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[Continued on next page]

(54) Title: COMPOUNDS FOR TARGETING DRUG DELIVERY AND ENHANCING SIRNA ACTIVITY

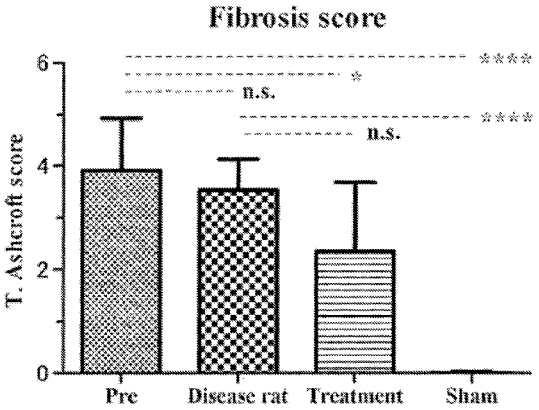
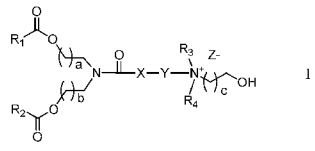


FIG. 7



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(57) Abstract: Here described are compounds of formula I: wherein R_1 and R_2 is independently selected from a group consisting of C_{10} to C_{18} alkyl, C_{12} to C_{18} alkenyl, and oleyl group; wherein R_3 and R_4 are independently selected from a group consisting of C_1 to C_6 alkyl, and C_2 to C_6 alkanol; wherein X is selected from a group consisting of $-CH_2-$, -S-, and -O- or absent; wherein Y is selected from $-(CH_2)n$, $-S(CH_2)_n$, $-O(CH_2)_n-$, thiophene, $-SO_2(CH_2)_n-$, and ester, wherein n = 1 -4; wherein a = 1 -4; wherein b=1 -4; wherein c=1-4; and wherein Z is a counterion; and compounds consisting of the structure $(\text{targeting molecule})_m$-linker-$(\text{targeting molecule})_n$, wherein the targeting molecule is a retinoid or a fat soluble vitamin having a specific receptor on the target cell; wherein m and n are independently 0, 1, 2 or 3; and wherein the linker comprises a polyethylene glycol (PEG) or PEG-like molecule, as well as compositions and pharmaceutical formulations including one or both of these compounds which are useful for the delivery of therapeutic agents; and methods of using these compositions and pharmaceutical formulations.

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AMENDED CLAIMS
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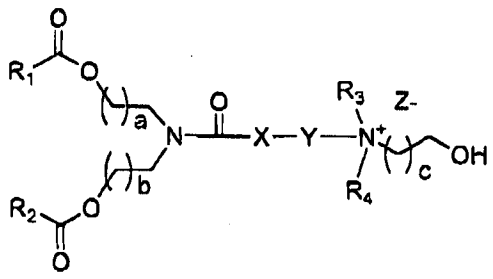
1. A compound of formula I



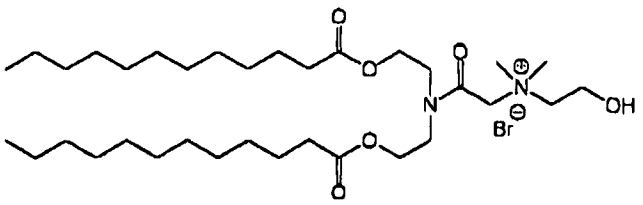
I

wherein R_1 and R_2 is independently selected from a group consisting of C_{12} to C_{18} alkyl, C_{12} to C_{18} alkenyl, and oleyl group; wherein R_3 and R_4 are independently selected from a group consisting of C_1 to C_6 alkyl, and C_2 to C_6 alkanol; wherein X is selected from a group consisting of $-CH_2-$, -S-, and -O- or absent; wherein Y is selected from $-(CH_2)_n$, $-S(CH_2)_n$, $-O(CH_2)_n-$, thiophene, $-SO_2(CH_2)_n-$, and $-OCO(CH_2)_n$, wherein n = 1-4; wherein a = 1-4; wherein b=1-4; wherein c=1-4; and wherein Z is a counterion.

2. The compound of claim 1, wherein the counterion is a halogen or mesylate.

AMENDED SHEET (ARTICLE 19)

3. The compound of claim 1 that is selected from the group consisting of



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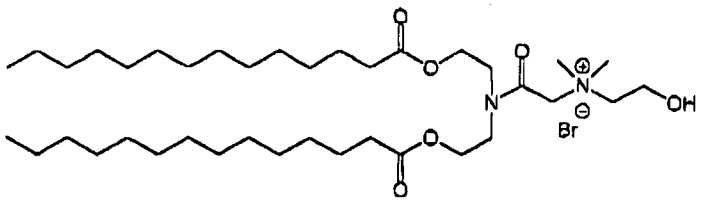

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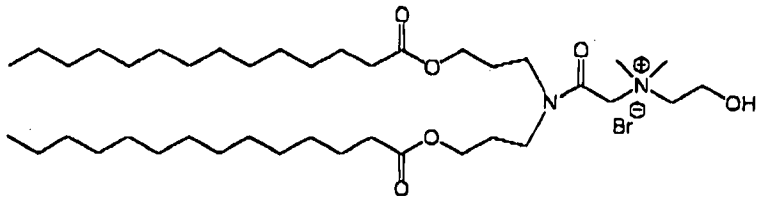
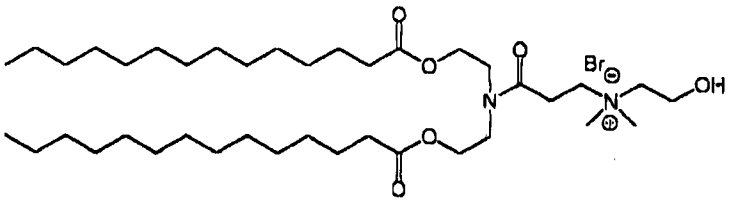
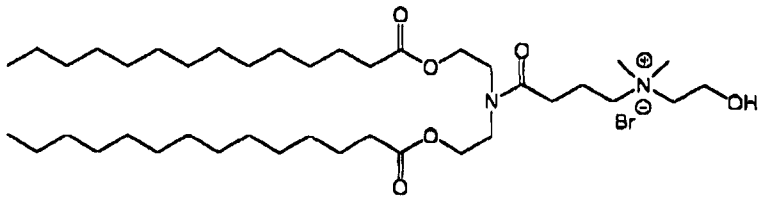


Pr-HEDC



HE-Et-DC



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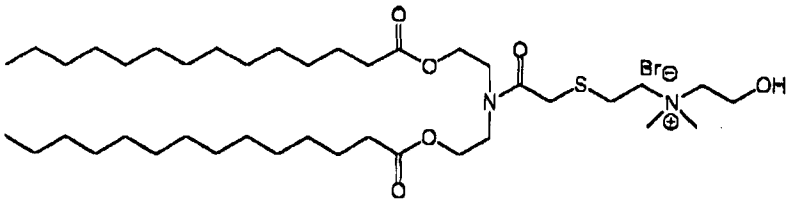

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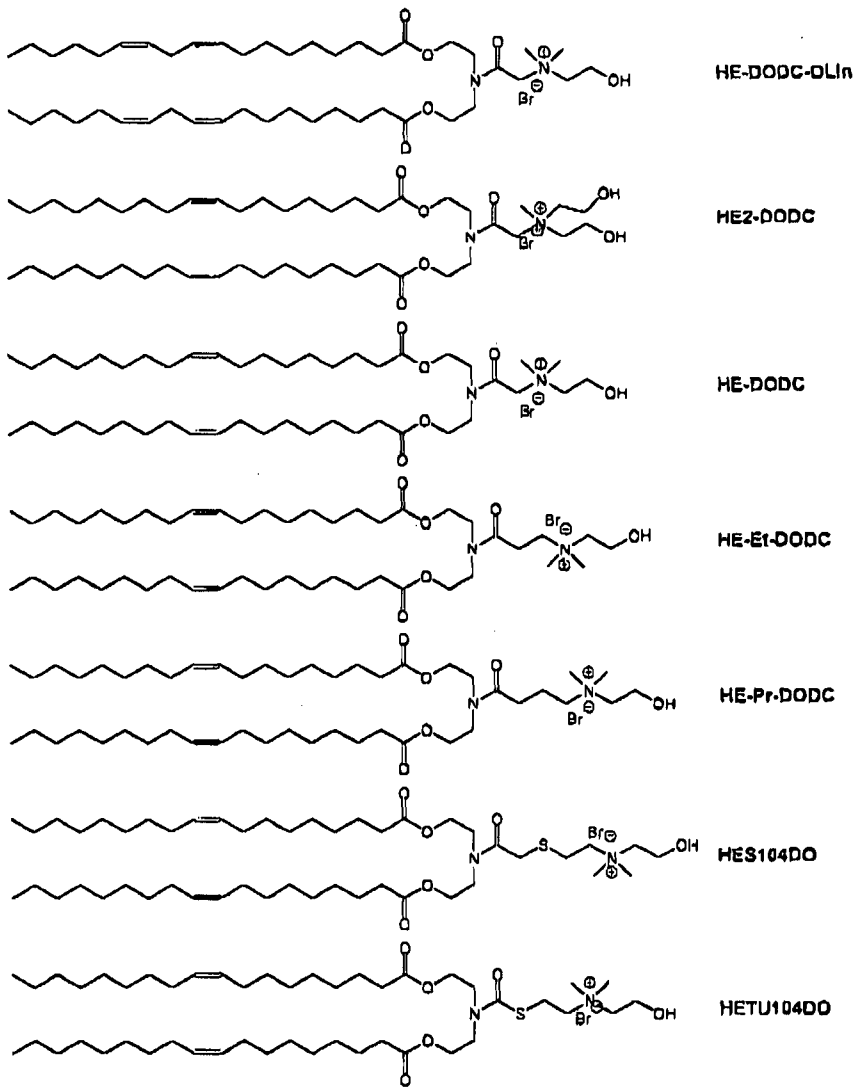
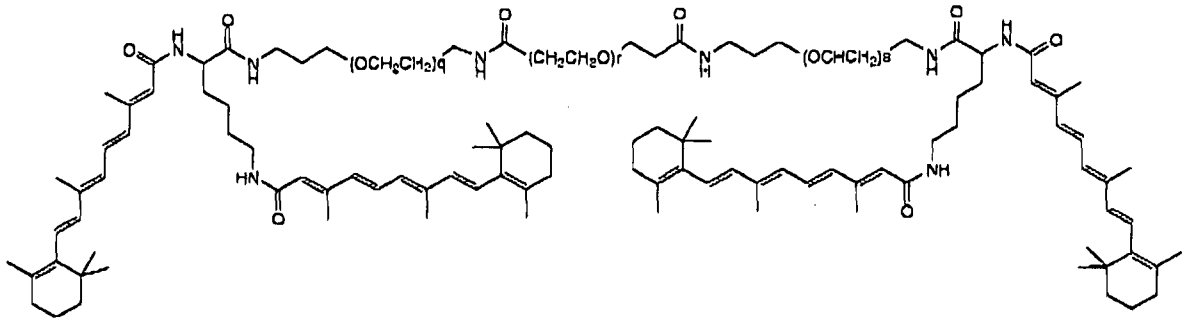


4. A stellate-cell-specific drug carrier comprising a stellate cell specific amount of a retinoid molecule and a cationic lipid consisting of the compound according to claim 3.

5. The drug carrier of claim 4, further comprising a liposomal composition.

6. The drug carrier of claim 5, wherein the liposomal composition comprises a lipid vesicle comprising a bilayer of lipid molecules.

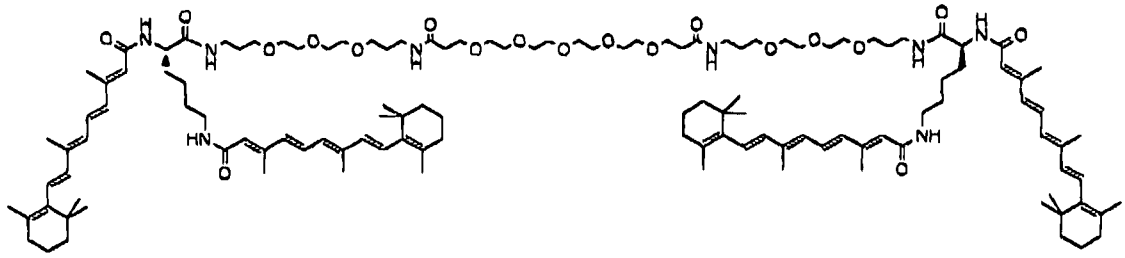
7. The drug carrier of claim 4, wherein the retinoid conjugate is a compound of formula II:



II

wherein q, r, and s are each independently 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10; or a enantiomer, diastereomer, or mixture of stereoisomers thereof.

8. The drug carrier of claim 7, wherein the compound of formula II is

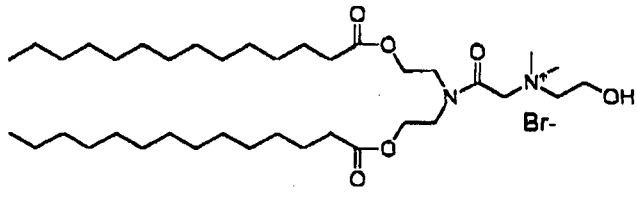


9. The drug carrier of claim 6, wherein the retinoid molecule is at least partially exposed on the exterior of the drug carrier before the drug carrier reaches the stellate cell.

10. The drug carrier of claim 4, wherein the retinoid is 0.2 mol% to 20 mol% of the lipid molecules.

11. The drug carrier of claim 6, wherein the cationic lipid is at a concentration of 5-50 mol %.

12. The drug carrier of claim 6, wherein cationic lipid has the structure



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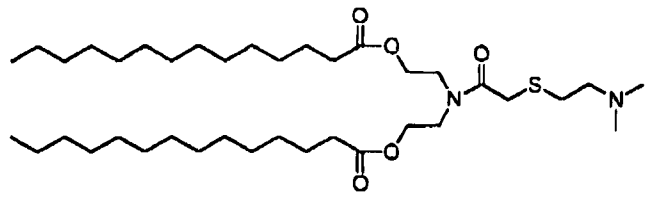
13. The drug carrier of claim 6, wherein the lipid molecules further comprise a PEG-lipid.

14. The drug carrier of claim 13, wherein the PEG-lipid is at a concentration of 1 to 10 mol %.

15. The drug carrier of claim 13, wherein the PEG-lipid is PEG-DMPE.

16. The drug carrier of claim 6, wherein the lipid molecules further comprise an ionizable cationic lipid.

17. The drug carrier of claim 16, wherein the ionizable cationic lipid has the structure



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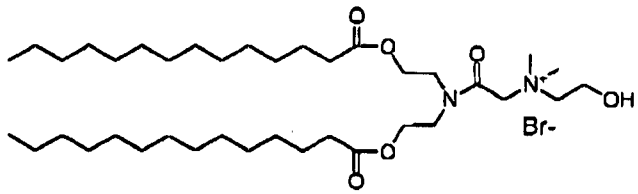
18. The drug carrier of claim 16, wherein the ionizable cationic lipid is present at a concentration of 5 to 45 mol %.

19. The drug carrier of claim 6, wherein the lipid molecules further comprise a combination of a quaternary amine cationic lipid and an ionizable cationic lipid.

20. The drug carrier of claim 19, wherein the ionizable cationic lipid is the immediate synthetic precursor to the quaternary amine cationic lipid.

21. The drug carrier of claim 19, wherein the quaternary amine cationic lipid has the structure



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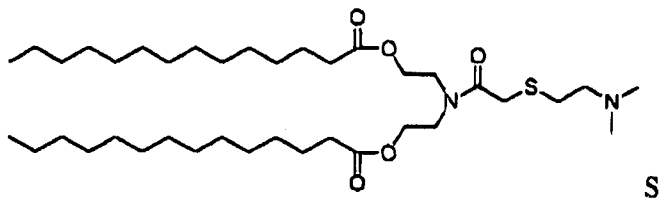
and the ionizable cationic lipid has the structure



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22. The drug carrier of claim 6, wherein the lipid molecules further comprise a non-cationic lipid.

23. The drug carrier of claim 22, wherein the non-cationic lipid is a phospholipid.

24. The drug carrier of claim 22, wherein the phospholipid is DOPE.

25. The drug carrier of claim 22, wherein the phospholipid is at a concentration of 0 to 55 mol %.

26. The drug carrier of claim 22, wherein the non-cationic lipid is cholesterol.

27. The drug carrier of claim 22, wherein cholesterol is at a concentration of 0 to 55 mol %.

28. The drug carrier of claim 4, further comprising a nucleic acid.

29. The drug carrier of claim 28, wherein the nucleic acid is an siRNA that is capable of knocking down expression of hsp47 mRNA in the stellate cell.

30. The drug carrier of claim 28, further comprising siRNA.

31. The drug carrier of claim 30, wherein the siRNA is encapsulated by the liposome and is inaccessible to the aqueous medium.

32. The drug carrier of claim 30, wherein the siRNA is complexed on the outer surface of the liposome and accessible to the aqueous medium.

33. A compound for facilitating drug delivery to a target cell, consisting of the structure (targeting molecule)$_n$-linker-(targeting molecule)$_n$, wherein the targeting molecule is a retinoid or a fat soluble vitamin having a specific receptor on the target cell; wherein n=0, 1, 2 or 3; and wherein the linker comprises a polyethylene glycol (PEG) or PEG-like molecule.

34. The compound of claim 33, wherein the retinoid is selected from the group consisting of vitamin A, retinoic acid, tretinoin, adapalene, 4-hydroxy(phenyl)retinamide (4-HPR), retinyl palmitate, retinal, saturated retinoic acid, and saturated, demethylated retinoic acid.

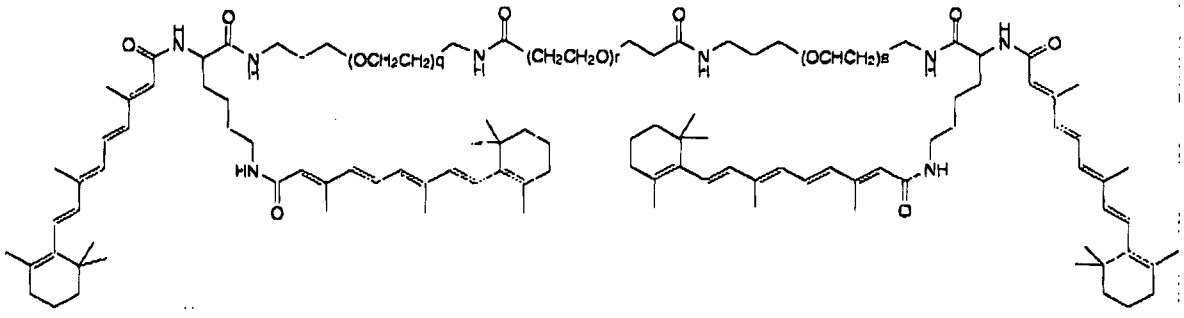
35. The compound of claim 33, wherein the fat-soluble vitamin is vitamin D, vitamin E, or vitamin K.

36. The compound of claim 33, wherein the linker is selected from the group consisting of bis-amido-PEG, tris-amido-PEG, tetra-amido-PEG, Lys-bis-amido-PEG Lys, Lys-tris-amido-PEG-Lys, Lys-tetr-amido-PEG-Lys, Lys-PEG-Lys, PEG2000, PEG1250, PEG1000, PEG750, PEG550, PEG-Glu, Glu, C6, Gly3, and GluNH.

37. The compound of claim 33, wherein the compound is selected from the group consisting of retinoid-PEG-retinoid, (retinoid)$_2$-PEG-(retinoid)$_2$, VA-PEG2000-VA, (retinoid)$_2$-bis-amido-PEG-(retinoid)$_2$, (retinoid)$_2$-Lys-bis-amido-PEG-Lys-(retinoid)$_2$.

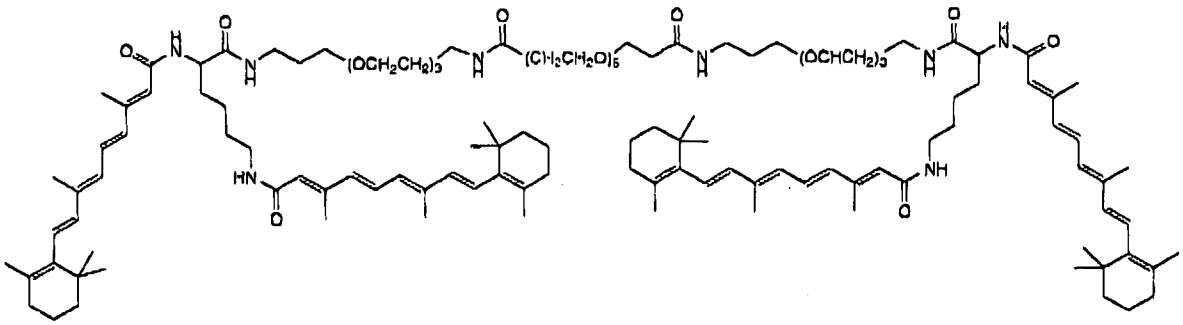
38. The compound of claim 37, wherein the retinoid is selected from the group consisting of vitamin A, retinoic acid, tretinoin, adapalene, 4-hydroxy(phenyl)retinamide (4-HPR), retinyl palmitate, retinal, saturated retinoic acid, and saturated, demethylated retinoic acid.

39. The compound of claim 38, wherein the compound is a composition of formula



wherein q, r, and s are each independently 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10.

40. The compound of claim 38, wherein the composition of formula is



41. The compound of claim 33, wherein the PEG is mono disperse.

42. A stellate-cell-specific drug carrier comprising a stellate cell specific amount of a retinoid molecule consisting of the structure $(retinoid)_m$-linker-$(retinoid)_n$; wherein m and n are independently 0, 1, 2, or 3; and wherein the linker comprises a polyethylene glycol (PEG) or PEG-like molecule, and a liposomal composition comprising the compound of claim 1.

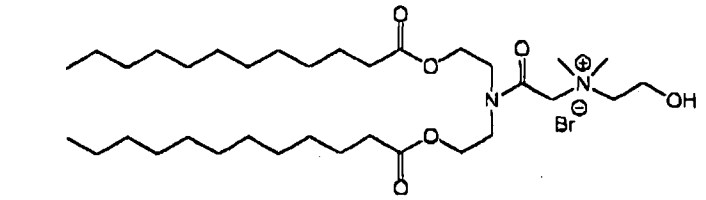
43. Cancelled.

44. The drug carrier of claim 42, wherein the liposomal composition comprises a lipid vesicle comprising a bilayer of lipid molecules.

45. The drug carrier of claim 42, wherein the retinoid molecule is at least partially exposed on the exterior of the drug carrier before the drug carrier reaches the stellate cell.

46. The drug carrier of claim 44, wherein the retinoid is 0.1 mol% to 20 mol% of the lipid molecules.

47. The drug carrier of claim 44, wherein the lipid molecules comprise one or more lipids selected from the group consisting of



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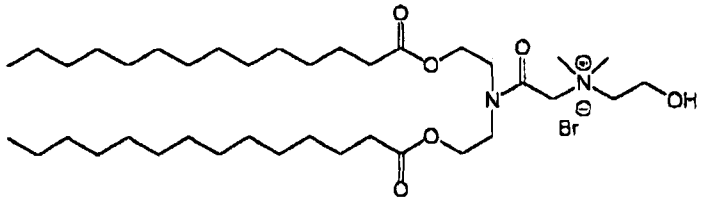

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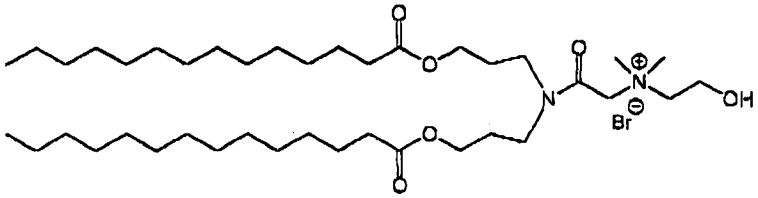

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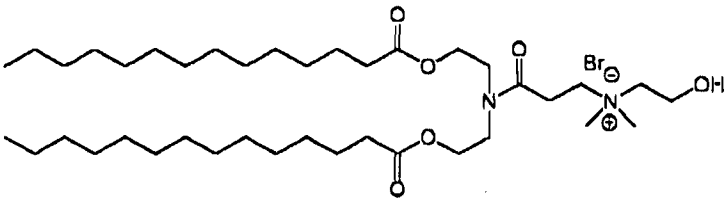

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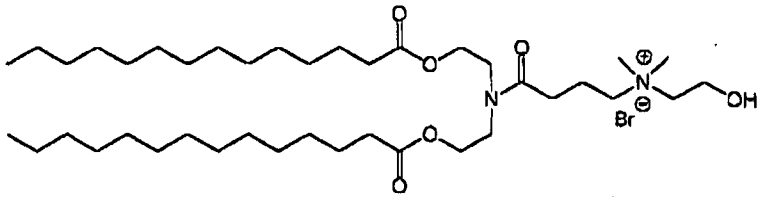

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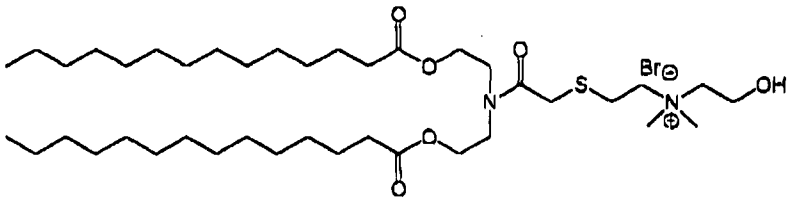

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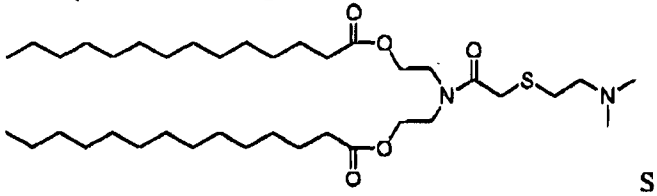
48. The drug carrier of claim 47, wherein the lipid molecules further comprise a compound consisting of the structure



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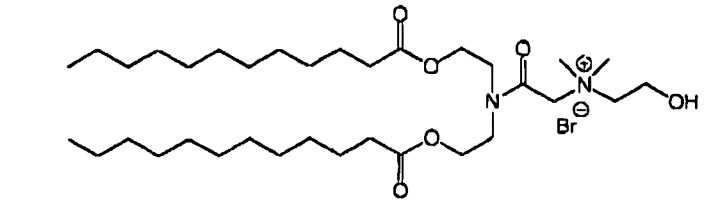
49. The drug carrier of claim 44, further comprising a nucleic acid.

50. The drug carrier of claim 49, wherein the nucleic acid is an siRNA that is capable of knocking down expression of hsp47 mRNA in the stellate cell.

51. A compound for facilitating drug delivery to a target cell, consisting of the structure $(lipid)_m$-linker-$(targeting\ molecule)_n$, wherein the targeting molecule is a retinoid or a fat soluble vitamin having a specific receptor on the target cell; wherein m and n are independently 0, 1, 2, or 3; and wherein the linker comprises a polyethylene glycol (PEG) molecule, and the lipid consists of the compound of claim 1.

52. The compound of claim 51, wherein the lipid is selected from one or more of the group consisting of



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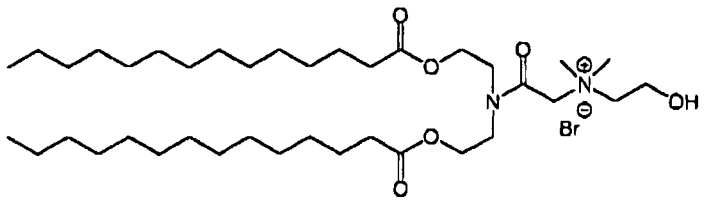

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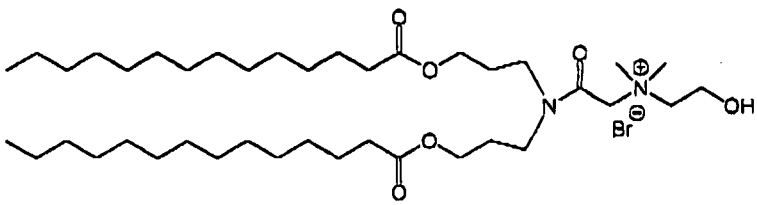

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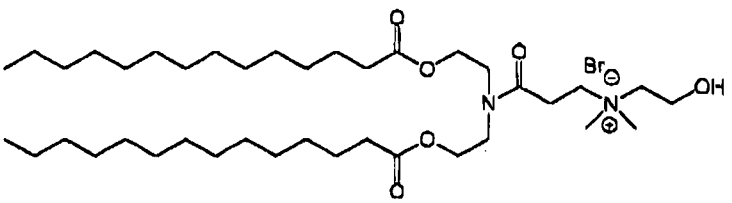

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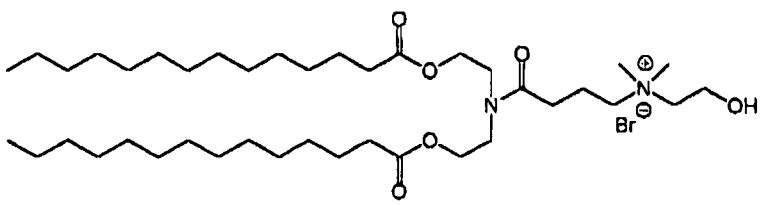

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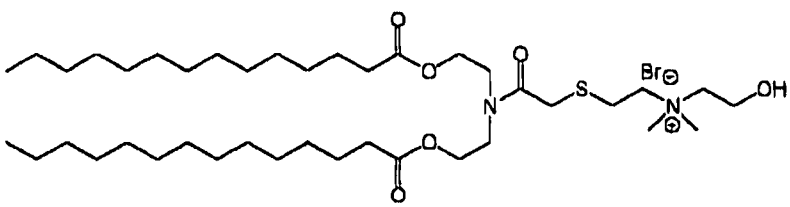

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53. The compound of claim 52, wherein the retinoid is selected from the group consisting of vitamin A, retinoic acid, tretinoin, adapalene, 4-hydroxy(phenyl)retinamide (4-HPR), retinyl palmitate, retinal, saturated retinoic acid, and saturated, demethylated retinoic acid.

54. The compound of claim 52, wherein the fat-soluble vitamin is vitamin D, vitamin E, or vitamin K.

55. The compound of claim 52, wherein the linker is selected from the group consisting of bis-amido-PEG, tris-amido-PEG, tetra-amido-PEG, Lys-bis-amido-PEG Lys, Lys-tris-amido-PEG-Lys, Lys-tetr-amido-PEG-Lys, Lys-PEG-Lys, PEG2000, PEG1250, PEG1000, PEG750, PEG550, PEG-Glu, Glu, C6, Gly3, and GluNH.

56. The compound of claim 55, selected from the group consisting of DSPE-PEG-VA, DSPE-PEG2000-Glu-VA, DSPE-PEG550-VA, DOPE-VA, DOPE-Glu-VA, DOPE-Glu-NH-VA, DOPE-Gly3-VA, DC-VA, DC-6-VA, and AR-6-VA.

57. A stellate-cell-specific drug carrier comprising a stellate cell specific amount of a targeting molecule consisting of the molecule $(lipid)_m$-linker-$(retinoid)_n$, wherein m and n are independently 0, 1, 2 or 3; and wherein the linker comprises a polyethylene glycol (PEG) or PEG-like molecule, and the lipid consists of the compound of claim 1.

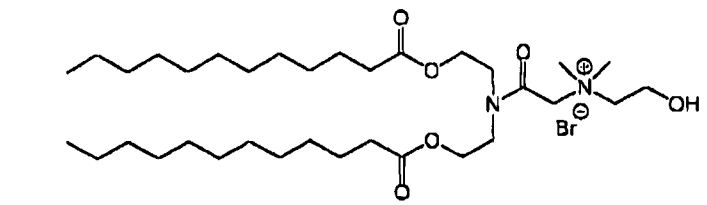
58. The drug carrier of claim 57, further comprising a liposomal composition.

59. The drug carrier of claim 58, wherein the liposomal composition comprises a lipid vesicle comprising a bilayer of lipid molecules.

60. The drug carrier of claim 59, wherein the retinoid molecule is at least partially exposed on the exterior of the drug carrier before the drug carrier reaches the stellate cell.

61. The drug carrier of claim 59, wherein the retinoid is 0.1 mol% to 20 mol% of the lipid molecules.

62. The drug carrier of claim 59, wherein the lipid molecules comprise one or more lipids selected from the group consisting of



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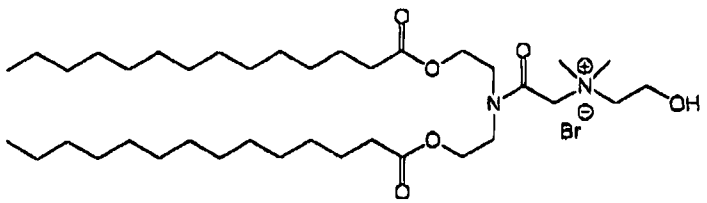

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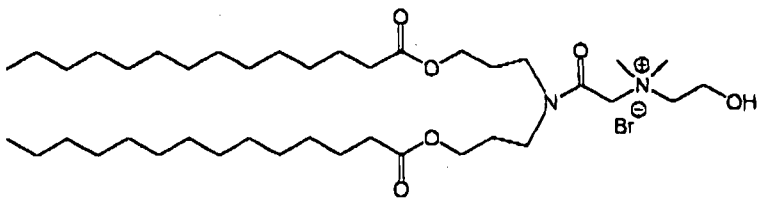
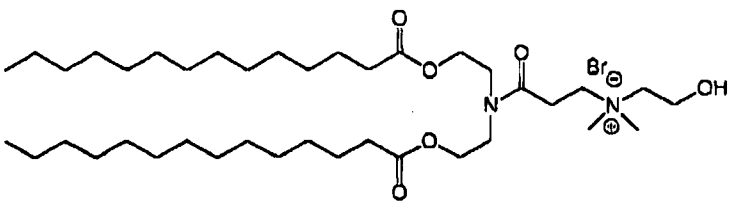
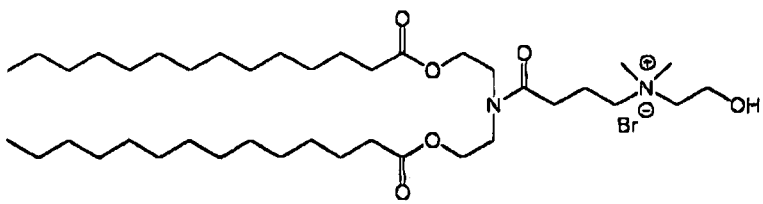


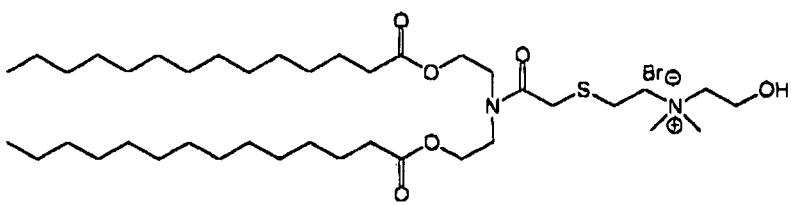
Pr-HEDC



HE-Et-DC



HE-Pr-DC



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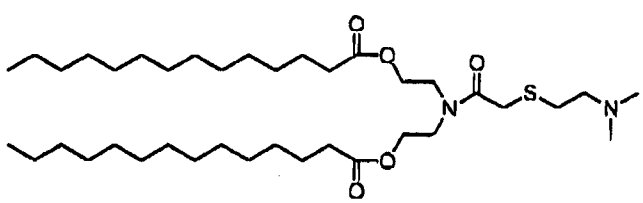
63. The drug carrier of claim 62, wherein the lipid molecules further comprise a compound consisting of the structure



S104.

64. The drug carrier of claim 59, further comprising a nucleic acid.

65. The drug carrier of claim 64, wherein the nucleic acid is an siRNA that is capable of knocking down expression of hsp47 mRNA in the stellate cell.