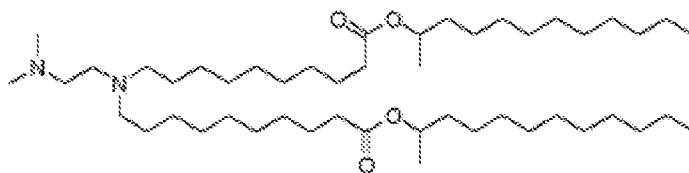
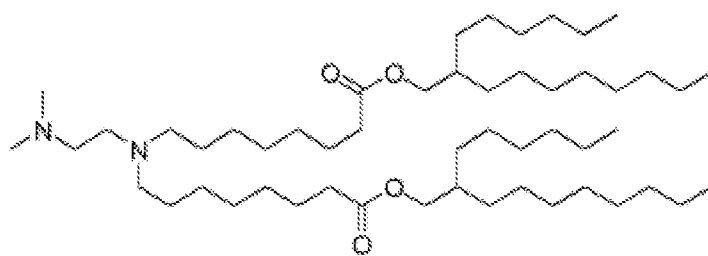
5. LNP za uporabu prema bilo kojem od zahtjeva 1-4, gdje je kationski lipid formiran iz lipidne strukture odabrane između:

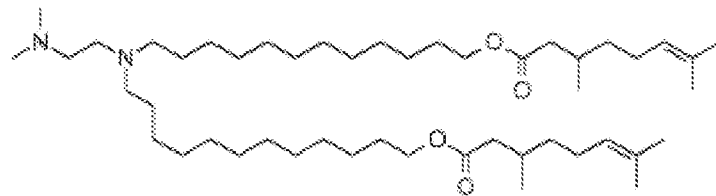
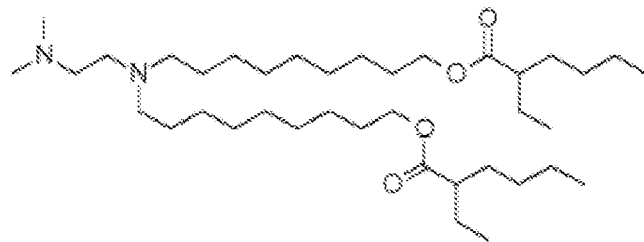
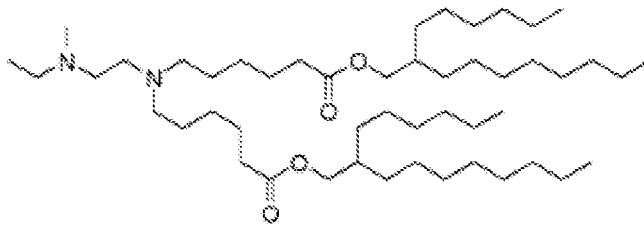
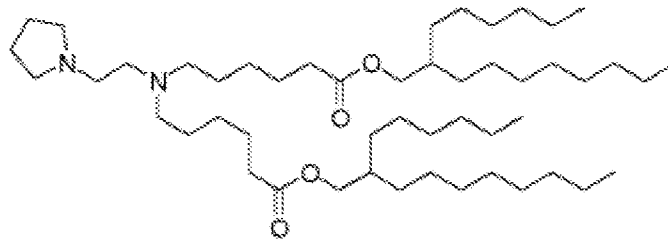
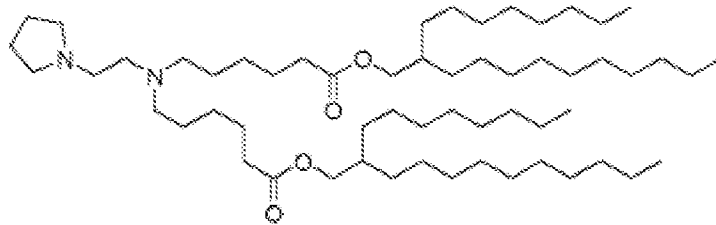
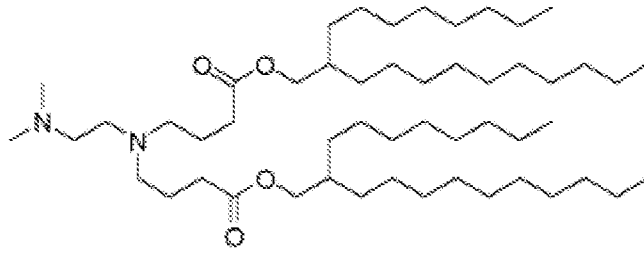


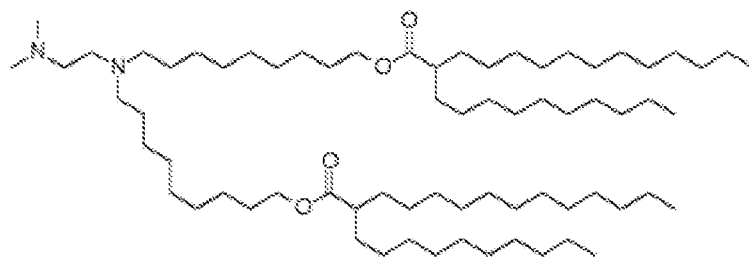
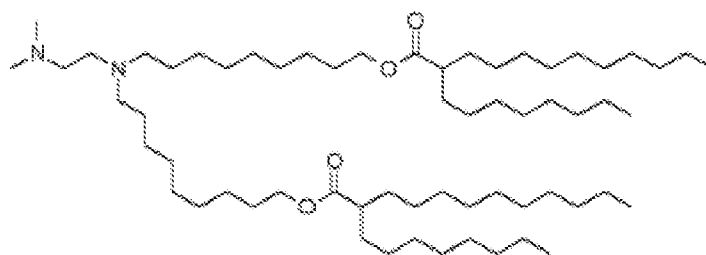
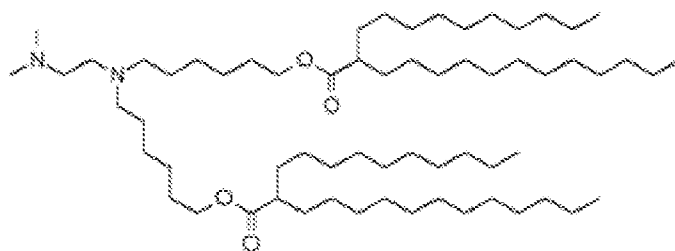
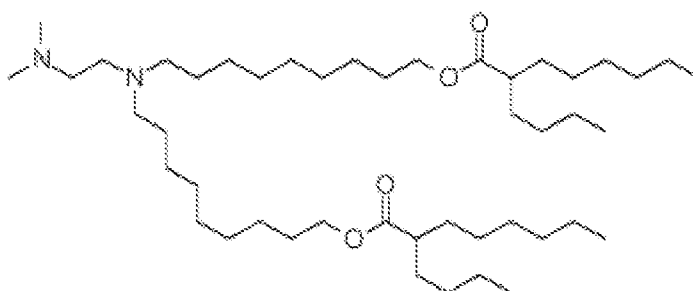
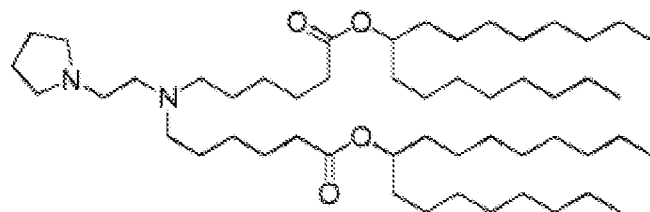
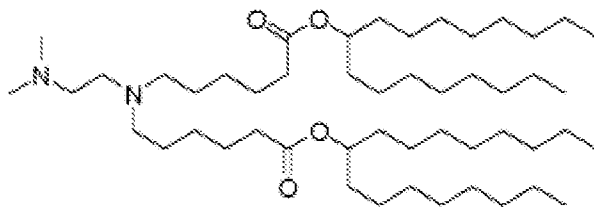


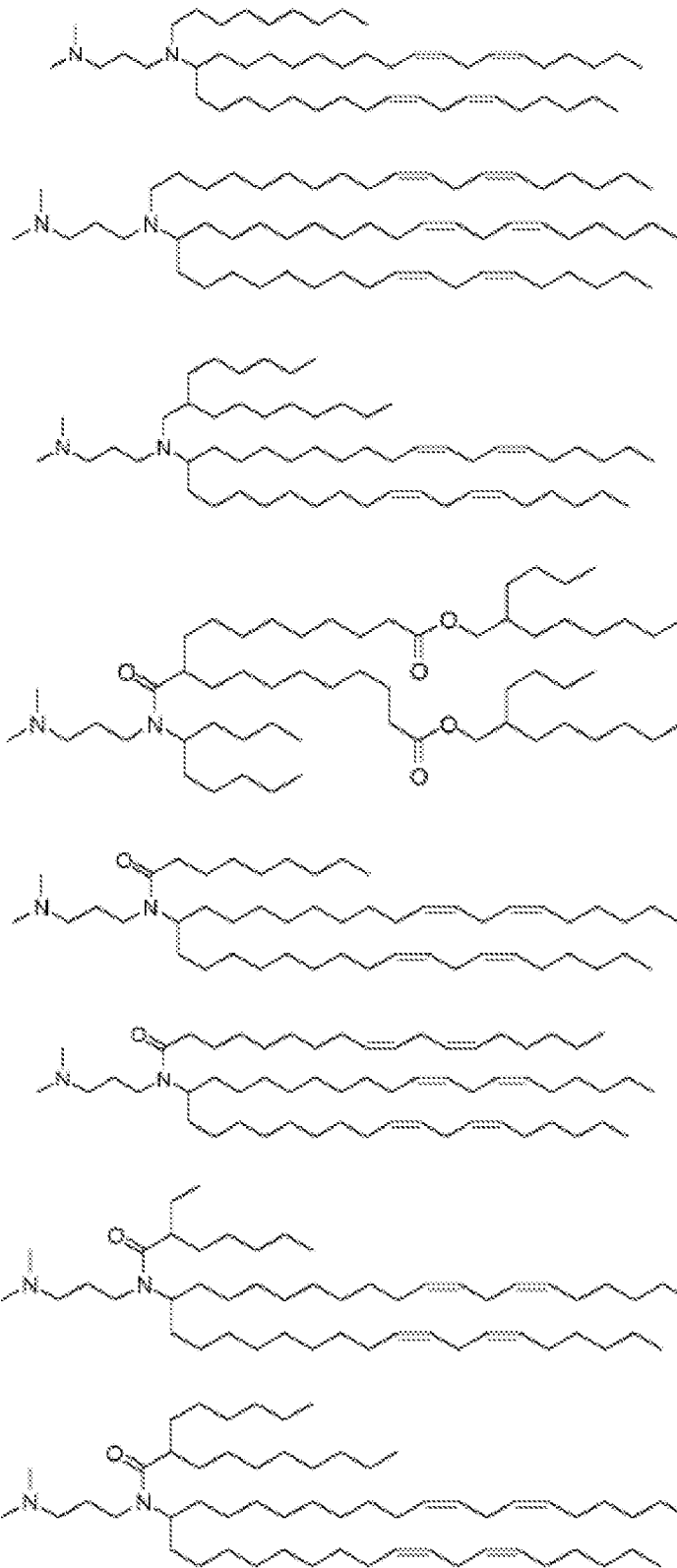


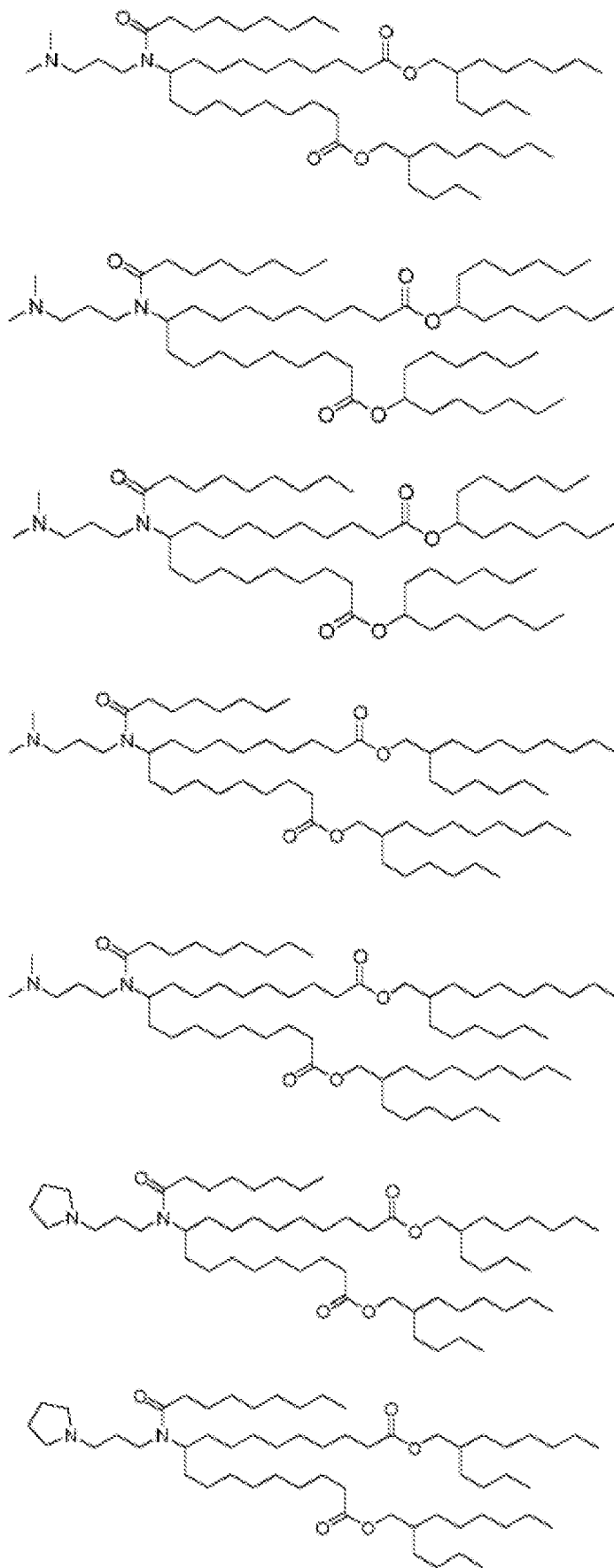


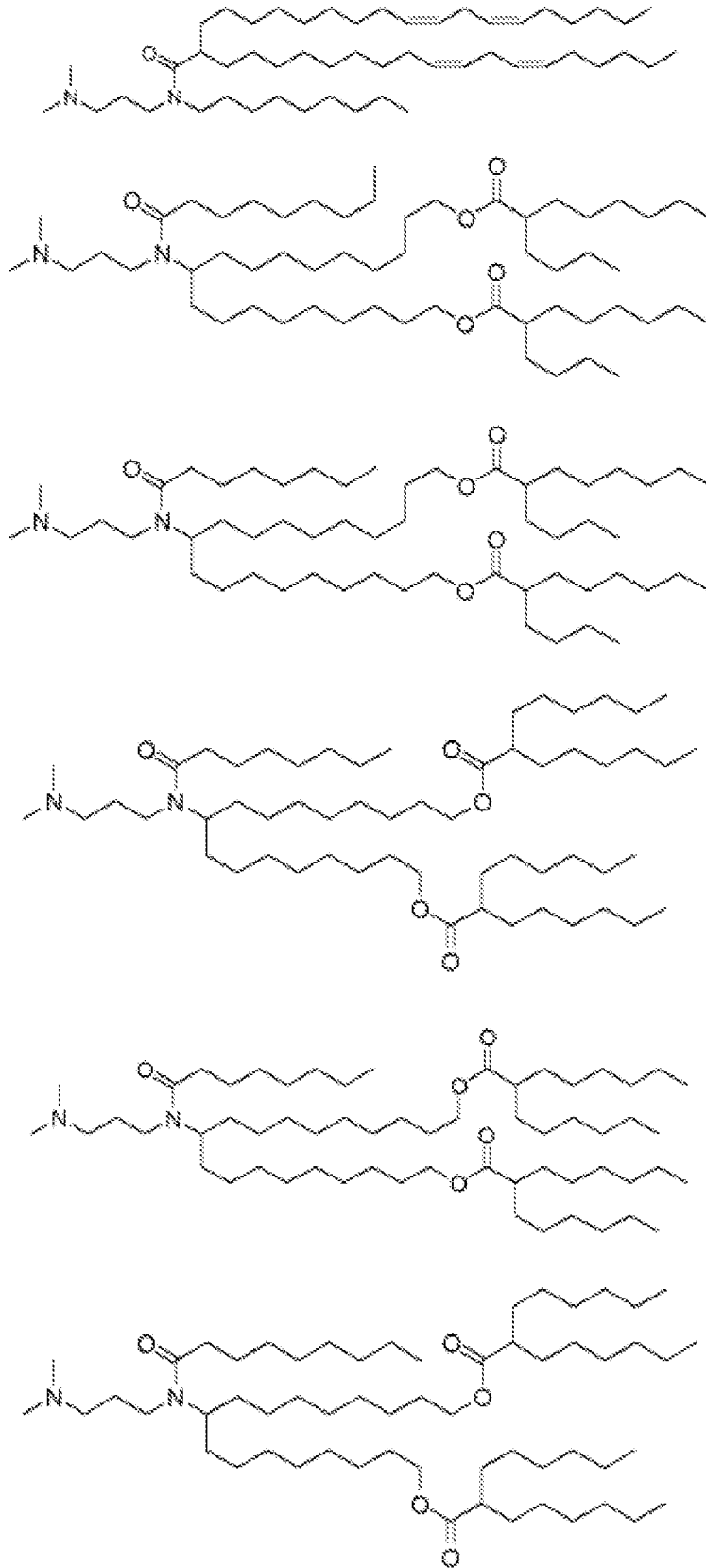


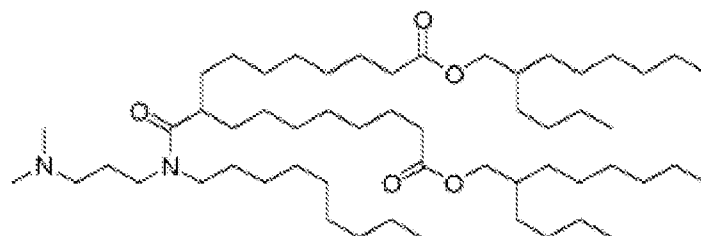
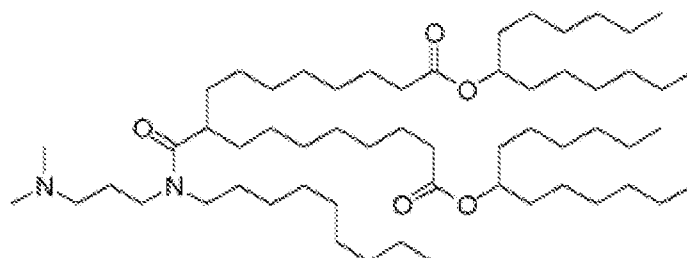
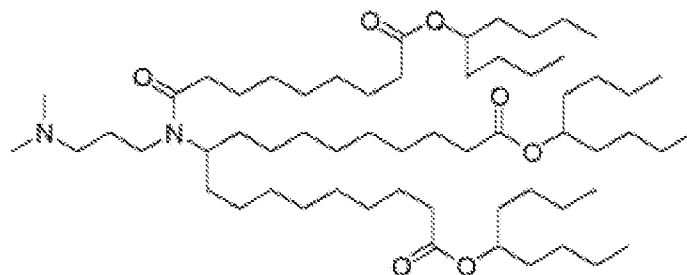
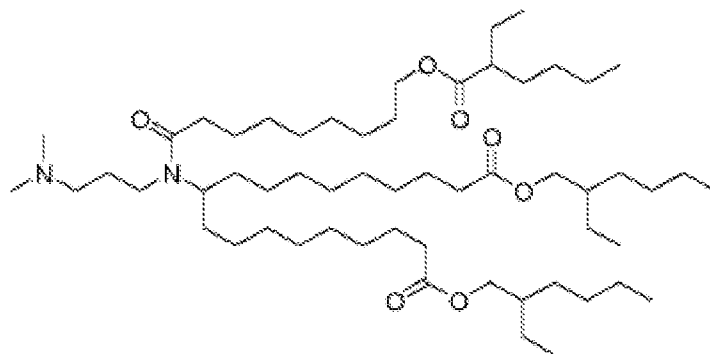
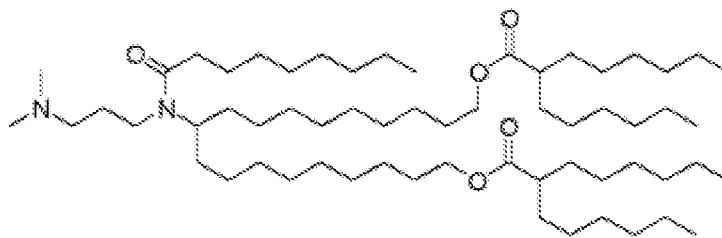


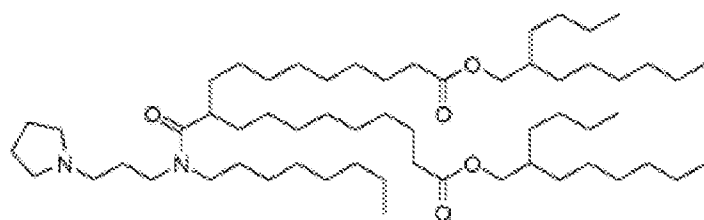
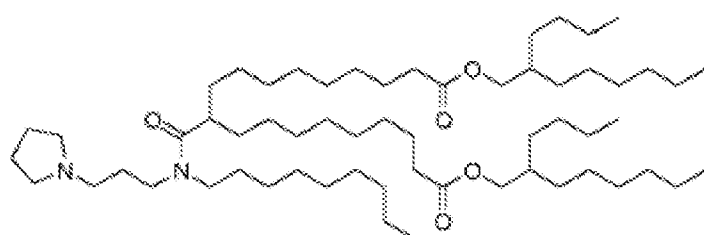
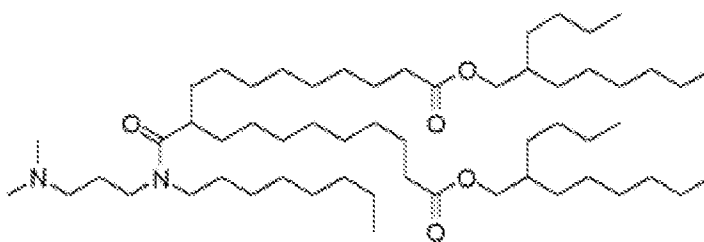
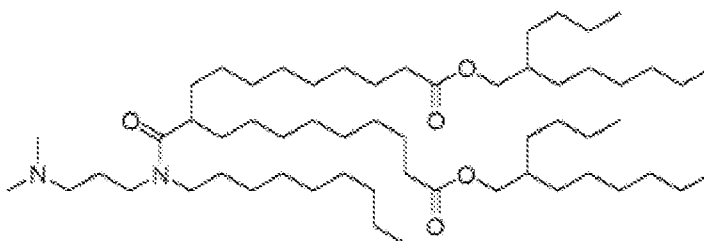
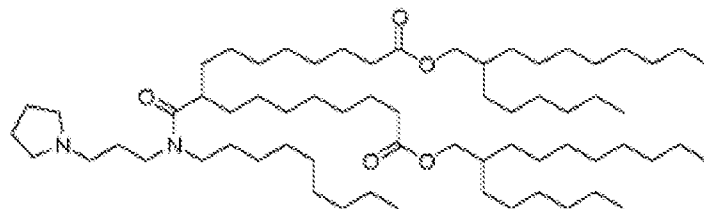
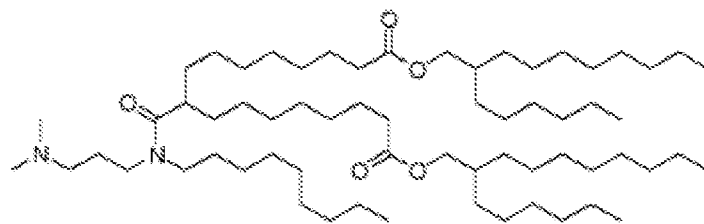


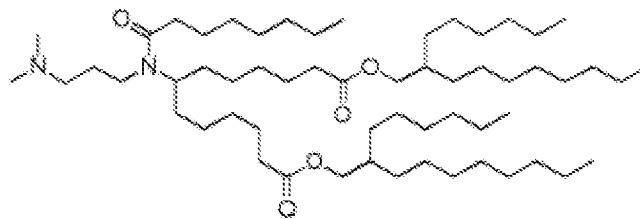
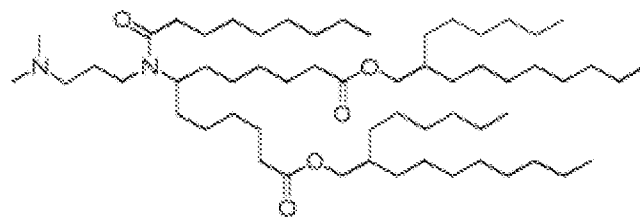
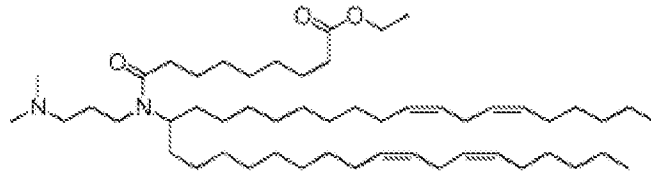
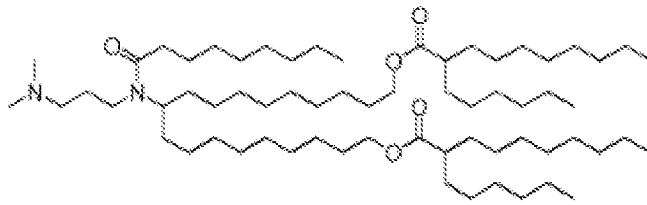
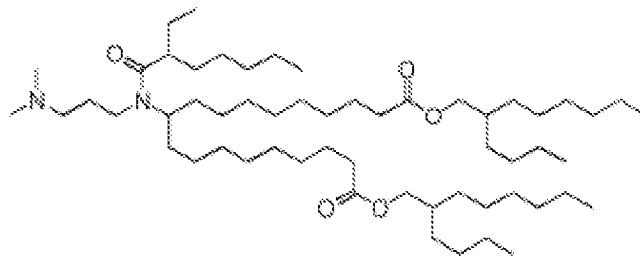
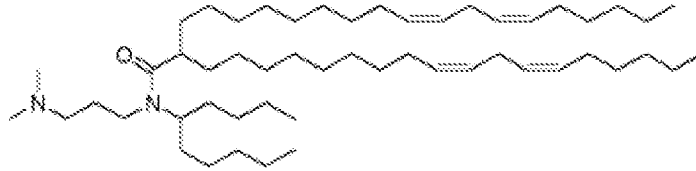
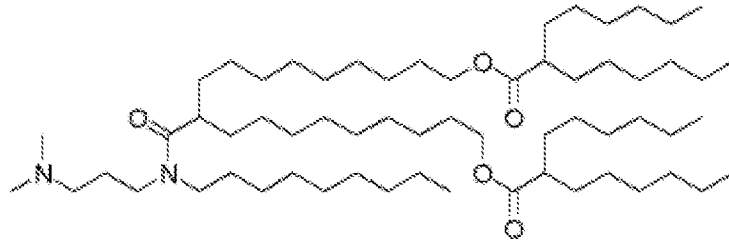


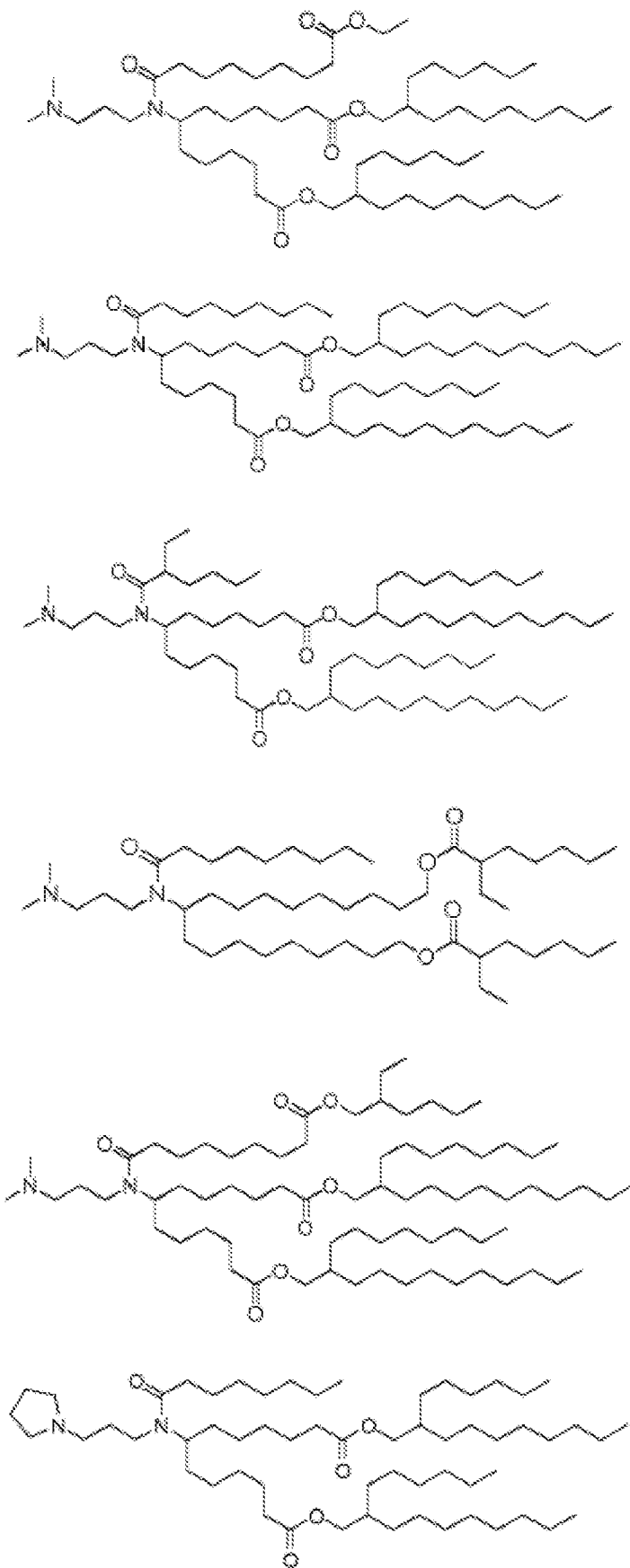


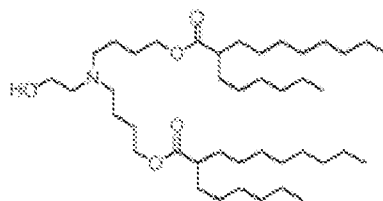
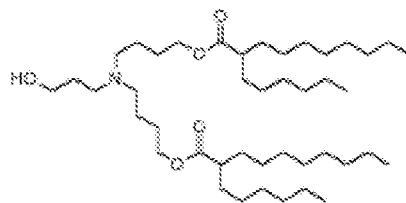
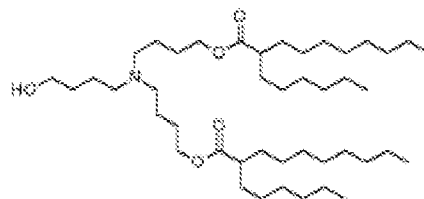
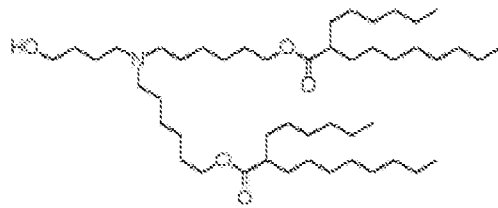
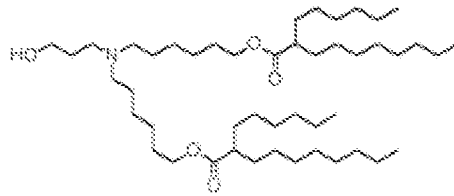
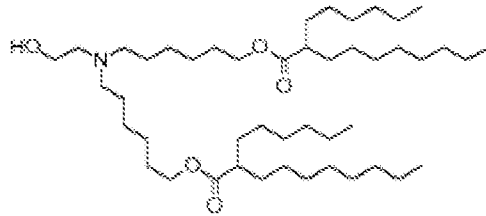
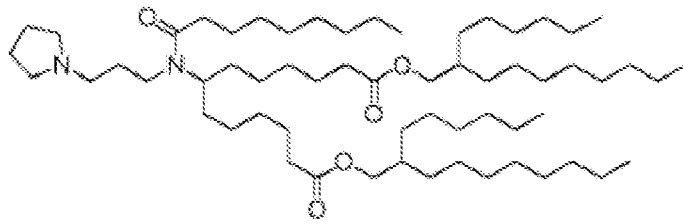


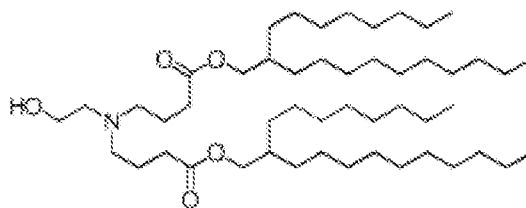
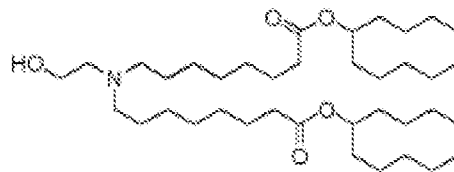
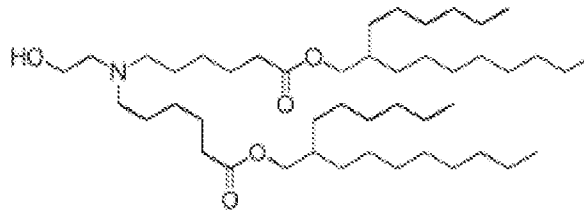
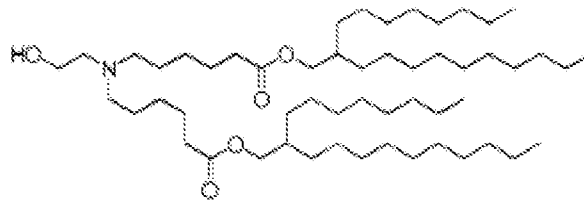
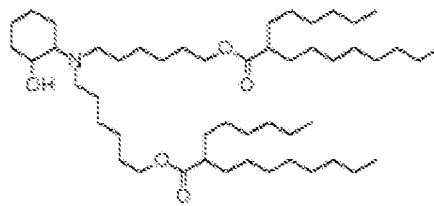
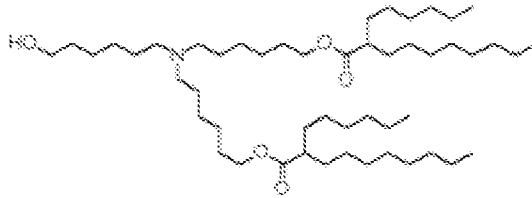
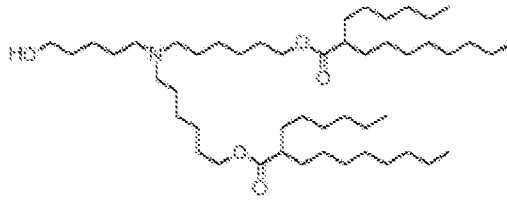


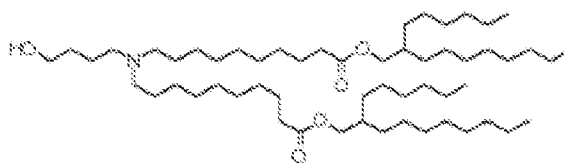
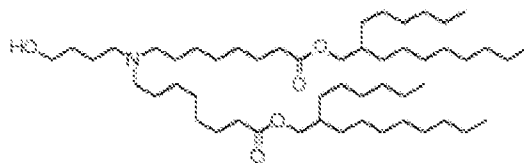
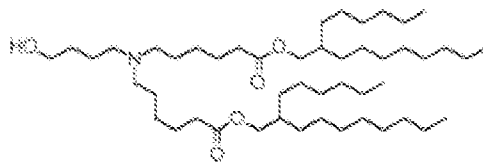
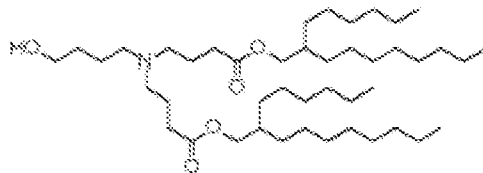
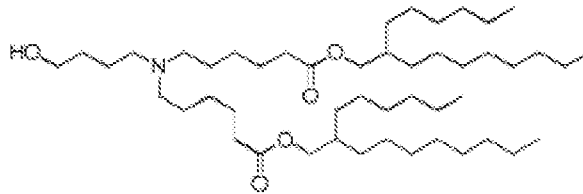
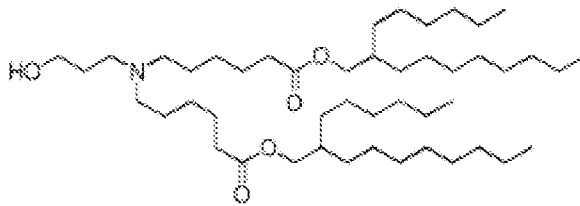
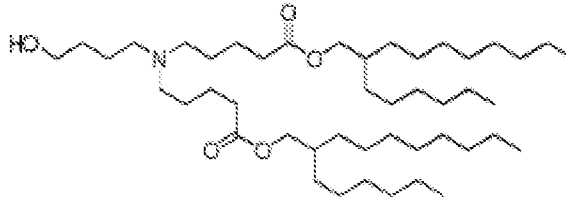
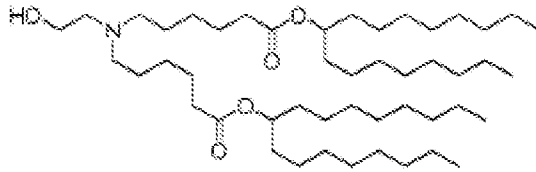


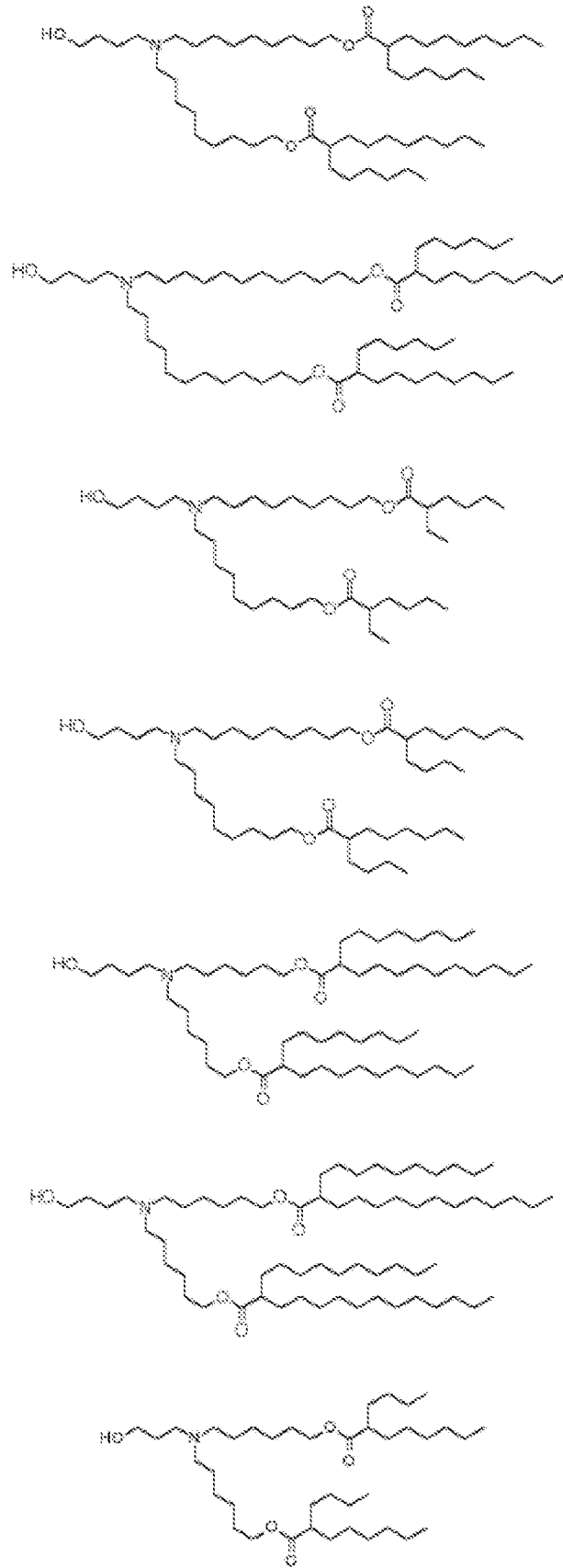


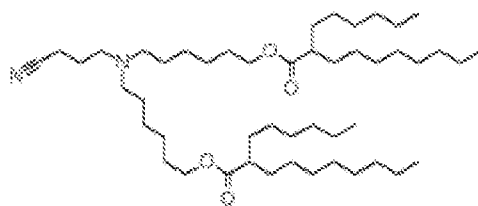
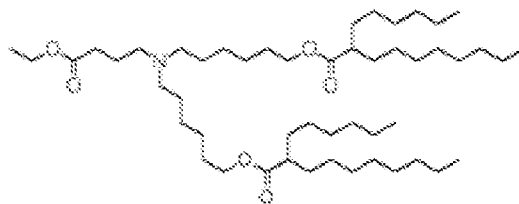
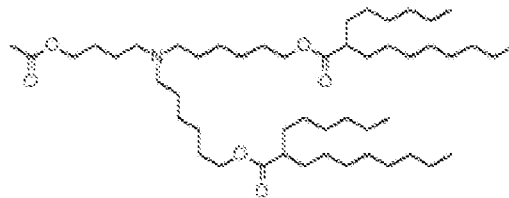
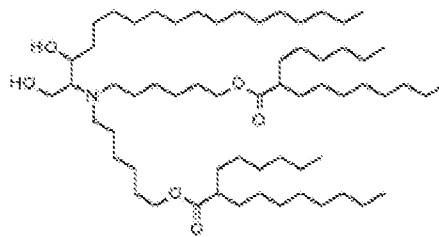
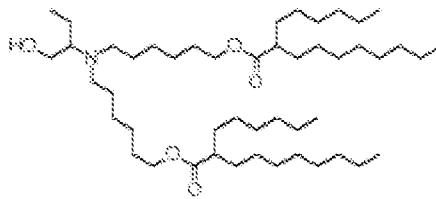
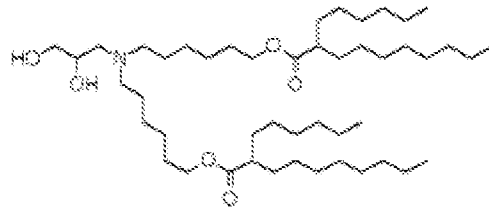
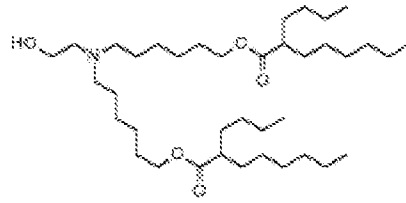


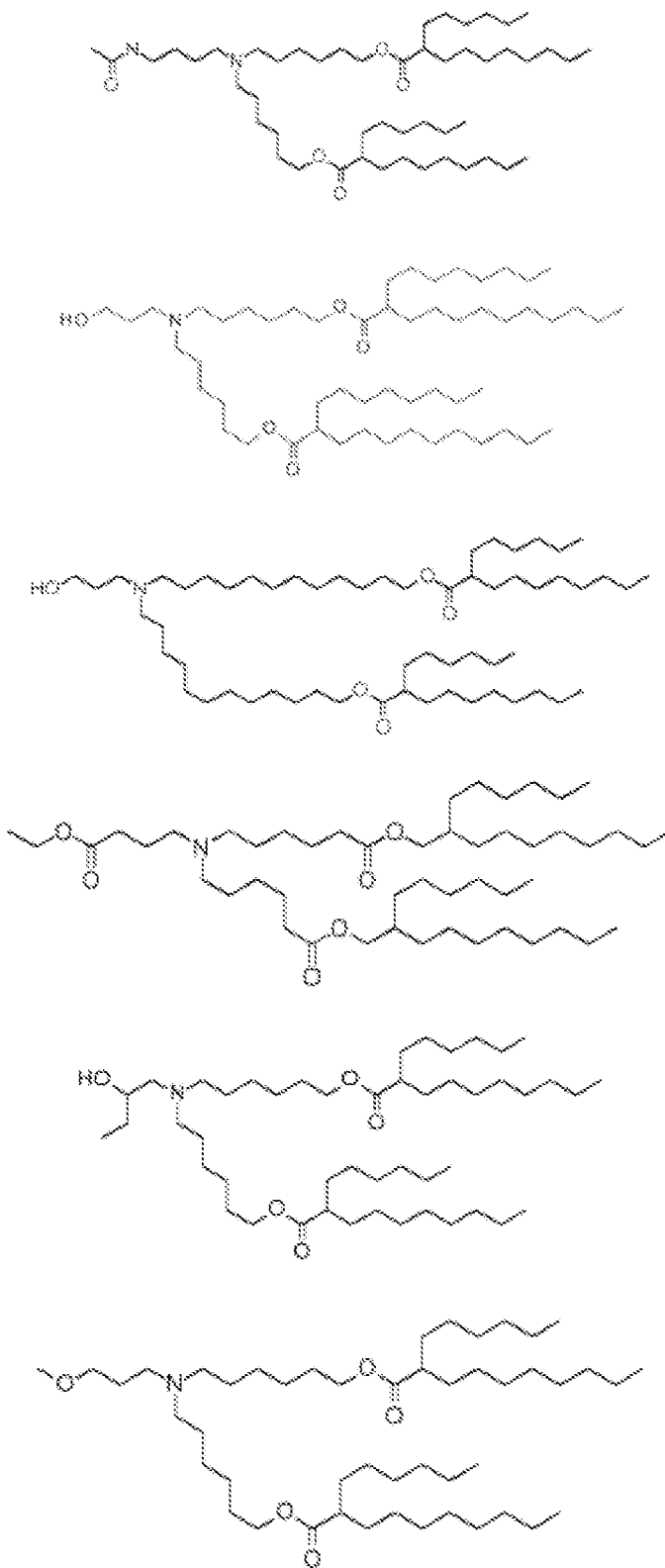


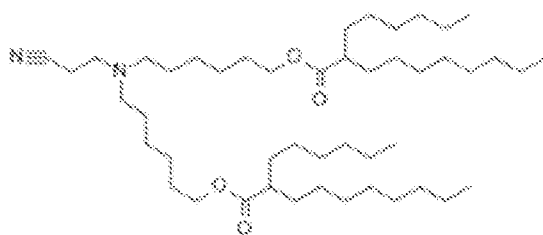
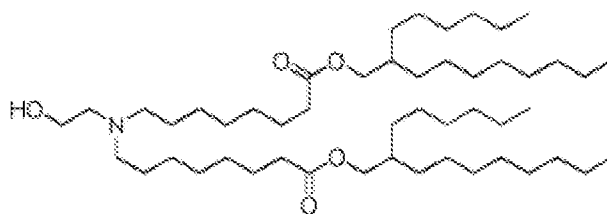
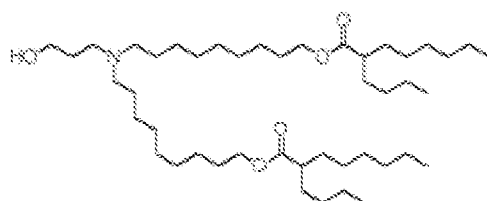
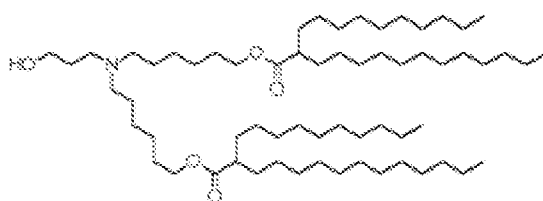
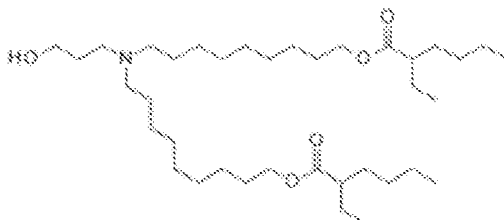
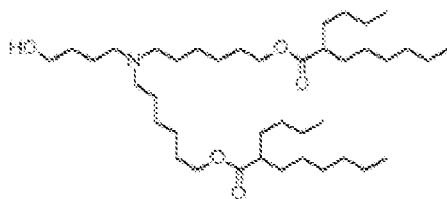


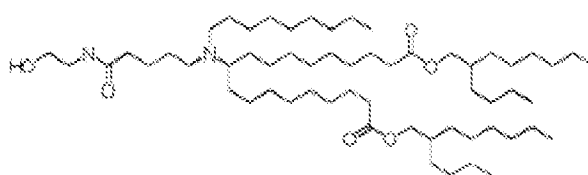
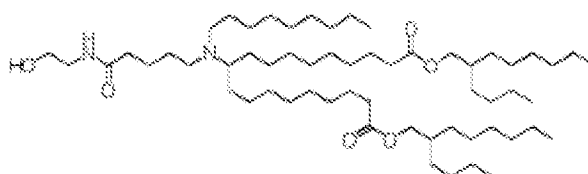
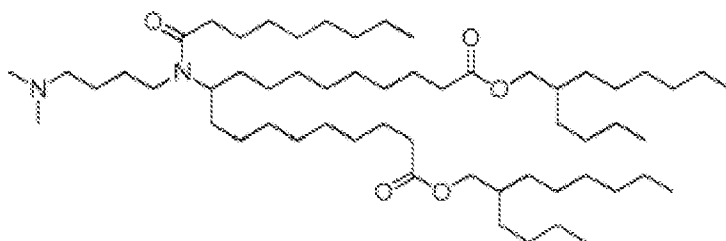
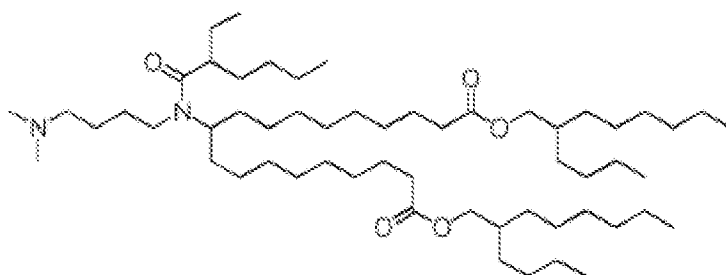
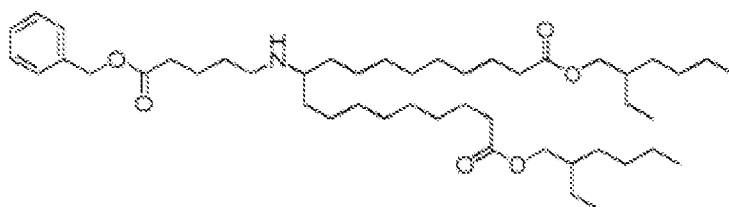
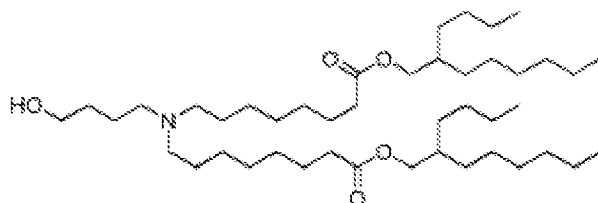
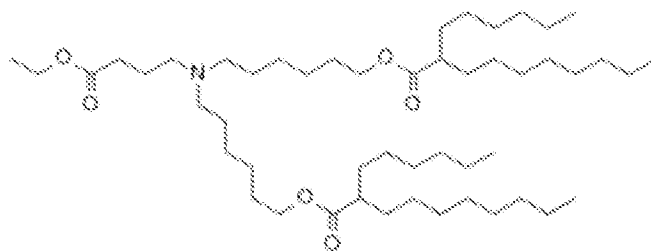


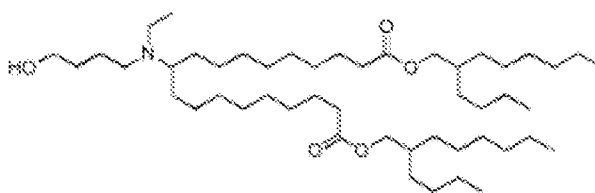
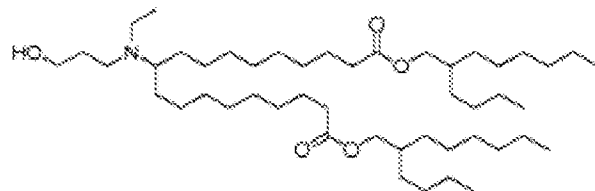
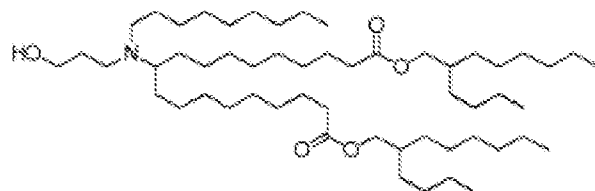
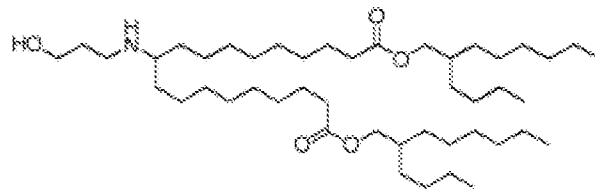
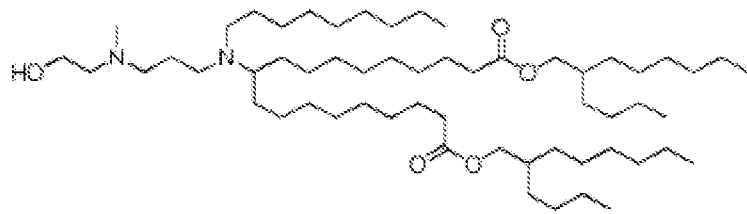
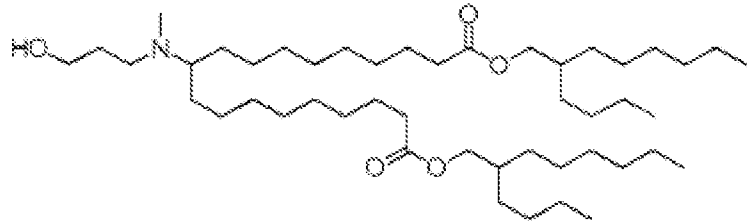
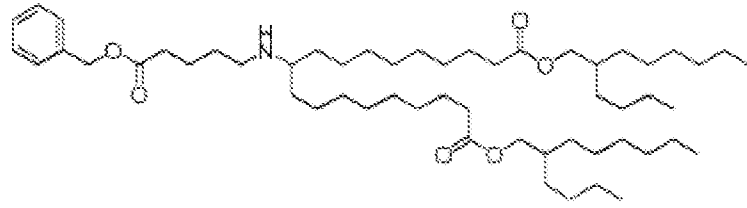


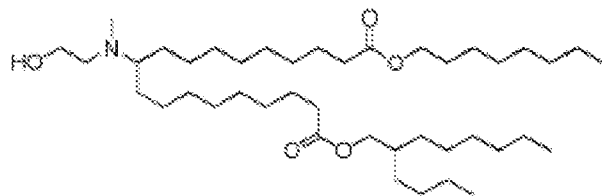
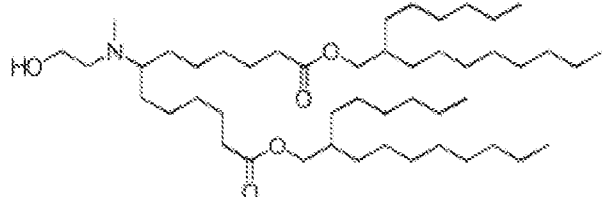
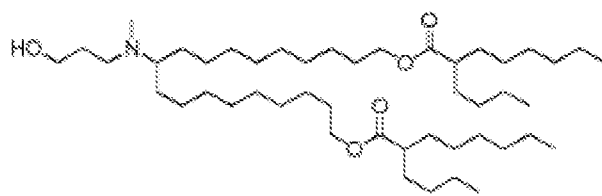
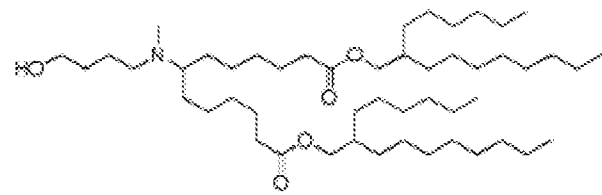
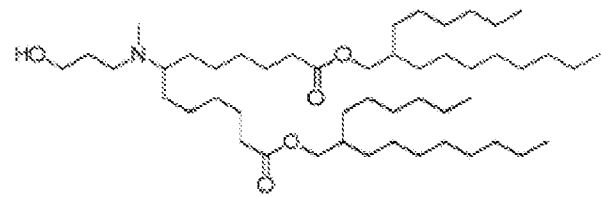
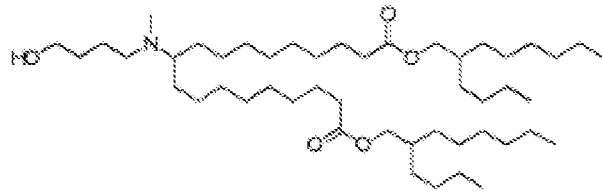
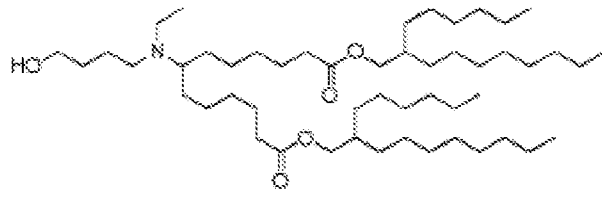


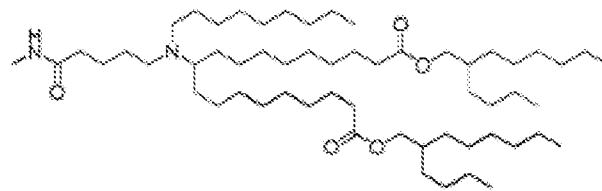
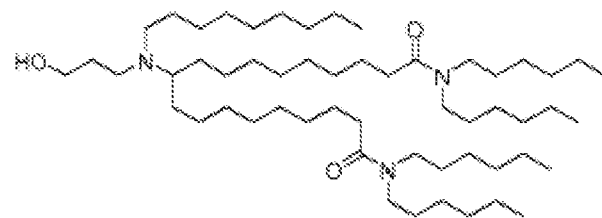
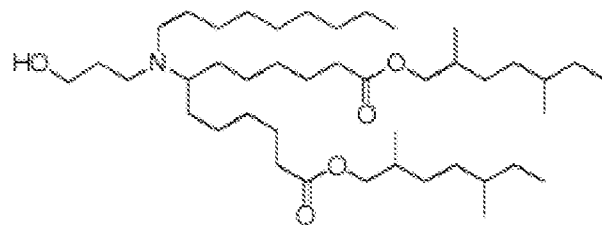
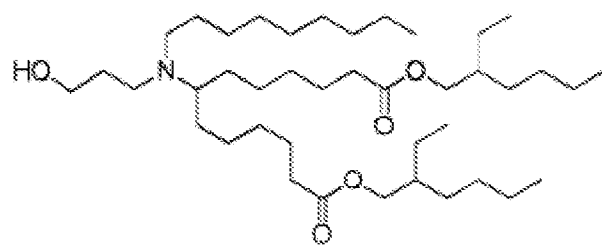
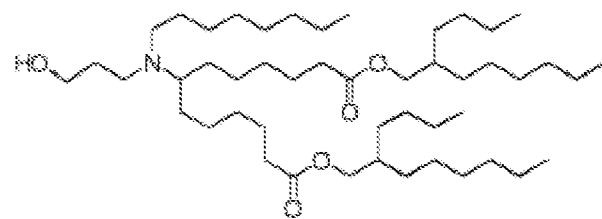
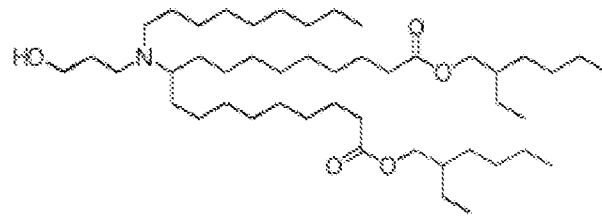
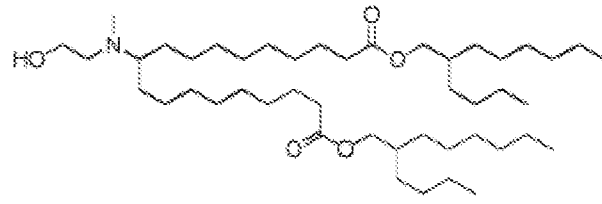


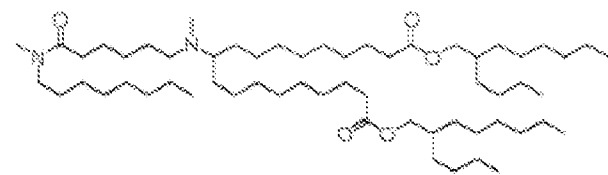
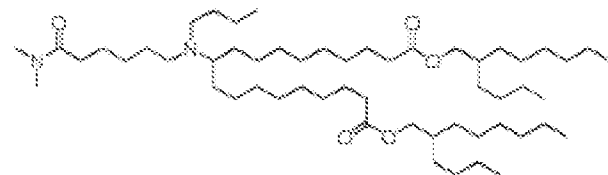
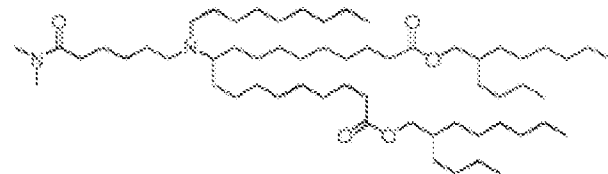
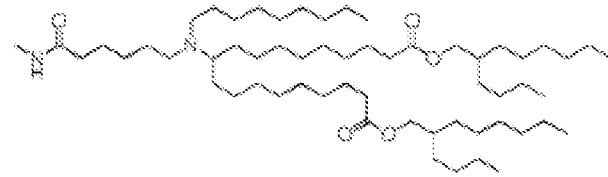
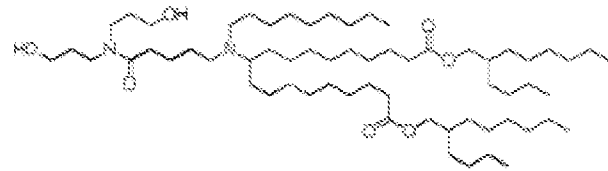
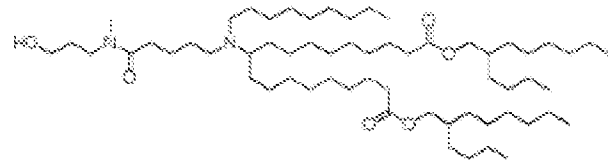
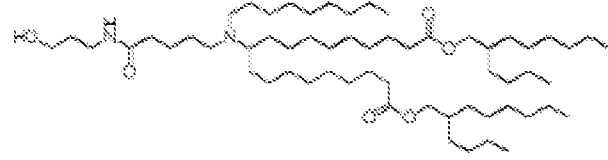
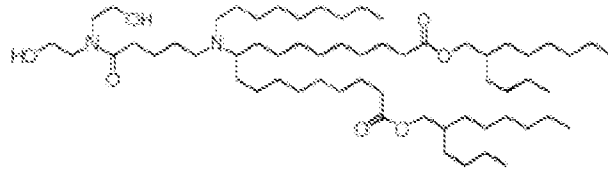


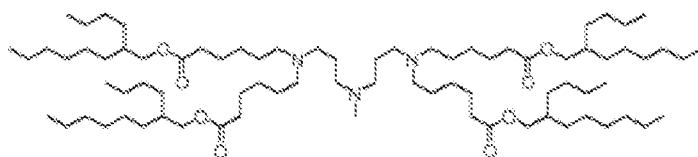
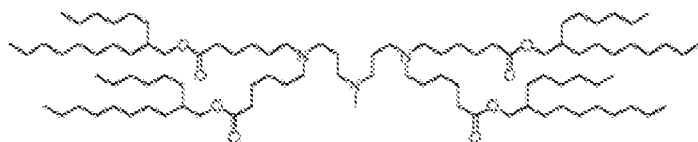
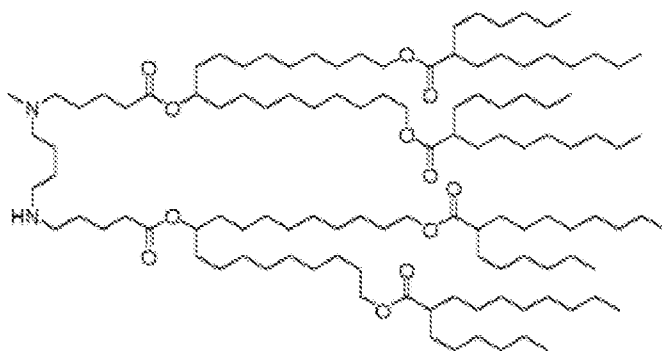
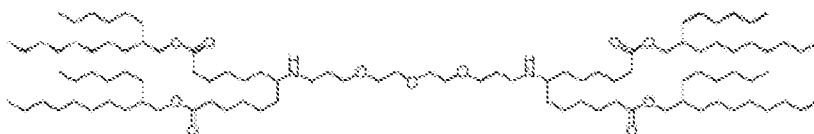
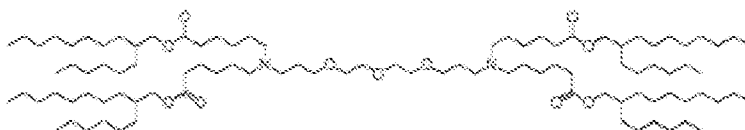
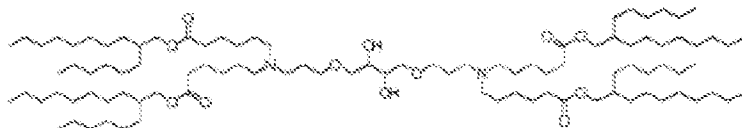
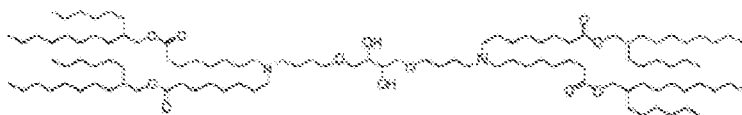
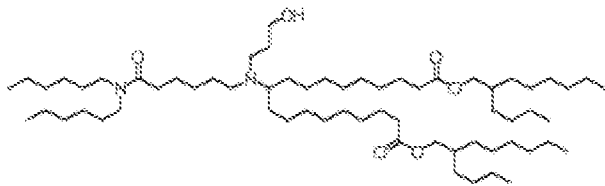


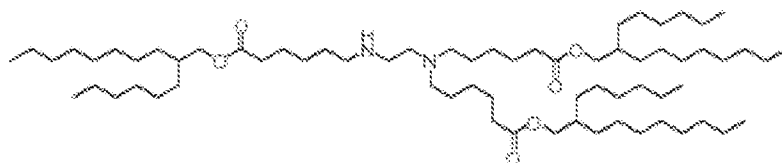
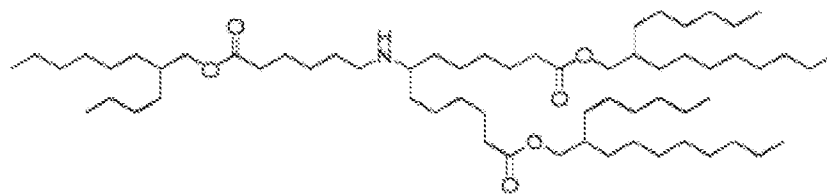
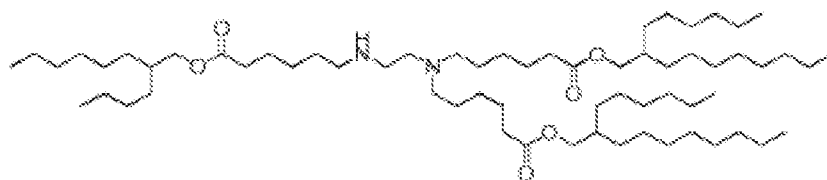
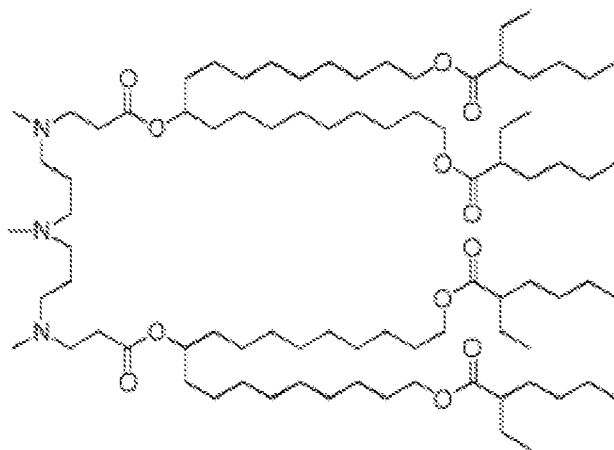
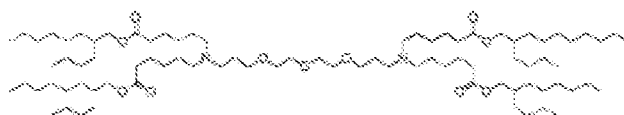
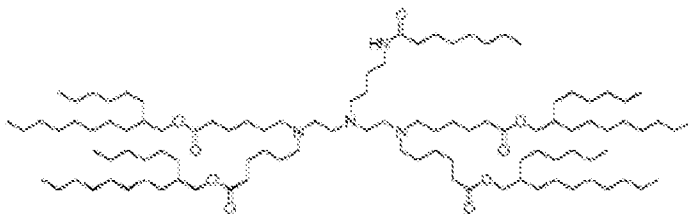
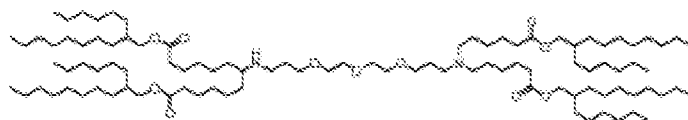


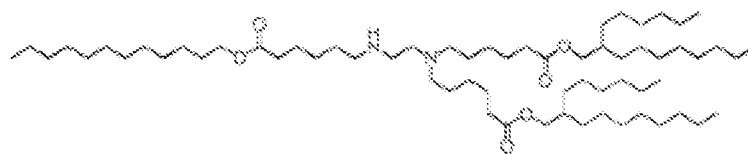
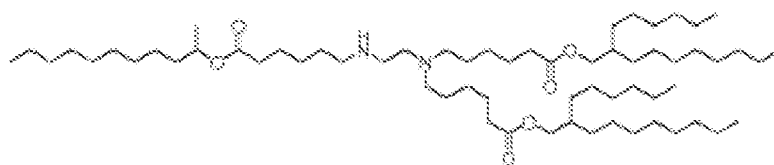
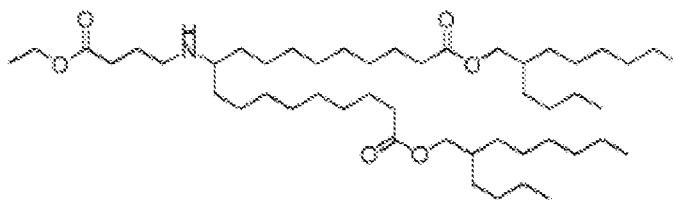
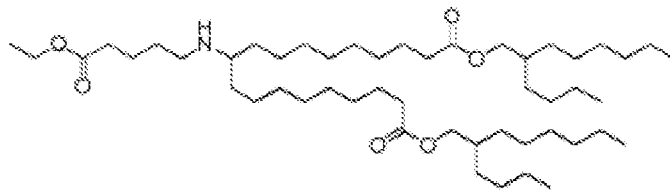
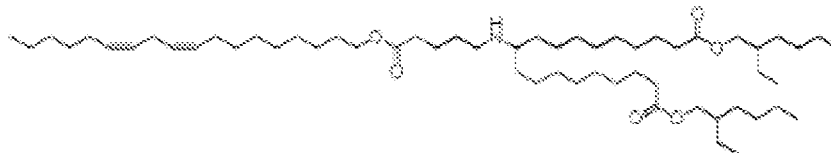
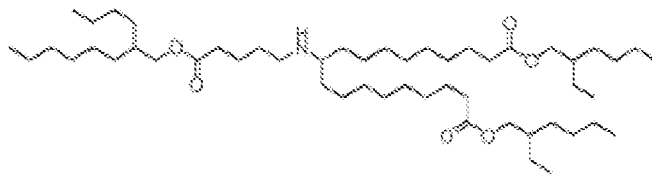
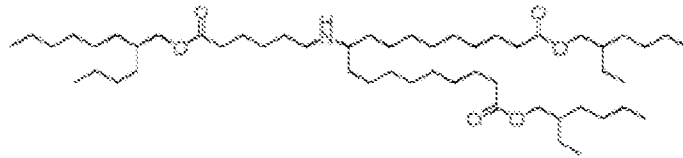
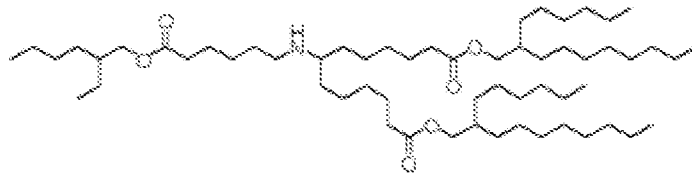


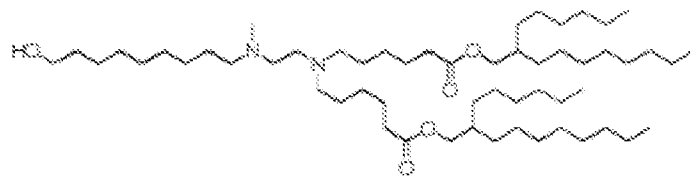
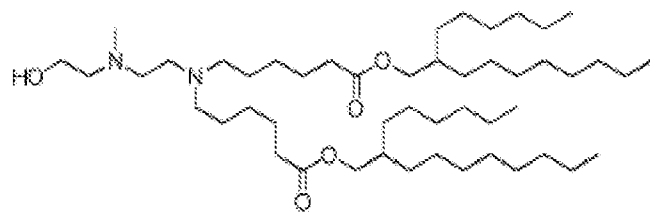
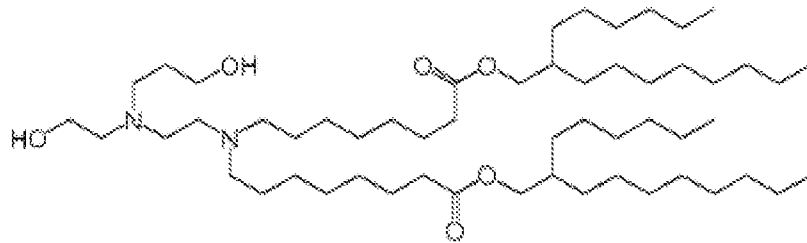
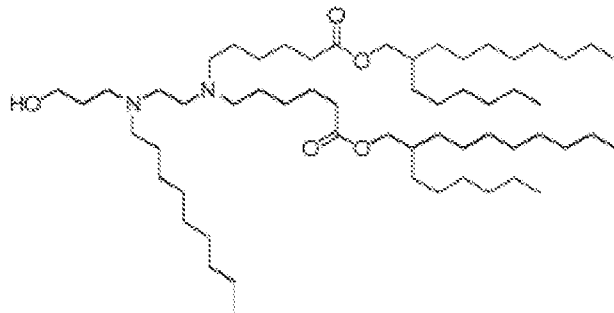
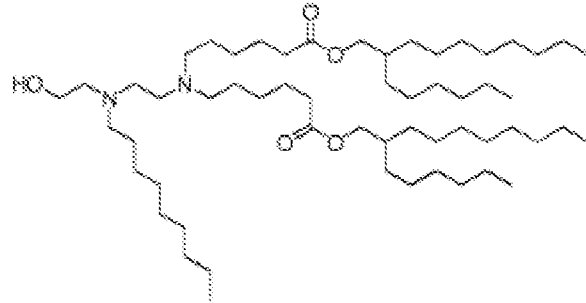
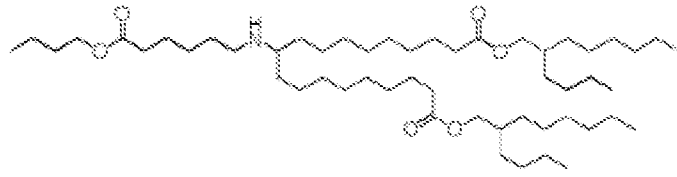


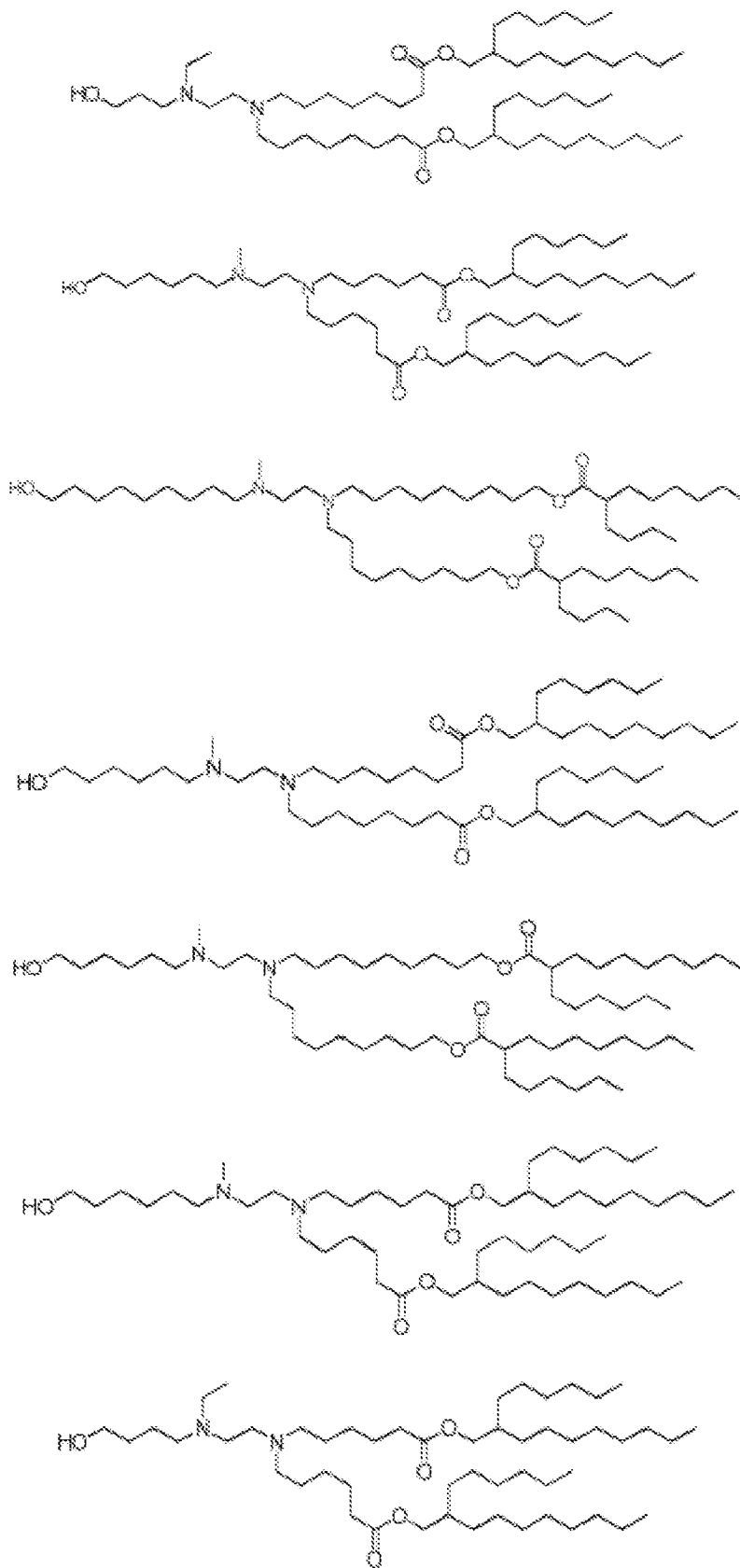


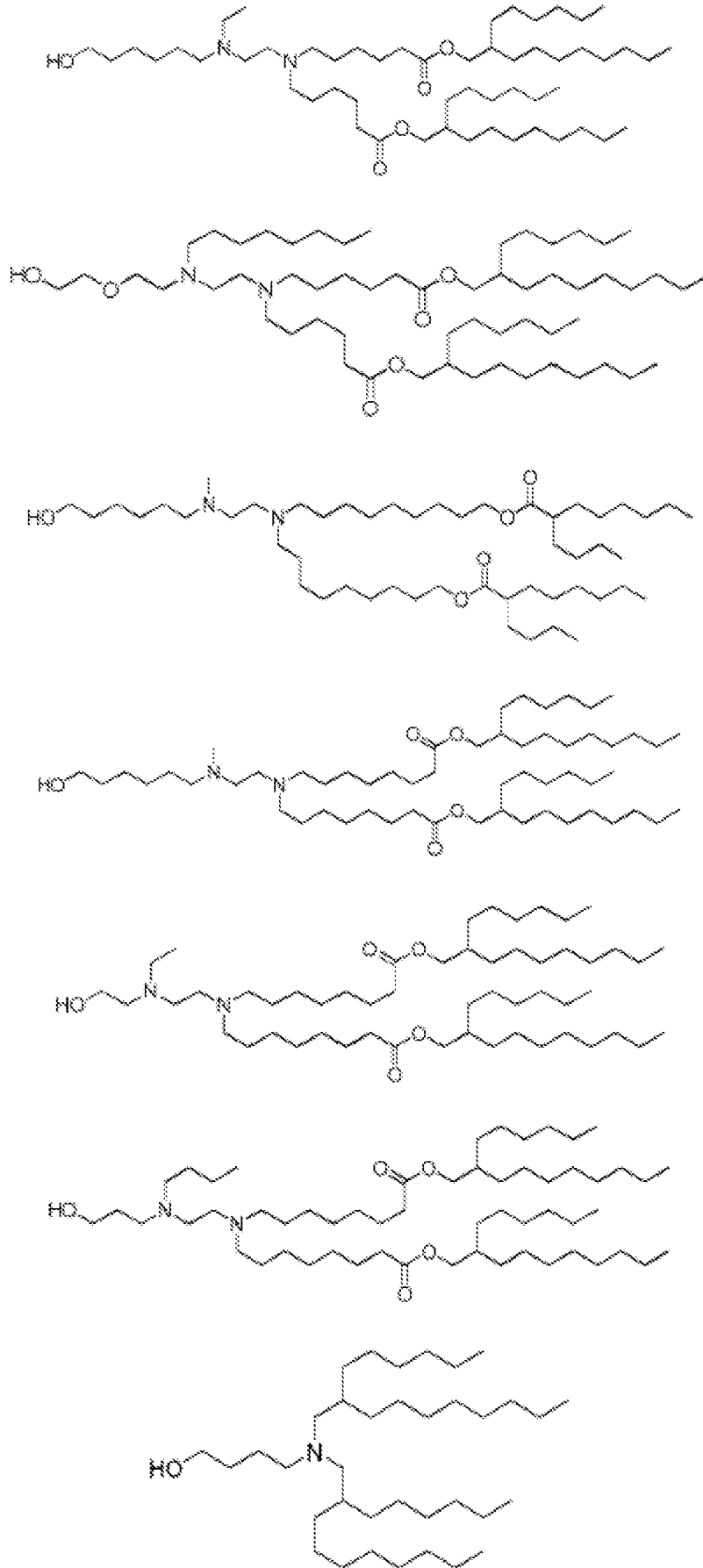


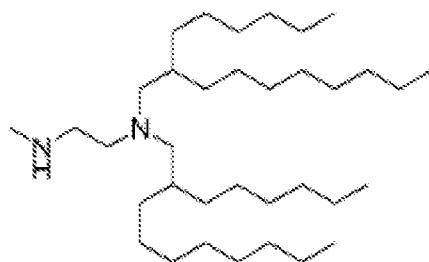
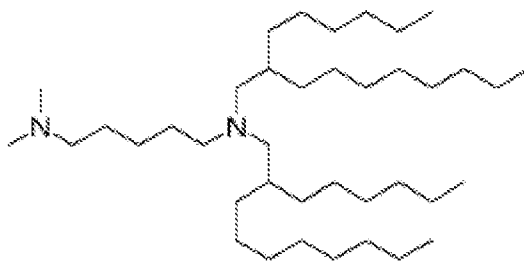
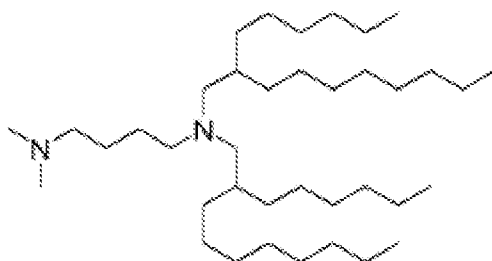
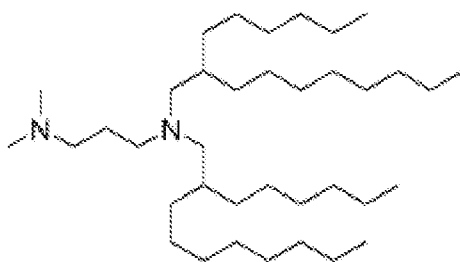
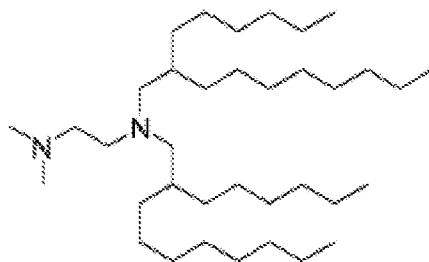


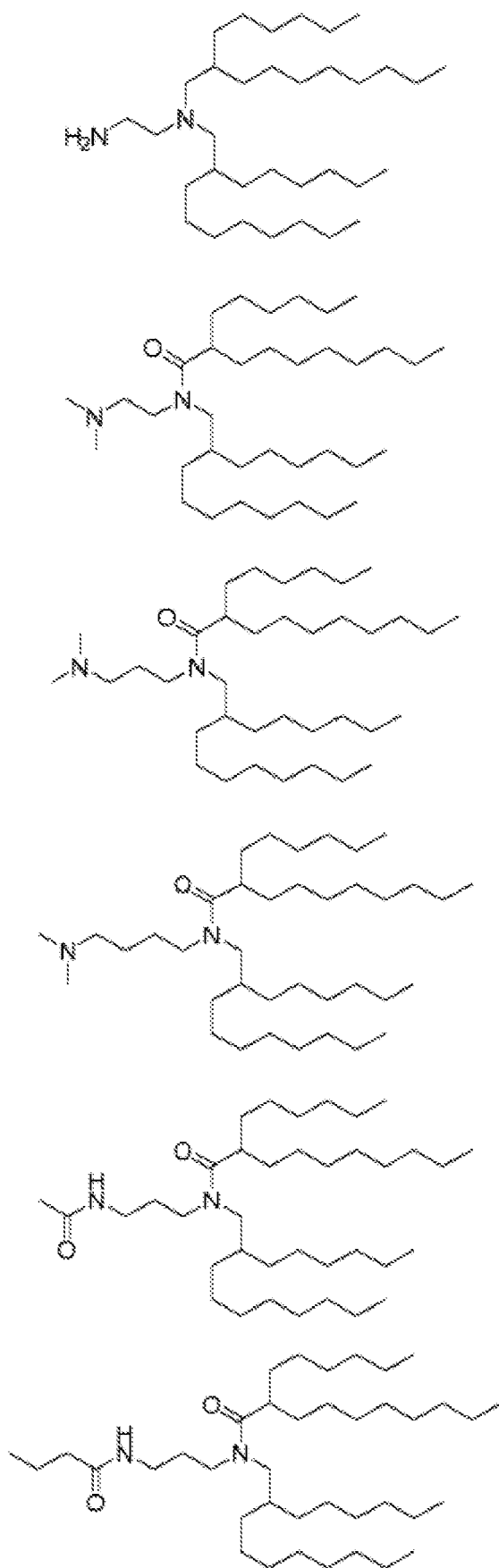


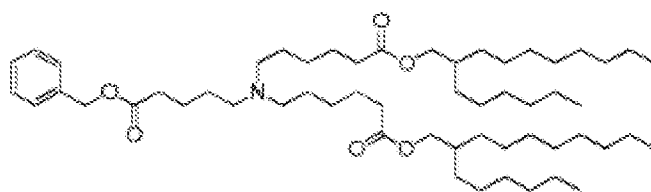
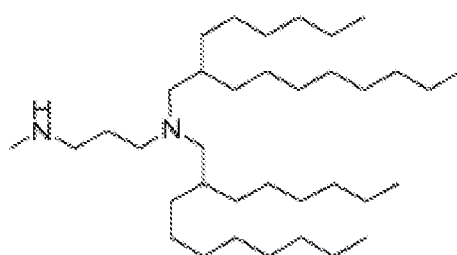
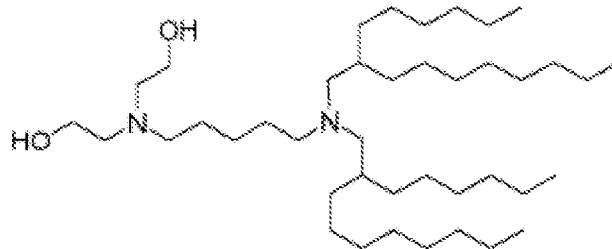
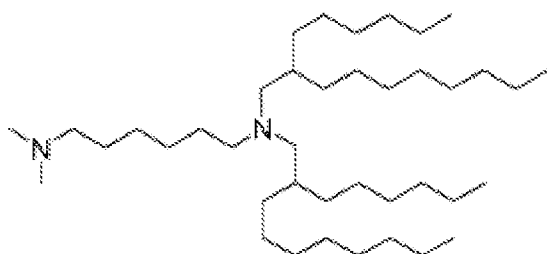
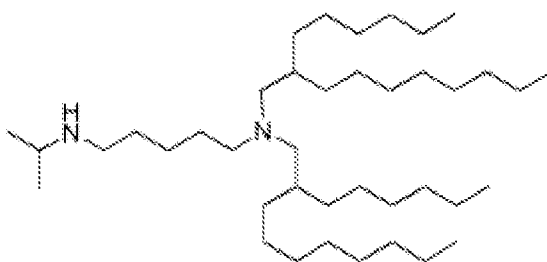
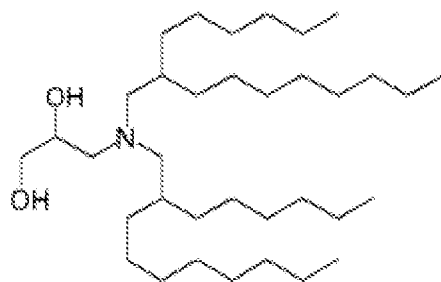


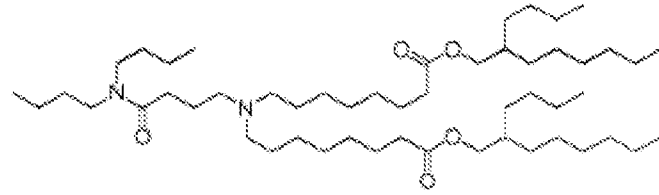
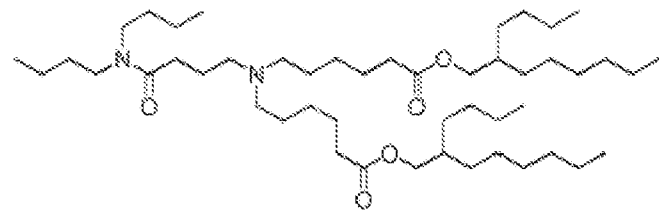
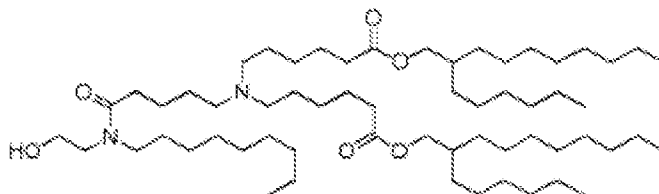
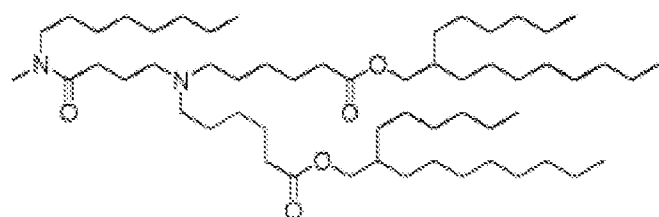
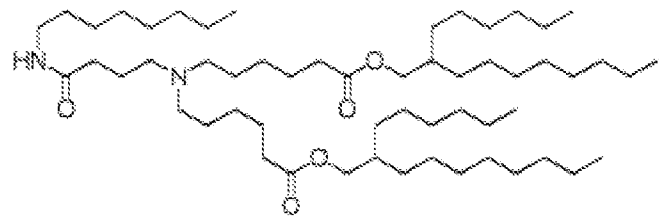
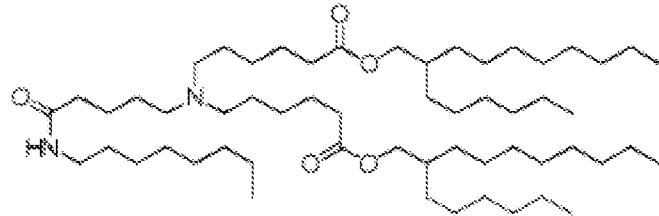
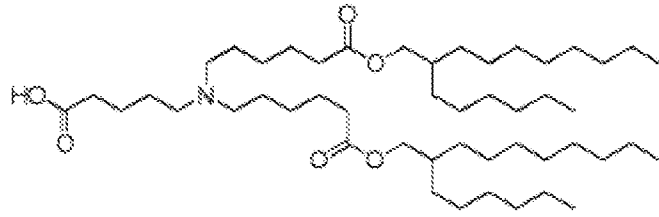


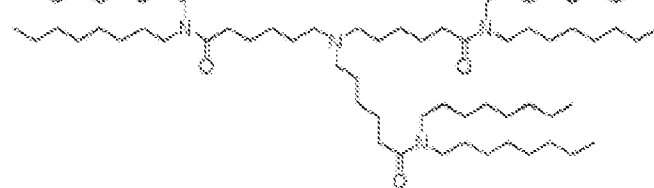
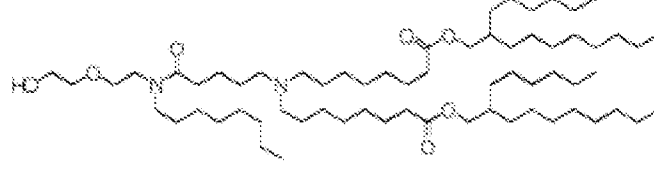
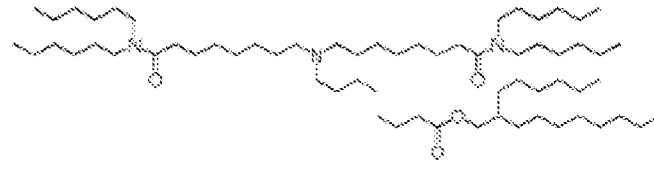
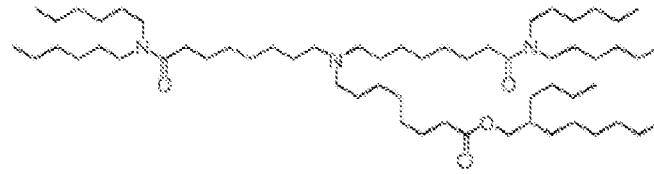
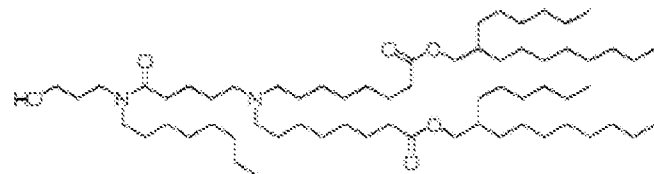
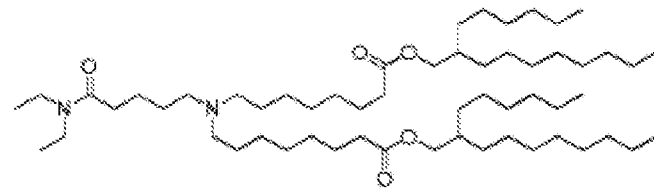
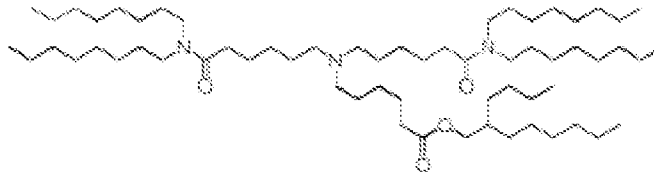
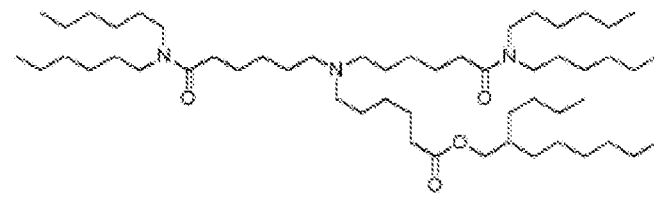


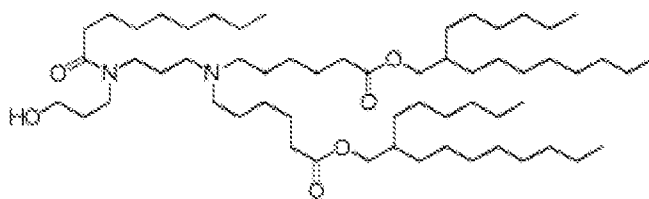
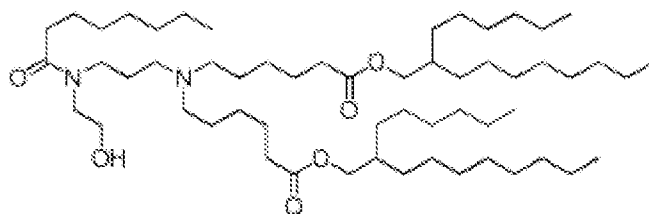
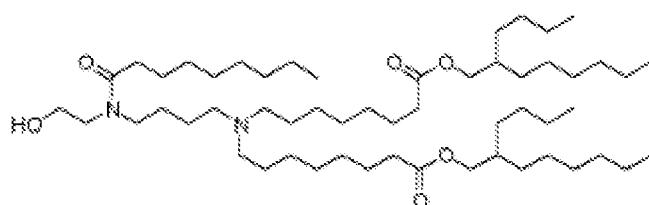
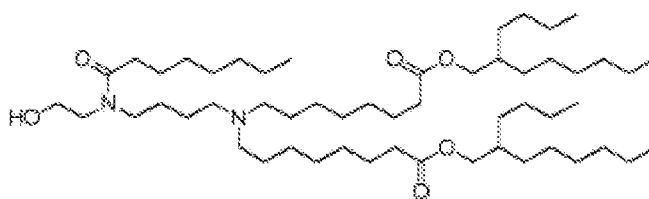
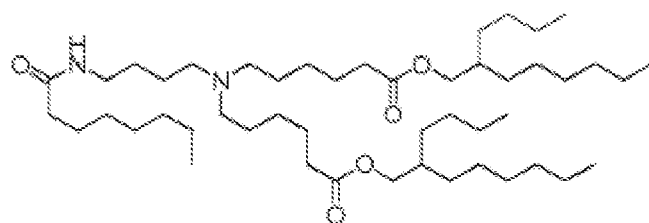
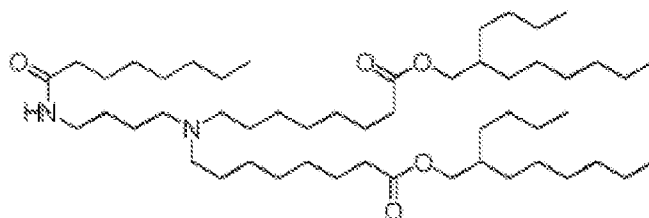
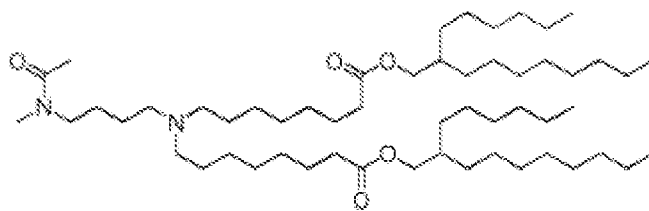


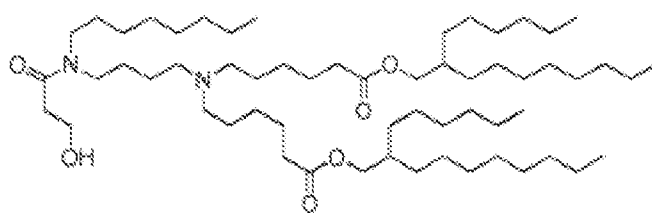
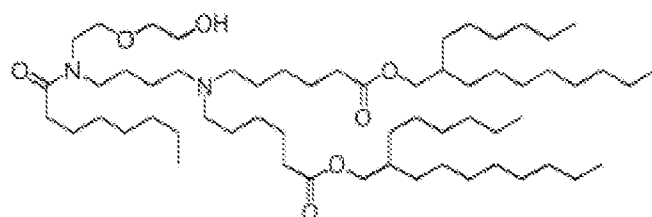
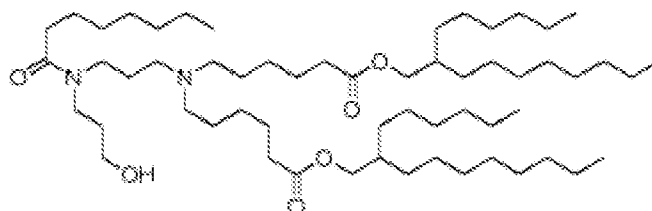
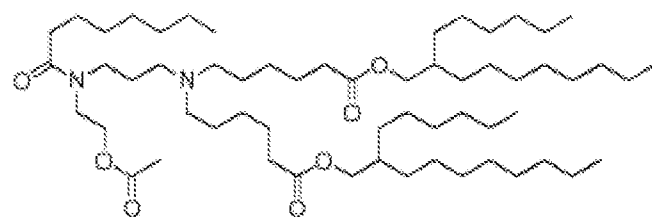
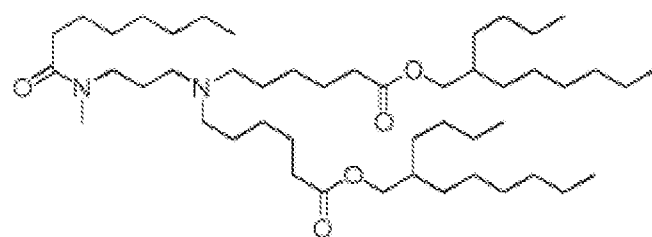
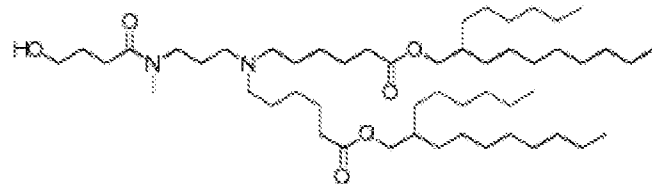
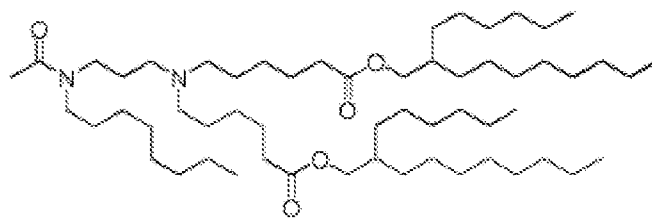


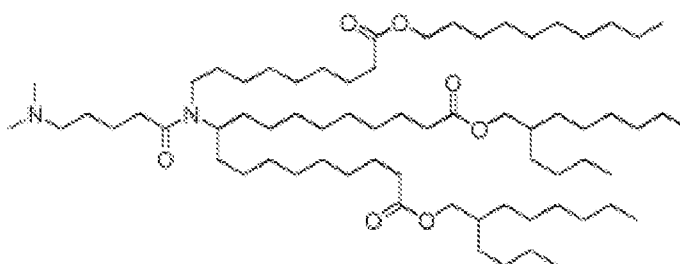
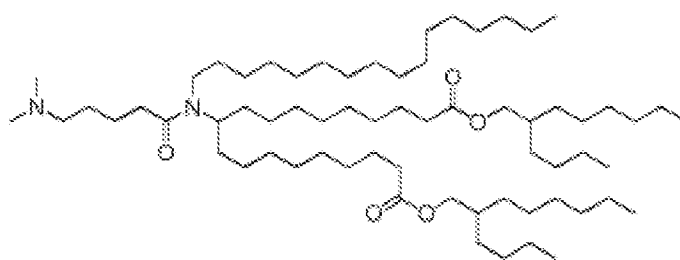
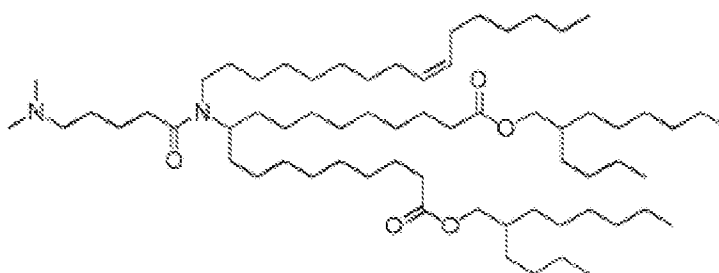
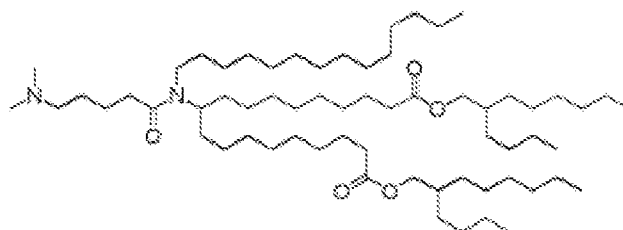
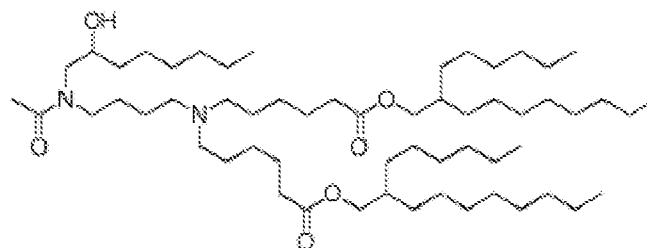
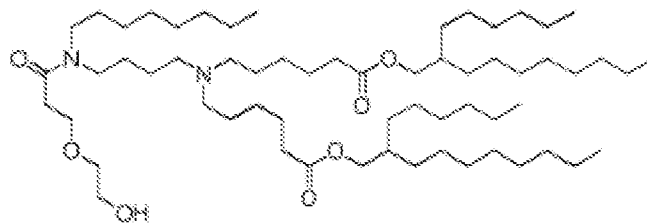


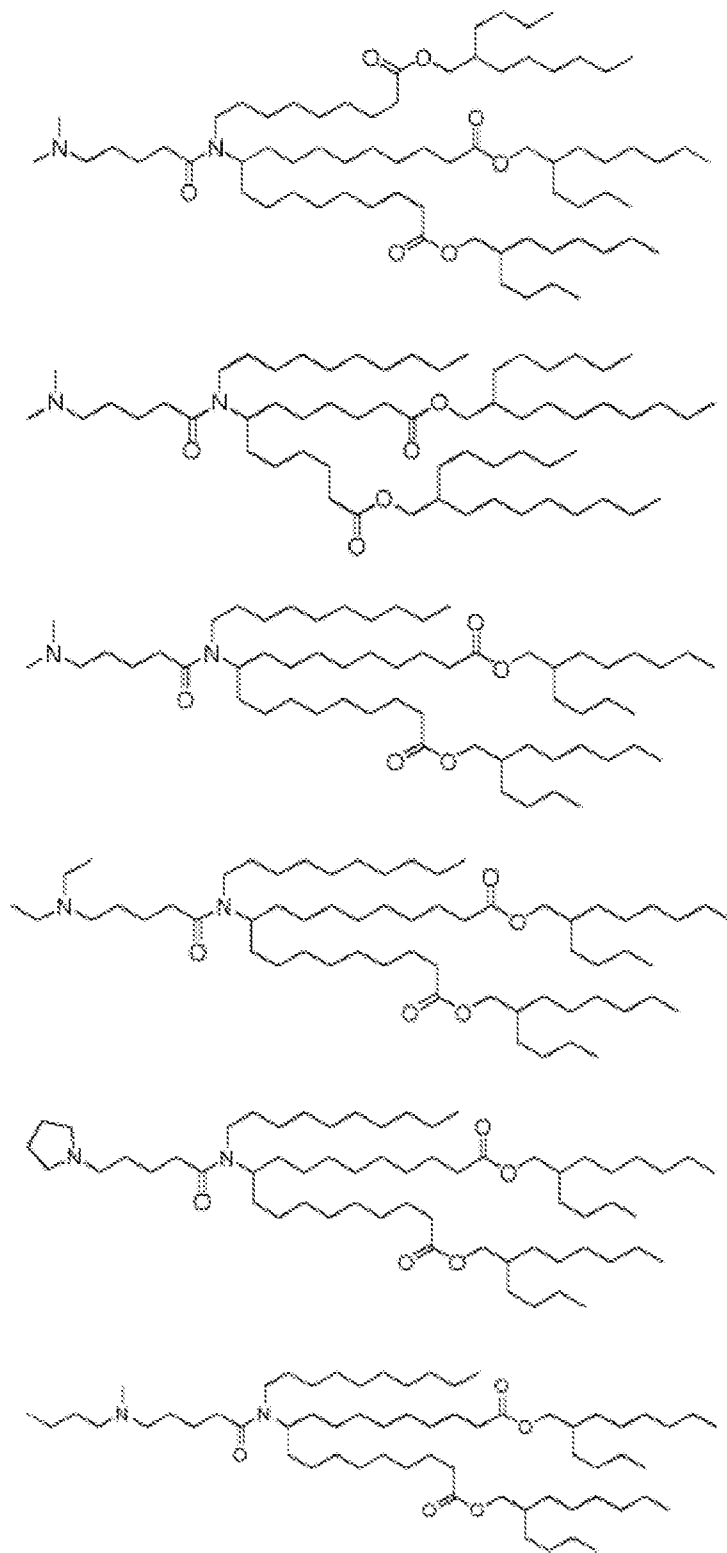


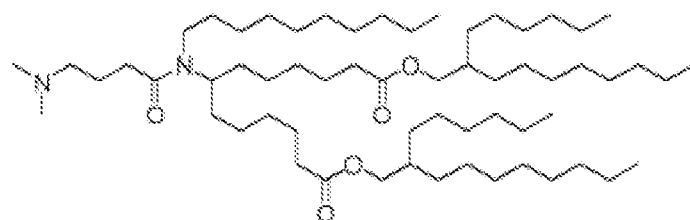
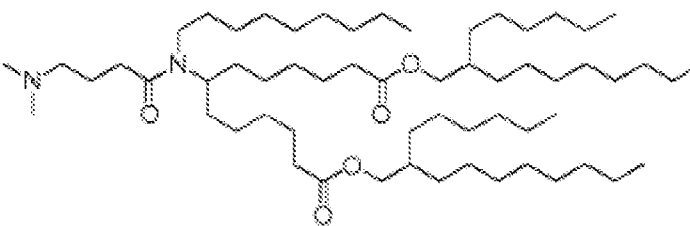
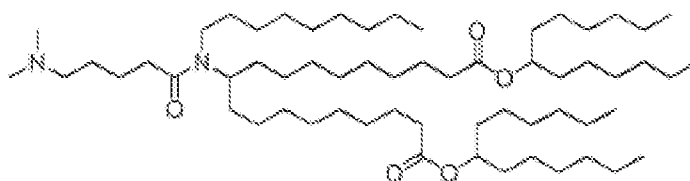
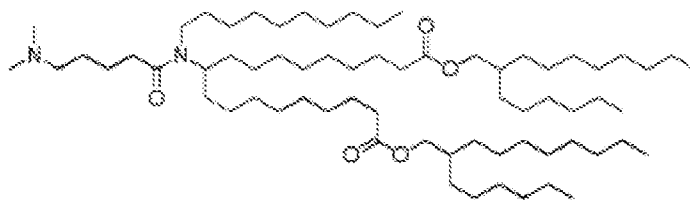
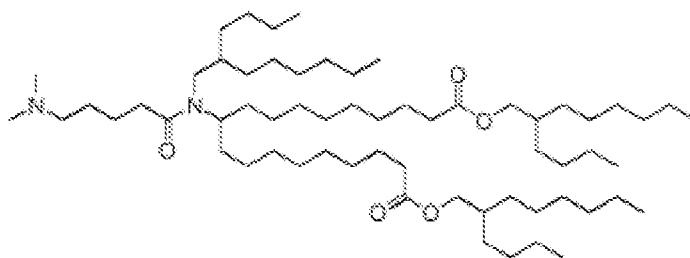
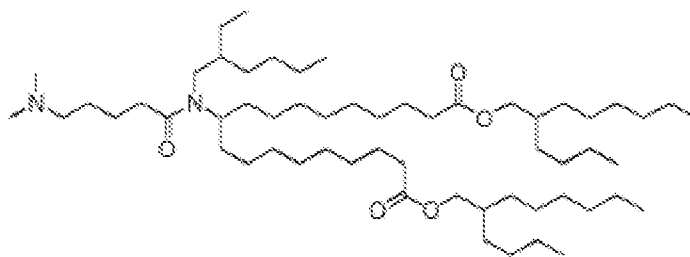


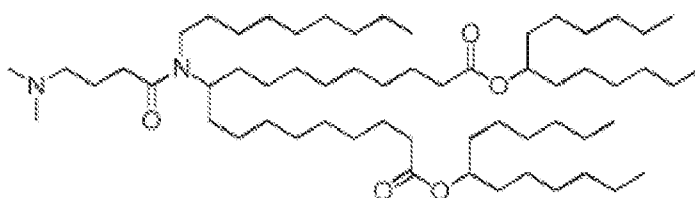
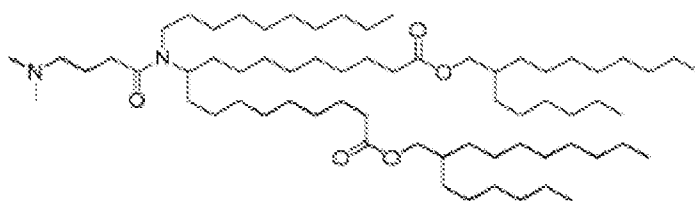
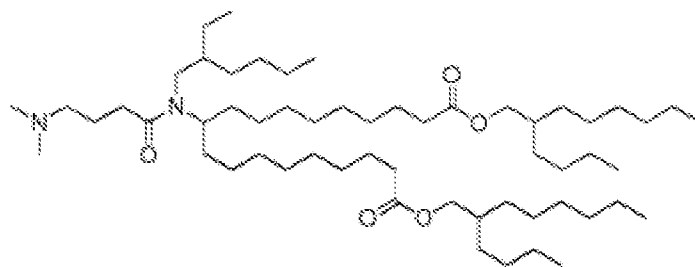
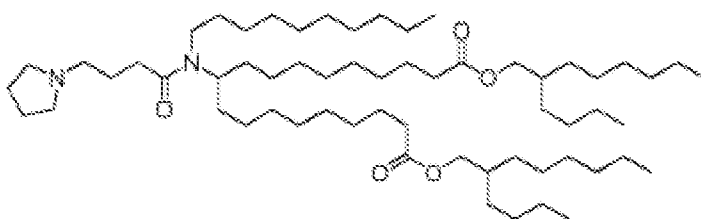
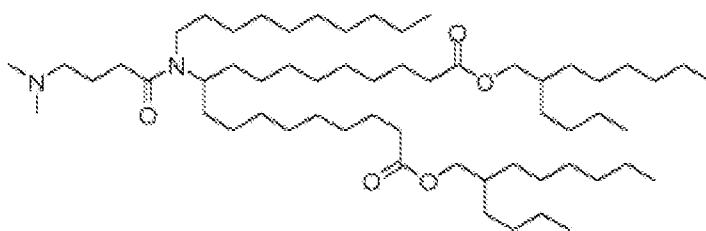
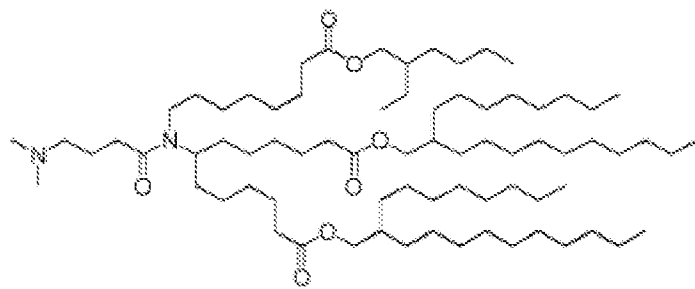


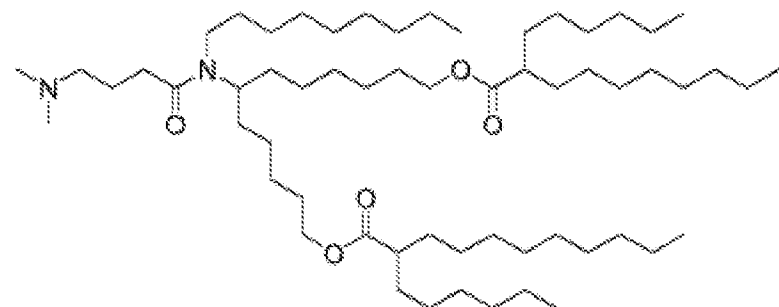
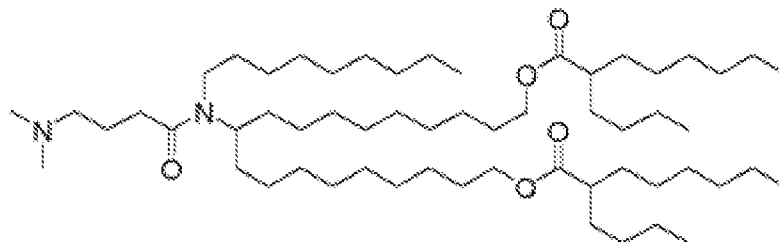
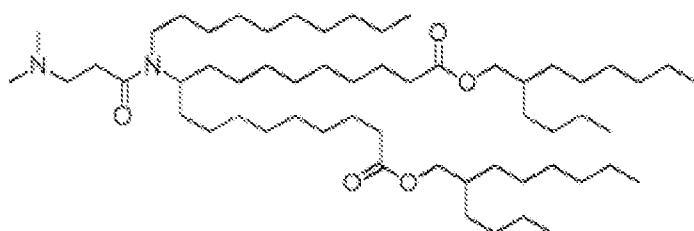
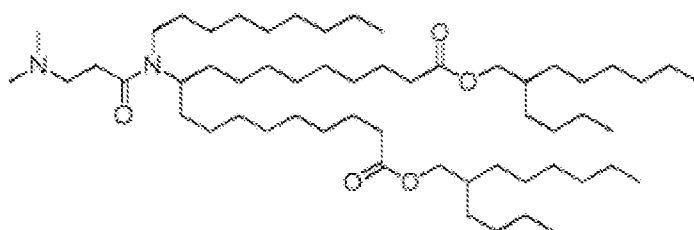
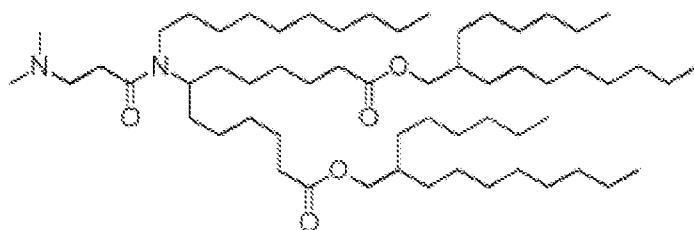
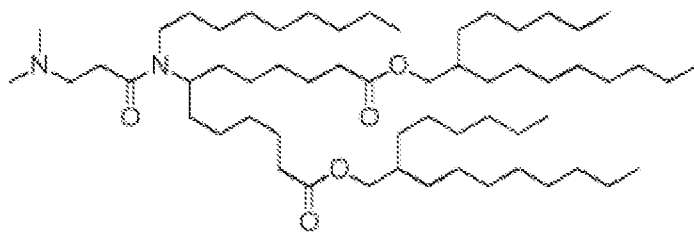


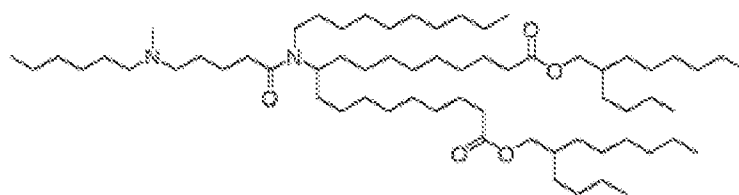
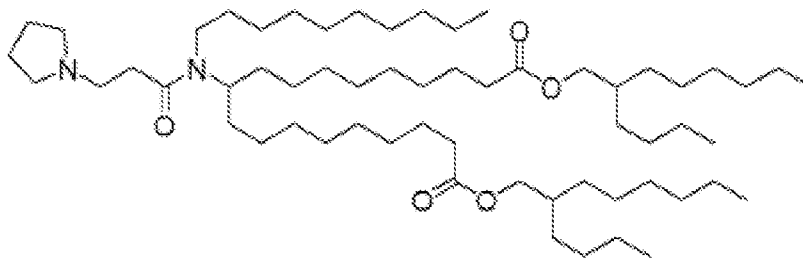
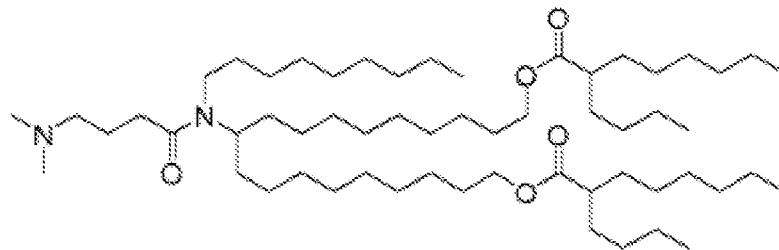
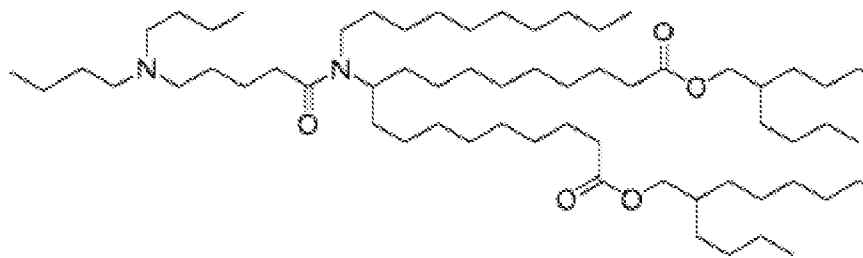
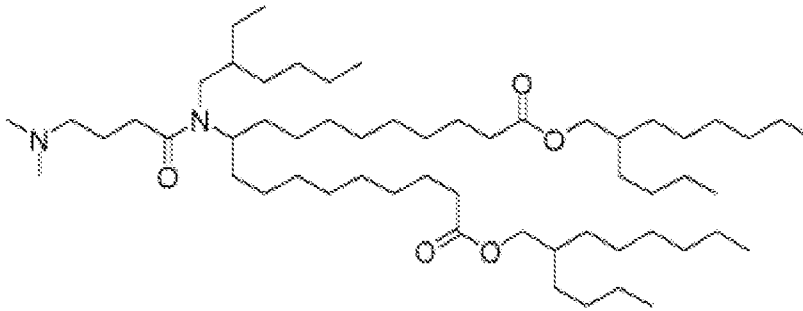
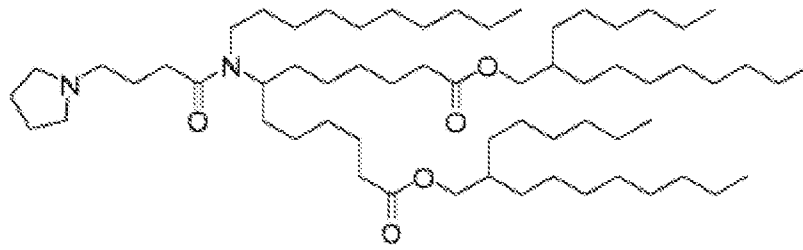


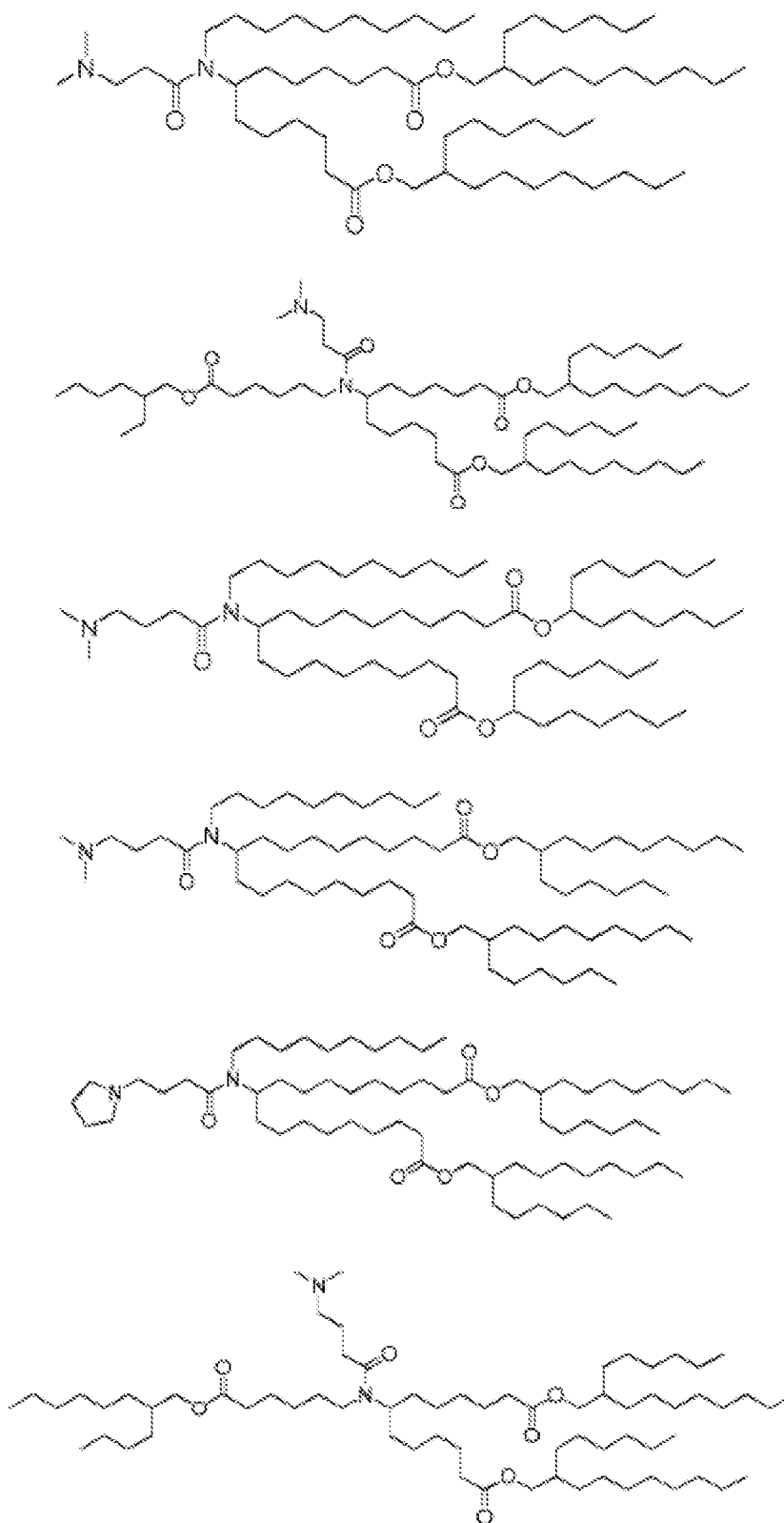












6. LNP za uporabu prema bilo kojem od zahtjeva 1-5, naznačen time što je molarni omjer kationskog lipida prema neutralnom lipidu u rasponu od oko 2:1 do oko 8:1.
7. LNP za uporabu prema bilo kojem od zahtjeva 1-6, naznačen time što je neutralni lipid distearoilfosfatidilkolin (DSPC), dioleoilfosfatidilkolin (DOPC), dipalmitoilfosfatidilkolin (DPPC), dioleoilfosfatidilglicerol (DOPG), dipalmitoilfosfatidilglicerol (DPPG), dioleoilfosfatidiletanolamin (DOPE), palmitoiloleo ilfosfatidilkolin (POPC), palmitoiloleoilfosfatidiletanolamin (POPE) i dioleoilfosfatidiletanolamin 4-(N-maleimidometil)-cikloheksan-1 karboksilat (DOPE-mal), dipalmitoil fosfatidil etanolamin (DPPE), dimiristoilfosfoetanolamin (DMPE), distearoil-
- 5

fosfatidiletanolamin (DSPE), 16-O -monometil PE, 16-O-dimetil PE, 18-1-trans PE, 1-stearioil-2-oleoilfosfatidijetanol amin (SOPE) ili 1,2-dielaidoylsn-glicero-3-fofoetanolamin (transDOPE).

8. LNP-ovi za uporabu prema bilo kojem od zahtjeva 1-6, naznačeni time što je neutralni lipid DSPC, DPPC, DMPC, DOPC, POPC, DOPE ili SM.
- 5 9. LNP-ovi za uporabu prema bilo kojem od zahtjeva 1-6, naznačeni time što je neutralni lipid DSPC.
10. LNP-ovi za uporabu prema bilo kojem od zahtjeva 1-9, naznačeni time što je steroid kolesterol.
11. LNP-ovi za uporabu prema bilo kojem od zahtjeva 1-10, naznačeni time što je molarni omjer kationskog lipida prema steroidu u rasponu od 5:1 do 1:1.
- 10 12. LNP-ovi za uporabu prema bilo kojem od zahtjeva 1-11, naznačeni time što je molarni omjer kationskog lipida prema lipidu konjugiranom polimerom u rasponu od oko 100:1 do oko 20:1.
13. LNP-ovi za uporabu prema bilo kojem od zahtjeva 1-12, naznačeni time što je nukleinska kiselina odabrana između antisens i messenger RNA.
14. LNP-ovi za uporabu prema bilo kojem od zahtjeva 1-13, naznačeni time što nukleinska kiselina sadrži mRNA sposobnu prevesti imunogeni protein.
- 15 15. LNP-ovi za uporabu prema bilo kojem od zahtjeva 1-14, naznačeni time što davanje uključuje intravenozno davanje.