CLAIMS:

1. An oligomeric compound comprising a modified oligonucleotide consisting of 14 to 30 linked nucleosides and having a nucleobase sequence comprising at least 14, at least 15, or at least 16 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOs: 12-15, wherein the modified oligonucleotide comprises at least one modification selected from a modified sugar moiety and a modified internucleoside linkage.

2. An oligomeric compound comprising a modified oligonucleotide consisting of 14 to 30 linked nucleosides and having a nucleobase sequence comprising at least 14, at least 15, or at least 16 contiguous nucleobases complementary to:

an equal length portion of nucleobases 2046-2061 of SEQ ID NO: 1;
an equal length portion of nucleobases 2271-2286 of SEQ ID NO: 1;
an equal length portion of nucleobases 2272-2287 of SEQ ID NO: 1;

wherein the modified oligonucleotide comprises at least one modification selected from a modified sugar moiety and a modified internucleoside linkage.

3. An oligomeric compound comprising a modified oligonucleotide consisting of 16 linked nucleosides and having a nucleobase sequence comprising the nucleobase sequence of SEQ ID NO: 12, wherein the modified oligonucleotide comprises at least one modification selected from a modified sugar moiety and a modified internucleoside linkage.

4. An oligomeric compound comprising a modified oligonucleotide consisting of 16 linked nucleosides and having a nucleobase sequence comprising the nucleobase sequence of SEQ ID NO: 13, wherein the modified oligonucleotide comprises at least one modification selected from a modified sugar moiety and a modified internucleoside linkage.

5. An oligomeric compound comprising a modified oligonucleotide consisting of 16 linked nucleosides and having a nucleobase sequence comprising the nucleobase sequence of SEQ ID NO: 14, wherein the modified oligonucleotide comprises at least one modification selected from a modified sugar moiety and a modified internucleoside linkage.

6. An oligomeric compound comprising a modified oligonucleotide consisting of 16 linked nucleosides and having a nucleobase sequence comprising the nucleobase sequence of SEQ ID NO: 15, wherein the modified oligonucleotide comprises at least one modification selected from a modified sugar moiety and a modified internucleoside linkage.

7. The oligomeric compound of any of claims 1-6, wherein the modified oligonucleotide has a nucleobase sequence that is at least 80%, at least 85%, at least 90%, at least 95%, or 100% complementary to

the nucleobase sequence of any SEQ ID NO: 1 or SEQ ID NO: 2, when measured across the entire nucleobase sequence of the modified oligonucleotide.

8. The oligomeric compound of any of claims 1-7, wherein the modified oligonucleotide comprises at least one bicyclic sugar moiety.

9. The oligomeric compound of claim 8, wherein the bicyclic sugar moiety has a 4'-2' bridge, wherein the 4'-2' bridge is selected from $-CH_2-O-$; and $-CH(CH_3)-O-$.

10. The oligomeric compound of any of claims 1-9, wherein the modified oligonucleotide comprises at least one non-bicyclic modified sugar moiety.

11. The oligomeric compound of claim 10, wherein the non-bicyclic modified sugar moiety is a 2'-MOE sugar moiety or a 2'-OMe sugar moiety.

12. The oligomeric compound of any of claims 1-11, wherein the modified oligonucleotide comprises at least one sugar surrogate.

13. The oligomeric compound of claim 12, wherein the sugar surrogate is any of morpholino, modified morpholino, PNA, THP, and F-HNA.

14. The oligomeric compound of any of claims 1-13, wherein the modified oligonucleotide is a gapmer.

15. The oligomeric compound of claim 14, wherein the modified oligonucleotide has a sugar motif comprising:

a 5'-region consisting of 1-6 linked 5'-region nucleosides;

a central region consisting of 6-10 linked central region nucleosides; and

a 3'-region consisting of 1-6 linked 3'-region nucleosides; wherein

each of the 5'-region nucleosides and each of the 3'-region nucleosides comprises a modified sugar moiety and at least 6 of the central region nucleosides comprises a 2'-β-D-deoxyribosyl sugar moiety.

16. The oligomeric compound of claim 14, wherein the modified oligonucleotide has a sugar motif comprising:

a 5'-region consisting of 1-6 linked 5'-region nucleosides;

a central region consisting of 6-10 linked central region nucleosides; and

a 3'-region consisting of 1-6 linked 3'-region nucleosides; wherein

each of the 5'-region nucleosides and each of the 3'-region nucleosides comprises a modified sugar moiety and each of the central region nucleosides comprises a 2'-deoxyribosyl sugar moiety

17. The oligomeric compound of claim 14, wherein the modified oligonucleotide has a sugar motif comprising:

a 5'-region consisting of 3 linked 5'-region nucleosides;

a central region consisting of 10 linked central region nucleosides; and

a 3'-region consisting of 3 linked 3'-region nucleosides; wherein

each of the 5'-region nucleosides and each of the 3'-region nucleosides comprises a 2'-MOE modified sugar moiety or a cEt modified sugar moiety, and each of the central region nucleosides comprises a 2'-β-D-deoxyribosyl sugar moiety.

18. The oligomeric compound of claim 14, wherein the modified oligonucleotide has a sugar motif comprising:

a 5'-region consisting of 3 linked 5'-region nucleosides;

a central region consisting of 10 linked central region nucleosides; and

a 3'-region consisting of 43 linked 3'-region nucleosides; wherein

each of the 5'-region nucleosides and each of the 3'-region nucleosides comprises a 2'-MOE modified sugar moiety or a cEt modified sugar moiety, and at least 6 of the central region nucleosides comprises a 2'-β-D-deoxyribosyl sugar moiety.

19. The oligomeric compound of any of claims 1-18, wherein the modified oligonucleotide has a sugar motif (5' to 3') selected from eekddddddddddkke, ekkddddddddddkke, kkkdyddddddddkkk, kkkddyddddddddkkk, kkkdddyddddddkkk, kkkddddddddddkkk, or eeeeddddddddddeeeee; wherein 'e' represents a 2'-MOE sugar moiety, 'k' represents a cEt sugar moiety, 'd' represents a 2'-β-D-deoxyribosyl sugar moiety, and 'y' represents a 2'-OMe sugar moiety.

20. The oligomeric compound of any of claims 1-19, wherein the modified oligonucleotide comprises at least one modified internucleoside linkage.

21. The oligomeric compound of claim 20, wherein each internucleoside linkage of the modified oligonucleotide is a modified internucleoside linkage.

22. The oligomeric compound of claim 20 or claim 21, wherein at least one internucleoside linkage is a phosphorothioate internucleoside linkage.

23. The oligomeric compound of any of claims 20 and claim 22, wherein the modified oligonucleotide comprises at least one phosphodiester internucleoside linkage.

24. The oligomeric compound of any of claims 20, 22 and 23, wherein each internucleoside linkage is either a phosphodiester internucleoside linkage or a phosphorothioate internucleoside linkage.

25. The oligomeric compound of claim 21, wherein each internucleoside linkage is a phosphorothioate internucleoside linkage.

26. The oligomeric compound of any of claims 1-20 or 22-24, wherein the modified oligonucleotide has an internucleoside linkage motif of soosssssssssssos; wherein,

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

27. The oligomeric compound of any of claims 1-26, wherein the modified oligonucleotide comprises at least one modified nucleobase.

28. The oligomeric compound of claim 27, wherein the modified nucleobase is a 5-methylcytosine.

29. The oligomeric compound of any of claims 1-28, wherein the modified oligonucleotide consists of 14-30, 14-22, 14-20, 14-18, 14-20, 15-17, 15-25, or 16-20 linked nucleosides.

30. The oligomeric compound of any of claims 1-28, wherein the modified oligonucleotide consists of 16 linked nucleosides.

31. The oligomeric compound of any of claims 1-30, comprising a conjugate group.

32. The oligomeric compound of claim 31, wherein the conjugate group comprises a GalNAc cluster comprising 1-3 GalNAc ligands.

33. The oligomeric compound of any one of claims 31 and 32, wherein the conjugate group comprises a conjugate linker consisting of a single bond.

34. The oligomeric compound of any one of claims 31-33, wherein the conjugate group comprises a cleavable linker.

35. The oligomeric compound of any one of claims 31-34, wherein the conjugate group comprises a conjugate linker comprising 1-3 linker-nucleosides.

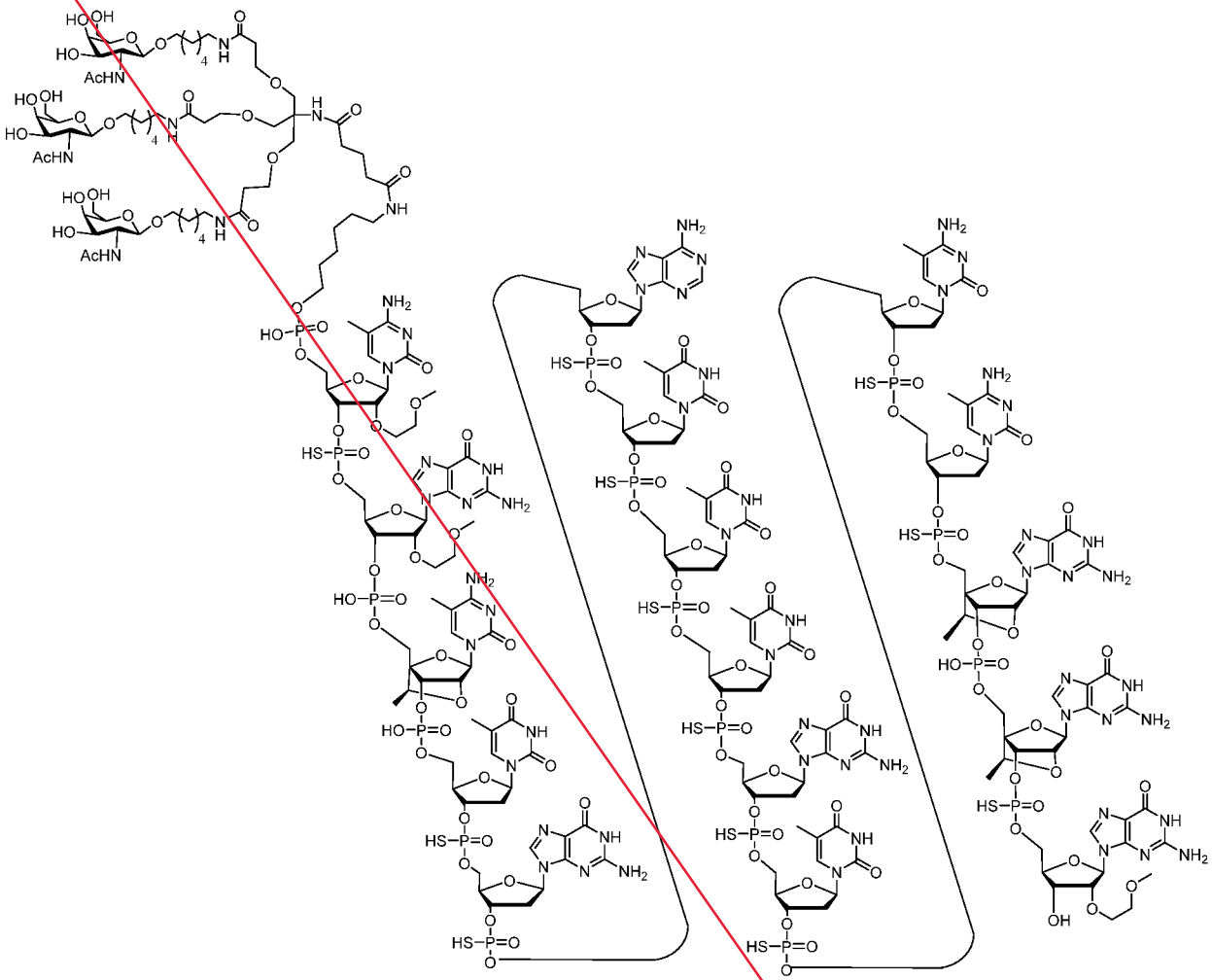
36. The oligomeric compound of any one of claims 31-35, wherein the conjugate group is attached to the modified oligonucleotide at the 5'-nucleoside of the modified oligonucleotide.

37. The oligomeric compound of any one of claims 31-35, wherein the conjugate group is attached to the modified oligonucleotide at the 3'-nucleoside of the modified oligonucleotide.

38. The oligomeric compound of any of claims 1-37, wherein the oligomeric compound is a singled-stranded oligomeric compound.

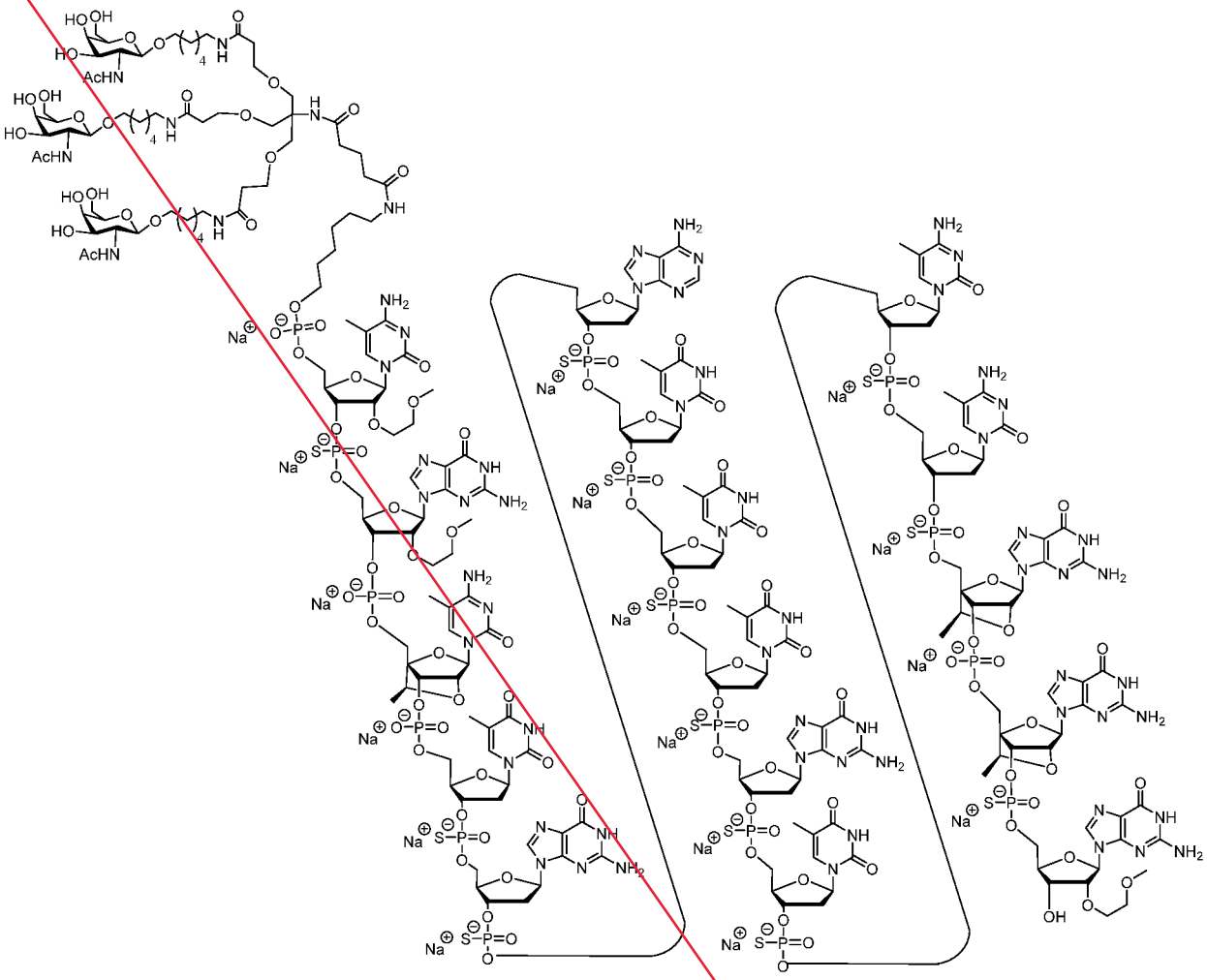
39. The oligomeric compound of any of claims 1-30, consisting of the modified oligonucleotide.

40. An oligomeric compound according to the following chemical structure:



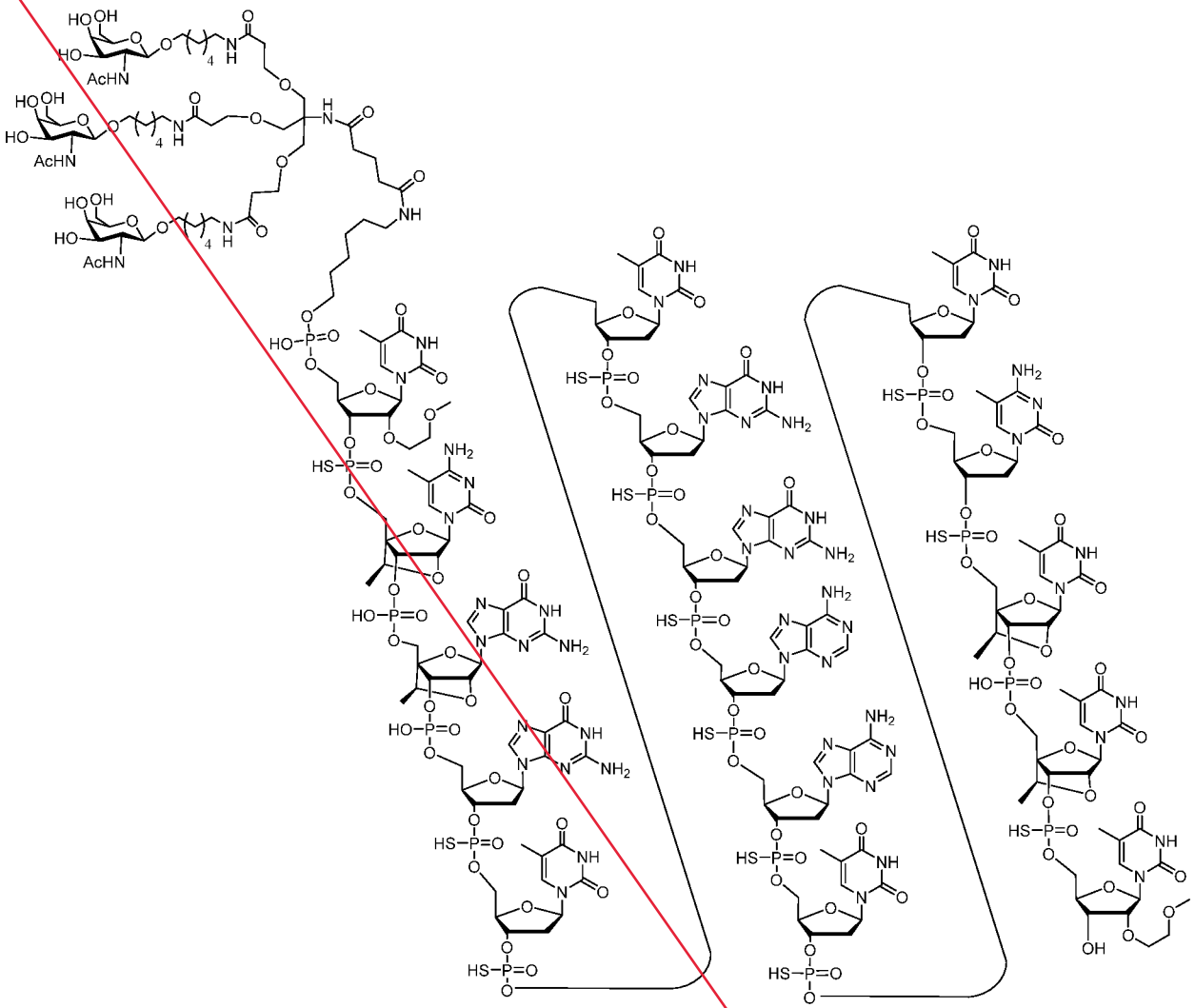
(SEQ ID NO: 12), or a salt thereof.

41. An oligomeric compound according to the following chemical structure:



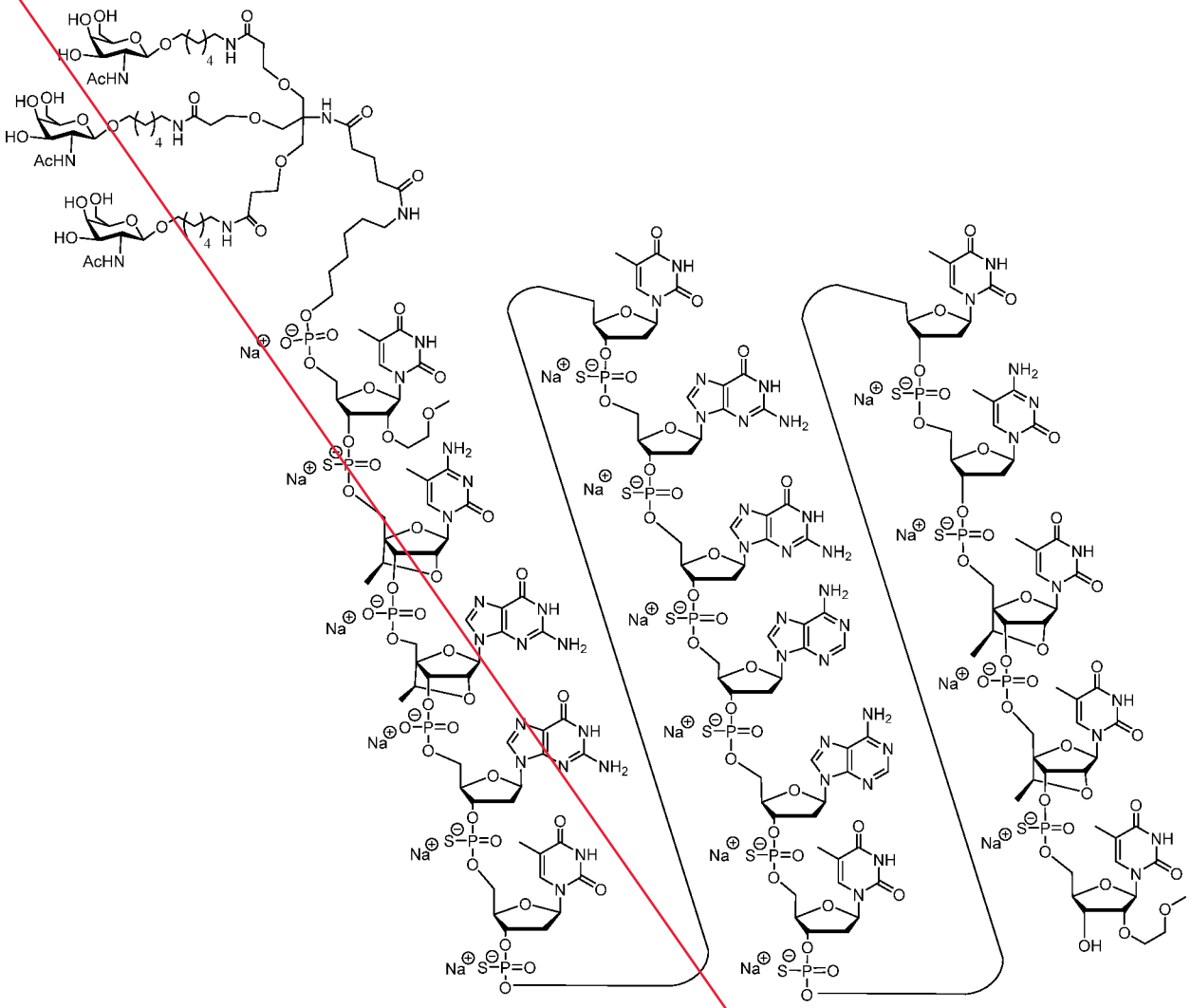
(SEQ ID NO: 12).

42. An oligomeric compound according to the following chemical structure:



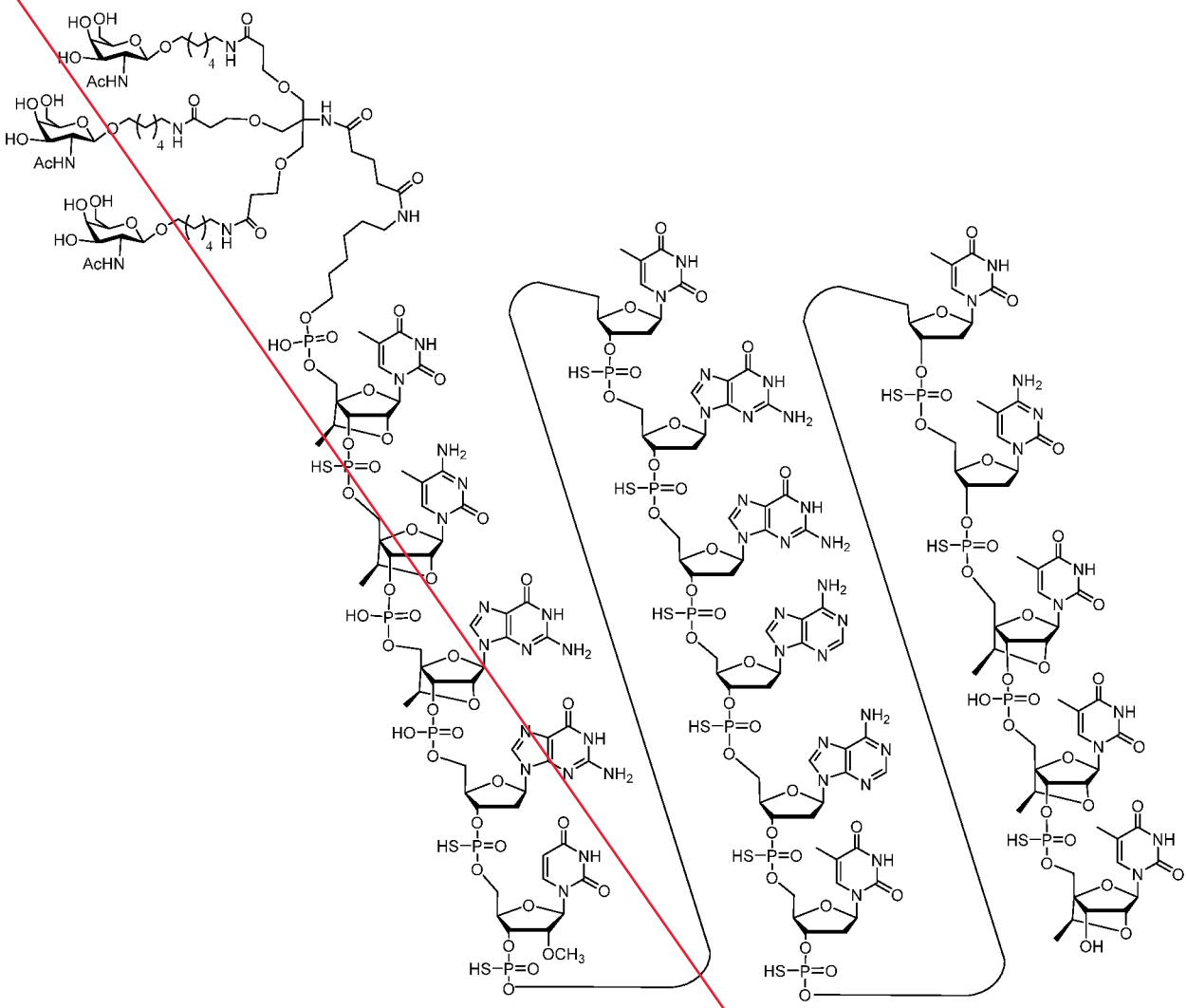
(SEQ ID NO: 13), or a salt thereof.

43. An oligomeric compound according to the following chemical structure:



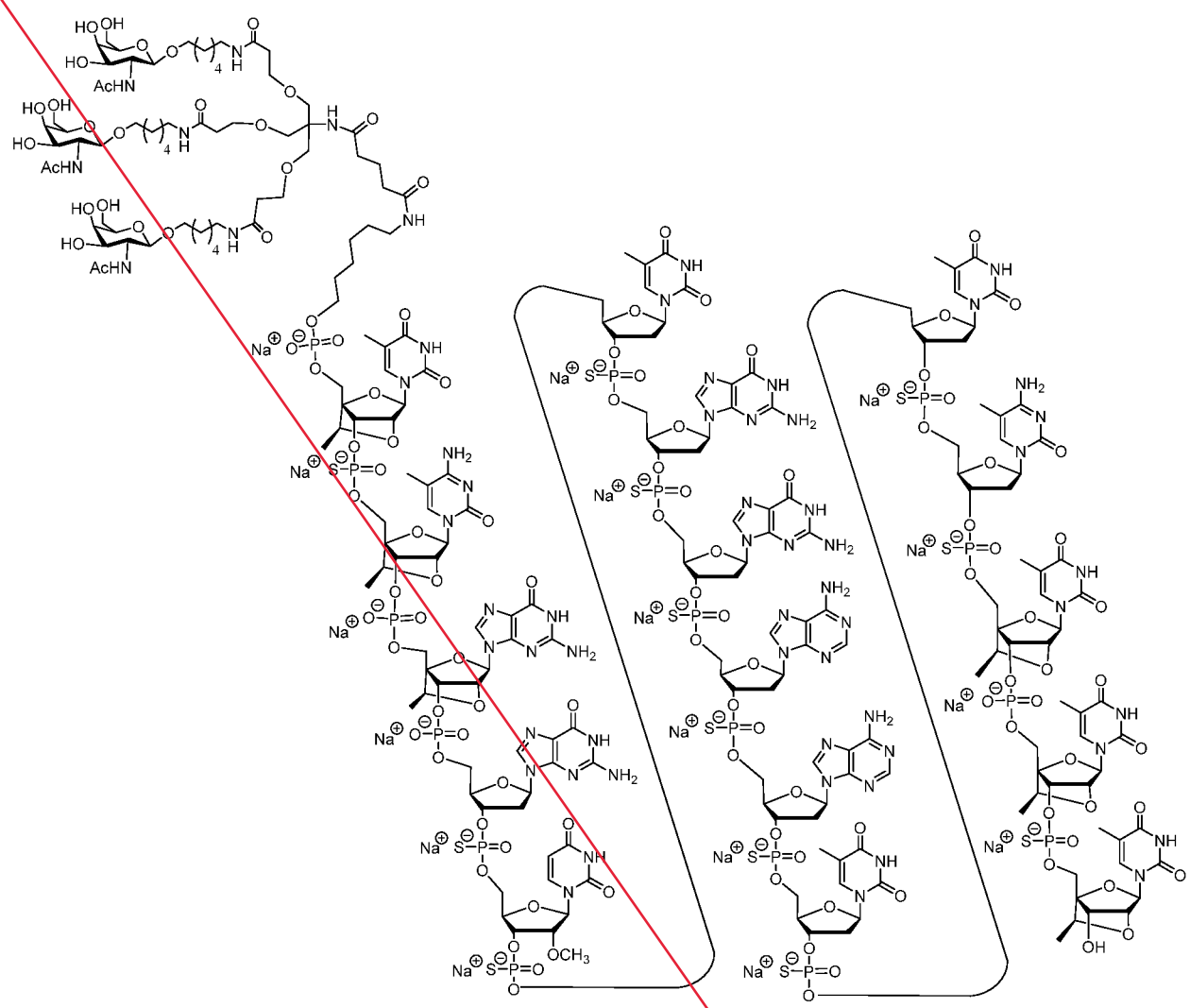
(SEQ ID NO: 13).

44. An oligomeric compound according to the following chemical structure:



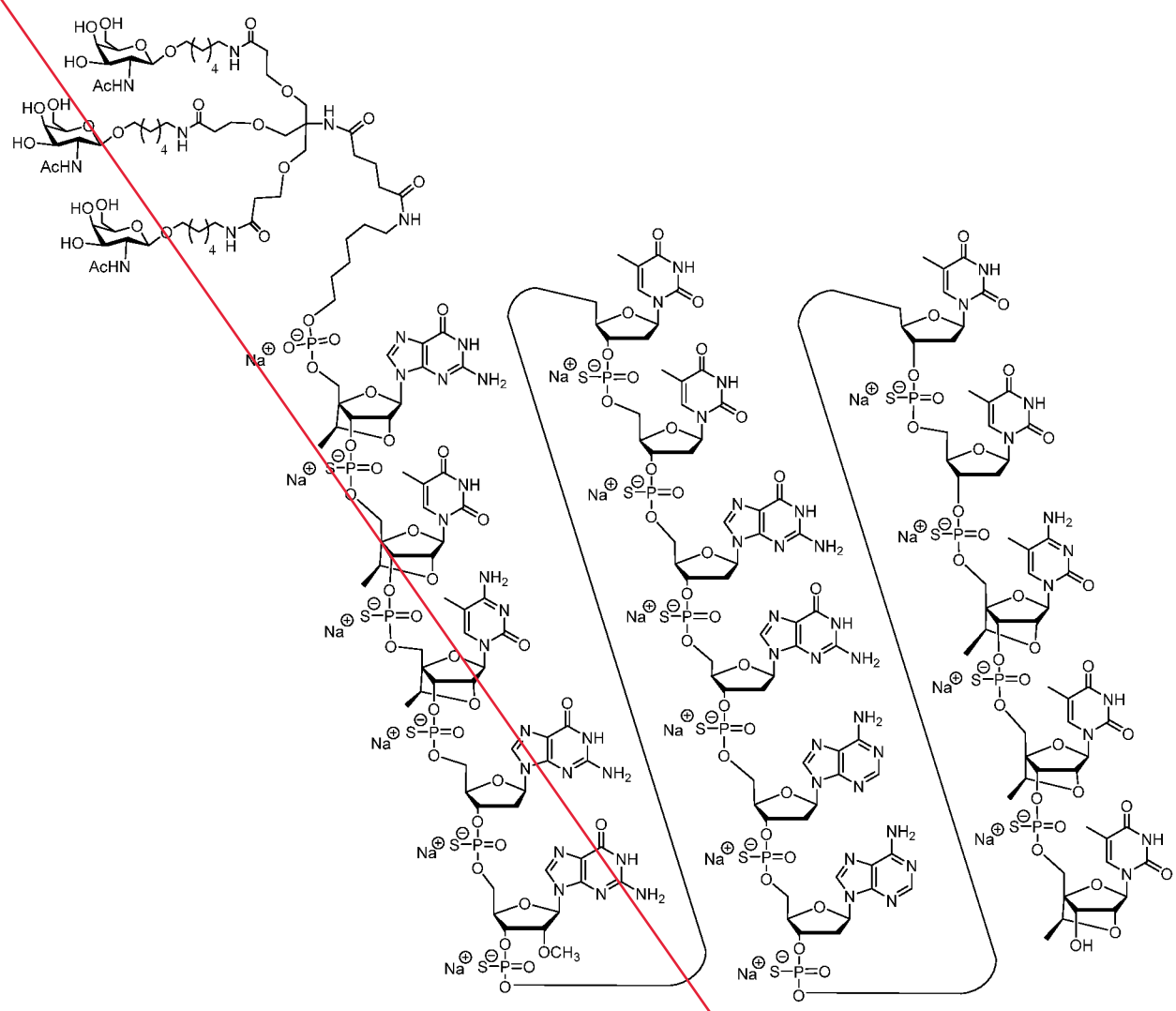
(SEQ ID NO: 14), or a salt thereof.

45. An oligomeric compound according to the following chemical structure:



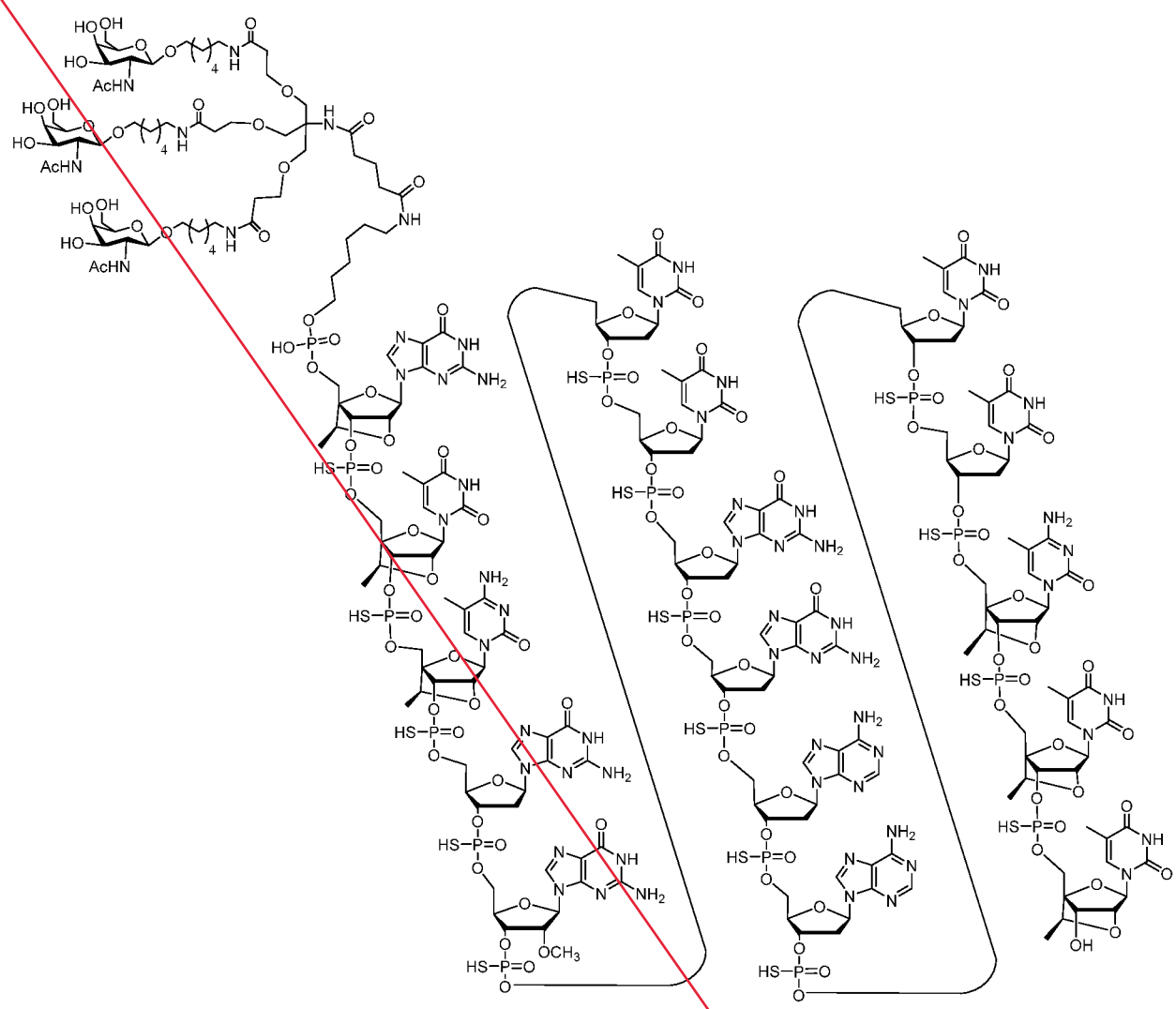
(SEQ ID NO: 14).

46. An oligomeric compound according to the following chemical structure:



(SEQ ID NO: 15), or salt thereof.

47. An oligomeric compound according to the following chemical structure:



(SEQ ID NO: 15).

48. The oligomeric compound of any of claims 40, 42, 44, and 47, which is the sodium salt or potassium salt.

49. An oligomeric compound comprising a modified oligonucleotide according to the following chemical notation: $^{m}C_{es}G_{eo}{}^{m}C_{ko}T_{ds}G_{ds}A_{ds}T_{ds}T_{ds}T_{ds}G_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}G_{ko}G_{ks}G_{e}$ (SEQ ID NO: 12), wherein:

A = an adenine nucleobase,

^{m}C = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'-β-D-MOE sugar moiety,

k = a cEt sugar moiety,

d = a 2'-β-D-deoxyribosyl sugar moiety,

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

50. An oligomeric compound comprising a modified oligonucleotide according to the following chemical notation: $T_{es}{}^{m}C_{ko}G_{ko}G_{ds}T_{ds}T_{ds}G_{ds}G_{ds}A_{ds}A_{ds}T_{ds}T_{ds}{}^{m}C_{ds}T_{ko}T_{ks}T_{e}$ (SEQ ID NO: 13), wherein:

A = an adenine nucleobase,

^{m}C = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'-β-D-MOE sugar moiety,

k = a cEt sugar moiety,

d = a 2'-β-D-deoxyribosyl sugar moiety,

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

51. An oligomeric compound comprising a modified oligonucleotide according to the following chemical notation: $G_{ks}T_{ks}{}^{m}C_{ks}G_{ds}G_{ys}T_{ds}T_{ds}G_{ds}G_{ds}A_{ds}A_{ds}T_{ds}T_{ds}{}^{m}C_{ks}T_{ks}T_{k}$ (SEQ ID NO: 15), wherein:

A = an adenine nucleobase,

^{m}C = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

k = a cEt sugar moiety,

d = a 2'-β-D-deoxyribosyl sugar moiety,

y = a 2'-OMe ribose sugar moiety, and

s = a phosphorothioate internucleoside linkage.

52. An oligomeric compound comprising a modified oligonucleotide according to the following chemical notation: $T_{ks}{}^{m}C_{ko}G_{ko}G_{ds}U_{ys}T_{ds}G_{ds}G_{ds}A_{ds}A_{ds}T_{ds}T_{ds}{}^{m}C_{ds}T_{ko}T_{ks}T_{k}$ (SEQ ID NO: 14), wherein:

A = an adenine nucleobase,

^{m}C = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

U = a uracil nucleobase,

k = a cEt sugar moiety,

d = a 2'-β-D-deoxyribosyl sugar moiety,

y = a 2'-OMe ribose sugar moiety,

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

53. The oligomeric compound of any of claims 49-52, comprising the modified oligonucleotide covalently linked to a conjugate group.

54. An oligomeric duplex comprising an oligomeric compound of any of claims 1-53.

55. An antisense compound comprising or consisting of an oligomeric compound of any of claims 1-53 or an oligomeric duplex of claim 54.

56. A chirally enriched population of oligomeric compounds of any of claims 40-53, wherein the population is enriched for compounds comprising at least one particular phosphorothioate internucleoside linkage having a particular stereochemical configuration.

57. The chirally enriched population of claim 56, wherein the population is enriched for compounds comprising at least one particular phosphorothioate internucleoside linkage having the (*S*p) configuration.

58. The chirally enriched population of claim 56, wherein the population is enriched for compounds comprising at least one particular phosphorothioate internucleoside linkage having the (*R*p) configuration.

59. The chirally enriched population of claim 56, wherein the population is enriched for compounds having a particular, independently selected stereochemical configuration at each phosphorothioate internucleoside linkage.

60. The chirally enriched population of claim 56, wherein the population is enriched for compounds having the (*S*p) configuration at each phosphorothioate internucleoside linkage or for modified oligonucleotides having the (*R*p) configuration at each phosphorothioate internucleoside linkage.

61. The chirally enriched population of claim 56, wherein the population is enriched for compounds having the (Rp) configuration at one particular phosphorothioate internucleoside linkage and the (Sp) configuration at each of the remaining phosphorothioate internucleoside linkages.

62. The chirally enriched population of claim 56, wherein the population is enriched for compounds having at least 3 contiguous phosphorothioate internucleoside linkages in the Sp, Sp, and Rp configurations, in the 5' to 3' direction.

63. A population of oligomeric compounds of any of claims 40-53, in which all phosphorothioate internucleoside linkages of the oligomeric compound are stereorandom.

64. A pharmaceutical composition comprising the oligomeric compound of any of claims 1-53, the oligomeric duplex of claim 54, the antisense compound of claim 55, or the population of any of claims 56-63 and a pharmaceutically acceptable carrier or diluent.

65. A method comprising administering to an individual the pharmaceutical composition of claim 64.

66. A method of treating a disease associated with the RAAS pathway, comprising administering to an individual having or at risk of having a disease associated with the RAAS pathway a therapeutically effective amount of the pharmaceutical composition according to claim 64, thereby treating the disease associated with

the RAAS pathway.

67. The method of claim 66, wherein the disease is a cardiovascular disease.

68. The method of any of claims 66 and 67, wherein the disease is selected from hypertension, resistant hypertension, Marfan syndrome, heart failure, kidney disease, obesity, metabolic syndrome, NASH, and NAFLD.

69. The method of any of claims 66-68, wherein at least one symptom or hallmark of the disease is ameliorated.

70. The method of claim 69, wherein the symptom or hallmark is any of hypertension, hypertensive emergency (i.e. malignant hypertension), stroke, pre-eclampsia, aneurysms of the blood vessels, abdominal aneurysm, peripheral artery disease, organ damage, or pulmonary arterial hypertension.

71. The method of any of claims 65 to 70, wherein the pharmaceutical composition is administered systemically.

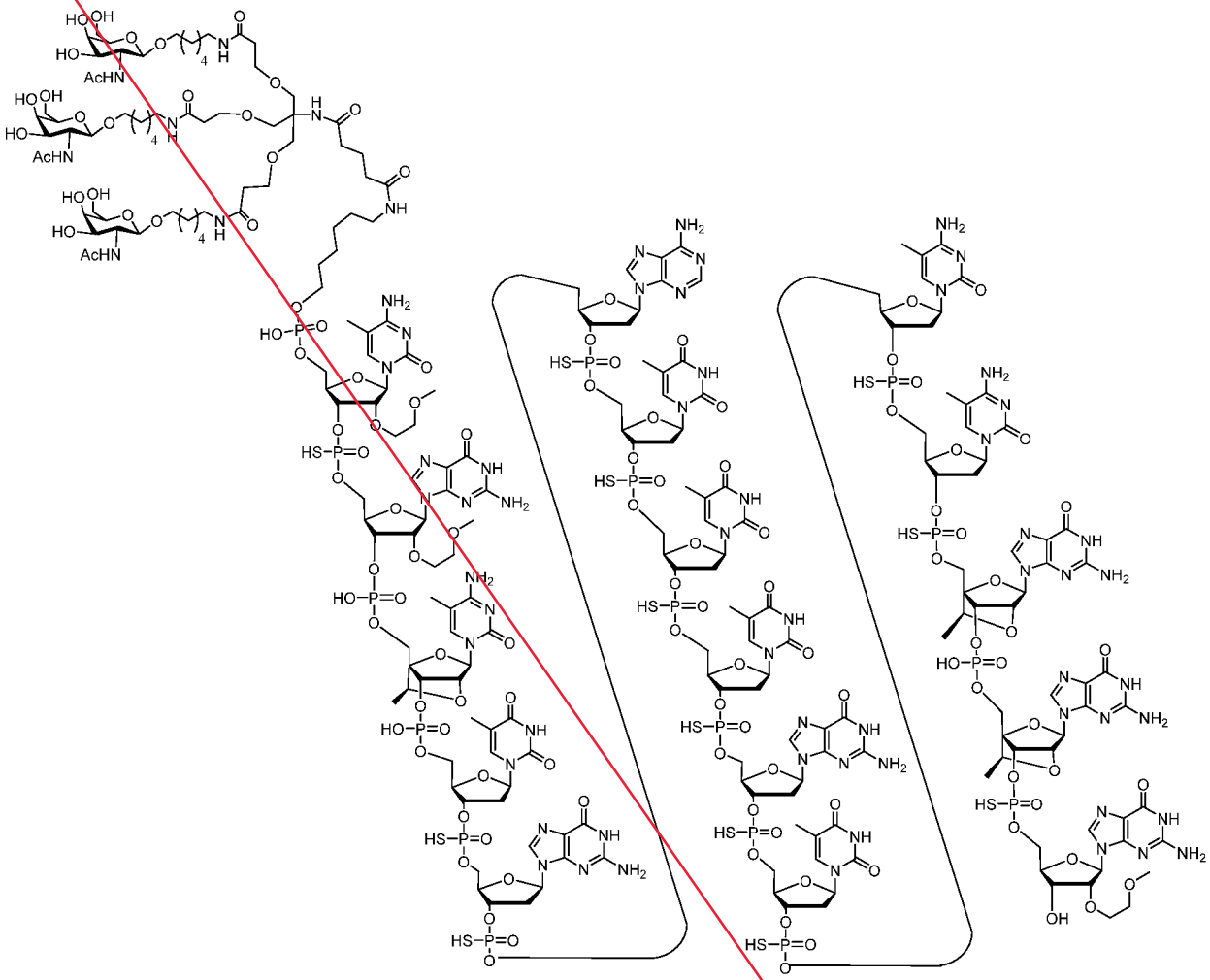
72. The method of any of claims 65 to 71, wherein the pharmaceutical composition is administered subcutaneously or intramuscularly.

73. Use of the oligomeric compound of any of claims 1-53, the oligomeric duplex of claim 54, the antisense compound of claim 55, or the population of any of claims 56-63 for reducing AGT expression in a cell.

74. The use of claim 73, wherein the level of AGT RNA is reduced.

75. The use of claim 73, wherein the level of AGT protein is reduced.

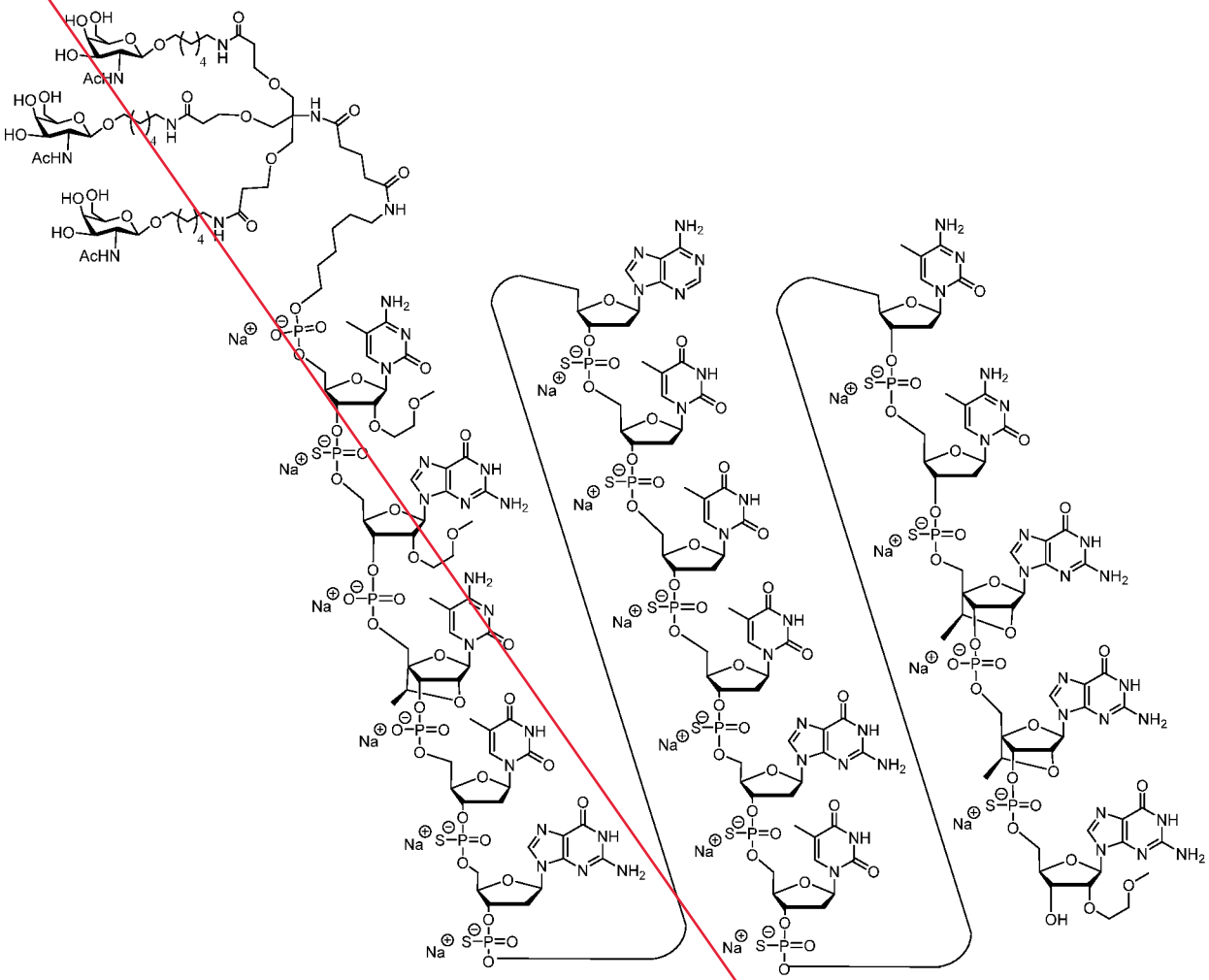
76. An oligomeric compound according to the following chemical structure:



(SEQ ID NO: 12), or a salt thereof.

77. The oligomeric compound of claim 76, which is the sodium salt or potassium salt.

78. An oligomeric compound according to the following chemical structure:



(SEQ ID NO: 12).

79. An oligomeric compound comprising a modified oligonucleotide according to the following chemical notation: $^{m}C_{es}G_{eo}{}^{m}C_{ko}T_{ds}G_{ds}A_{ds}T_{ds}T_{ds}T_{ds}G_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}G_{ko}G_{ks}G_{e}$ (SEQ ID NO: 12), wherein:

A = an adenine nucleobase,

^{m}C = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'-β-D-MOE sugar moiety,

k = a cEt sugar moiety,

d = a 2'-β-D-deoxyribosyl sugar moiety,

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

80. The oligomeric compound of claim 79, comprising the modified oligonucleotide covalently linked to a conjugate group.

81. A population of oligomeric compounds of claim 76, in which all phosphorothioate internucleoside linkages of the oligomeric compound are stereorandom.

82. A pharmaceutical composition comprising the oligomeric compound of claim 76 and a pharmaceutically acceptable carrier or diluent.

83. The pharmaceutical composition of claim 82, wherein the pharmaceutically acceptable diluent is water or PBS.

84. A pharmaceutical composition comprising the population of claim 81 and a pharmaceutically acceptable carrier or diluent.

85. A population of oligomeric compounds of claim 77, in which all phosphorothioate internucleoside linkages of the oligomeric compound are stereorandom.

86. A pharmaceutical composition comprising the oligomeric compound of claim 77 and a pharmaceutically acceptable carrier or diluent.

87. The pharmaceutical composition of claim 86, wherein the pharmaceutically acceptable diluent is water or PBS.

88. A pharmaceutical composition comprising the population of claim 85 and a pharmaceutically acceptable carrier or diluent.

89. A population of oligomeric compounds of claim 78, in which all phosphorothioate internucleoside linkages of the oligomeric compound are stereorandom.

90. A pharmaceutical composition comprising the oligomeric compound of claim 78 and a pharmaceutically acceptable carrier or diluent.

91. The pharmaceutical composition of claim 90, wherein the pharmaceutically acceptable diluent is water or PBS.

92. A pharmaceutical composition comprising the population of claim 89 and a pharmaceutically acceptable carrier or diluent.

93. A population of oligomeric compounds of claim 79 in which all phosphorothioate internucleoside linkages of the oligomeric compound are stereorandom.

94. A pharmaceutical composition comprising the oligomeric compound of claim 79 and a pharmaceutically acceptable carrier or diluent.

95. The pharmaceutical composition of claim 94, wherein the pharmaceutically acceptable diluent is water or PBS.

96. A pharmaceutical composition comprising the population of claim 93 and a pharmaceutically acceptable carrier or diluent.

97. A population of oligomeric compounds of claim 80, in which all phosphorothioate internucleoside linkages of the oligomeric compound are stereorandom.

98. A pharmaceutical composition comprising the oligomeric compound of claim 80 and a pharmaceutically acceptable carrier or diluent.

99. The pharmaceutical composition of claim 98, wherein the pharmaceutically acceptable diluent is water or PBS.

100. A pharmaceutical composition comprising the population of claim 97 and a pharmaceutically acceptable carrier or diluent.

CLAIMS

1. An oligomeric compound comprising a modified oligonucleotide according to the following chemical notation: $^{m}C_{es}G_{eo}{}^{m}C_{ko}T_{ds}G_{ds}A_{ds}T_{ds}T_{ds}T_{ds}G_{ds}T_{ds}{}^{m}C_{ds}{}^{m}C_{ds}G_{ko}G_{ks}G_{e}$ (SEQ ID NO: 12), wherein:

A = an adenine nucleobase,

^{m}C = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'-β-D-MOE sugar moiety,

k = a cEt sugar moiety,

d = a 2'-β-D-deoxyribosyl sugar moiety,

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

2. The oligomeric compound of claim 1, comprising the modified oligonucleotide covalently linked to a conjugate group.

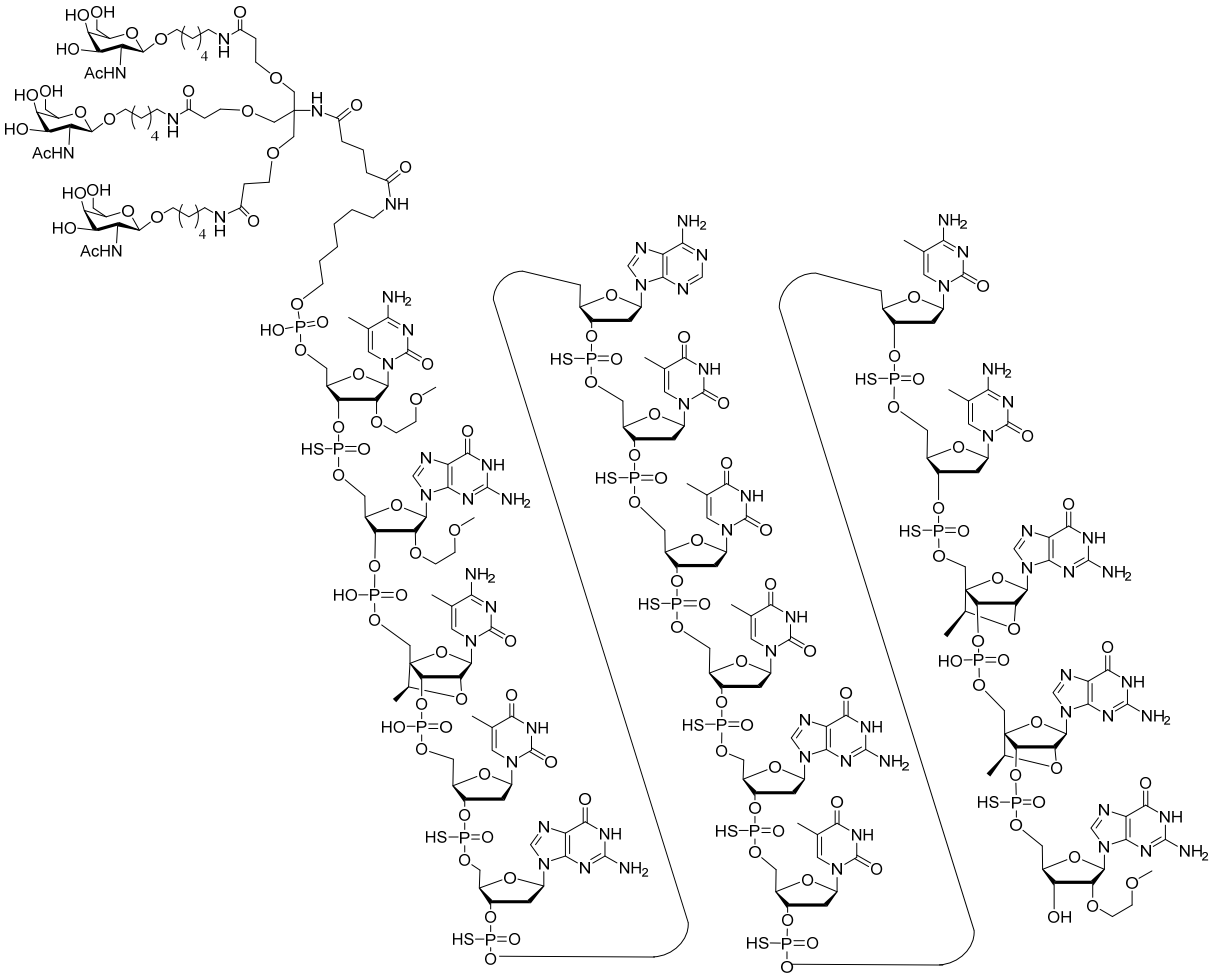
3. The oligomeric compound of claim 2, wherein the conjugate group comprises a conjugate linker consisting of a single bond.

4. The oligomeric compound of claim 2 or claim 3, wherein the conjugate group comprises a cleavable linker.

5. The oligomeric compound of any one of claims 2-4, wherein the conjugate group comprises a conjugate linker comprising 1-3 linker-nucleosides.

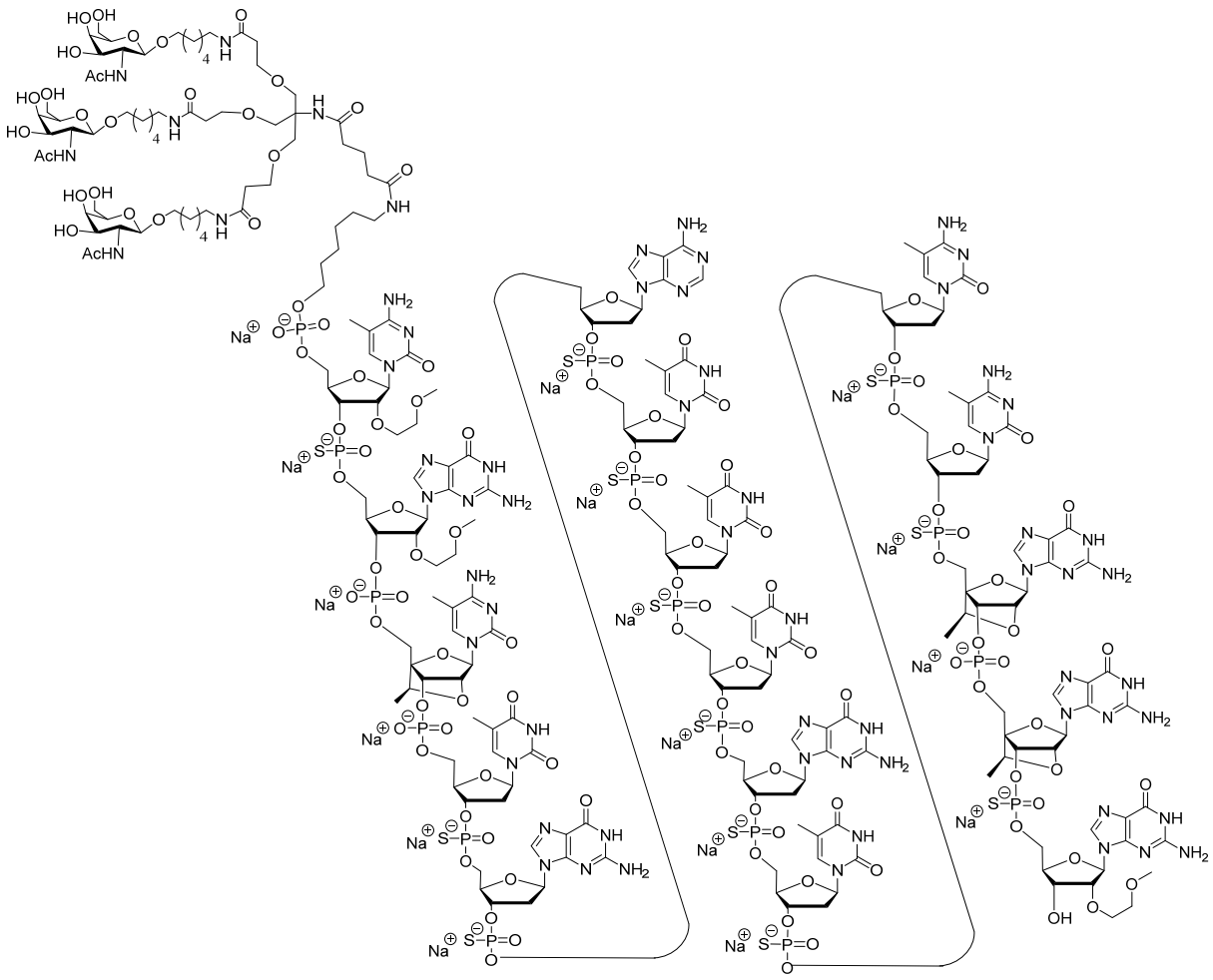
6. The oligomeric compound of any one of claims 2-5, wherein the conjugate group is attached to the modified oligonucleotide at the 3' and/or the 5'-end of the modified oligonucleotide.

7. The oligomeric compound of claim 2, according to the following chemical structure:



(SEQ ID NO: 12), or a salt thereof.

8. The oligomeric compound of claim 2, according to the following chemical structure:



(SEQ ID NO: 12).

9. The oligomeric compound of claim 7, which is the sodium salt or potassium salt.

10. A population of oligomeric compounds of any of claims 1-9, in which all phosphorothioate internucleoside linkages of the oligomeric compound are stereorandom.

11. A pharmaceutical composition comprising the oligomeric compound of any of claims 1-9, or the population of claim 10 and a pharmaceutically acceptable carrier or diluent.

12. The pharmaceutical composition of claim 11, wherein the pharmaceutically acceptable diluent is water or PBS.

13. Use of the pharmaceutical composition of claim 11 or claim 12, in the manufacture of a

medicament for treating a disease associated with the RAAS pathway, wherein a therapeutically effective amount of the pharmaceutical composition is to be administered to an individual having or at risk of having a disease associated with the RAAS pathway, thereby treating the disease associated with the RAAS pathway, wherein:

(i) the disease is a cardiovascular disease; and/or

(ii) the disease is selected from hypertension, resistant hypertension, Marfan syndrome, heart failure, kidney disease, obesity, metabolic syndrome, NASH, and NAFLD.

14. The use according to claim 13, wherein at least one symptom or hallmark of the disease is ameliorated, wherein the symptom or hallmark is any of hypertension, hypertensive emergency (i.e. malignant hypertension), stroke, pre-eclampsia, aneurysms of the blood vessels, abdominal aneurysm, peripheral artery disease, organ damage, or pulmonary arterial hypertension.

15. The use according to claim 13 or claim 14, wherein the pharmaceutical composition is to be administered systemically.

16. The use according to claim 15, wherein the pharmaceutical composition is to be administered subcutaneously or intramuscularly.