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(71) Demandeur/Applicant:
AARHUS UNIVERSITET, DK

(72) Inventeurs/Inventors:
GUSTAFSEN, CAMILLA, DK;
MADSEN, SONDERGAARD PEDER, DK;
PEDERSEN, GLERUP SIMON, DK

(74) Agent: BCF LLP

(54) Titre : COMPOSES DESTINES AU TRAITEMENT DE TROUBLES DU METABOLISME DES LIPOPROTEINES
(54) Title: COMPOUNDS FOR TREATMENT OF LIPOPROTEIN METABOLISM DISORDERS

(57) Abrégé/Abstract:
The present disclosure relates to use of heparin analogues as inhibitors of proprotein convertase subtilisin-like/kexin type 9 (PCSK9) for the treatment of lipoprotein metabolism disorders.

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(71) Applicant: **AARHUS UNIVERSITET** [DK/DK]; Nordre Ringgade 1, 8000 Aarhus C (DK).

(72) Inventors: **GUSTAFSEN, Camilla**; Langelandsgade 19, 8000 Aarhus C (DK). **MADSEN, SØNDERGAARD, Peder**; Krogagre 9, 8240 Risskov (DK). **PEDERSEN, GLERUP, Simon**; Solsikkevej 8, 8240 Risskov (DK).

(74) Agent: **HØIBERG P/S**; Adelgade 12, 1304 Copenhagen K (DK).

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(54) Title: COMPOUNDS FOR TREATMENT OF LIPOPROTEIN METABOLISM DISORDERS

(57) Abstract: The present disclosure relates to use of heparin analogues as inhibitors of proprotein convertase subtilisin-like/kexin type 9 (PCSK9) for the treatment of lipoprotein metabolism disorders.

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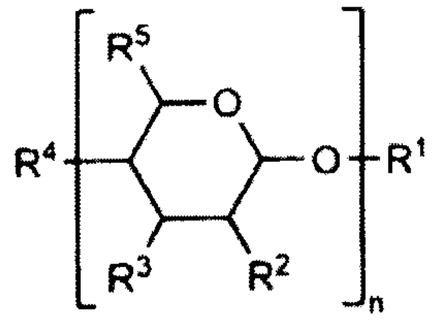
Claims

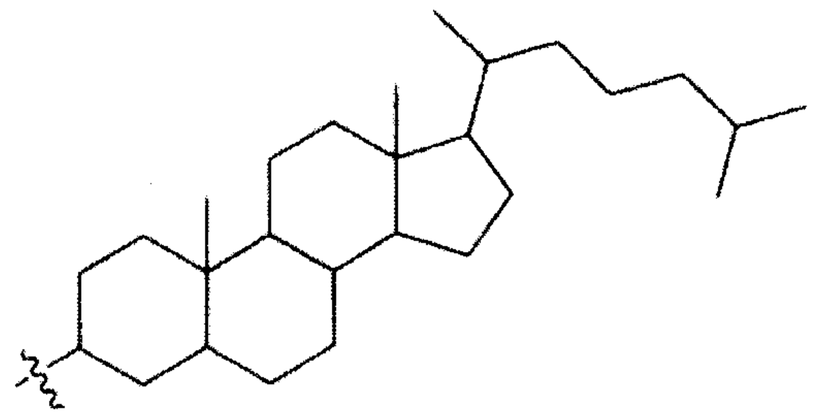
1. A composition comprising a compound having the general structure of formula (I):



(I)

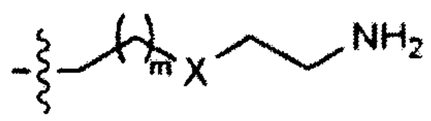
or a pharmaceutically acceptable salt, solvate, polymorph, or tautomer thereof, wherein:

- R^1 comprises a group with a formula selected from:
  a) Formula (XI):



(XI); or

  b) Formula (II):



(II)

wherein:

X is SO_2

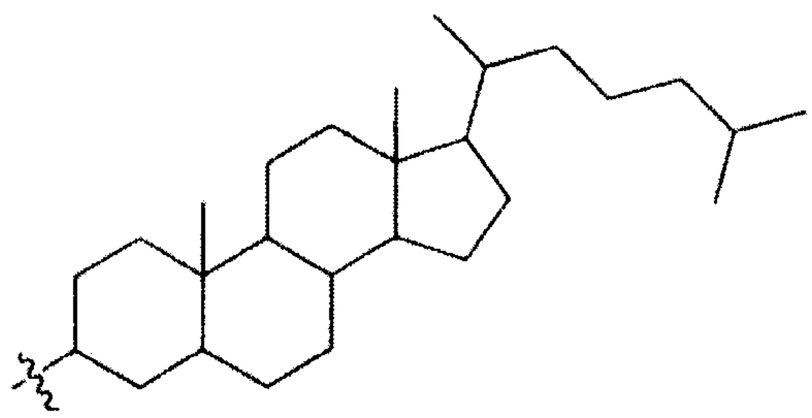
m is an integer independently equal to, or greater than 1;

- each R^2 is independently selected from the group consisting of $-OSO_3^-$, -OH, $-NH_2$, $-NHSO_3^-$, $-NHOCH_3$ and $-OPO_3^{2-}$;
- each R^3 is independently selected from the group consisting of $-OSO_3^-$, -OH and $-OPO_3^{2-}$;
- each R^4 is independently selected from the group consisting of $-OSO_3^-$, -OH, $-OPO_3^{2-}$ and –H;

- each R^5 is independently selected from the group consisting of $-CH_2OSO_3^-$, $-CH_2OH$, $-COO^-$ and $-CH_2OPO_3^{2-}$;
- n is an integer between 3 and 10;

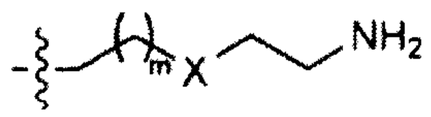
for use in the treatment of a disorder of lipoprotein metabolism in a subject, wherein said disorder of lipoprotein metabolism is selected from the group consisting of diabetes, obesity, metabolic syndrome, xanthoma, hypercholesterolemia, familial hypercholesterolemia, dyslipidemia , hypertriglyceridemia, hyperlipidemia, sitosterolemia, hypertension, angina, acute coronary syndrome, coronary heart disease, atherosclerosis, arteriosclerosis, vascular inflammation and sepsis.

2. The composition for use according to claim 1, wherein R^1 comprises a group of formula (XI):



(XI).

3. The composition for use according to claim 0, wherein R^1 comprises a group of formula (II):

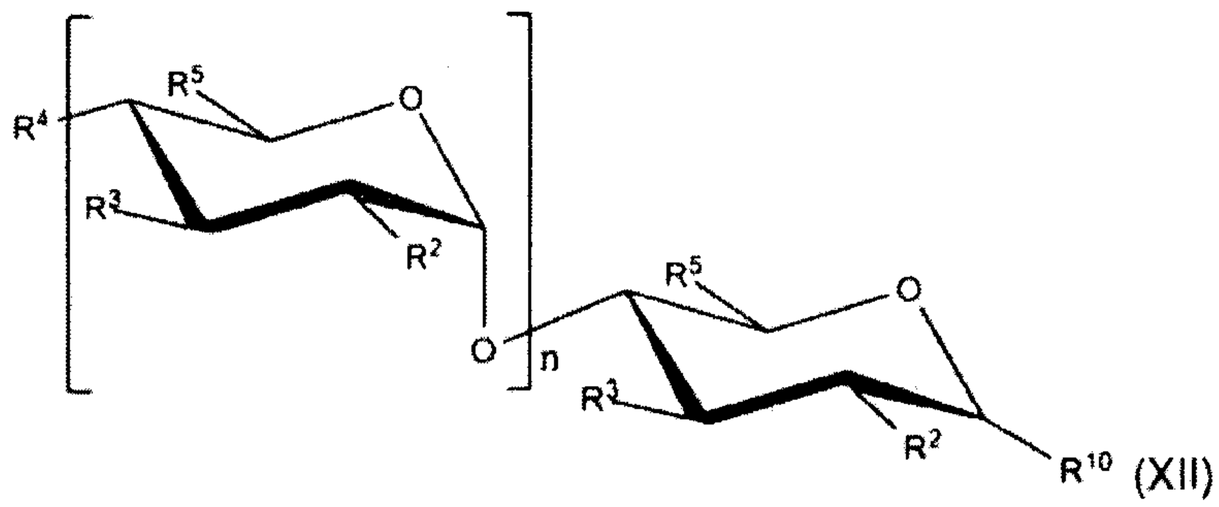


(II)

wherein:

- X is SO_2
- m is an integer independently equal to, or greater than 1.

4. The composition for use according to any one of the preceding claims, wherein the compound has the general structural formula (XII):



(XII)

wherein R^{10} is –O-R^1, and n is an integer between 2 and 9.

5. The composition for use according to any one of the preceding claims, wherein R^2 is $-OSO_3^-$.

6. The composition for use according to any one of the preceding claims, wherein R^3 is $-OSO_3^-$.

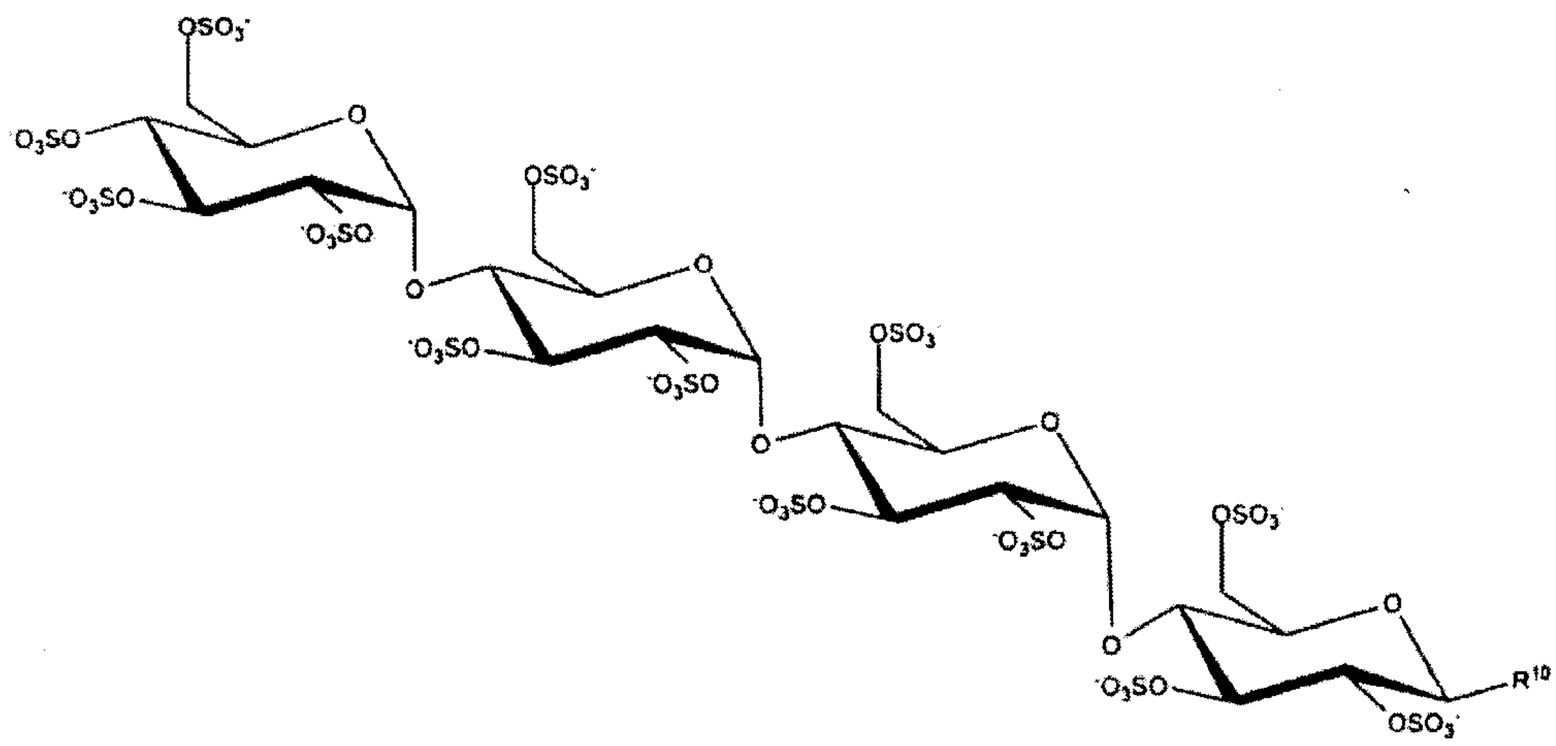
7. The composition for use according to any one of the preceding claims, wherein R^4 is $-OSO_3^-$.

8. The composition for use according to any one of the preceding claims, wherein R^5 is $-CH_2OSO_3^-$.

9. The composition for use according to any one of the preceding claims, wherein R^2, R^3 and R^4 are $-OSO_3^-$ and R^5 is $-CH_2OSO_3^-$.

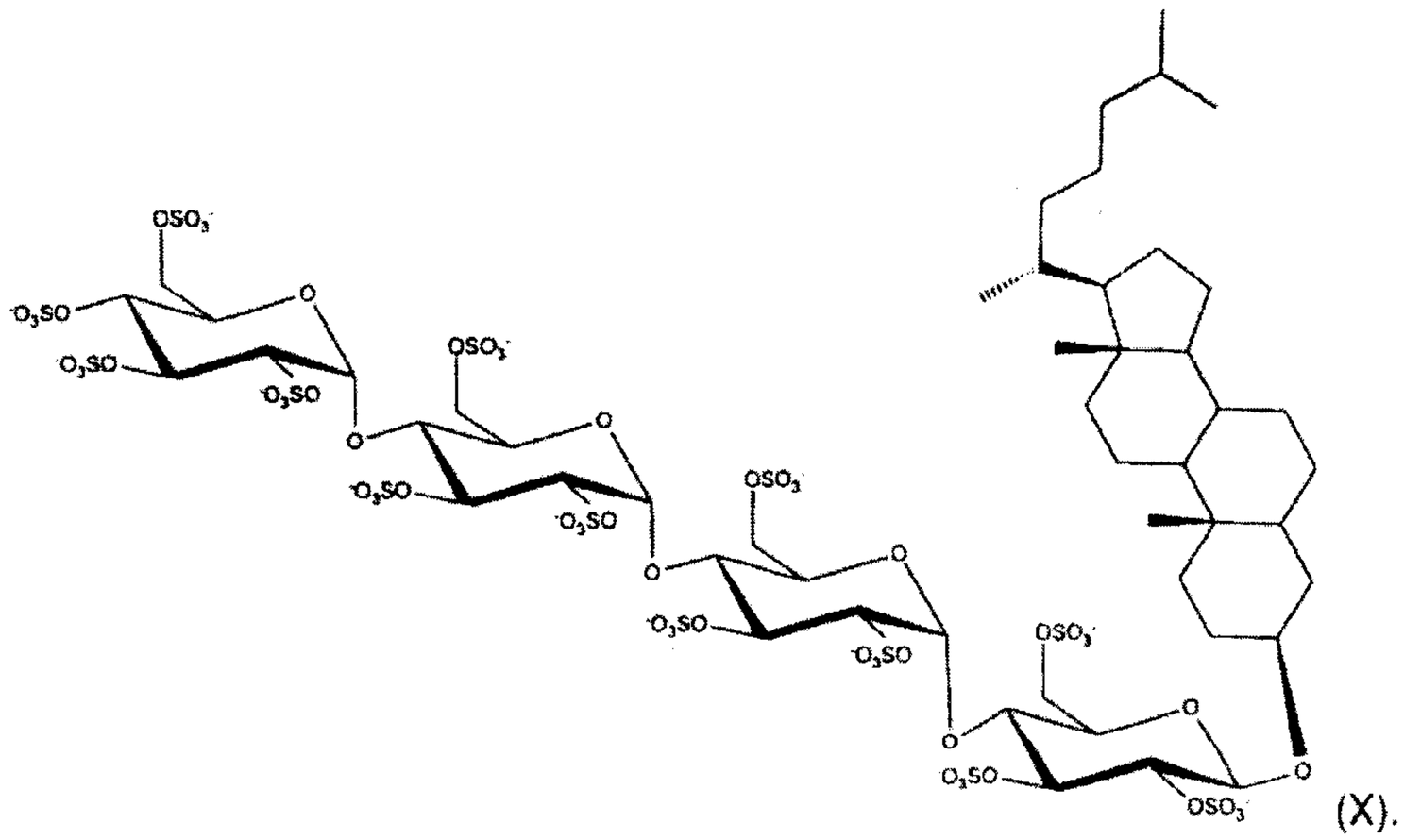
10. The composition for use according to any one of the preceding claims, wherein the salt is sodium salt.

11. The composition for use according to any one of the preceding claims, wherein the compound has the general structural formula (XIV):



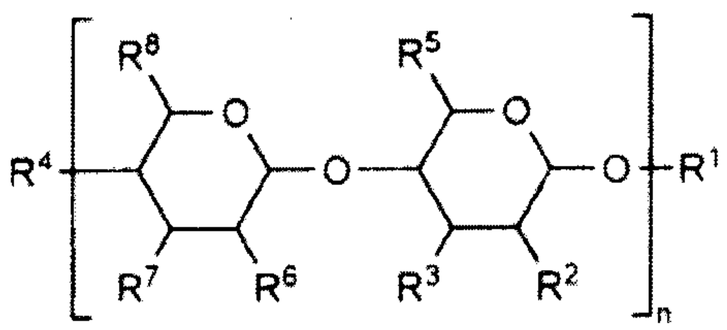
(XIV).

12. The composition for use according to any one of the preceding claims, wherein the compound of formula (I) is compound (X):



(X).

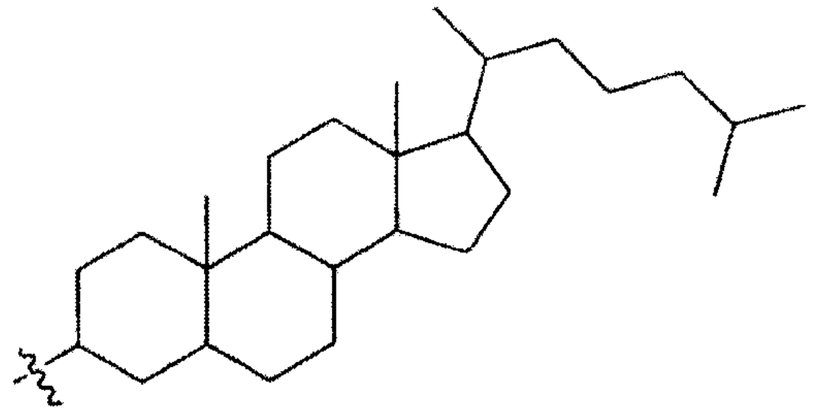
13. The composition for use according to any one of the preceding claims, wherein said compound has the general structure (III):



(III)

wherein:

- R^1 comprises a group with a formula selected from:
  a) Formula (XI):



(XI); or

  b) Formula (II):

(II)

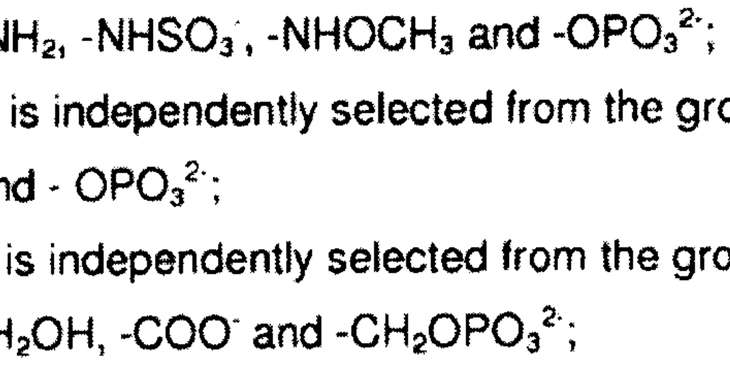
wherein:

X is SO_2

m is an integer independently equal to, or greater than 1;

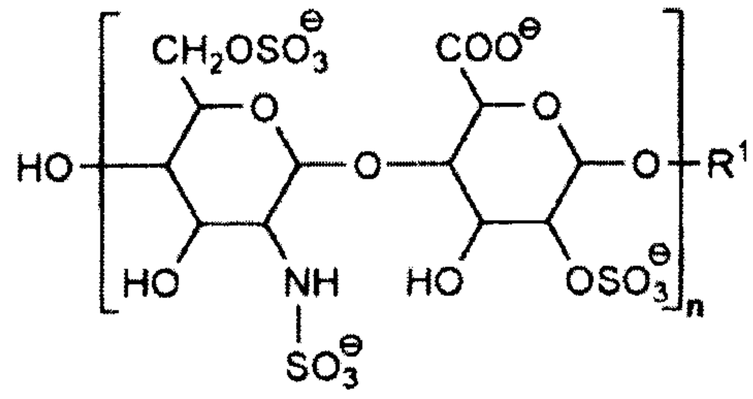
- each R^2 and R^6 is independently selected from the group consisting of $-OSO_3^-$, -OH, $-NH_2$, $-NHSO_3^-$, $-NHOCH_3$ and $-OPO_3^{2-}$;
- each R^3 and R^7 is independently selected from the group consisting of $-OSO_3^-$, -OH and $-OPO_3^{2-}$;
- each R^5 and R^8 is independently selected from the group consisting of $-CH_2OSO_3^-$, $-CH_2OH$, $-COO^-$ and $-CH_2OPO_3^{2-}$;
- each R^4 is independently selected from the group consisting of $-OSO_3^-$, -OH, $-OPO_3^{2-}$ and –H;
- n is an integer between 2 and 5.

14. The composition for use according to any one of the preceding claims, wherein said compound has the general structure (IV):



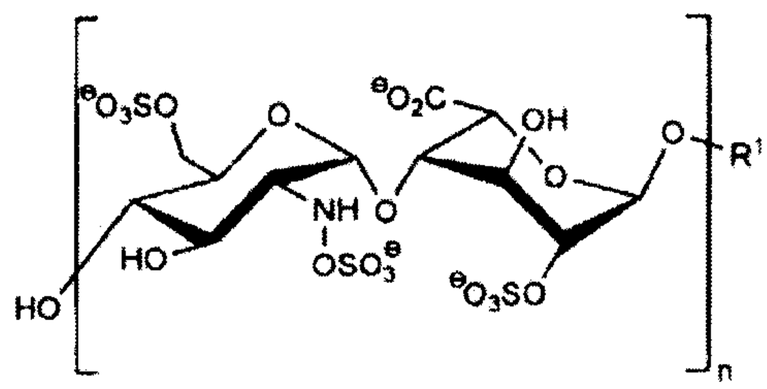
(IV).

15. The composition for use according to any one of the preceding claims, wherein said compound has the general structure (V):



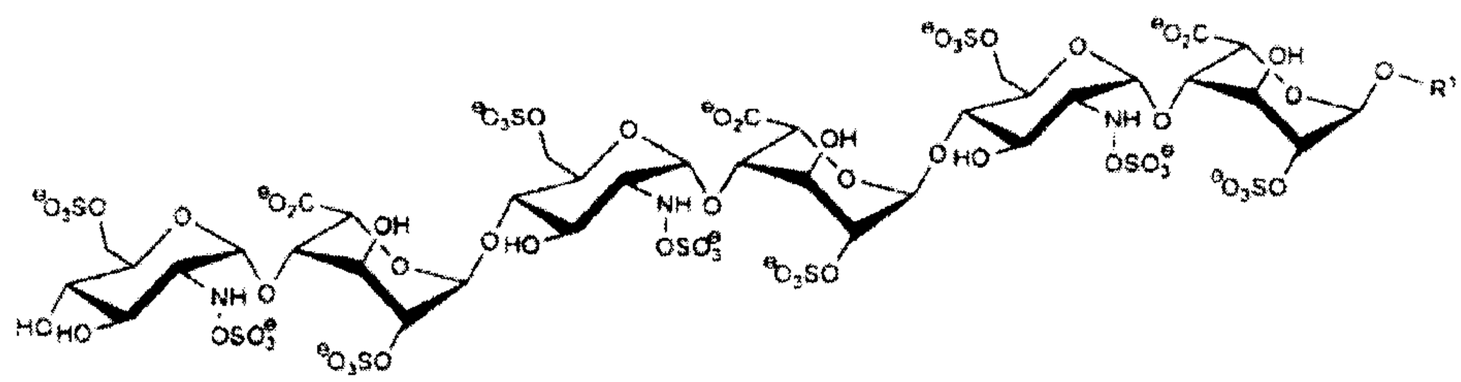
(V).

16. The composition for use according to any one of the preceding claims, wherein said compound has the general structure (VI):



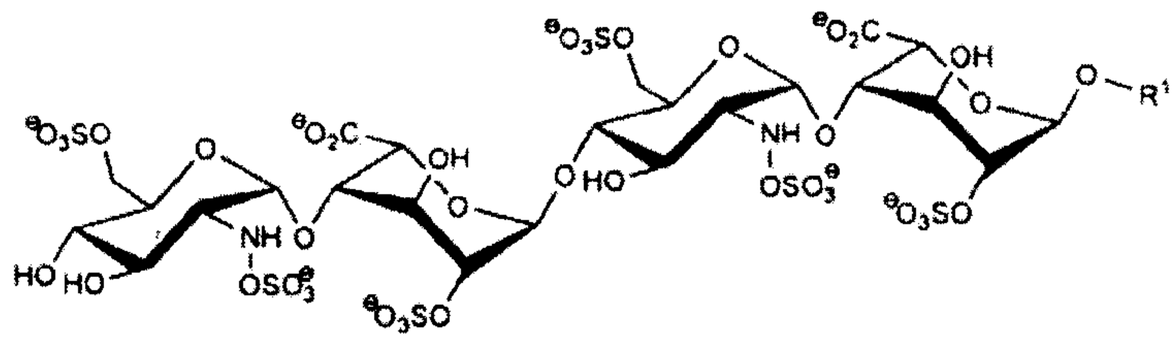
(VI).

17. The composition for use according to any one of the preceding claims, wherein said compound has the general structure (VII):



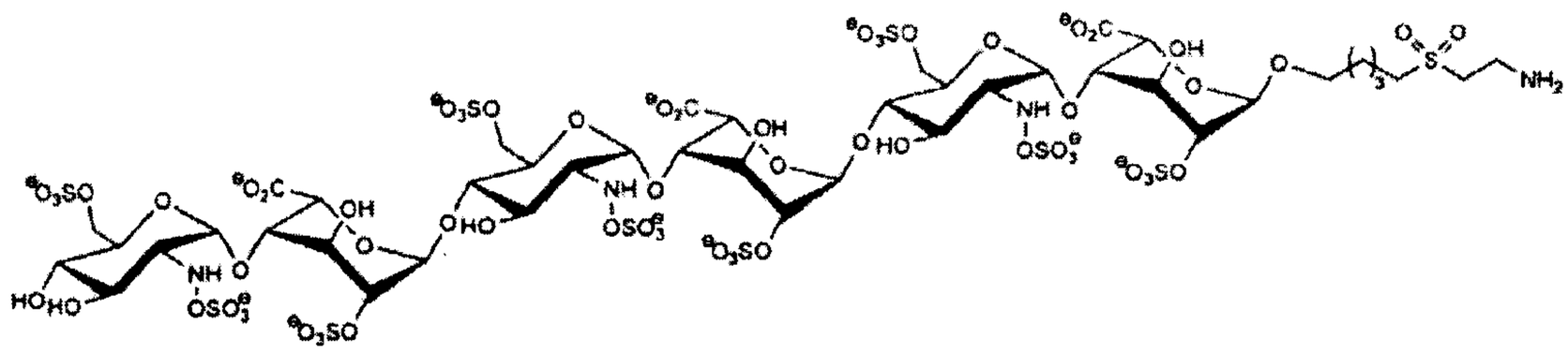
(VII).

18. The composition for use according to any one of the preceding claims, wherein said compound has the general structure (VIII):



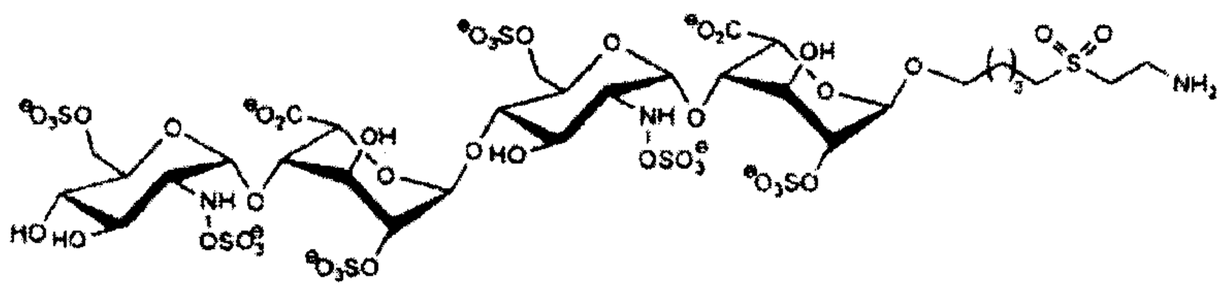
(VIII).

19. The composition for use according to any one of the preceding claims, wherein the compound of formula (I) is Heparin I and has the following structure:



Heparin I.

20. The composition for use according to any one of the preceding claims, wherein the compound of formula (I) is Heparin VII and has the following structure:

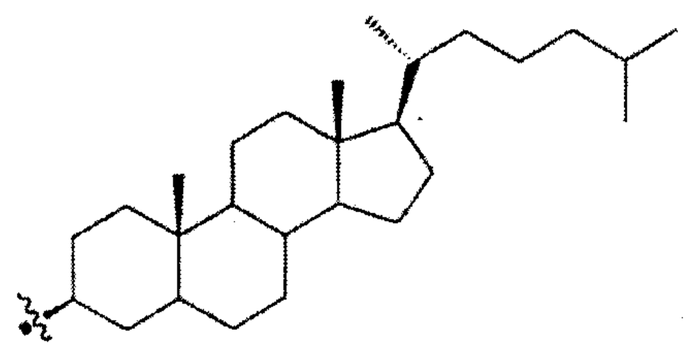


Heparin VII.

21. The composition for use according to claim 1, wherein R^1 comprises at least one monosaccharide unit, such as at least two monosaccharide units, such as at least three monosaccharide units, such as at least four monosaccharide units.

22. The composition for use according to any one of the preceding claims, wherein R^1 further comprises a moiety selected from the group consisting of alkyl, substituted alkyl, heteroalkyl, substituted heteroalkyl, alkylsulfonyl, substituted alkylsulfonyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substituted alkoxy, ester, amide, acyl, substituted acyl, amino, substituted amino, thioalkyl, substituted thioalkyl, aryl, heteroaryl, substituted aryl, hydrogen, and halogen.

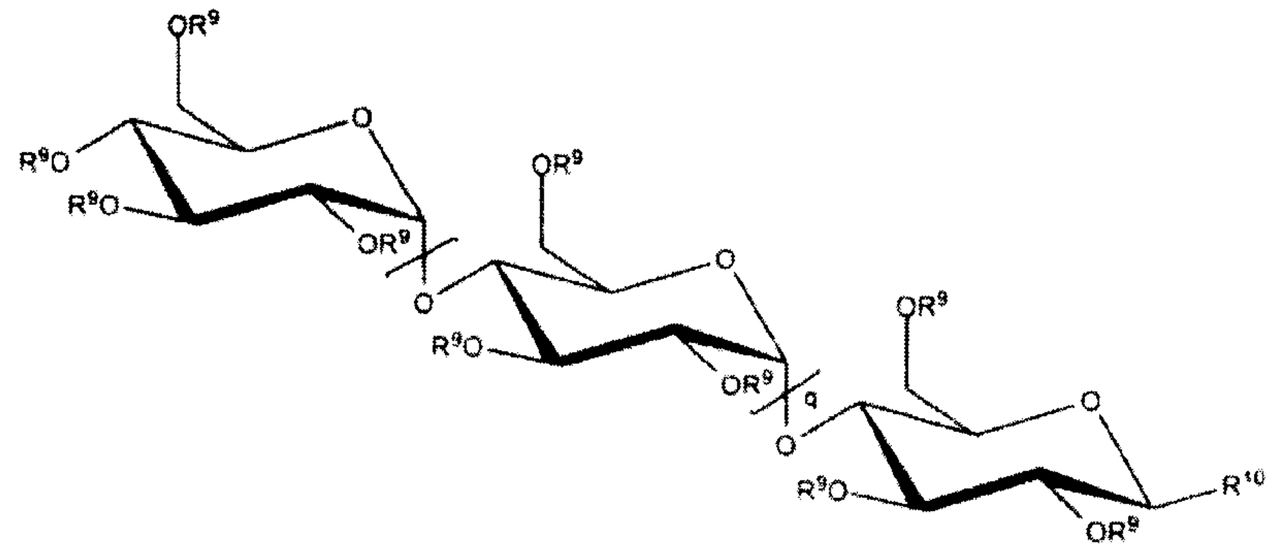
23. The composition for use according to claim 1, wherein R^1 comprises a group of formula (XVII):



(XVII)

24. The composition for use according to any one of the preceding claims, wherein R^1 consists of a group of formula (XVII).

25. The composition for use according to any one of the preceding claims, wherein the compound of formula (I) is a compound of formula (XXVI):



(XXVI)

wherein q is an integer between 1 and 8 and R^9 is individually $-SO_3^-$ or -H.

26. The composition for use according to any one of the preceding claims, wherein R^{10} comprises a group of -O-formula (XVII).

27. The composition for use according to any one of the preceding claims, wherein R^{10} consists of a group of -O-formula (XVII).

28. The composition for use according to any one of the preceding claims, wherein R^{10} is $-O-R^1$.

29. The composition for use according to any one of the preceding claims, wherein the compound is

L. A compound of formula (XXVI), wherein q is 2 and R^{10} is –O-formula (XVII); or

M. A compound of formula (XXVI), wherein q is 1 and R^{10} is –O-formula (XVII).

30. The composition for use according to any one of the preceding claims, wherein said compound further comprises an albumin binding moiety conjugated to said compound.

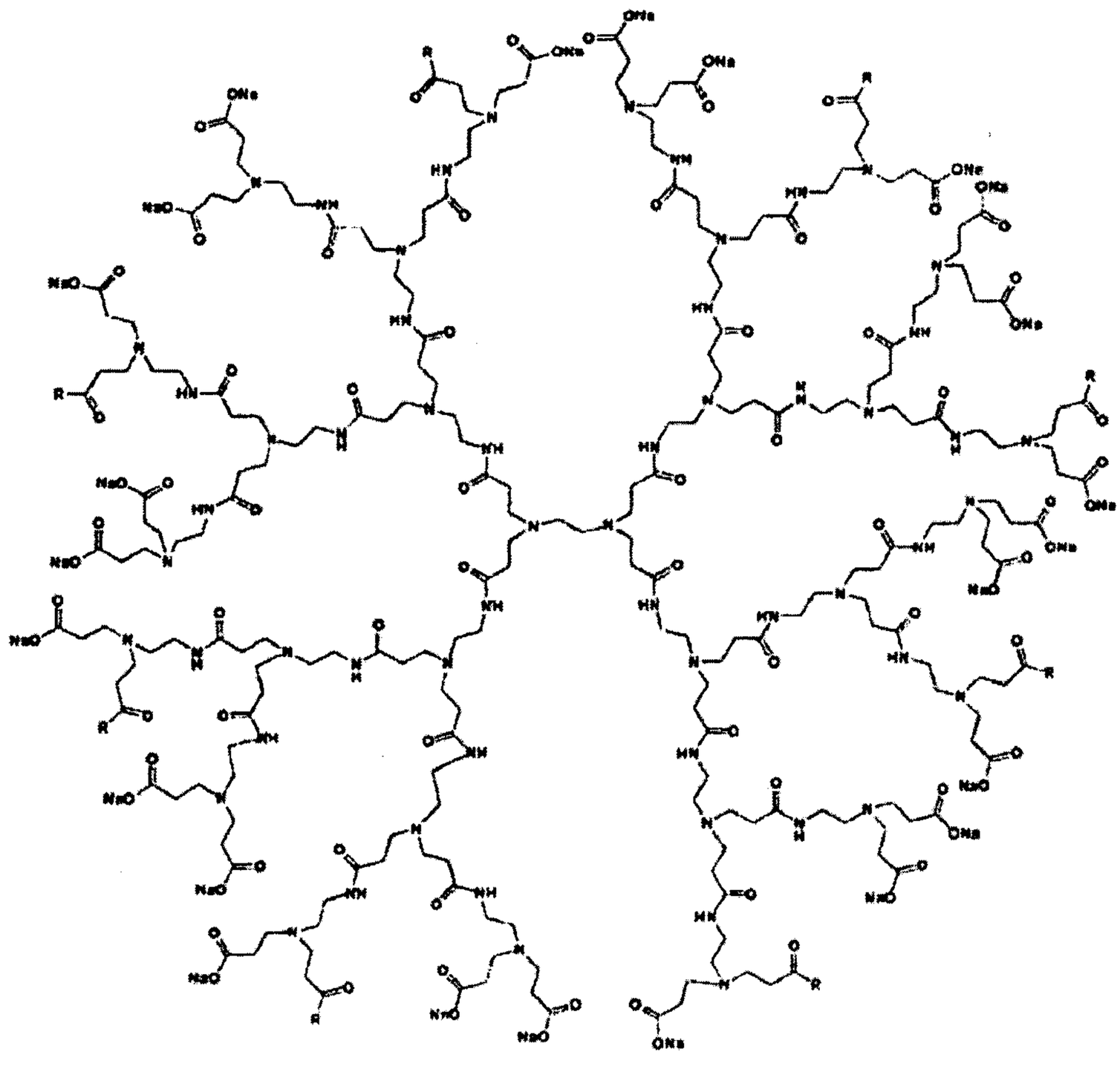
31. The composition for use according to any one of the preceding claims, wherein the albumin binding moiety is a fatty acid.

32. The composition for use according to any one of the preceding claims, wherein the albumin binding moiety conjugated to said compound is a fatty acid selected from the group consisting of caprylic acid, capric acid, lauric acid, myristic acid, palmitic acid, stearic acid, arachidic acid, behenic acid, lignoceric acid, cerotic acid, myristoleic acid, palmitoleic acid, sapienic acid, oleic acid, elaidic acid, vaccenic acid, linoleic acid, linoelaidic acid, α-linolenic acid, arachidonic acid, eicosapentaenoic acid, erucic acid and docosahexaenoic acid.

33. The composition for use according to any one of the preceding claims, wherein a bile acid is conjugated to the compound of formula (I).

34. The composition for use according to any one of the preceding claims, wherein the conjugated bile acid is selected from the group consisting of cholic acid, taurocholic acid, glycocholic acid, taurochenodeoxycholic acid, glycochenodeoxycholic acid, chenodeoxycholic acid, deoxycholic acid, and lithocholic acid.

35. The composition for use according to any one of the preceding claims, wherein the compound is covalently attached via the terminal amino group (as R) to a dendritic structure of the formula:



36. The composition for use according to any one of the preceding claims, wherein said compound specifically recognizes and binds at least one of amino acid residues 78 to 167 of PCSK9 (SEQ ID NO: 1), such as at least one of amino acid residues 78 to 92, such as at least one of amino acid residues 93 to 97, such as at least one of amino acid residues 98 to 103, such as at least one of amino acid residues 104 to 105, such

as at least one of amino acid residues 106 to 135, such as at least one of amino acid residues 136 to 139, such as at least one of amino acid residues 140 to 164, such as at least one of amino acid residues 165 to 167 of PCSK9 (SEQ ID NO: 1).

37. The composition for use according to any one of the preceding claims, wherein said compound binds to one or more amino acids selected from the group consisting of R93, R96, R97, R104, R105, K136, H139, R165 and R167 of PCSK9 (SEQ ID NO: 1).

38. The composition for use according to any one of the preceding claims, wherein said compound binds to at least one, such as to at least two, such as to at least three, such as to at least four, such as to at least five, such as to all six of R93, R96, R97, R104, R105 and H139 of PCSK9 (SEQ ID NO: 1).

39. The composition for use according to any one of the preceding claims, wherein the compound is a heparin analogue.

40. The composition for use according to any one of the preceding claims, wherein binding of the compound of formula (I) to PCSK9 results in increased protein level of LDL receptor (LDLR), compared to the levels in the absence of the compound.

41. The composition for use according to any one of the preceding claims wherein the binding of the compound to PCSK9 results in increased protein level of the LDLR in hepatocytes, compared to the levels in the absence of the compound.

42. The composition for use according to any one of the preceding claims, wherein binding of the compound to PCSK9 results in decreased lysosomal degradation of LDLR compared to the degradation in the absence of said compound.

43. The composition for use according to any one of the preceding claims, wherein binding of the compound to PCSK9 results in decreased plasma levels of LDL-C compared to the levels in the absence of said compound.

44. The composition for use according to any one of the preceding claims, wherein the plasma levels of LDL-C are determined in vitro.

45. The composition for use according to any one of the preceding claims, wherein the plasma levels of LDL-C are determined by Western Blot, immuno-staining, ELISA, ultracentrifugation, FPLC, or by enzymatic colorimetric determination.

46. The composition for use according to any one of the preceding claims, wherein said compound does not bind to the LDLR-binding site of PCSK9 (SEQ ID NO: 1).

47. The composition for use according to any one of the preceding claims, wherein the disorder of lipoprotein metabolism is linked to abnormal levels of LDL-C.

48. The composition for use according to any one of the preceding claims, wherein the disorder of lipoprotein metabolism is linked to elevated levels of LDL-C.

49. The composition for use according to any one of the preceding claims, wherein the disorder of lipoprotein metabolism is linked to abnormal PCSK9 plasma levels and/or abnormal LDLR levels of LDLR-expressing cells.

50. The composition for use according to any one of the preceding claims, wherein the disorder of lipoprotein metabolism is linked to abnormal PCSK9 plasma levels and/or abnormal LDLR levels of hepatocytes.

51. The composition for use according to any one of the preceding claims, wherein the disorder of lipoprotein metabolism is diabetes.

52. The composition for use according to any one of the preceding claims, wherein the disorder of lipoprotein metabolism is obesity.

53. The composition for use according to any one of the preceding claims, wherein the disorder of lipoprotein metabolism is metabolic syndrome.

54. The composition for use according to any one of the preceding claims, wherein the disorder of lipoprotein metabolism is xanthoma.

55. The composition for use according to any one of the preceding claims, wherein the disorder of lipoprotein metabolism is hypercholesterolemia.

56. The composition for use according to any one of the preceding claims, wherein the disorder of lipoprotein metabolism is familial hypercholesterolemia.

57. The composition for use according to any one of the preceding claims, wherein the disorder of lipoprotein metabolism is dyslipidemia.

58. The composition for use according to any one of the preceding claims, wherein the disorder of lipoprotein metabolism is hypertriglyceridemia.

59. The composition for use according to any one of the preceding claims, wherein the disorder of lipoprotein metabolism is hyperlipidemia.

60. The composition for use according to any one of the preceding claims, wherein the disorder of lipoprotein metabolism is sitosterolemia.

61. The composition for use according to any one of the preceding claims, wherein the disorder of lipoprotein metabolism is hypertension.

62. The composition for use according to any one of the preceding claims, wherein the disorder of lipoprotein metabolism is angina.

63. The composition for use according to any one of the preceding claims, wherein the disorder of lipoprotein metabolism is acute coronary syndrome.

64. The composition for use according to any one of the preceding claims, wherein the disorder of lipoprotein metabolism is coronary heart disease.

65. The composition for use according to any one of the preceding claims, wherein the disorder of lipoprotein metabolism is atherosclerosis.

66. The composition for use according to any one of the preceding claims, wherein the disorder of lipoprotein metabolism is vascular inflammation.

67. The composition for use according to any one of the preceding claims, wherein the disorder of lipoprotein metabolism is arteriosclerosis.

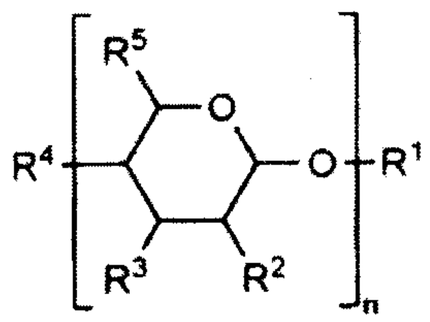
68. The composition for use according to any one of the preceding claims, wherein the disorder of lipoprotein metabolism is sepsis.

69. The composition for use according to any one of the preceding claims, wherein the treatment is prophylactic.

70. The composition for use according to any one of the preceding claims, wherein the subject is a mammal.

71. The composition for use according to any one of the preceding claims, wherein the mammal is a human.

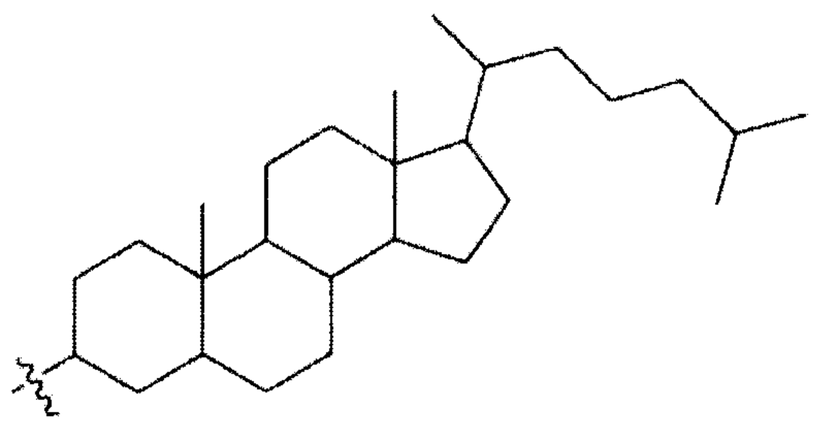
72. Use of a composition comprising a compound having the general structure of formula (I):



(I)

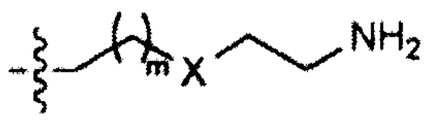
or a pharmaceutically acceptable salt, solvate, polymorph, or tautomer thereof, wherein:

- R^1 comprises a group with a formula selected from:
  a) Formula (XI):



(XI); or

b) Formula (II):



(II)

wherein:

X is SO_2

m is an integer independently equal to, or greater than 1;

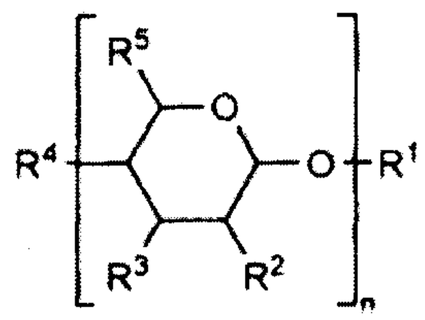
;

- each R^2 is independently selected from the group consisting of $-OSO_3^-$, -OH, $-NH_2$, $-NHSO_3^-$, $-NHOCH_3$ and $-OPO_3^{2-}$;
- each R^3 is independently selected from the group consisting of $-OSO_3^-$, -OH and $-OPO_3^{2-}$;
- each R^4 is independently selected from the group consisting of $-OSO_3^-$, -OH, $-OPO_3^{2-}$ and –H;
- each R^5 is independently selected from the group consisting of $-CH_2OSO_3^-$, $-CH_2OH$, $-COO^-$ and $-CH_2OPO_3^{2-}$;
- n is an integer between 3 and 10;

for the preparation of a medicament for the treatment of a disorder of lipoprotein metabolism in a subject, wherein said disorder of lipoprotein metabolism is selected from the group consisting of, diabetes, obesity, metabolic syndrome, xanthoma, hypercholesterolemia, familial hypercholesterolemia, dyslipidemia , hypertriglyceridemia, hyperlipidemia, sitosterolemia, hypertension, angina, acute coronary syndrome, coronary heart disease, atherosclerosis, arteriosclerosis, vascular inflammation and sepsis.

73. A method of treatment of a disorder of lipoprotein metabolism, wherein said disorder of lipoprotein metabolism is selected from the group consisting of, diabetes, obesity, metabolic syndrome, xanthoma, hypercholesterolemia, familial

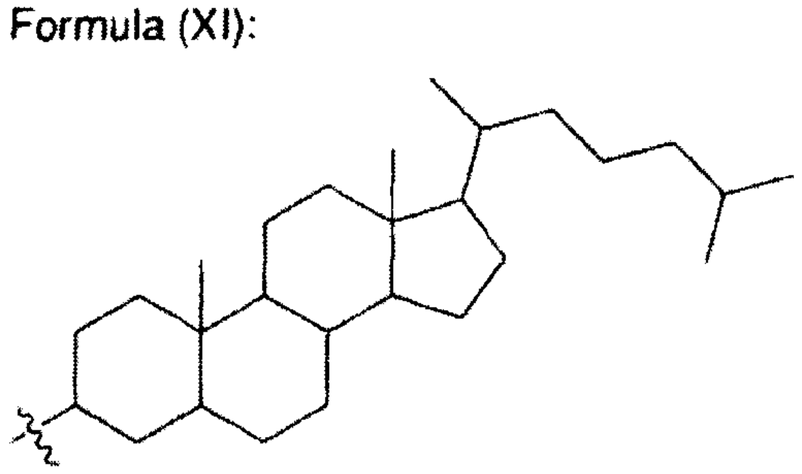
hypercholesterolemia, dyslipidemia , hypertriglyceridemia, hyperlipidemia, sitosterolemia, hypertension, angina, acute coronary syndrome, coronary heart disease, atherosclerosis, arteriosclerosis, vascular inflammation and sepsis, the method comprising administering to a subject in need thereof, a therapeutically effective amount of a composition comprising a compound having the general structure of formula (I):



(I)

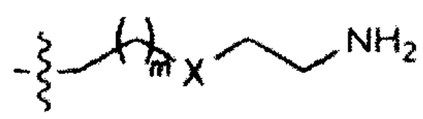
or a pharmaceutically acceptable salt, solvate, polymorph, or tautomer thereof, wherein:

- R^1 comprises a group with a formula selected from:
  a) Formula (XI):



(XI); or

  b) Formula (II):



(II)

wherein:

X is SO_2

m is an integer independently equal to, or greater than 1;

- each R^2 is independently selected from the group consisting of $-OSO_3^-$, -OH, $-NH_2$, $-NHSO_3^-$, $-NHOCH_3$ and $-OPO_3^{2-}$;
- each R^3 is independently selected from the group consisting of $-OSO_3^-$, -OH and $-OPO_3^{2-}$;

- each R^4 is independently selected from the group consisting of $-OSO_3^-$, $-OH$, $-OPO_3^{2-}$ and $-H$;
- each R^5 is independently selected from the group consisting of $-CH_2OSO_3^-$, $-CH_2OH$, $-COO^-$ and $-CH_2OPO_3^{2-}$;
- n is an integer between 3 and 10.

74. A method of inhibiting degradation of LDLR, said method comprising administering a composition as defined in any one of claims 1 to 71.

75. The composition according to any one of the preceding claims, wherein the composition is a pharmaceutical composition comprising at least one compound as defined in any one of claims 1 to 71.

76. The pharmaceutical composition according to claim 75, wherein said composition further comprises at least one of a statin or an anti-PCK9 antibody.

77. The pharmaceutical composition according to claim 76, wherein said composition further comprises an anti-PCK9 antibody which specifically binds to the LDLR-binding site of PCSK9.

78. The pharmaceutical composition according to any one of claims 75 to 77, wherein said composition further comprises at least one further compound, such as a compound selected from the group consisting of lodelcizumab, ralpancizumab, alirocumab, evolocumab and bococizumab

79. The pharmaceutical composition according to any one of claims 75 to 78, wherein the composition further comprises at least one of:

- an antibody inhibiting binding of PCSK9 to LDLR;
- a statin;
- cholestyramine;
- ezetimibe.

80. The pharmaceutical composition according to any one of claims 75 to 79, further comprising one or more pharmaceutically acceptable excipients.

81. The pharmaceutical composition according to any one of claims 75 to80, wherein the pH of the composition is between pH 4 and pH 10.

82. The pharmaceutical composition according to any one of claims 75 to 81, wherein the composition is formulated for oral administration.

83. The pharmaceutical composition according to any one of claims 75 to 82, wherein the composition is formulated for parenteral administration.

84. The pharmaceutical composition according to any one of claims 75 to 81 or 83, wherein the parenteral administration is by injection.

85. The pharmaceutical composition according to any one of claims 75 to 81 or 83 to 84, wherein the parenteral administration is intravenous, intramuscular, intraspinal, intraperitoneal, subcutaneous, a bolus or a continuous administration.

86. The pharmaceutical composition according to any one of claims75 to 85, wherein the compound is administered at a daily dosage of between 0.1 mg and 1000 mg per kg bodyweight.

87. A method for reducing plasma lipoprotein levels in a subject in need thereof, said method comprising the step of administering to said subject a composition as defined in any one of claims 1 to 71 or a pharmaceutical composition as defined in any one of claims75 to 86.

88. The method of claim 87, wherein lipoprotein is LDL-C.

89. The method according to any one of claims 87 to 88, wherein said subject does not respond to statin treatment.

90. The composition for use according to any one of the preceding claims, wherein the compound is stable in serum.

91. The composition for use according to any one of the preceding claims, wherein the compound is non-toxic after administration.