CLAIMS:

The present disclosure provides the following non-limiting numbered claims:

1. An oligomeric compound comprising a modified oligonucleotide consisting of 12 to 50 linked nucleosides wherein the nucleobase sequence of the modified oligonucleotide is at least 90% complementary to an equal length portion of a LRRK2 nucleic acid, and wherein the modified oligonucleotide comprises at least one modification selected from a modified sugar and a modified internucleoside linkage.

2: An oligomeric compound comprising a modified oligonucleotide consisting of 12 to 50 linked nucleosides and having a nucleobase sequence comprising at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or at least 20 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NOS: 30-3847.

3: An oligomeric compound comprising a modified oligonucleotide consisting of 12 to 50 linked nucleosides and having a nucleobase sequence comprising a portion of at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, or at least 20 contiguous nucleobases, wherein the portion is complementary to :

an equal length portion of nucleobases 18,633-18,658 of SEQ ID NO: 2;
an equal length portion of nucleobases 21,721-21,755 of SEQ ID NO: 2;
an equal length portion of nucleobases 27,963-28,016 of SEQ ID NO: 2;
an equal length portion of nucleobases 35,415-35,446 of SEQ ID NO: 2;
an equal length portion of nucleobases 77,221-77,264 of SEQ ID NO: 2;
an equal length portion of nucleobases 81,581-81,612 and/or 87,838-87,869 of SEQ ID NO: 2;
an equal length portion of nucleobases 81,627-81,651 of SEQ ID NO: 2;
an equal length portion of nucleobases 82,058-82,081 of SEQ ID NO: 2;
an equal length portion of nucleobases 82,180-82,220 of SEQ ID NO: 2;
an equal length portion of nucleobases 82,500-82,525 of SEQ ID NO: 2;
an equal length portion of nucleobases 91,038-91,067 of SEQ ID NO: 2;
an equal length portion of nucleobases 92,148-92,173 of SEQ ID NO: 2;
am equal length portion of nucleobases 98,186-98,220 of SEQ ID NO: 2;
an equal length portion of nucleobases 98,218-98,242 of SEQ ID NO: 2;
an equal length portion of nucleobases 99,199-99,223 of SEQ ID NO: 2;
an equal length portion of nucleobases 119,903-119,936 of SEQ ID NO: 2; or
an equal length portion of nucleobases 4,062-4,086 of SEQ ID NO: 1.

4. The oligomeric compound of any of claims 1-3, 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 sequences of SEQ ID NO: 1 or SEQ ID NO: 2, when measured across the entire nucleobase sequence of the modified oligonucleotide.

5. The oligomeric compound of any of claims 1-4, wherein the modified oligonucleotide comprises at least one modified nucleoside.

6. The oligomeric compound of claim 5, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a modified sugar moiety.

7. The oligomeric compound of claim 6, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a bicyclic sugar moiety.

8. The oligomeric compound of claim 7, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a bicyclic sugar moiety having a 2'-4' bridge, wherein the 2'-4' bridge is selected from $-O-CH_2-$; and $-O-CH(CH_3)-$.

9. The oligomeric compound of any of claims 5-8, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a non-bicyclic modified sugar moiety.

10. The oligomeric compound of claim 9, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a non-bicyclic modified sugar moiety comprising a 2'-MOE modified sugar or 2'-OMe modified sugar.

11. The oligomeric compound of any of claims 5-10, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a sugar surrogate.

12. The oligomeric compound of claim 11, wherein the modified oligonucleotide comprises at least one modified nucleoside comprising a sugar surrogate selected from morpholino and PNA.

13. The oligomeric compound of any of claims 1-12, wherein the modified oligonucleotide has a sugar motif comprising:

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

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

a 3'-region consisting of 1-5 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 an unmodified 2'-deoxyribosyl sugar moiety.

14. The oligomeric compound of any of claims 1-13, wherein the modified oligonucleotide comprises at least one modified internucleoside linkage.

15. The oligomeric compound of claim 14, wherein each internucleoside linkage of the modified oligonucleotide is a modified internucleoside linkage.

16. The oligomeric compound of claim 14 or 15 wherein at least one internucleoside linkage is a phosphorothioate internucleoside linkage.

17. The oligomeric compound of claim 14 or 16 wherein the modified oligonucleotide comprises at least one phosphodiester internucleoside linkage.

18. The oligomeric compound of any of claims 14, 16, or 17, wherein each internucleoside linkage is either a phosphodiester internucleoside linkage or a phosphorothioate internucleoside linkage.

19. The oligomeric compound of any of claims 1-18, wherein the modified oligonucleotide comprises at least one modified nucleobase.

20. The oligomeric compound of claim 19, wherein the modified nucleobase is a 5-methyl cytosine.

21. The oligomeric compound of any of claims 1-20, wherein the modified oligonucleotide consists of 12-30, 12-22, 12-20, 14-20, 15-25, 16-20, 18-22 or 18-20 linked nucleosides.

22. The oligomeric compound of any of claims 1-21, wherein the modified oligonucleotide consists of 17 or 20 linked nucleosides.

23. The oligomeric compound of any of claims 1-22 consisting of the modified oligonucleotide.

24. The oligomeric compound of any of claims 1-22 comprising a conjugate group comprising a conjugate moiety and a conjugate linker.

25. The oligomeric compound of claim 24, wherein the conjugate group comprises a GalNAc cluster comprising 1-3 GalNAc ligands.

26. The oligomeric compound of claims 24 or 25, wherein the conjugate linker consists of a single bond.

27. The oligomeric compound of claim 25, wherein the conjugate linker is cleavable.

28. The oligomeric compound of claim 27, wherein the conjugate linker comprises 1-3 linker-nucleosides.

29. The oligomeric compound of any of claims 24-28, wherein the conjugate group is attached to the modified oligonucleotide at the 5'-end of the modified oligonucleotide.

30. The oligomeric compound of any of claims 24-28, wherein the conjugate group is attached to the modified oligonucleotide at the 3'-end of the modified oligonucleotide.

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

32. The oligomeric compound of any of claims 1-31 wherein the oligomeric compound is a singled-stranded oligomeric compound.

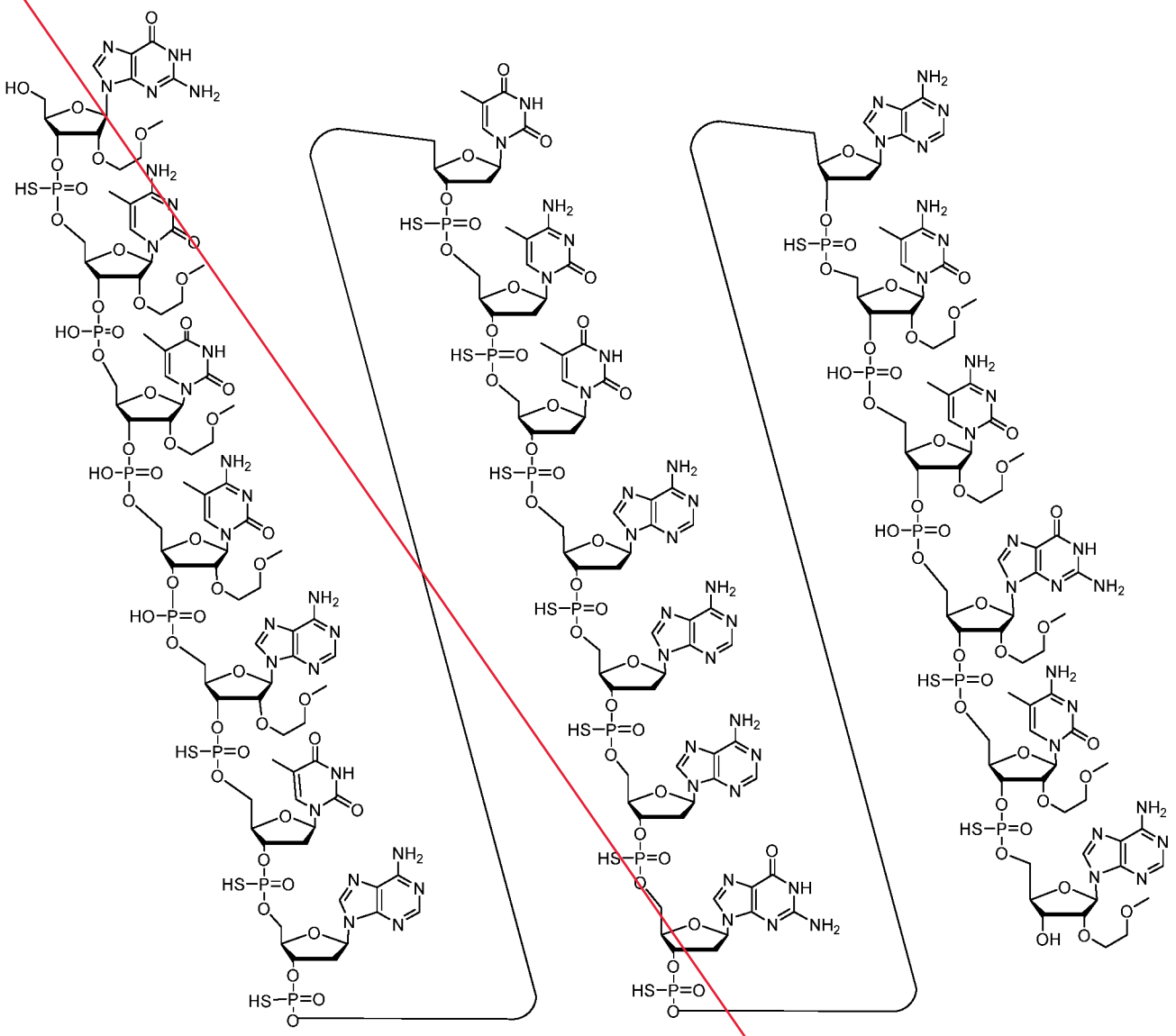
33. The oligomeric compound of any of claims 1-27 or 29-31, wherein the oligomeric compound does not comprise linker-nucleosides.

34. An oligomeric duplex comprising an oligomeric compound of any of claims 1-31 or 33.

35. An antisense compound comprising or consisting of an oligomeric compound of any of claims 1-33 or an oligomeric duplex of claim 34.

36. A pharmaceutical composition comprising an oligomeric compound of any of claims 1-33 or an oligomeric duplex of claim 34 and a pharmaceutically acceptable carrier or diluent.

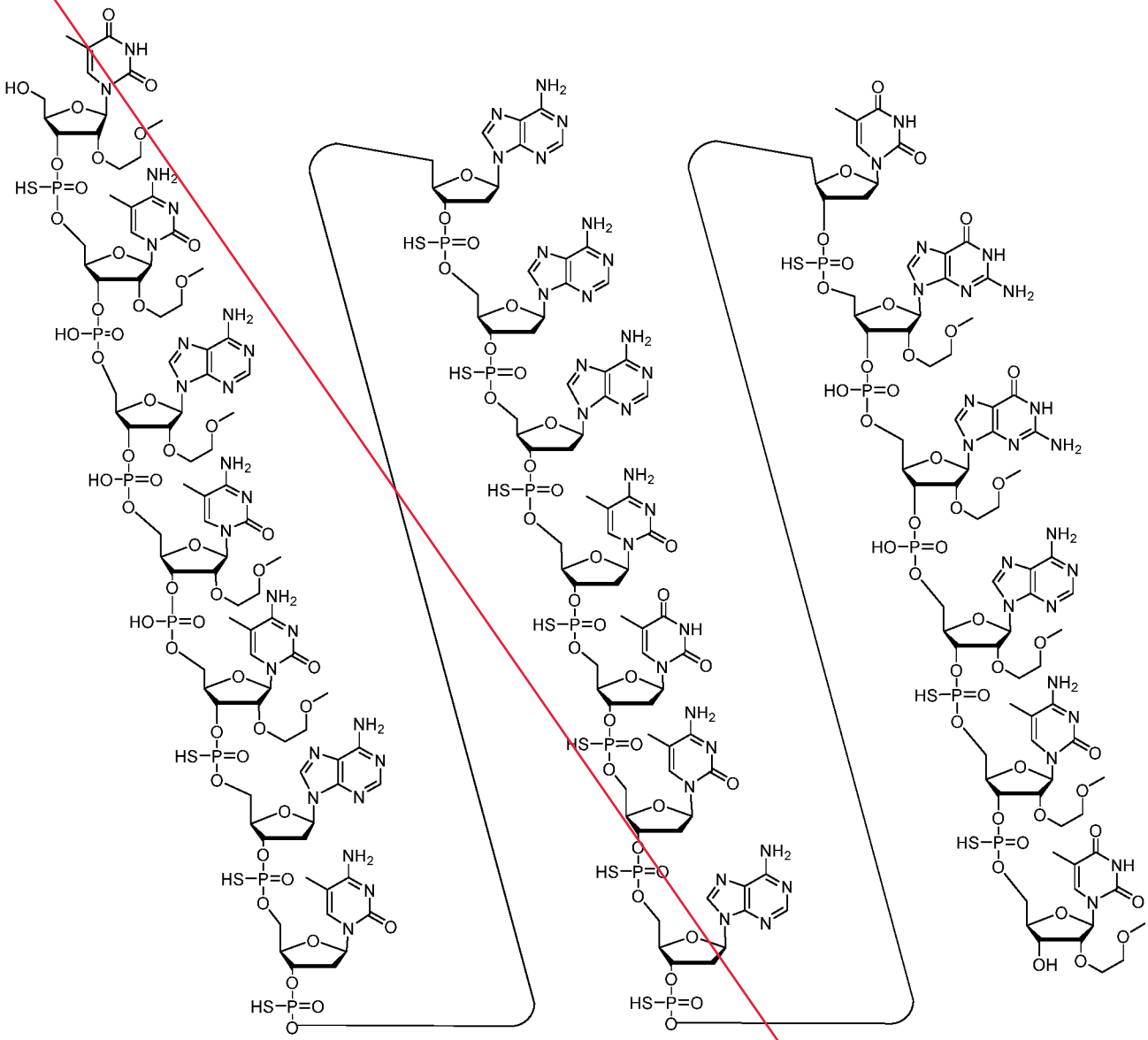
37. A modified oligonucleotide according to the following formula:



(SEQ ID NO: 222)

or a salt thereof.

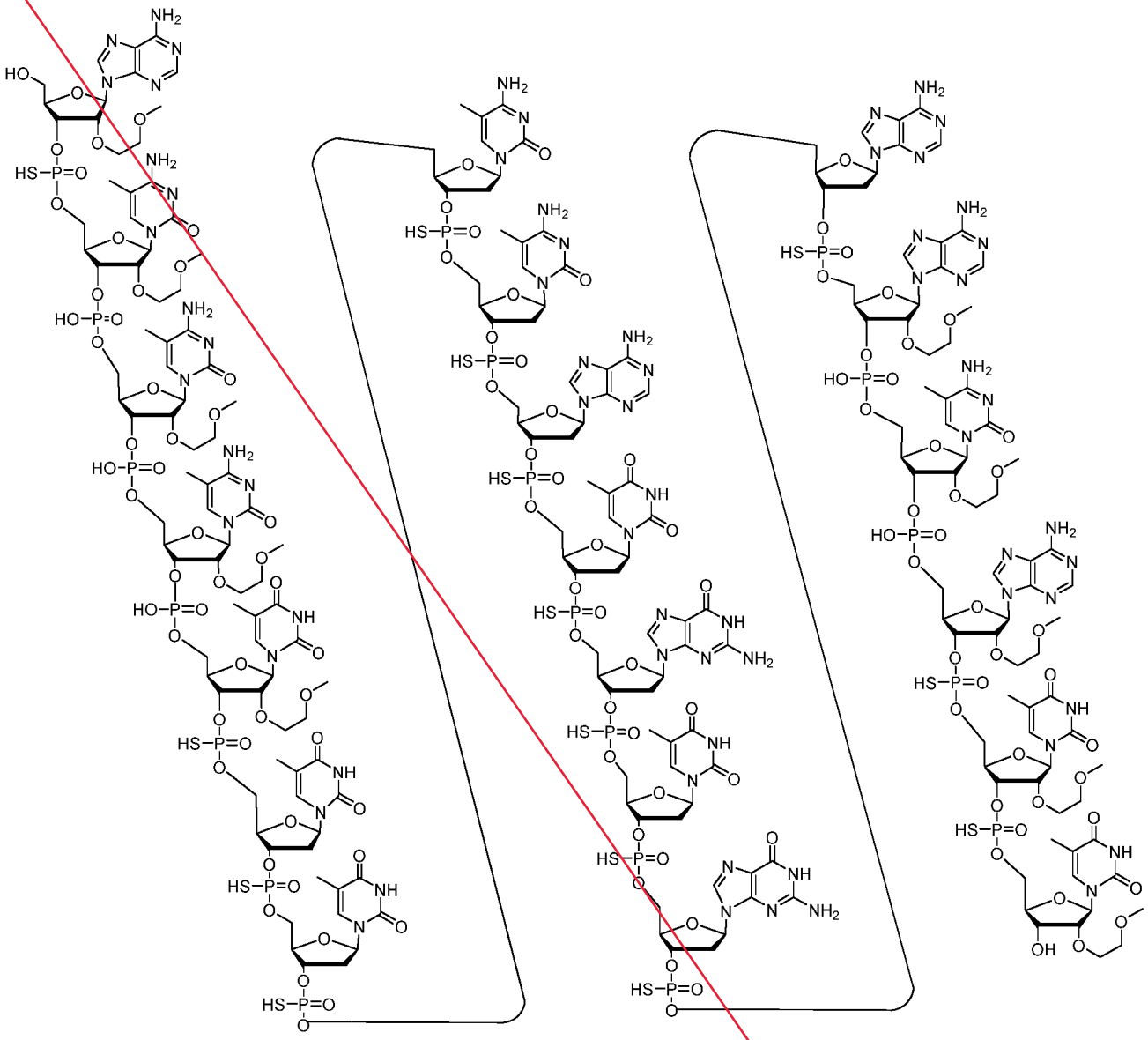
38. A modified oligonucleotide according to the following formula:



(SEQ ID NO: 888)

or a salt thereof.

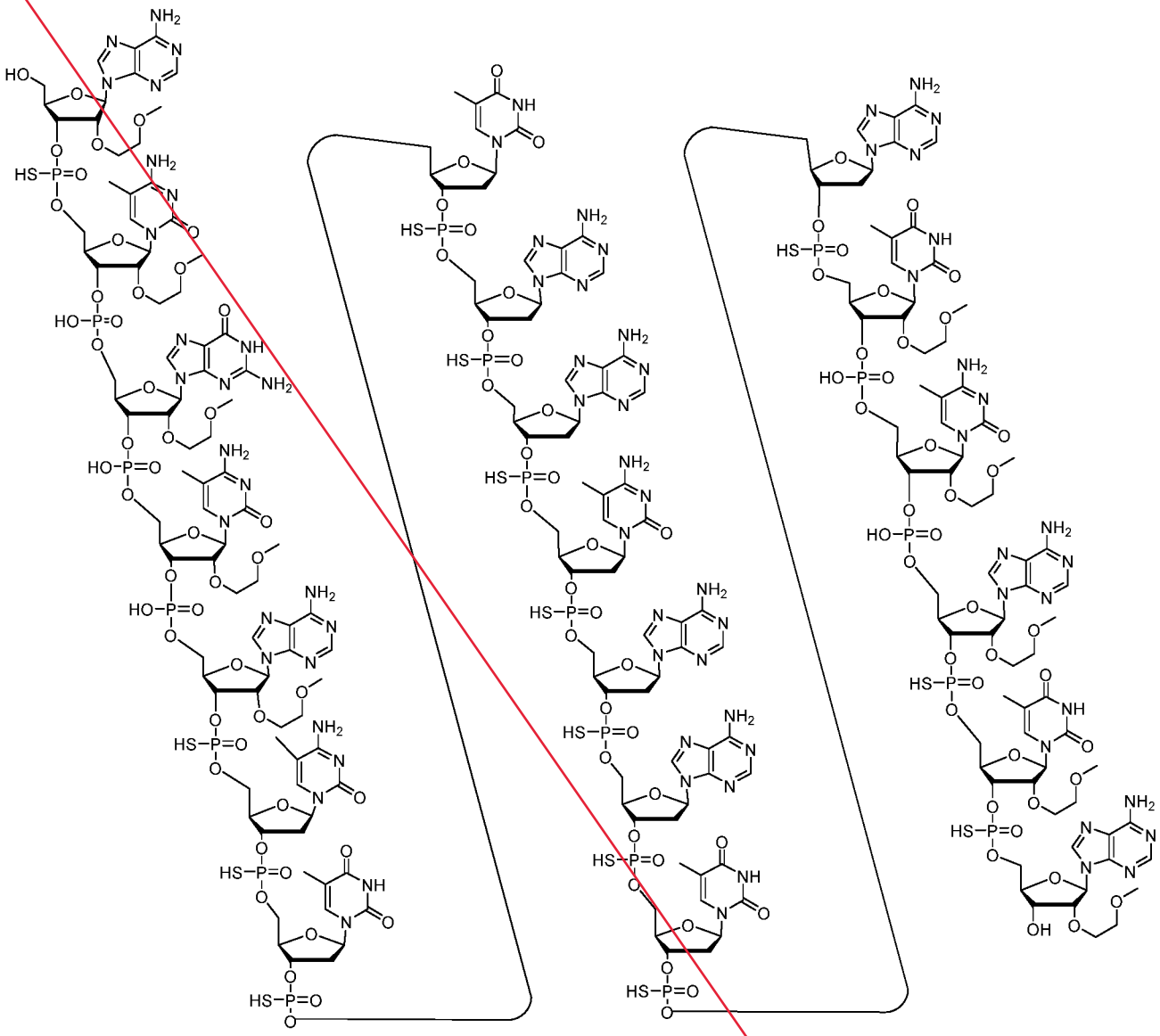
39. A modified oligonucleotide according to the following formula:



(SEQ ID NO: 1431)

or a salt thereof.

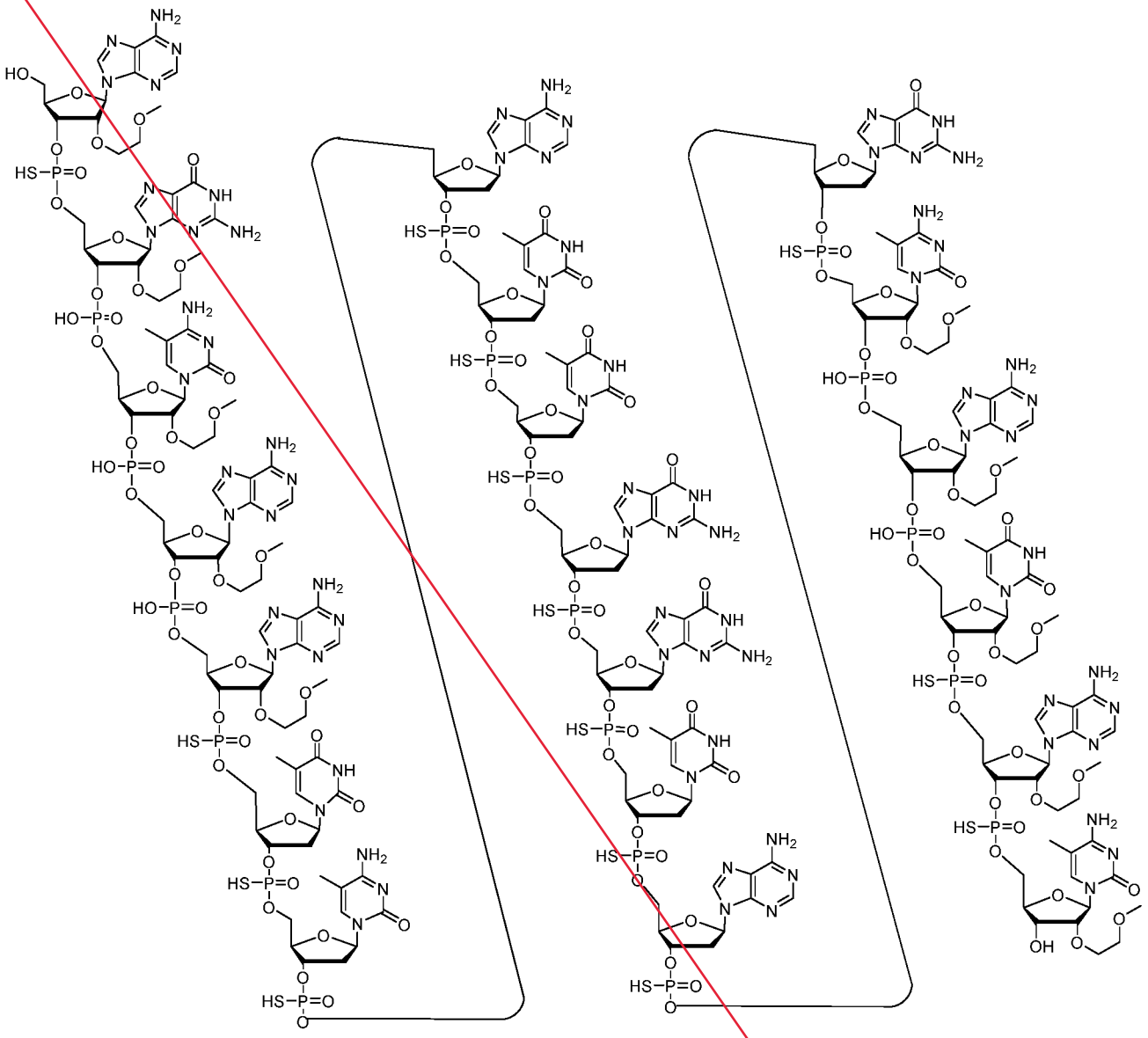
40. A modified oligonucleotide according to the following formula:



(SEQ ID NO: 3590)

or a salt thereof.

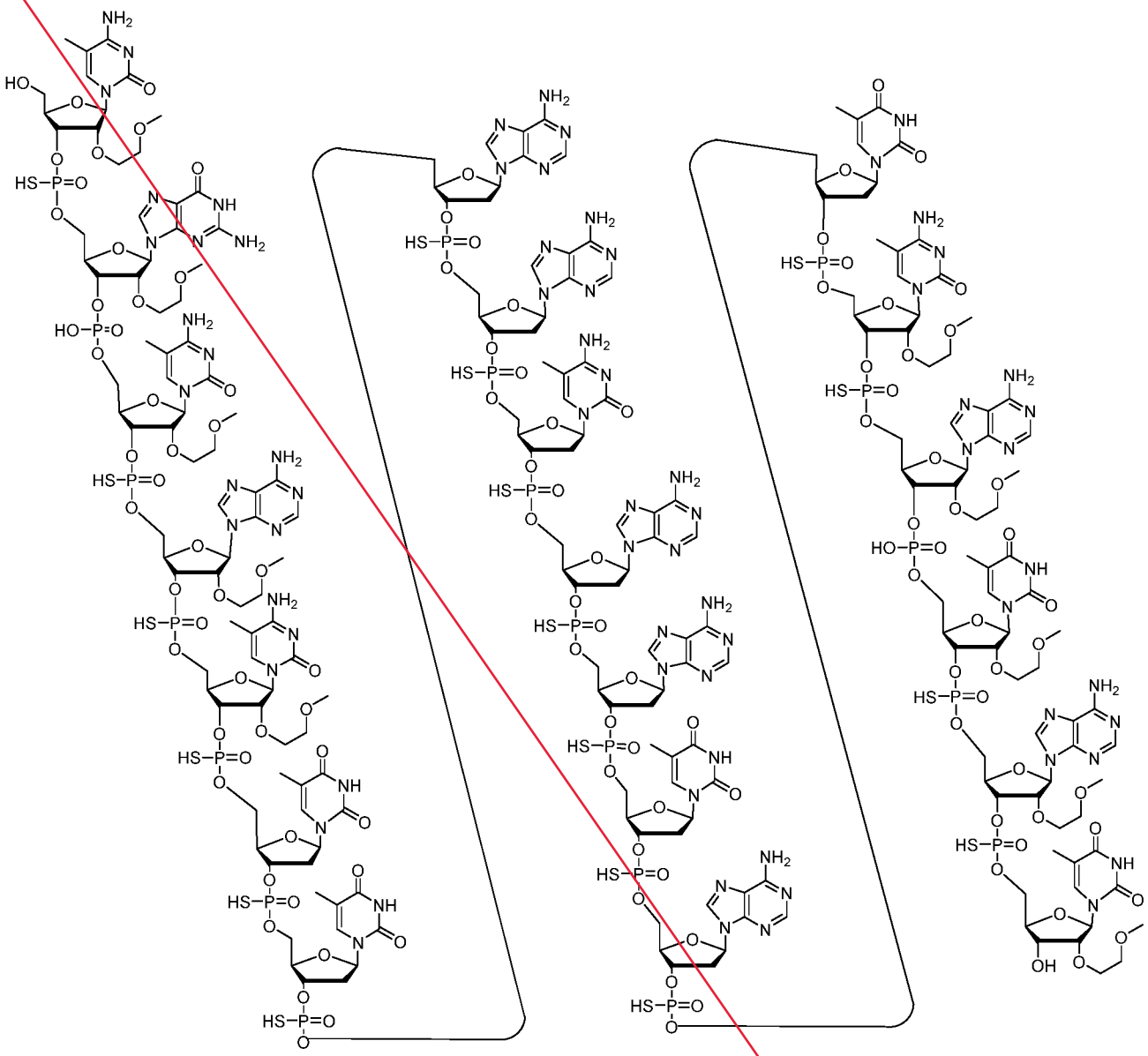
41. A modified oligonucleotide according to the following formula:



(SEQ ID NO: 3385)

or a salt thereof.

42. A modified oligonucleotide according to the following formula:

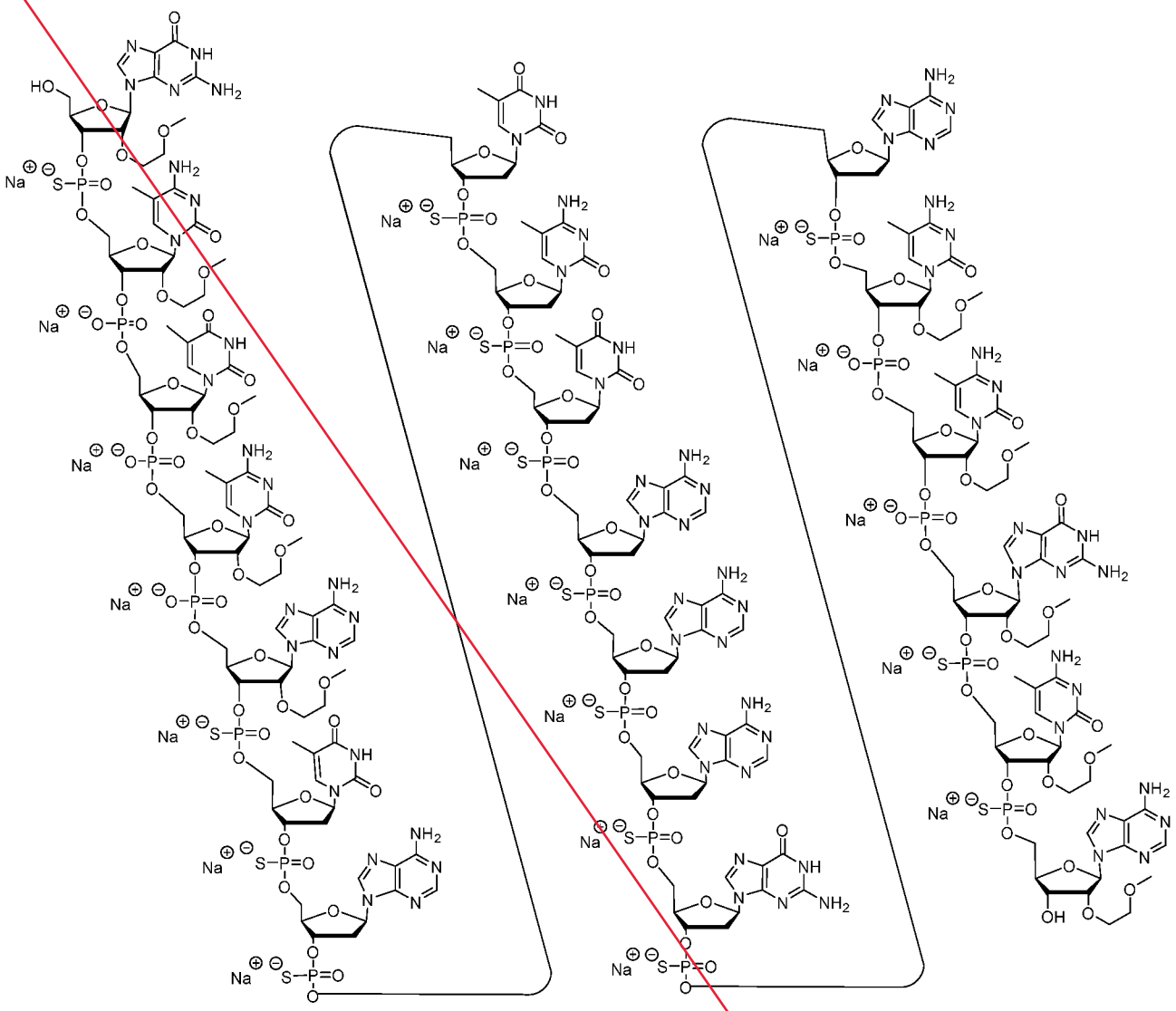


(SEQ ID NO: 852)

or a salt thereof.

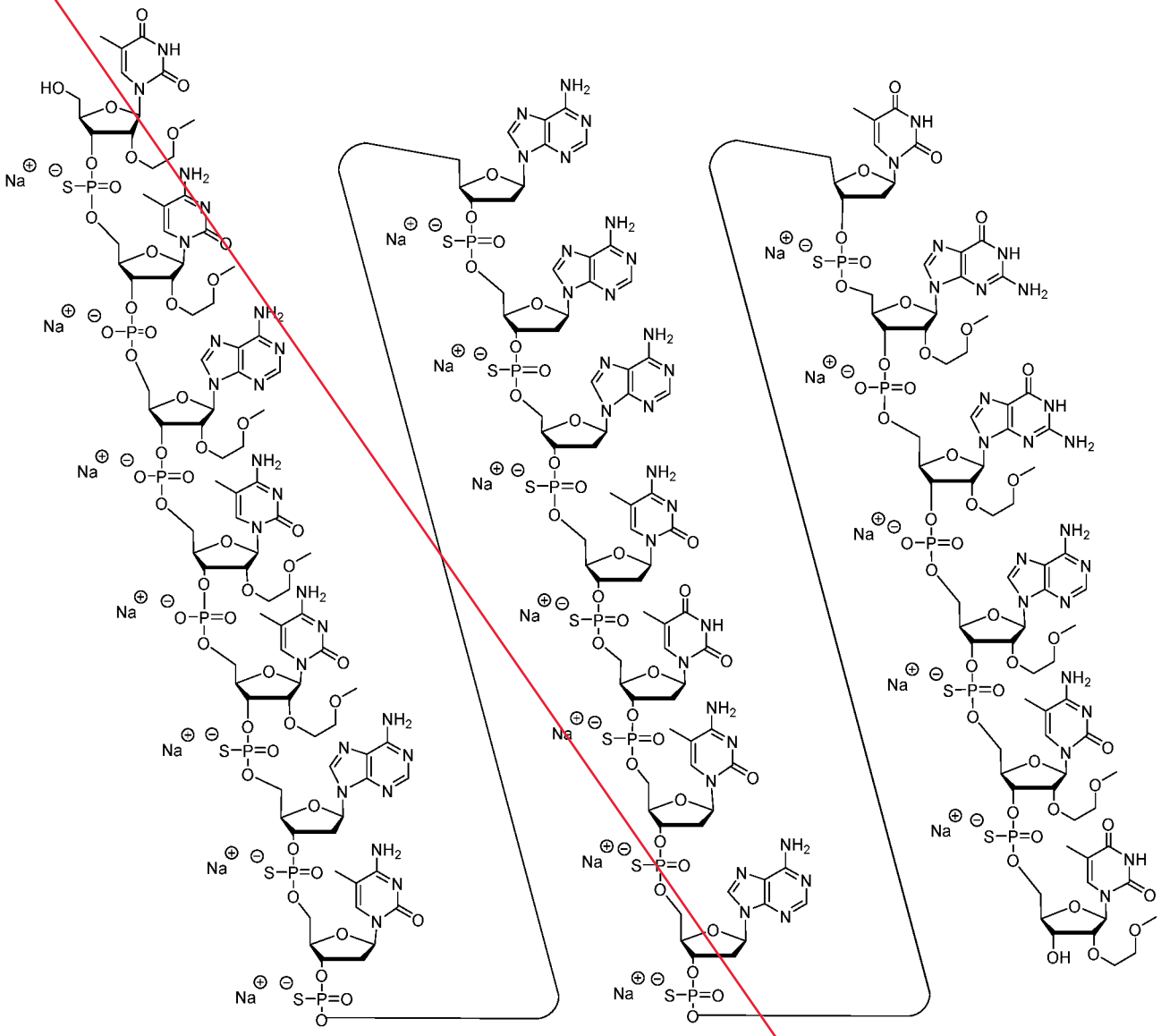
43. The modified oligonucleotide of any of claims 37-42, which is a sodium salt of the formula.

44. A modified oligonucleotide according to the following formula:



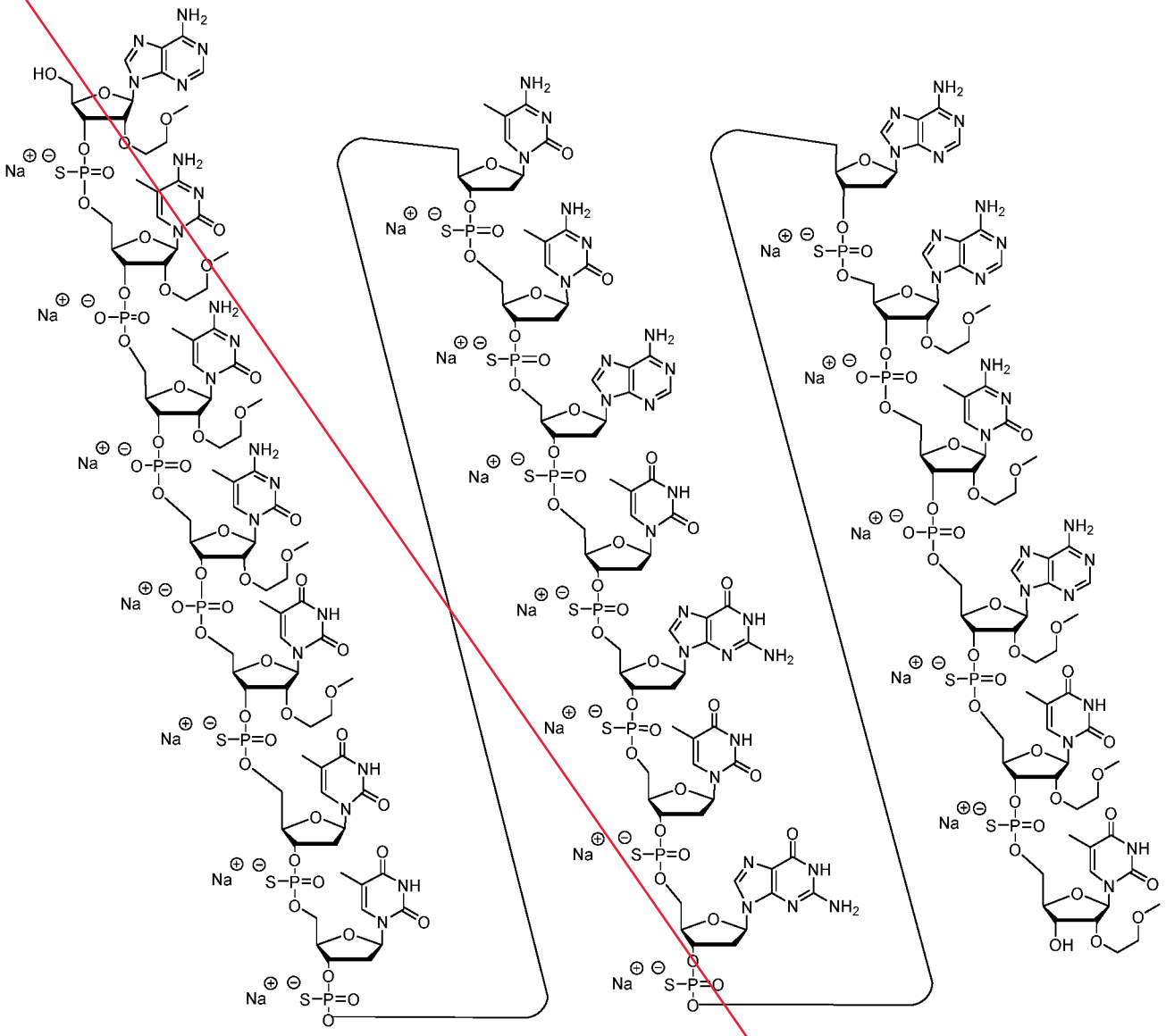
(SEQ ID NO: 222).

45. A modified oligonucleotide according to the following formula:



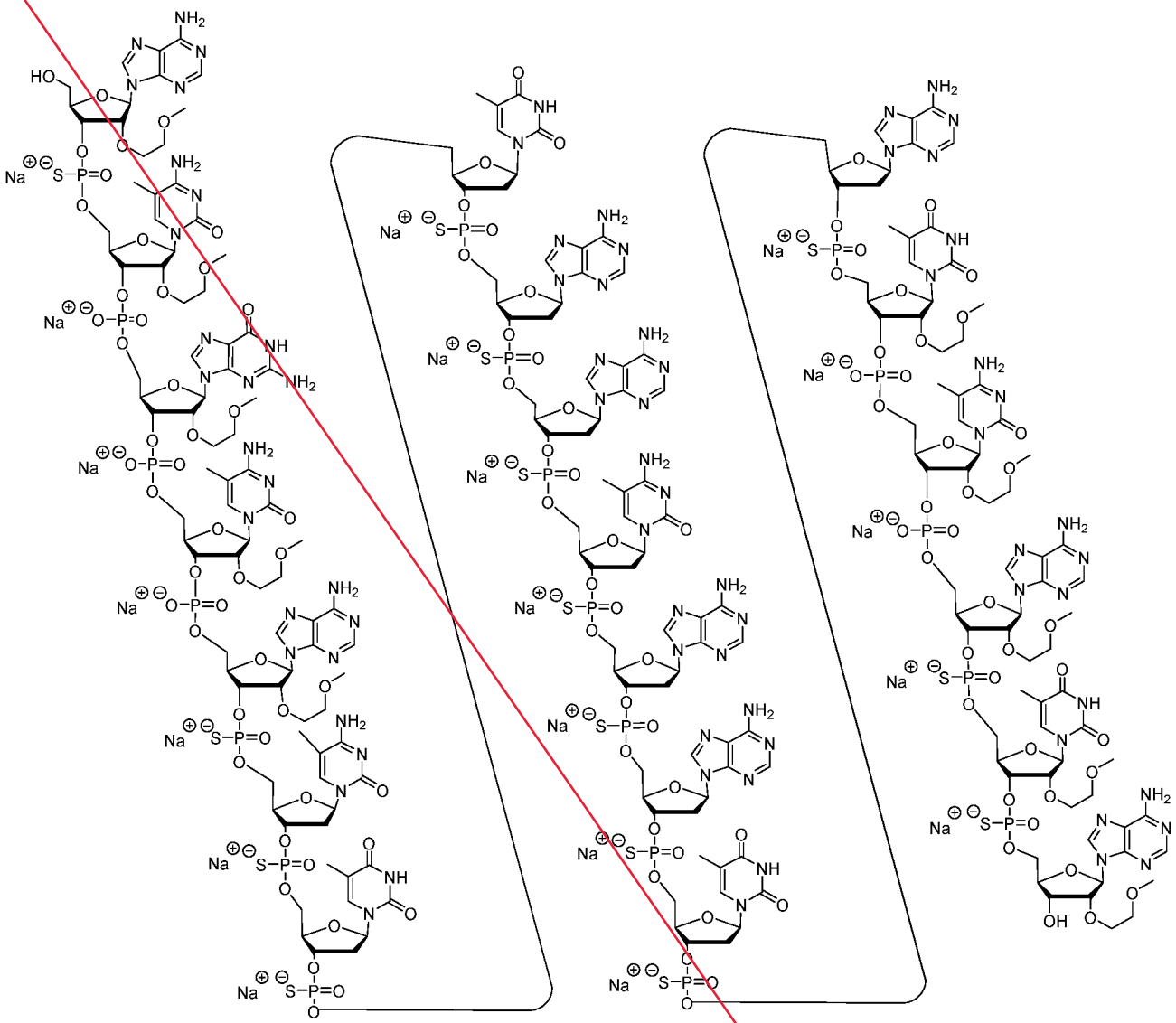
(SEQ ID NO: 888).

46. A modified oligonucleotide according to the following formula:



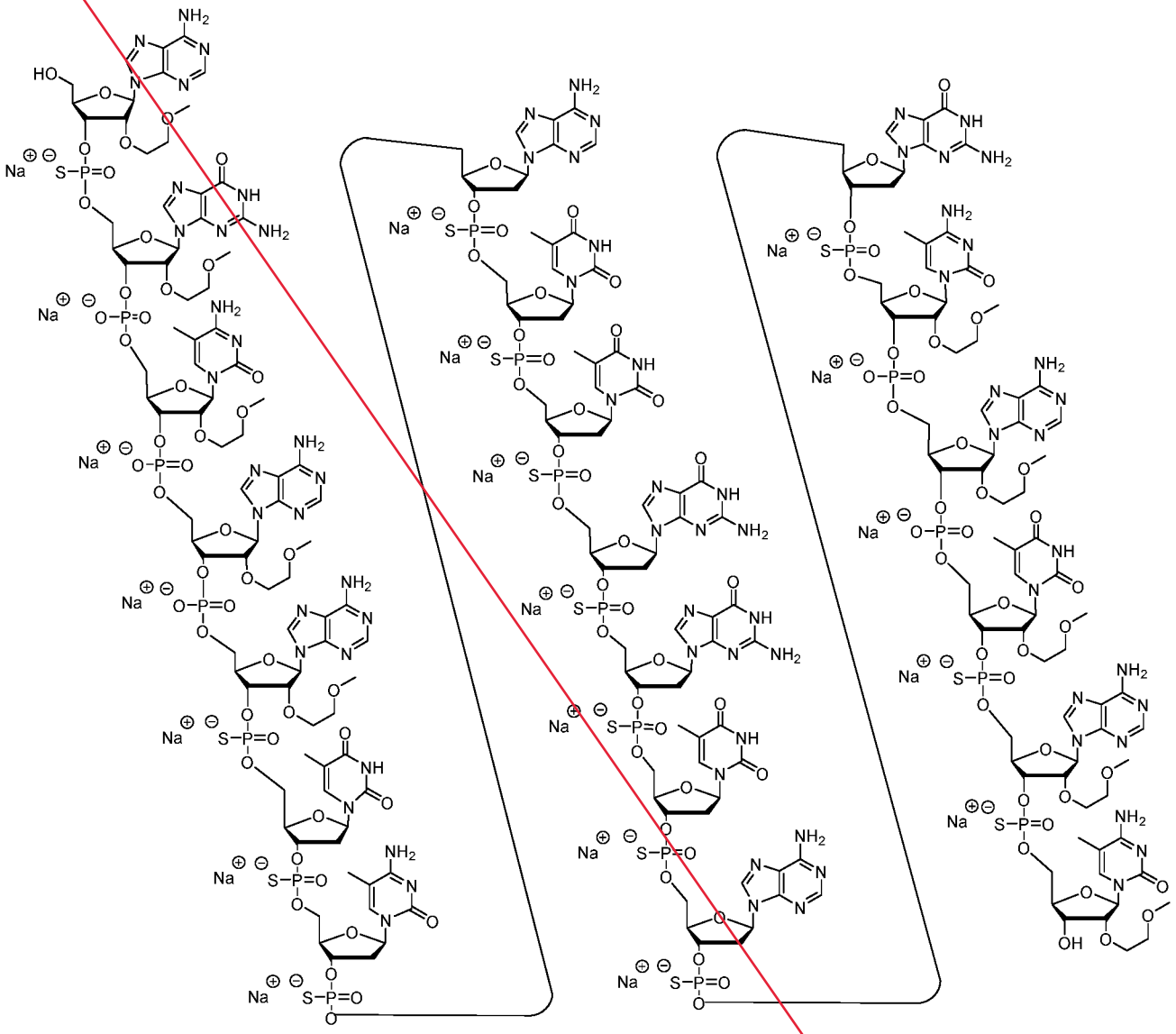
(SEQ ID NO: 1431).

47. A modified oligonucleotide according to the following formula:



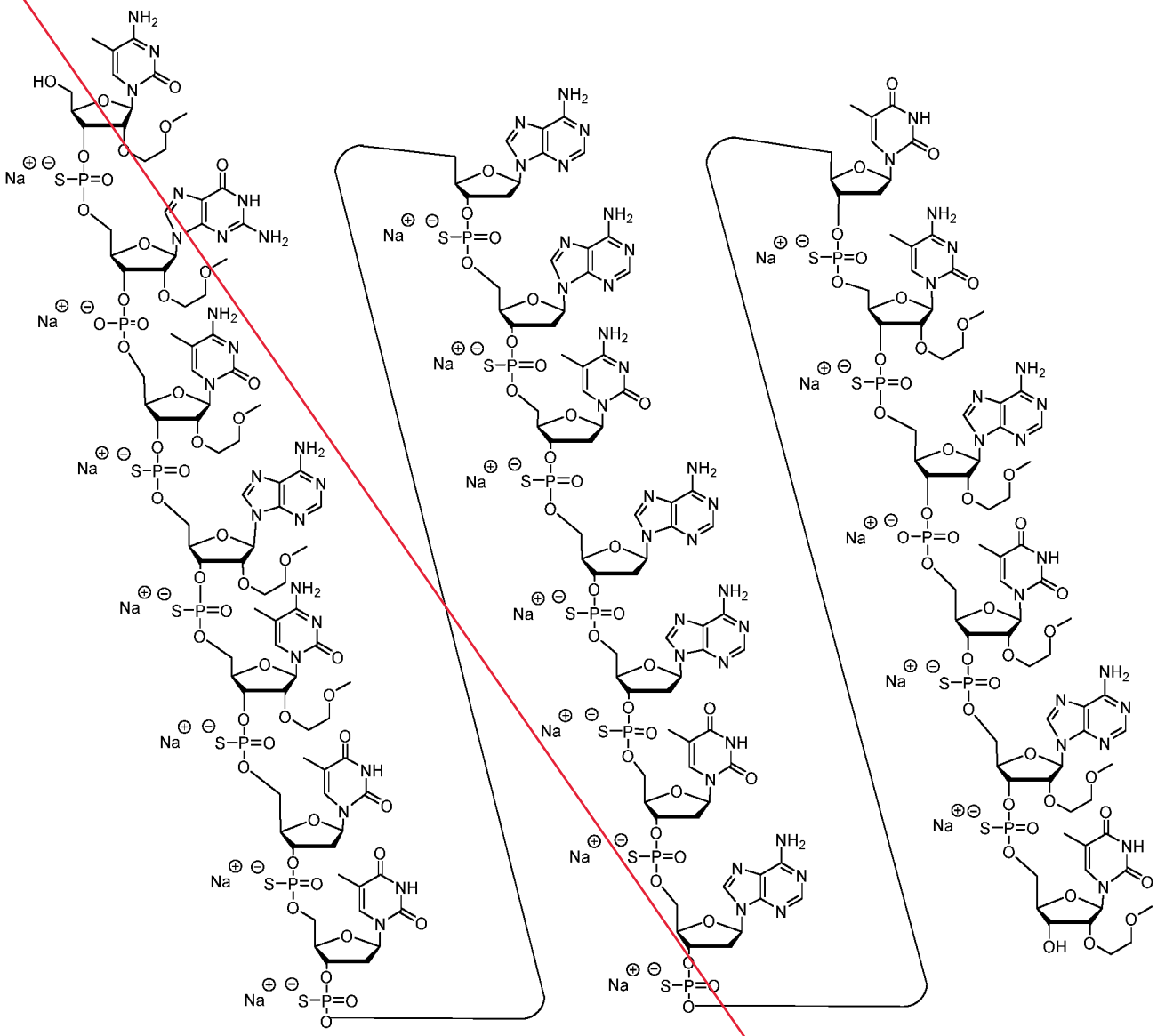
(SEQ ID NO: 3590).

48. A modified oligonucleotide according to the following formula:



(SEQ ID NO: 3385).

49. A modified oligonucleotide according to the following formula:



(SEQ ID NO: 852).

50. A chirally enriched population of the modified oligonucleotide of any of claims 37-49 wherein the population is enriched for modified oligonucleotides comprising at least one particular phosphorothioate internucleoside linkage having a particular stereochemical configuration.

51. The chirally enriched population of claim 50, wherein the population is enriched for modified oligonucleotides comprising at least one particular phosphorothioate internucleoside linkage having the (*S*p) configuration.

52. The chirally enriched population of claim 50 or 51, wherein the population is enriched for modified oligonucleotides comprising at least one particular phosphorothioate internucleoside linkage having the (*R*p) configuration.

53. The chirally enriched population of claim 50, wherein the population is enriched for modified oligonucleotides having a particular, independently selected stereochemical configuration at each phosphorothioate internucleoside linkage

54. The chirally enriched population of claim 53, wherein the population is enriched for modified oligonucleotides having the (*S*p) configuration at each phosphorothioate internucleoside linkage.

55. The chirally enriched population of claim 53, wherein the population is enriched for modified oligonucleotides having the (*R*p) configuration at each phosphorothioate internucleoside linkage.

56. The chirally enriched population of claim 50 or claim 53, wherein the population is enriched for modified oligonucleotides having at least 3 contiguous phosphorothioate internucleoside linkages in the *S*p-*S*p-*R*p configuration, in the 5' to 3' direction.

57. A population of modified oligonucleotides of any of claims 37-49, wherein all of the phosphorothioate internucleoside linkages of the modified oligonucleotide are stereorandom.

58. A pharmaceutical composition comprising the modified oligonucleotide of any of claims 37-49 and a pharmaceutically acceptable diluent or carrier.

59. The pharmaceutical composition of claim 58, wherein the pharmaceutically acceptable diluent is artificial cerebrospinal fluid.

60. The pharmaceutical composition of claim 59, wherein the pharmaceutical composition consists essentially of the modified oligonucleotide and artificial cerebrospinal fluid.

61. A method comprising administering to an animal a pharmaceutical composition of any of claims 36 or 58-60.

62. A method of treating a disease associated with LRRK2 comprising administering to an individual having or at risk for developing a disease associated with LRRK2 a therapeutically effective amount of a pharmaceutical composition according to any of claims 36 or 58-60; and thereby treating the disease associated with LRRK2.

63. The method of claim 62, wherein the disease associated with LRRK2 is a neurodegenerative disease.

64. The method of claim 63, wherein the neurodegenerative disease is Parkinson's disease.

65. The method of claim 64, wherein at least one symptom or hallmark of the neurodegenerative disease is ameliorated.

66. The method of claim 65, wherein the symptom or hallmark is any of ataxia, neuropathy, and aggregate formation.

67. An oligomeric compound comprising a modified oligonucleotide according to the following formula: Ges mCeo Teo mCeo Aes Tds Ads Tds mCds Tds Ads Ads Ads Gds Ads mCeo mCeo Ges mCes Ae (SEQ ID NO: 222); wherein,

A = an adenine nucleobase,

mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'- MOE modified sugar,

d = a 2'-deoxyribose sugar,

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

68. An oligomeric compound comprising a modified oligonucleotide according to the following formula:

Tes mCeo Aeo mCeo mCes Ads mCds Ads Ads Ads mCds Tds mCds Ads Tds Geo Geo Aes mCes Te (SEQ ID NO: 888); wherein,

A = an adenine nucleobase,

mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'- MOE modified sugar,

d = a 2'-deoxyribose sugar,

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

69. An oligomeric compound comprising a modified oligonucleotide according to the following formula:

Aes mCeo mCeo mCeo Tes Tds Tds mCds mCds Ads Tds Gds Tds Gds Ads Aeo mCeo Aes Tes Te (SEQ ID NO: 1431); wherein,

A = an adenine nucleobase,

mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'- MOE modified sugar,

d = a 2'-deoxyribose sugar,

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

70. An oligomeric compound comprising a modified oligonucleotide according to the following formula:

Aes mCeo Geo mCeo Aes mCds Tds Tds Ads Ads mCds Ads Ads Tds Ads Teo mCeo Aes Tes Ae (SEQ ID NO: 3590); wherein,

A = an adenine nucleobase,

mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'- MOE modified sugar,

d = a 2'-deoxyribose sugar,

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

71. An oligomeric compound comprising a modified oligonucleotide according to the following formula: Aes Geo mCeo Aeo Aes Tds mCds Ads Tds Tds Gds Gds Tds Ads Gds mCeo Aeo Tes Aes mCe (SEQ ID NO: 3385); wherein,

A = an adenine nucleobase,

mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'- MOE modified sugar,

d = a 2'-deoxyribose sugar,

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

72. An oligomeric compound comprising a modified oligonucleotide according to the following formula: mCes Geo mCes Aes mCes Tds Tds Ads Ads mCds Ads Ads Tds Ads Tds mCes Aeo Tes Aes Te (SEQ ID NO: 852); wherein,

A = an adenine nucleobase,

mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'- MOE modified sugar,

d = a 2'-deoxyribose sugar,

s = a phosphorothioate internucleoside linkage, and

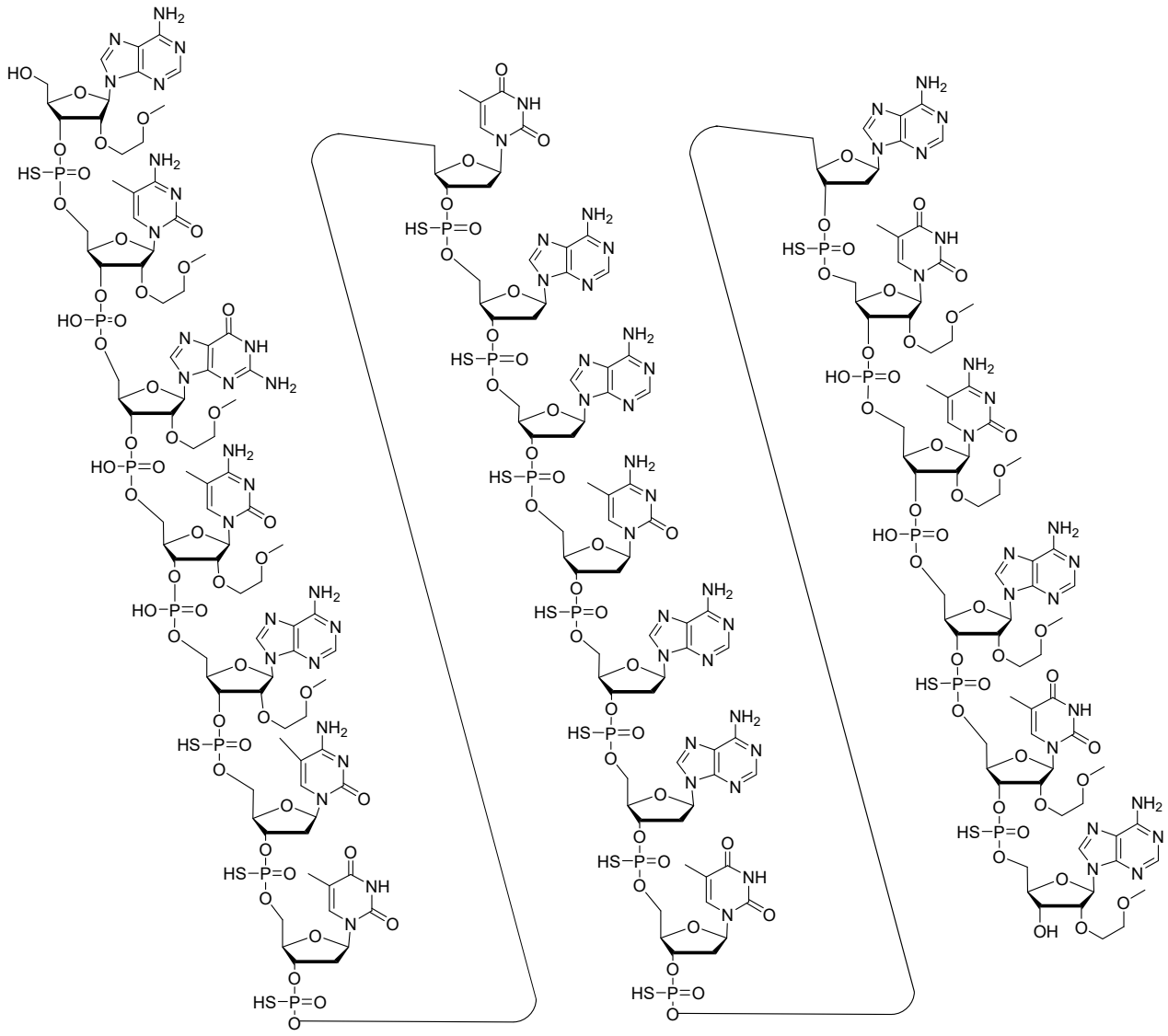
o = a phosphodiester internucleoside linkage.

Claim 73.The oligomeric compound of claim 3, wherein the modified oligonucleotide is an RNAi compound.

Claim 74.The oligomeric compound of claim 73, wherein the RNAi compound is an ssRNA or an siRNA.

CLAIMS:

1. A modified oligonucleotide according to the following chemical structure:

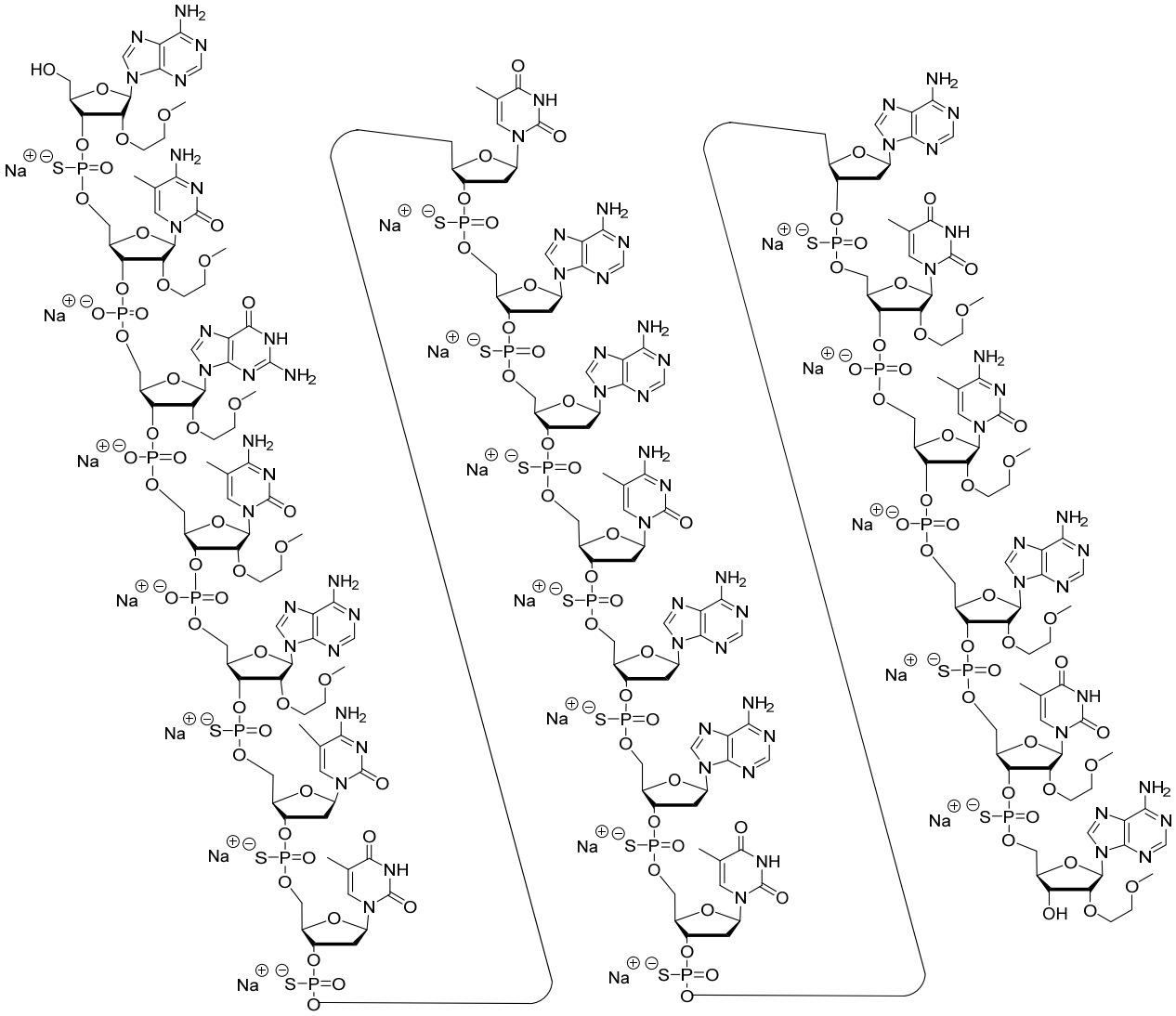


(SEQ ID NO: 3590)

or a salt thereof.

2. The modified oligonucleotide of claim 1, which is the sodium salt or the potassium salt.

3. A modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 3590).

4. An oligomeric compound comprising a modified oligonucleotide according to the following chemical notation:

Aes mCeo Geo mCeo Aes mCds Tds Tds Ads Ads mCds Ads Ads Tds Ads Teo mCeo Aes Tes Ae (SEQ ID NO: 3590); wherein,

A = an adenine nucleobase,

mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'-$OCH_2CH_2OCH_3$ ribosyl sugar moiety,

d = a 2'-deoxyribosyl sugar moiety,

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

5. A population of modified oligonucleotides of any of claims 1-3 or a population of oligomeric compounds of claim 4, wherein all of the phosphorothioate internucleoside linkages of the modified oligonucleotide are stereorandom.

6. A pharmaceutical composition comprising a modified oligonucleotide of any of claims 1-3, an oligomeric compound of claim 4, or a population of modified oligonucleotides or oligomeric compounds of claim 5, and a pharmaceutically acceptable diluent.

7. The pharmaceutical composition of claim 6, wherein:

i) the pharmaceutically acceptable diluent is artificial cerebrospinal fluid or phosphate-buffered saline (PBS); or

ii) the pharmaceutical composition consists essentially of a modified oligonucleotide of any of claims 1-3, an oligomeric compound of claim 4, or a population of modified oligonucleotides or oligomeric compounds of claim 5, and:

a) artificial cerebrospinal fluid; or

b) PBS.

8. A modified oligonucleotide of any of claims 1-3, an oligomeric compound of claim 4, a population of modified oligonucleotides or oligomeric compounds of claim 5, or a pharmaceutical composition of claim 6 or claim 7 for use in therapy in an animal.

9. The modified oligonucleotide, oligomeric compound, population of modified oligonucleotides or oligomeric compounds, or pharmaceutical composition for use according to claim 8, wherein the therapy comprises reducing expression of LRRK2 in a cell, optionally wherein the cell is a human cell.

10. Use of a modified oligonucleotide of any of claims 1-3, an oligomeric compound of claim 4, a population of modified oligonucleotides or oligomeric compounds of claim 5, or a pharmaceutical composition of claim 6 or claim 7 in the manufacture of a medicament for treating a disease associated with LRRK2.

11. The use according to claim 10, wherein the disease associated with LRRK2 is a neurodegenerative disease.

12. The use according to claim 11, wherein the neurodegenerative disease is Parkinson’s disease.

13. The use according to claim 11 or claim 12, wherein at least one symptom or hallmark of the neurodegenerative disease is ameliorated.

14. The use according to claim 13, wherein the symptom or hallmark is any of ataxia, neuropathy, and aggregate formation.