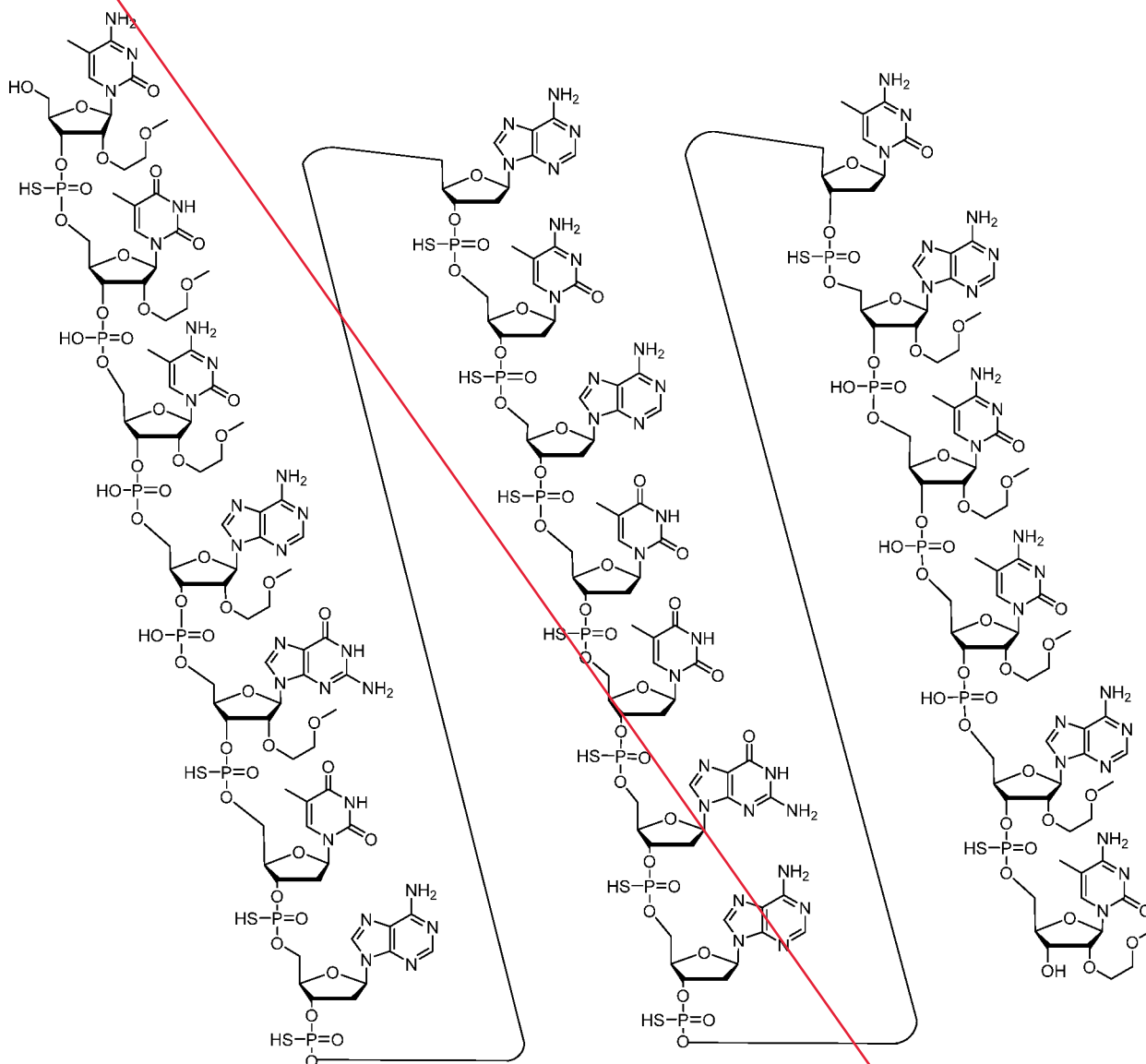


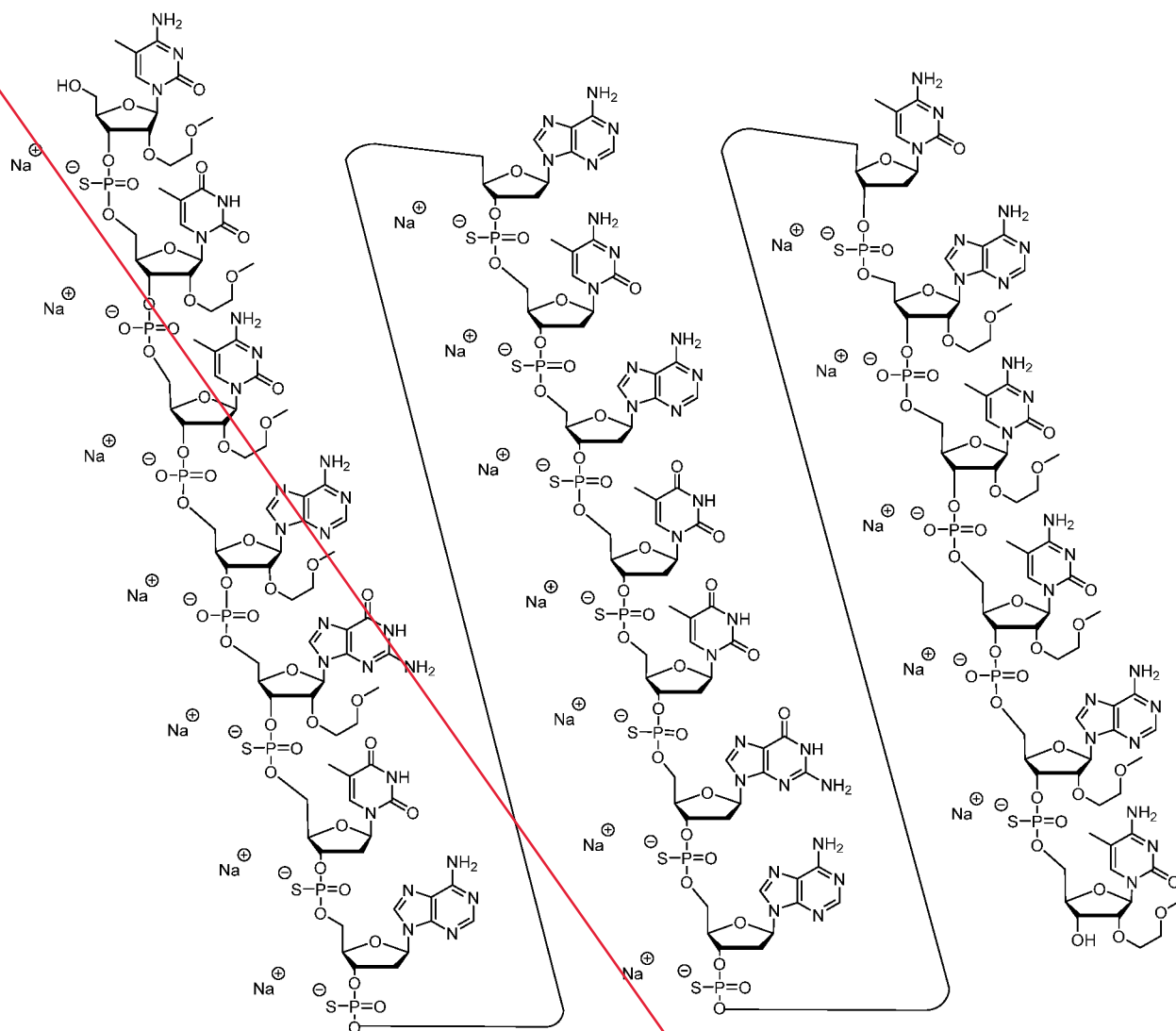
CLAIMS:

1. A method of ameliorating Huntington's disease (HD) in a human subject in need thereof, the method comprising administering to the human subject a therapeutically effective amount of a modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 4), or a salt thereof.

2. The method of claim 1, wherein the modified oligonucleotide is the sodium salt or the potassium salt.
3. A method of ameliorating HD in a human subject in need thereof, the method comprising administering to the human subject a therapeutically effective amount of a modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 4).

4. A method of ameliorating HD in a human subject in need thereof, the method comprising administering to the human subject a therapeutically effective amount of a modified oligonucleotide, wherein the modified oligonucleotide has the following chemical notation (5' to 3'): mCes Teo mCeo Aeo Ges Tds Ads Ads mCds Ads Tds Tds Gds Ads mCds Aeo mCeo mCeo Aes mCe (SEQ ID NO: 4); wherein,

A = an adenine nucleobase,

mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'-MOE sugar moiety,

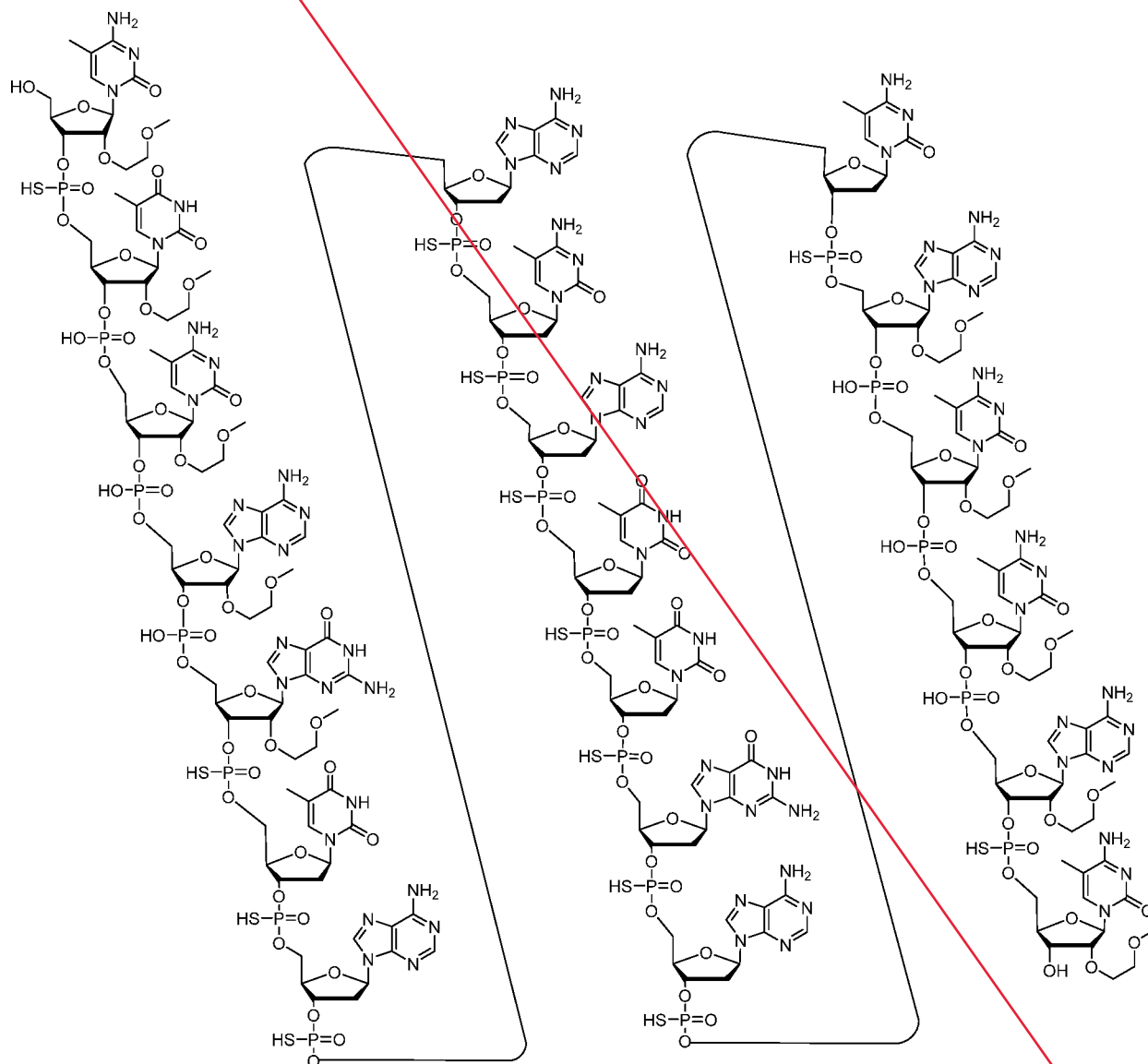
d = a 2'-β-D-deoxyribose sugar moiety,

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

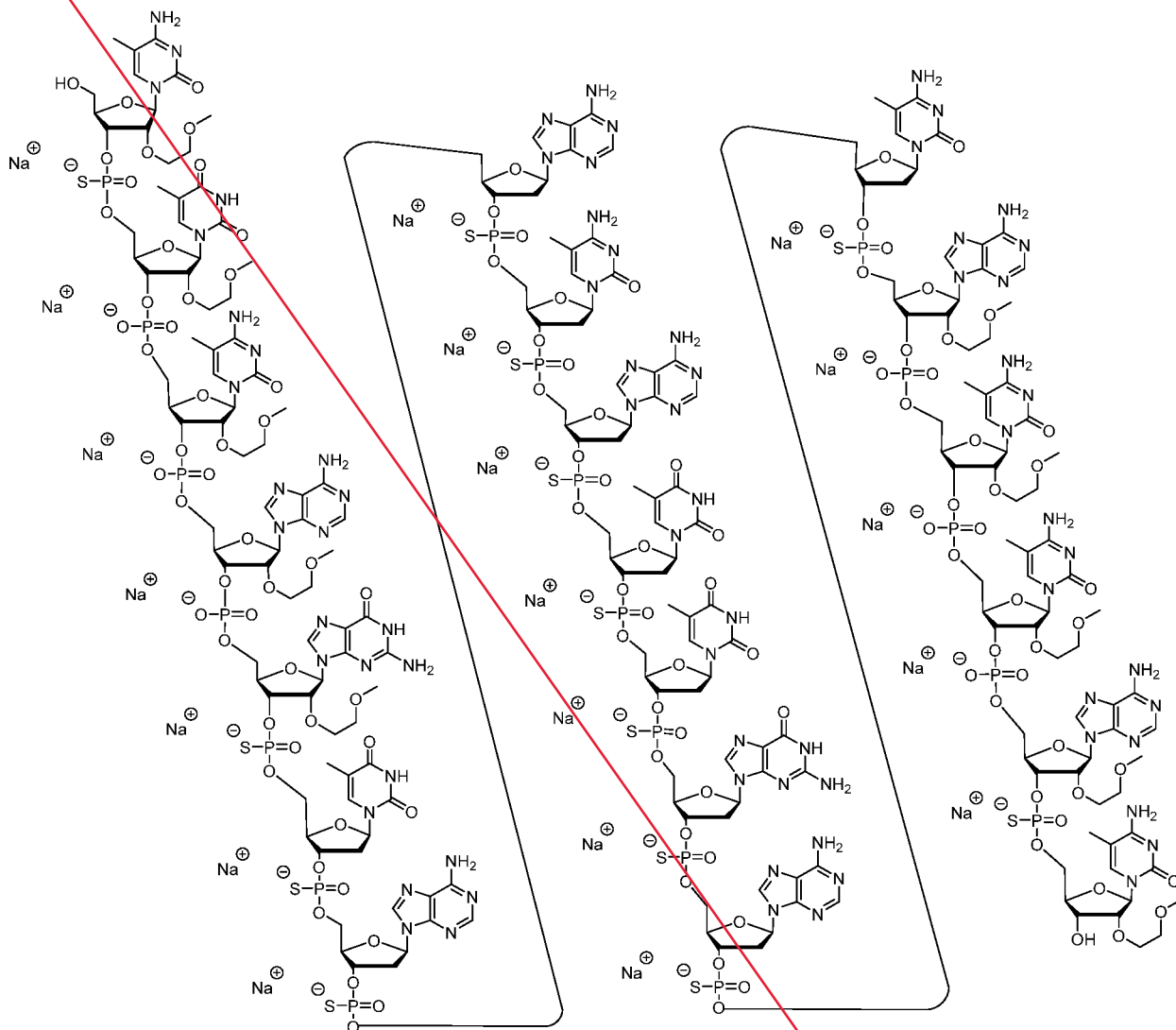
5. The method of any one of claims 1-4, wherein at least one symptom of HD is ameliorated.

6. The method of claim 5, wherein the at least one symptom comprises brain atrophy, reduced brain activity, reduced brain connectivity, muscle atrophy, nerve degeneration, cardiac failure, impaired glucose tolerance, weight loss, osteoporosis, testicular atrophy, impaired global function, impaired motor function, impaired cognitive function, impaired daily function, impaired attention, impaired visuo perceptual processing, impaired working memory, impaired psychomotor speed, impaired verbal motor output, impaired degree of independence, impaired apathy, impaired learning ability, impaired mental concentration, impaired speech, depression, irritability, anger, impaired mobility, impaired self-care, pain, discomfort, anxiety, suicidal ideation, suicidal behavior, or a combination thereof.
7. A method of reducing HTT RNA in a human subject in need thereof, the method comprising administering to the human subject a therapeutically effective amount of a modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 4), or a salt thereof.

8. The method of claim 7, wherein the modified oligonucleotide is the sodium salt or the potassium salt.
9. A method of reducing HTT RNA in a human subject in need thereof, the method comprising administering to the human subject a therapeutically effective amount of a modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 4).

10. A method of reducing HTT RNA in a human subject in need thereof, the method comprising administering to the human subject a therapeutically effective amount of a modified oligonucleotide, wherein the modified oligonucleotide has the following chemical notation (5' to 3'): mCes Teo mCeo Aeo Ges Tds Ads Ads mCds Ads Tds Tds Gds Ads mCds Aeo mCeo mCeo Aes mCe (SEQ ID NO: 4); wherein,

A = an adenine nucleobase,

mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

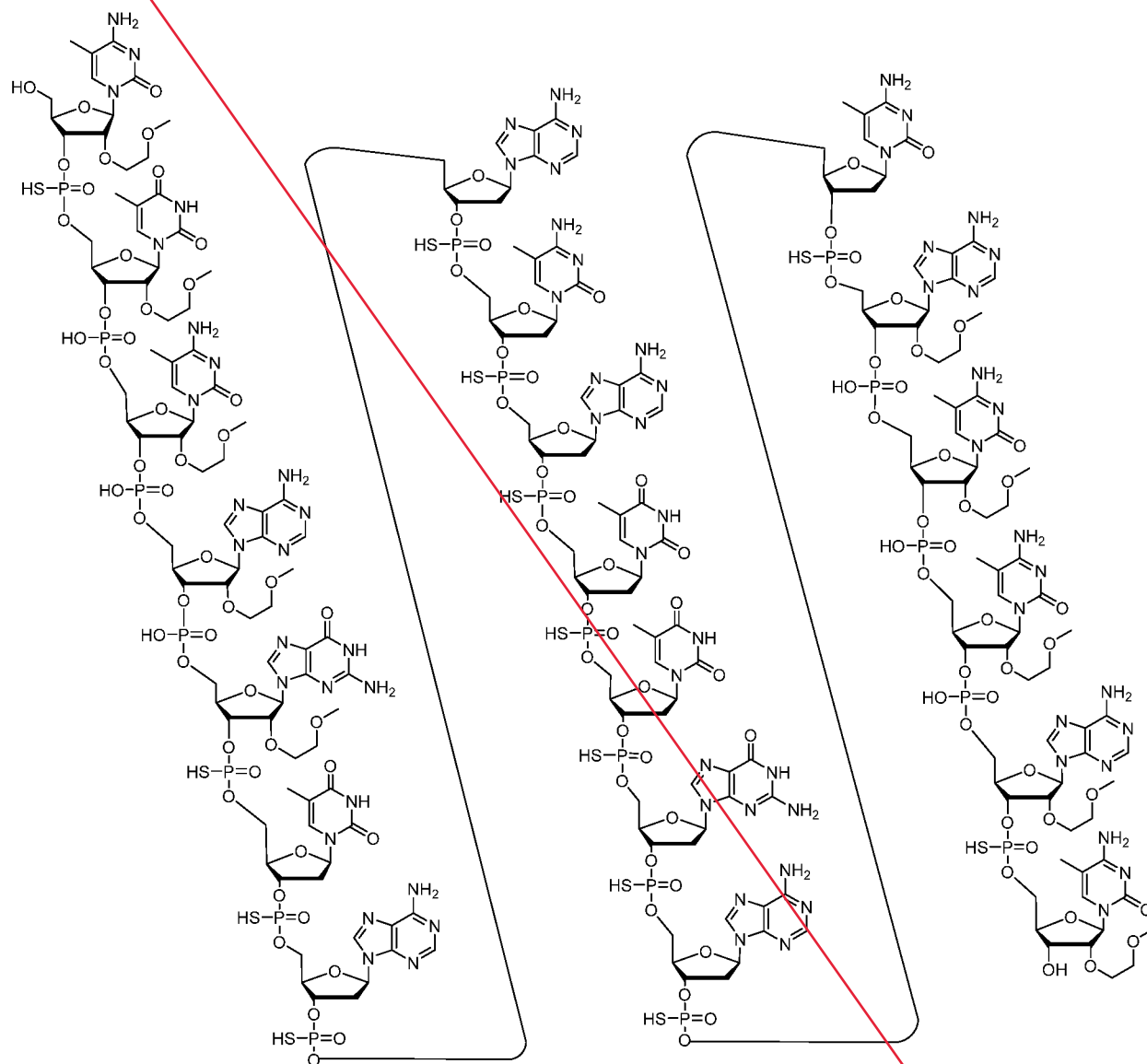
e = a 2'-MOE sugar moiety,

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

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

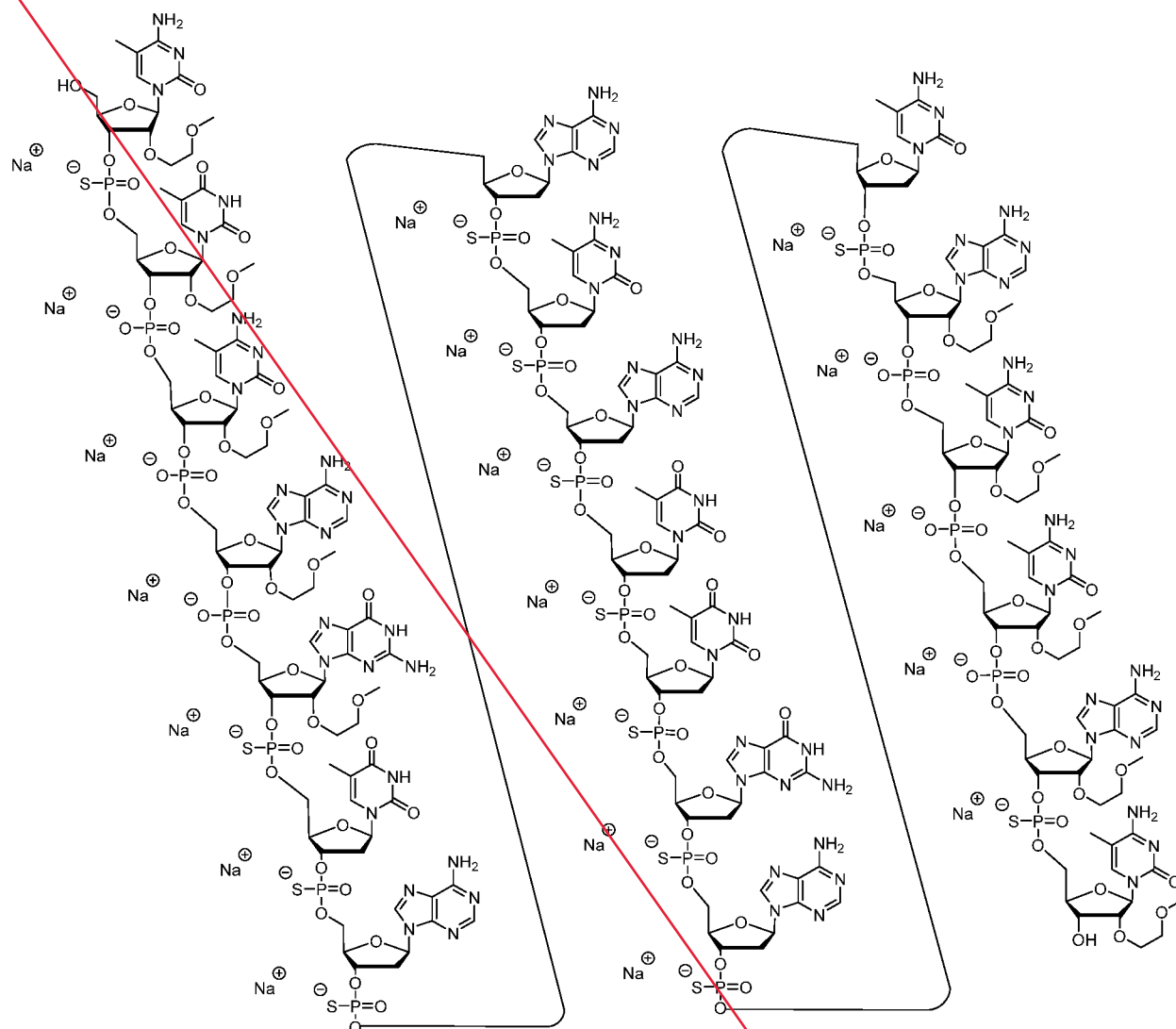
11. A method of reducing HTT protein in a human subject in need thereof, the method comprising administering to the human subject a therapeutically effective amount of a modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 4), or a salt thereof.

12. The method of claim 11, wherein the modified oligonucleotide is the sodium salt or the potassium salt.

13. A method of reducing HTT protein in a human subject in need thereof, the method comprising administering to the human subject a therapeutically effective amount of a modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 4).

14. A method of reducing HTT protein in a human subject in need thereof, the method comprising administering to the human subject a therapeutically effective amount of a modified oligonucleotide, wherein the modified oligonucleotide has the following chemical notation (5' to 3'): mCes Teo mCeo Aeo Ges Tds Ads Ads mCds Ads Tds Tds Gds Ads mCds Aeo mCeo mCeo Aes mCe (SEQ ID NO: 4); wherein,

A = an adenine nucleobase,
 mC = a 5-methyl cytosine nucleobase,
 G = a guanine nucleobase,
 T = a thymine nucleobase,
 e = a 2'-MOE sugar moiety,

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

s = a phosphorothioate internucleoside linkage, and

o = a phosphodiester internucleoside linkage.

15. The method of any one of claims 1-14, wherein the therapeutically effective amount is 10 mg.
16. The method of any one of claims 1-14, wherein the therapeutically effective amount is 30 mg.
17. The method of any one of claims 1-14, wherein the therapeutically effective amount is 60 mg.
18. The method of any one of claims 1-14, wherein the therapeutically effective amount is 90 mg.
19. The method of any one of claims 1-14, wherein the therapeutically effective amount is 120 mg.
20. The method of any one of claims 1-14, wherein the therapeutically effective amount is about 10 mg.
21. The method of any one of claims 1-14, wherein the therapeutically effective amount is about 30 mg.
22. The method of any one of claims 1-14, wherein the therapeutically effective amount is about 60 mg.
23. The method of any one of claims 1-14, wherein the therapeutically effective amount is about 90 mg.
24. The method of any one of claims 1-14, wherein the therapeutically effective amount is about 120 mg.
25. The method of any one of claims 1-14, wherein the therapeutically effective amount is any of 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 55 mg, 60 mg, 65 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg, 100 mg, 105 mg, 110 mg, 115 mg, 120 mg, 125 mg, 130 mg, 135 mg, 140 mg, 145 mg, 150 mg, 155 mg, 160 mg, 165 mg, 170 mg, 175 mg, 180 mg, 185 mg, 190 mg, 195 mg, 200 mg, 205 mg, 210 mg, 215 mg, 220 mg, 225 mg, 230 mg, 235 mg, 240 mg, 245 mg, 250 mg, 255 mg, 260 mg, 265 mg, 270 mg, 275 mg, 280 mg, 285 mg, 290 mg, 295 mg, and 300 mg.
26. The method of any one of claims 1-14, wherein the therapeutically effective amount is any of about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 145 mg, about 150 mg, about 155 mg, about 160 mg, about 165 mg, about 170 mg, about 175 mg, about 180 mg, about 185 mg, about 190 mg, about 195 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, and about 300 mg.
27. The method of any one of claims 1-14, wherein the therapeutically effective amount is any of 115.0 mg, 115.1 mg, 115.2 mg, 115.3 mg, 115.4 mg, 115.5 mg, 115.6 mg, 115.7 mg, 115.8 mg, 115.9 mg, 116.0 mg, 116.1 mg, 116.2 mg, 116.3 mg, 116.4 mg, 116.5 mg, 116.6 mg, 116.7 mg, 116.8 mg, 116.9 mg, 117.0 mg, 117.1 mg, 117.2 mg, 117.3 mg, 117.4 mg, 117.5 mg, 117.6 mg, 117.7 mg, 117.8 mg, 117.9 mg, 118.0 mg, 118.1 mg, 118.2 mg, 118.3 mg, 118.4 mg, 118.5 mg, 118.6 mg, 118.7 mg, 118.8 mg, 118.9 mg, 119.0 mg, 119.1 mg, 119.2 mg, 119.3 mg, 119.4 mg, 119.5 mg, 119.6 mg, 119.7 mg, 119.8 mg, 119.9 mg, 120.0 mg, 120.1 mg, 120.2 mg, 120.3 mg, 120.4 mg, 120.5 mg, 120.6 mg, 120.7 mg, 120.8 mg, 120.9 mg, 121.0

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28. The method of any one of claims 1-14, wherein the therapeutically effective amount is any of about 115.0 mg, about 115.1 mg, about 115.2 mg, about 115.3 mg, about 115.4 mg, about 115.5 mg, about 115.6 mg, about 115.7 mg, about 115.8 mg, about 115.9 mg, about 116.0 mg, about 116.1 mg, about 116.2 mg, about 116.3 mg, about 116.4 mg, about 116.5 mg, about 116.6 mg, about 116.7 mg, about 116.8 mg, about 116.9 mg, about 117.0 mg, about 117.1 mg, about 117.2 mg, about 117.3 mg, about 117.4 mg, about 117.5 mg, about 117.6 mg, about 117.7 mg, about 117.8 mg, about 117.9 mg, about 118.0 mg, about 118.1 mg, about 118.2 mg, about 118.3 mg, 118.4 mg, about 118.5 mg, about 118.6 mg, about 118.7 mg, about 118.8 mg, about 118.9 mg, about 119.0 mg, about 119.1 mg, about 119.2 mg, about 119.3 mg, about 119.4 mg, about 119.5 mg, about 119.6 mg, about 119.7 mg, about 119.8 mg, about 119.9 mg, about 120.0 mg, about 120.1 mg, about 120.2 mg, about 120.3 mg, 120.4 mg, about 120.5 mg, about 120.6 mg, about 120.7 mg, about 120.8 mg, about 120.9 mg, about 121.0 mg, about 121.1 mg, about 121.2 mg, about 121.3 mg, about 121.4 mg, about 121.5 mg, about 121.6 mg, about 121.7 mg, about 121.8 mg, about 121.9 mg, about 122.0 mg, about 122.1 mg, about 122.2 mg, about 122.3 mg, 122.4 mg, about 122.5 mg, about 122.6 mg, about 122.7 mg, about 122.8 mg, about 122.9 mg, about 123.0 mg, about 123.1 mg, about 123.2 mg, about 123.3 mg, about 123.4 mg, about 123.5 mg, about 123.6 mg, about 123.7 mg, about 123.8 mg, about 123.9 mg, about 124.0 mg, about 124.1 mg, about 124.2 mg, about 124.3 mg, 124.4 mg, about 124.5 mg, about 124.6 mg, about 124.7 mg, about 124.8 mg, about 124.9 mg, and about 125.0 mg.

29. The method of any one of claims 1-14, wherein the therapeutically effective amount is within the range of any of 40 mg to 200 mg, 40 mg to 190 mg, 40 mg to 180 mg, 40 mg to 170 mg, from 40 mg to 160 mg, 40 mg to 150 mg, 40 mg to 140 mg, 40 mg to 120 mg, 40 mg to 110 mg, 40 mg to 100 mg, 40 mg to 80 mg, 40 mg to 70 mg, 40 mg to 60 mg, 40 mg to 50 mg, 50 mg to 200 mg, 50 mg to 190 mg, 50 mg to 180 mg, 50 mg to 170 mg, 50 mg to 160 mg, 50 mg to 150 mg, 50 mg to 140 mg, 50 mg to 120 mg, 50 mg to 110 mg, 50 mg to 100 mg, 50 mg to 80 mg, 50 mg to 70 mg, 50 mg to 60 mg, 60 mg to 200 mg, 60 mg to 190 mg, 60 mg to 180 mg, 60 mg to 170 mg, 60 mg to 160 mg, 60 mg to 150 mg, 60 mg to 140 mg, 60 mg to 120 mg, 60 mg to 110 mg, 60 mg to 100 mg, 60 mg to 80 mg, 60 mg to 70 mg, 70 mg to 200 mg, 70 mg to 190 mg, 70 mg to 180 mg, 70 mg to 170 mg, 70 mg to 160 mg, 70 mg to 150 mg, 70 mg to 140 mg, 70 mg to 120 mg, 70 mg to 110 mg, 70 mg to 100 mg, 70 mg to 80 mg, 80 mg to 200 mg, 80 mg to 190 mg, 80 mg to 180 mg, 80 mg to 170 mg, 80 mg to 160 mg, 80 mg to 150 mg, 80 mg to 140 mg, 80 mg to 120 mg, 80 mg to 110 mg, 80 mg to 100 mg, 80 mg to 90 mg, 90 mg to 200 mg, 90 mg to 190 mg, 90 mg to 180 mg, 90 mg to 170 mg, 90 mg to 160 mg, 90 mg to 150 mg, 90 mg to 140 mg, 90 mg to 120 mg, 90 mg to 110 mg, 90 mg to 100 mg, 100 mg to 200 mg, 100 mg to 190 mg, 100 mg to 180 mg, 100 mg to 170

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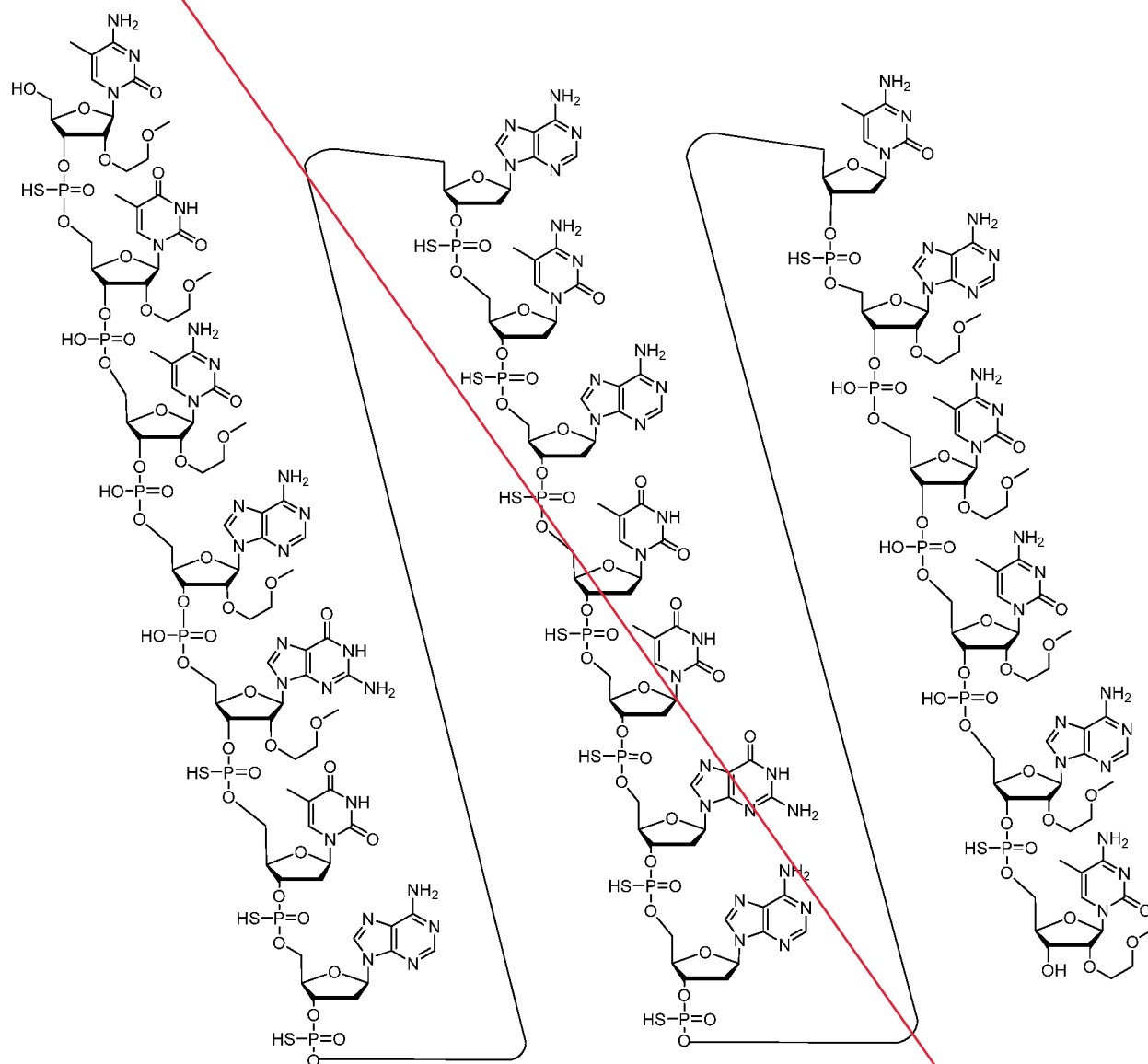
30. The method of any one of claims 1-14, wherein the therapeutically effective amount is any of less than 300 mg, less than 295 mg, less than 290 mg, less than 285 mg, less than 280 mg, less than 275 mg, less than 270 mg, less than 265 mg, less than 260 mg, less than 255 mg, less than 250 mg, less than 245 mg, less than 240 mg, less than 235 mg, less than 230 mg, less than 225 mg, less than 220 mg, less than 215 mg, less than 210 mg, less than 205 mg, less than 200 mg, less than 195 mg, less than 190 mg, less than 185 mg, less than 180 mg, less than 175 mg, less than 170 mg, less than 165 mg, less than 160 mg, less than 150 mg, less than 145 mg, less than 140 mg, less than 135 mg, less than 130 mg, less than 125 mg, less than 120 mg, less than 115 mg, less than 110 mg, less than 105 mg, less than 100 mg, less than 95 mg, less than 90 mg, less than 85 mg, less than 80 mg, less than 75 mg, less than 70 mg, less than 65 mg, less than 60 mg, less than 55 mg, less than 50 mg, less than 45 mg, less than 40 mg, less than 35 mg, less than 30 mg, less than 25 mg, less than 20 mg, less than 15 mg, less than 10 mg, and less than 5 mg.
31. The method of any one of claims 1-14, wherein the therapeutically effective amount is any of less than about 300 mg, less than about 295 mg, less than about 290 mg, less than about 285 mg, less than about 280 mg, less than about 275 mg, less than about 270 mg, less than about 265 mg, less than about 260 mg, less than about 255 mg, less than about 250 mg, less than about 245 mg, less than about 240 mg,

less than about 235 mg, less than about 230 mg, less than about 225 mg, less than about 220 mg, less than about 215 mg, less than about 210 mg, less than about 205 mg, less than about 200 mg, less than about 195 mg, less than about 190 mg, less than about 185 mg, less than about 180 mg, less than about 175 mg, less than about 170 mg, less than about 165 mg, less than about 160 mg, less than about 150 mg, less than about 145 mg, less than about 140 mg, less than about 135 mg, less than about 130 mg, less than about 125 mg, less than about 120 mg, less than about 115 mg, less than about 110 mg, less than about 105 mg, less than about 100 mg, less than about 95 mg, less than about 90 mg, less than about 85 mg, less than about 80 mg, less than about 75 mg, less than about 70 mg, less than about 65 mg, less than about 60 mg, less than about 55 mg, less than about 50 mg, less than about 45 mg, less than about 40 mg, less than about 35 mg, less than about 30 mg, less than about 25 mg, less than about 20 mg, less than about 15 mg, less than about 10 mg, and less than about 5 mg.

32. The method of any one of claims 1-14, wherein the therapeutically effective amount is any of at least 5 mg, at least 10 mg, at least 15 mg, at least 20 mg, at least 25 mg, at least 30 mg, at least 35 mg, at least 40 mg, at least 45 mg, at least 50 mg, at least 55 mg, at least 60 mg, at least 65 mg, at least 70 mg, at least 75 mg, at least 80 mg, at least 85 mg, at least 90 mg, at least 95 mg, at least about 100 mg, at least 105 mg, at least 115 mg, at least 120 mg, at least 125 mg, at least 130 mg, at least 135 mg, at least 140 mg, at least 145 mg, at least 150 mg, at least 155 mg, at least 160 mg, at least 165 mg, at least 170 mg, at least 175 mg, at least 180 mg, at least 185, at least 190 mg, at least 195 mg, and at least 200 mg.
33. The method of any one of claims 1-14, wherein the therapeutically effective amount is any of at least about 5 mg, at least about 10 mg, at least about 15 mg, at least about 20 mg, at least about 25 mg, at least about 30 mg, at least about 35 mg, at least about 40 mg, at least about 45 mg, at least about 50 mg, at least about 55 mg, at least about 60 mg, at least about 65 mg, at least about 70 mg, at least about 75 mg, at least about 80 mg, at least about 85 mg, at least about 90 mg, at least about 95 mg, at least about 100 mg, at least about 105 mg, at least about 115 mg, at least about 120 mg, at least about 125 mg, at least about 130 mg, at least about 135 mg, at least about 140 mg, at least about 145 mg, or at least about 150 mg, at least about 155 mg, at least about 160 mg, at least about 165 mg, at least about 170 mg, at least about 175 mg, at least about 180 mg, at least about 185, at least about 190 mg, at least about 195 mg, and at least about 200 mg.
34. The method of any one of claims 1-33, comprising administering the modified oligonucleotide once every 4 weeks.
35. The method of any one of claims 1-33, comprising administering the modified oligonucleotide once every 8 weeks.
36. The method of any one of claims 1-33, comprising administering the modified oligonucleotide once every 12 weeks.
37. The method of any one of claims 1-33, comprising administering the modified oligonucleotide once every 16 weeks.

38. The method of any one of claims 1-33, comprising administering the modified oligonucleotide once every 20 weeks.
39. The method of any one of claims 1-33, comprising administering the modified oligonucleotide about once every 4 weeks.
40. The method of any one of claims 1-33, comprising administering the modified oligonucleotide about once every 8 weeks.
41. The method of any one of claims 1-33, comprising administering the modified oligonucleotide about once every 12 weeks.
42. The method of any one of claims 1-33, comprising administering the modified oligonucleotide about once every 16 weeks.
43. The method of any one of claims 1-33, comprising administering the modified oligonucleotide about once every 20 weeks.
44. The method of any one of claims 1-33, comprising administering the modified oligonucleotide any of once every 1 week, once every 2 weeks, once every 3 weeks, once every 4 weeks, once every 5 weeks, once every 6 weeks, once every 7 weeks, once every 8 weeks, once every 9 weeks, once every 10 weeks, once every 11 weeks, once every 12 weeks, once every 13 weeks, once every 14 weeks, once every 15 weeks, once every 16 weeks, once every 17 weeks, once every 18 weeks, once every 19 weeks, and once every 20 weeks.
45. The method of any one of claims 1-33, comprising administering the modified oligonucleotide any of once about every 1 week, once about every 2 weeks, once about every 3 weeks, once about every 4 weeks, once about every 5 weeks, once about every 6 weeks, once about every 7 weeks, once about every 8 weeks, once about every 9 weeks, once about every 10 weeks, once about every 11 weeks, once about every 12 weeks, once about every 13 weeks, once about every 14 weeks, once about every 15 weeks, once about every 16 weeks, once about every 17 weeks, once about every 18 weeks, once about every 19 weeks, and once about every 20 weeks.
46. The method of any of claims 1-33, comprising administering to the human subject an initial loading dose of 120 mg of the modified oligonucleotide.
47. The method of claim 46, comprising administering to the human subject a second loading dose of 120 mg of the modified oligonucleotide 4 weeks after the initial loading dose.
48. The method of claim 47, comprising administering to the human subject a maintenance dose of 120 mg of the modified oligonucleotide 4 weeks after the second loading dose.
49. The method of claim 47, comprising administering to the human subject a maintenance dose of 120 mg of the modified oligonucleotide 8 weeks after the second loading dose.
50. The method of claim 47, comprising administering to the human subject a maintenance dose of 120 mg of the modified oligonucleotide 12 weeks after the second loading dose.

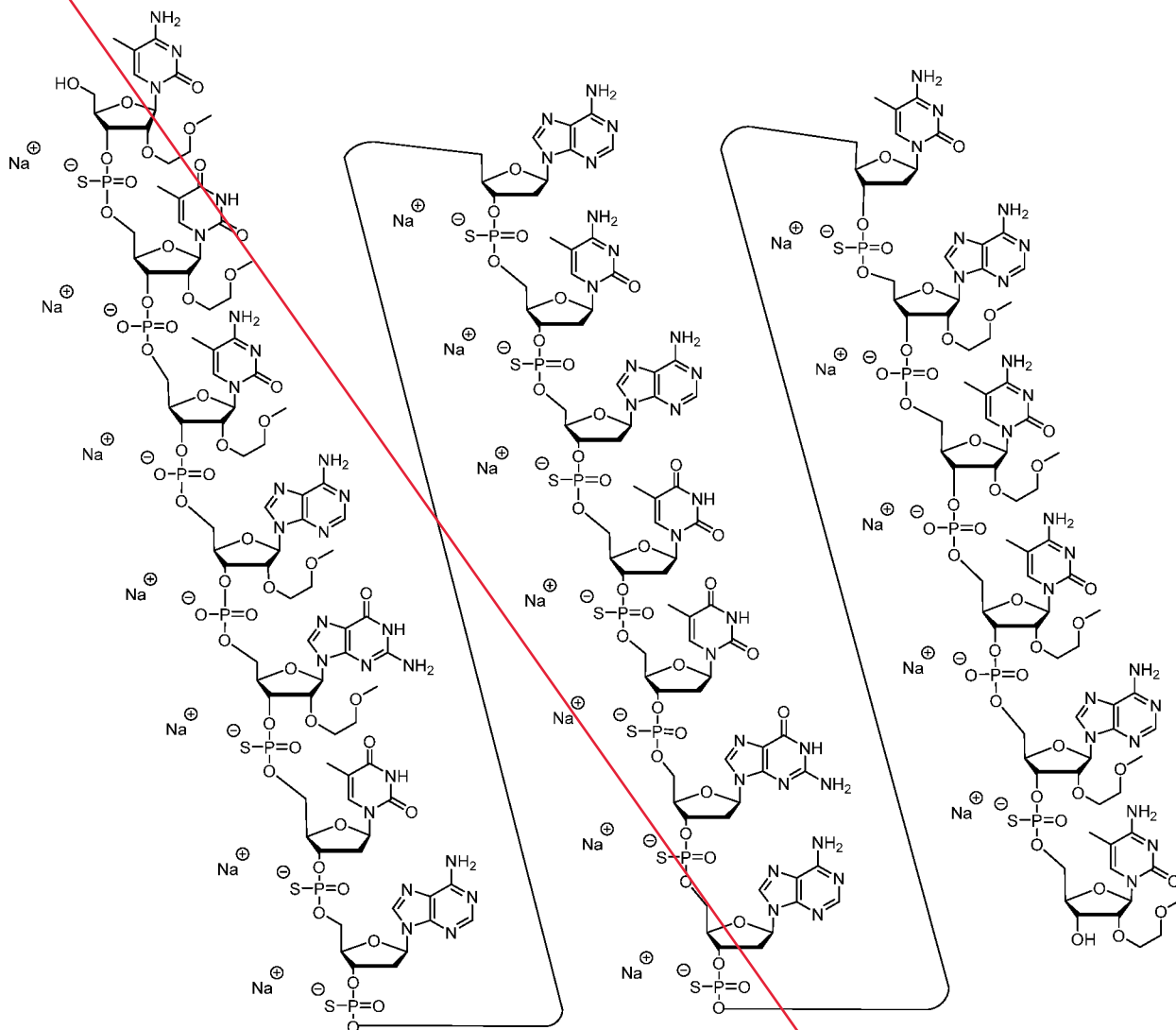
51. The method of claim 47, comprising administering to the human subject a maintenance dose of 120 mg of the modified oligonucleotide 16 weeks after the second loading dose.
52. The method of any of claims 7-10 and 15-51, wherein the HTT RNA is mHTT RNA.
53. The method of any of claim 11-51, wherein the HTT protein is mHTT protein.
54. A method of ameliorating HD, reducing HTT RNA, reducing HTT protein, reducing mHTT RNA, or reducing mHTT protein in a human subject in need thereof, the method comprising intrathecally administering to the human subject a therapeutically effective amount of 120 mg or about 120 mg of a modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 4), or a salt thereof.

55. The method of claim 54, wherein the modified oligonucleotide is the sodium salt or the potassium salt.

56. A method of ameliorating HD, reducing HTT RNA, reducing HTT protein, reducing mHTT RNA, or reducing mHTT protein in a human subject in need thereof, the method comprising intrathecally administering to the human subject a therapeutically effective amount of 120 mg or about 120 mg of a modified oligonucleotide according to the following chemical structure:



(SEQ ID NO: 4).

57. A method of ameliorating HD, reducing HTT RNA, reducing HTT protein, reducing HTT mRNA, or reducing mHTT protein in a human subject in need thereof, the method comprising intrathecally administering to the human subject a therapeutically effective amount of 120 mg or about 120 mg of a modified oligonucleotide, wherein the modified oligonucleotide has the following chemical notation (5' to 3'): mCes Teo mCeo Aeo Ges Tds Ads Ads mCds Ads Tds Tds Gds Ads mCds Aeo mCeo mCeo Aes mCe (SEQ ID NO: 4); wherein,

A = an adenine nucleobase,

mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,
e = a 2'-MOE sugar moiety,
d = a 2'-β-D-deoxyribosyl sugar moiety,
s = a phosphorothioate internucleoside linkage, and
o = a phosphodiester internucleoside linkage.

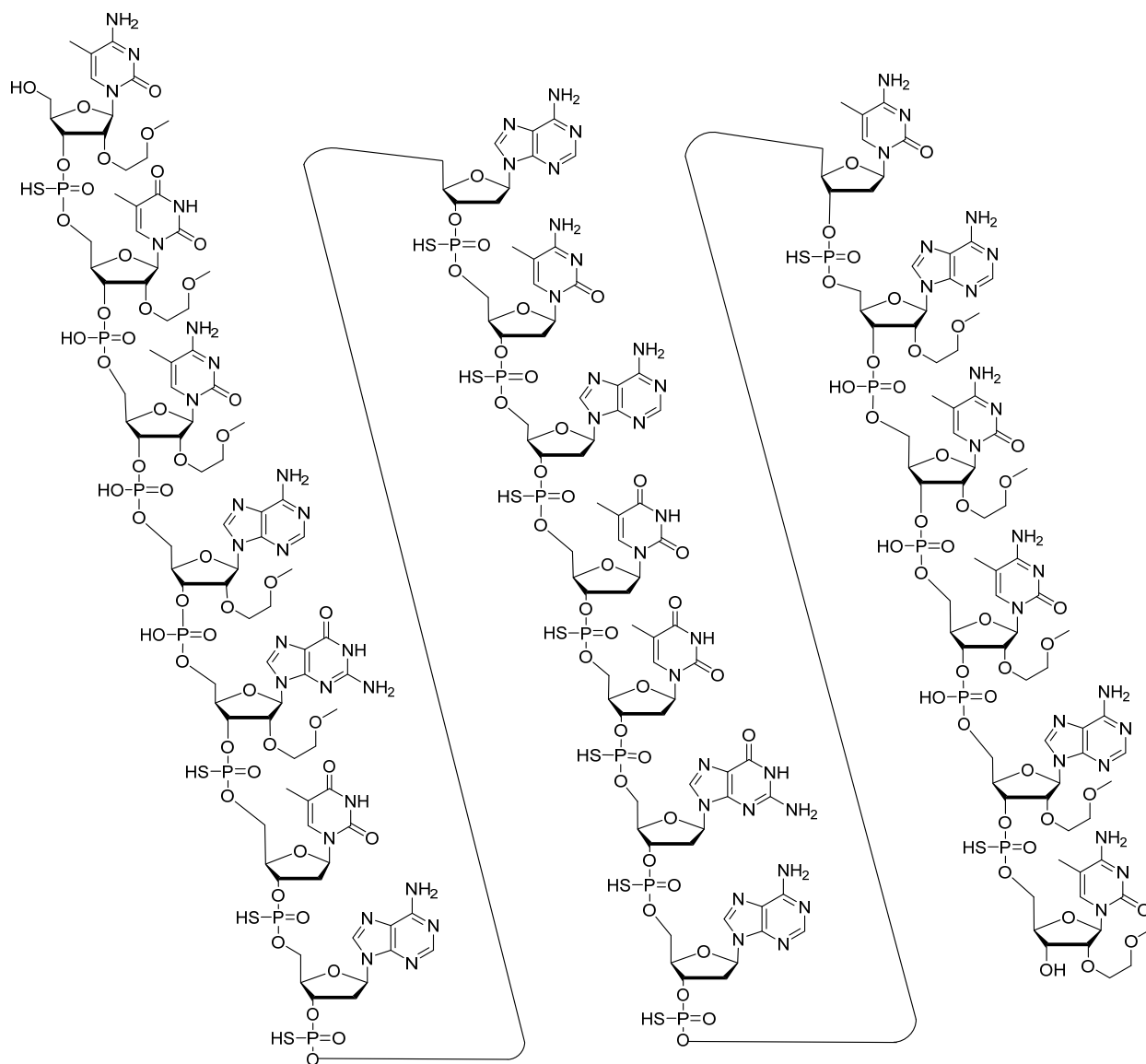
58. The method of any one of claims 54-57, comprising administering the modified oligonucleotide about once every 4 weeks.
59. The method of any one of claims 54-57, comprising administering the modified oligonucleotide about once every 8 weeks.
60. The method of any one of claims 54-57, comprising administering the modified oligonucleotide about once every 16 weeks.
61. The method of any of claims 54-57, comprising administering to the human subject:
- a) an initial loading dose of about 120 mg of the modified oligonucleotide,
 - b) a second loading dose of about 120 mg of the modified oligonucleotide about 4 weeks after administering the initial loading dose;
 - c) a first maintenance dose of about 120 mg of the modified oligonucleotide about 8 weeks after administering the second loading dose;
 - d) a second maintenance dose of about 120 mg of the modified oligonucleotide about 8 weeks after administering the first maintenance dose.
62. The method of any of claims 54-57, comprising administering to the human subject:
- a) an initial loading dose of about 120 mg of the modified oligonucleotide,
 - b) a second loading dose of about 120 mg of the modified oligonucleotide about 4 weeks after administering the initial loading dose;
 - c) a first maintenance dose of about 120 mg of the modified oligonucleotide about 16 weeks after administering the second loading dose;
 - d) a second maintenance dose of about 120 mg of the modified oligonucleotide about 16 weeks after administering the first maintenance dose.
63. The method of any one of claims 54-62, wherein at least one symptom of HD is ameliorated.
64. The method of claim 63, wherein the at least one symptom comprises brain atrophy, reduced brain activity, reduced brain connectivity, muscle atrophy, nerve degeneration, cardiac failure, impaired glucose tolerance, weight loss, osteoporosis, testicular atrophy, impaired global function, impaired motor function, impaired cognitive function, impaired daily function, impaired attention, impaired visuoperceptual processing, impaired working memory, impaired psychomotor speed, impaired verbal motor output, impaired degree of independence, impaired apathy, impaired learning ability, impaired mental concentration, impaired speech, depression, irritability, anger, impaired mobility, impaired self-care, pain, discomfort, anxiety, suicidal ideation, suicidal behavior, or a combination thereof.

65. The method of any of claims 1-64, wherein the human subject has a mutation in at least one *IT15* gene.
66. The method of any of claims 1-65, comprising identifying a mutation in at least one *IT15* gene of the human subject.
67. The method of claim 65 or claim 66, wherein the at least one *IT15* gene has any of at least 25, at least 26, at least 27, at least 28, at least 29, at least 30, at least 31, at least 32, at least 33, at least 34, at least 35, at least 36, at least 37, at least 38, at least 39, at least 40, at least 41, at least 42, at least 43, at least 44, at least 45, at least 46, at least 47, at least 48, at least 49, at least 50, at least 51, at least 52, at least 53, at least 54, at least 55, at least 56, at least 57, at least 58, at least 59, or at least 60 contiguous CAG repeats.
68. The method of claim 65 or claim 66, wherein the at least one *IT15* gene has 27 to 35 contiguous CAG repeats.
69. The method of claim 65 or claim 66, wherein the at least one *IT15* gene has 35 to 60 contiguous CAG repeats.
70. The method of claim 65 or claim 66, wherein the at least one *IT15* gene has greater than 60 contiguous CAG repeats.
71. The method of any of claims 1-70, wherein the modified oligonucleotide is administered to the CNS of the human subject.
72. The method of any of claims 1-71, wherein the modified oligonucleotide is administered by intrathecal administration.
73. The method of any of claims 1-72, wherein the modified oligonucleotide is administered by bolus intrathecal administration.
74. The method of any of claims 1-73, wherein HTT RNA is reduced.
75. The method of any of claims 1-74, wherein HTT protein is reduced.
76. The method of any of claims 1-75, wherein mHTT RNA is reduced.
77. The method of any of claims 1-76, wherein mHTT protein is reduced.
78. The method of any one of claims 1-77, comprising detecting an amount of mHTT RNA in a biological sample from the human subject.
79. The method of any one of claims 1-78, comprising detecting an amount of mHTT protein in a biological sample from the human subject.
80. The method of any one of claims 1-79, wherein the biological sample comprises cerebrospinal fluid.
81. The method of any of claims 78-80, wherein the detecting occurs before the administering.
82. The method of any of claims 78-80, wherein the detecting occurs after the administering.
83. The method of any of claims 78-80, wherein the detecting occurs before and after the administering.
84. The method of any one of claims 78-83, comprising adjusting the initial loading dose, the loading dose, maintenance dose, or therapeutically effective amount administered after detecting the amount of HTT RNA, HTT protein, mHTT RNA, mHTT protein, or combination thereof.

85. The method of any one of claims 1-84, comprising analyzing brain activity, brain size, or a combination thereof of the subject by performing an electroencephalogram (EEG) or magnetic resonance imaging (MRI) on the subject.
86. The method of claim 85, wherein performing the EEG or MRI occurs before administering, after administering, or a combination thereof.
87. The method of claim 86, comprising determining or adjusting the therapeutically effective amount after performing the EEG or MRI.
88. The method of claim 87, comprising performing the EEG or MRI after administering, and adjusting the frequency of administering after performing the EEG or MRI.
89. The method of any one of claims 85-88, wherein performing the EEG or MRI is performed within 1, 2, 4, 6, 8, 12 or 24 hours of administering.
90. The method of any one of claims 85-89, comprising performing the EEG before administering, and analyzing after administering, detecting less than a 4 Hz increase in EEG signal power from a first EEG to a second EEG, and subsequently increasing the frequency of administering the therapeutically effective amount of the modified oligonucleotide.
91. The method of claim 90, comprising administering a loading dose once about every 4 weeks and administering a maintenance dose once about every 8 or 16 weeks before recording the first EEG, and administering the maintenance dose less than about every 8 weeks or less than about every 16 weeks.
92. The method of any one of claims, 85-91, comprising recording a first EEG before administering, and recording a second EEG after administering, detecting less than a 4 Hz increase in EEG signal power from the first EEG to the second EEG, and subsequently administering a dose of the modified oligonucleotide that is greater than the therapeutically effective amount.
93. The method of claim 92, wherein the dose is at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 90%, or at least about 100% greater than the therapeutically effective amount.
94. The method of any one of claims 85-93, wherein the therapeutically effective amount is about 120 mg or 120 mg.

CLAIMS:

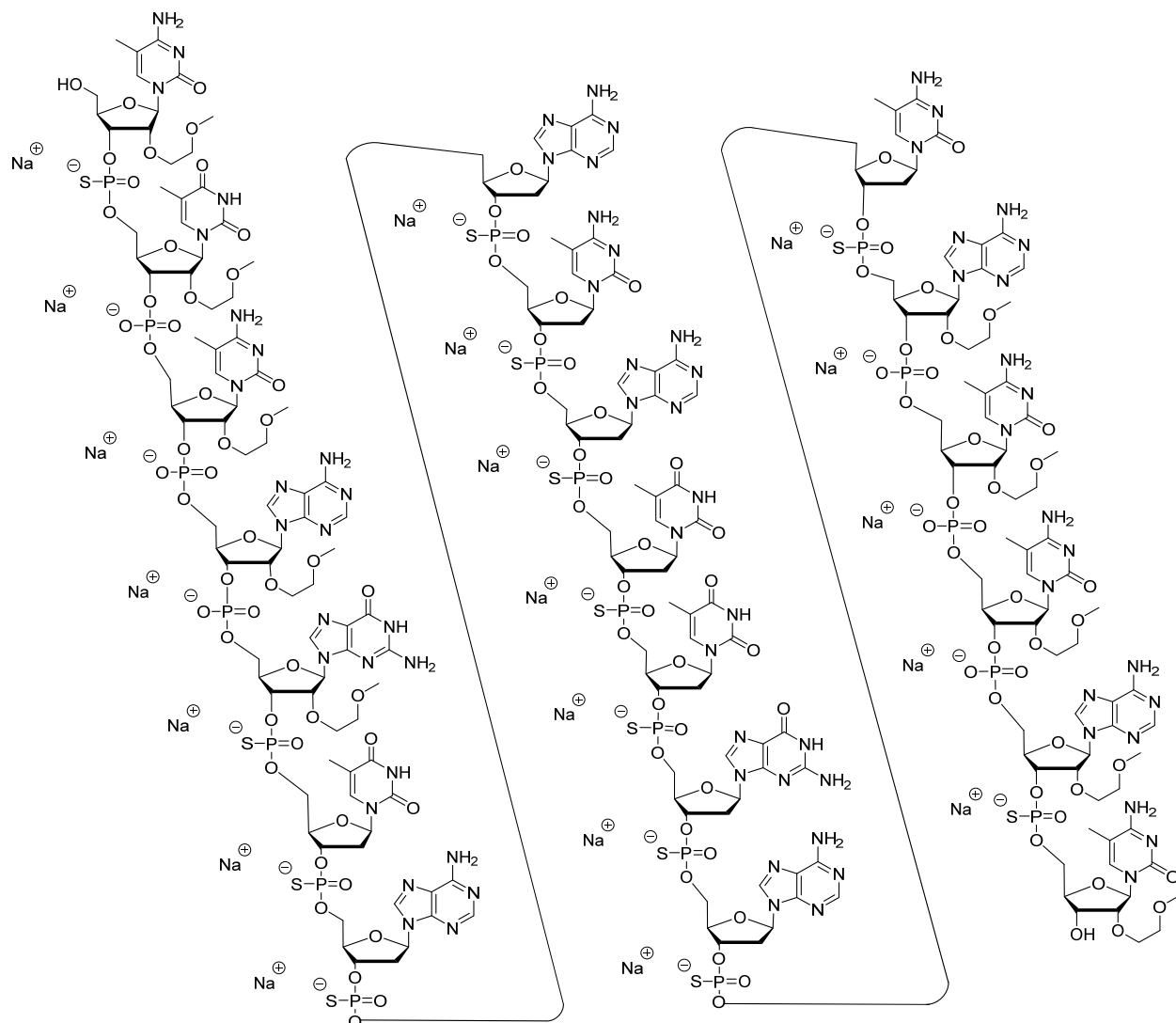
1. Use of a modified oligonucleotide in the manufacture of a medicament for ameliorating Huntington's disease (HD) in a human subject in need thereof, wherein a therapeutically effective amount of the modified oligonucleotide is to be administered to the human subject, wherein the modified oligonucleotide has the following chemical structure:



(SEQ ID NO: 4), or a salt thereof.

2. The use according to claim 1, wherein the modified oligonucleotide is the sodium salt or the potassium salt.
3. Use of a modified oligonucleotide in the manufacture of a medicament for ameliorating Huntington's disease (HD) in a human subject in need thereof, wherein a therapeutically effective amount

of the modified oligonucleotide is to be administered to the human subject, wherein the modified oligonucleotide has the following chemical structure:



(SEQ ID NO: 4).

- Use of a modified oligonucleotide in the manufacture of a medicament for ameliorating Huntington's disease (HD) in a human subject in need thereof, wherein a therapeutically effective amount of the modified oligonucleotide is to be administered to the human subject, wherein the modified oligonucleotide has the following chemical notation (5' to 3'): mCes Teo mCeo Aeo Ges Tds Ads Ads mCds Ads Tds Tds Gds Ads mCds Aeo mCeo mCeo Aes mCe (SEQ ID NO: 4); wherein,

A = an adenine nucleobase,

mC = a 5-methyl cytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'-MOE sugar moiety,

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

s = a phosphorothioate internucleoside linkage, and
o = a phosphodiester internucleoside linkage.

5. The use according to any one of claims 1-4, wherein at least one symptom of HD is ameliorated.
6. The use according to claim 5, wherein the at least one symptom comprises brain atrophy, reduced brain activity, reduced brain connectivity, muscle atrophy, nerve degeneration, cardiac failure, impaired glucose tolerance, weight loss, osteoporosis, testicular atrophy, impaired global function, impaired motor function, impaired cognitive function, impaired daily function, impaired attention, impaired visuoperceptual processing, impaired working memory, impaired psychomotor speed, impaired verbal motor output, impaired degree of independence, impaired apathy, impaired learning ability, impaired mental concentration, impaired speech, depression, irritability, anger, impaired mobility, impaired self-care, pain, discomfort, anxiety, suicidal ideation, suicidal behavior, or a combination thereof.
7. The use according to any one of claims 1-6, wherein the therapeutically effective amount is 60 mg.
8. The use according to any one of claims 1-7, wherein the therapeutically effective amount is any of 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 55 mg, 60 mg, 65 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg, 100 mg, 105 mg, 110 mg, 115 mg, 120 mg, 125 mg, 130 mg, 135 mg, 140 mg, 145 mg, 150 mg, 155 mg, 160 mg, 165 mg, 170 mg, 175 mg, 180 mg, 185 mg, 190 mg, 195 mg, 200 mg, 205 mg, 210 mg, 215 mg, 220 mg, 225 mg, 230 mg, 235 mg, 240 mg, 245 mg, 250 mg, 255 mg, 260 mg, 265 mg, 270 mg, 275 mg, 280 mg, 285 mg, 290 mg, 295 mg, and 300 mg.
9. The use according to any one of claims 1-8, wherein the modified oligonucleotide is to be administered once every 16 weeks.
10. The use according to any one of claims 1-9, wherein the human subject has a mutation in at least one *IT15* gene.
11. The use according to any one of claims 1-10, wherein the human subject has been identified to have a mutation in at least one *IT15* gene of the human subject.
12. The use according to claim 10 or claim 11, wherein the at least one *IT15* gene has any of at least 25, at least 26, at least 27, at least 28, at least 29, at least 30, at least 31, at least 32, at least 33, at least 34, at least 35, at least 36, at least 37, at least 38, at least 39, at least 40, at least 41, at least 42,

at least 43, at least 44, at least 45, at least 46, at least 47, at least 48, at least 49, at least 50, at least 51, at least 52, at least 53, at least 54, at least 55, at least 56, at least 57, at least 58, at least 59, or at least 60 contiguous CAG repeats.

13. The use according to claim 10 or claim 11, wherein the at least one IT15 gene has 27 to 35 contiguous CAG repeats.
14. The use according to claim 10 or claim 11, wherein the at least one IT15 gene has 35 to 60 contiguous CAG repeats.
15. The use according to claim 10 or claim 11, wherein the at least one IT15 gene has greater than 60 contiguous CAG repeats.
16. The use according to any one of claims 1-15, wherein the modified oligonucleotide is to be administered to the CNS of the human subject.
17. The use according to any one of claims 1-16, wherein the modified oligonucleotide is to be administered by intrathecal administration.
18. The use according to any one of claims 1-17, wherein the modified oligonucleotide is to be administered by bolus intrathecal administration.
19. The use according to any one of claims 1-18, wherein HTT RNA is reduced.
20. The use according to any one of claims 1-19, wherein HTT protein is reduced.
21. The use according to any one of claims 1-20, wherein mHTT RNA is reduced.
22. The use according to any one of claims 1-21, wherein mHTT protein is reduced.
23. The use according to any one of claims 1-22, wherein a biological sample from the human subject has been detected to have an amount of mHTT RNA.
24. The modified oligonucleotide for use according to any one of claims 1-23, wherein a biological sample from the human subject has been detected to have an amount of mHTT protein.

25. The use according to any one of claims 1-24, wherein the biological sample comprises cerebrospinal fluid.
26. The use according to any of claims 23-25, wherein the detection occurs before the administration.
27. The use according to any of claims 23-25, wherein the detection occurs after the administration.
28. The use according to any of claims 23-25, wherein the detection occurs before and after the administration.
29. The use according to any one of claims 1-28, wherein brain activity, brain size, or a combination thereof of the subject is analyzed by performing an electroencephalogram (EEG) or magnetic resonance imaging (MRI).
30. The use according to claim 29, wherein the EEG or MRI is performed before the administration, after the administration, or a combination thereof.
31. The use according to claim 30, wherein the therapeutically effective amount is determined or adjusted after performing the EEG or MRI.
32. The use according to claim 31, wherein the EEG or MRI is performed after the administration, and the frequency of the administration is adjusted after the EEG or MRI is performed.
33. The use according to any one of claims 29-32, wherein the EEG or MRI is performed within 1, 2, 4, 6, 8, 12 or 24 hours of the administration.
34. The use according to any one of claims 29-33, wherein the EEG is performed before the administration, and the analysis is performed after the administration, and wherein when an increase of less than 4 Hz in EEG signal power from a first EEG to a second EEG is detected, the frequency of the administration of the therapeutically effective amount of the modified oligonucleotide is subsequently increased.
35. The use according to claim 34, wherein a loading dose is to be administered once about every 4 weeks and a maintenance dose is to be administered once about every 8 or 16 weeks before recording the first EEG, and the administration of the maintenance dose less than about every 8 weeks or less than about every 16 weeks.

36. The use according to any one of claims 29-35, wherein a first EEG is recorded before the administration, and a second EEG is recorded after the administration, and wherein when an increase of less than a 4 Hz increase in EEG signal power is detected from the first EEG to the second EEG, a dose of the modified oligonucleotide that is greater than the therapeutically effective amount is to be subsequently administered.
37. The use according to claim 36, wherein the dose is at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 90%, or at least about 100% greater than the therapeutically effective amount.