

WHAT IS CLAIMED:

1. A compound comprising a modified oligonucleotide 8 to 80 linked nucleosides in length having a nucleobase comprising at least 8 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NO: 16-4679.
2. A compound comprising a modified oligonucleotide 8 to 80 linked nucleosides in length having a nucleobase comprising at least 9 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NO: 16-4679.
3. A compound comprising a modified oligonucleotide 8 to 80 linked nucleosides in length having a nucleobase comprising at least 10 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NO: 16-4679.
4. A compound comprising a modified oligonucleotide 8 to 80 linked nucleosides in length having a nucleobase comprising at least 11 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NO: 16-4679.
5. A compound comprising a modified oligonucleotide 8 to 80 linked nucleosides in length having a nucleobase comprising at least 12 contiguous nucleobases of any of the nucleobase sequences of SEQ ID NO: 16-4679.
6. A compound comprising a modified oligonucleotide 8 to 80 linked nucleosides in length having a nucleobase sequence comprising the nucleobase sequence of any one of SEQ ID NO: 16-4679.
7. A compound comprising a modified oligonucleotide having a nucleobase sequence consisting of any one of SEQ ID Nos: 16-4679.
8. A compound comprising a modified oligonucleotide 8 to 80 linked nucleosides in length having a nucleobase sequence complementary to nucleobases 25636-31076 (intron 2) of SEQ ID NO: 2, wherein said modified oligonucleotide is at least 85%, 90%, 95%, or 100% complementary to SEQ ID NO: 2.
9. A compound comprising a modified oligonucleotide 8 to 80 linked nucleosides in length complementary to nucleobases 26711-26802, 26778-26797, 9930-9949, 9953-9973, 9959-9978, 9961-9981, 9970-9992, 9975-9994, 9984-10003, 10040-10059, 10043-10063, 10045-10064, 10046-10065, 10049-10068, 10054-10073, 10160-10179, 10209-10229, 10212-10231, 10214-10235, 10217-10236, 10218-10238, 10327-10346, 10389-10413, 10490-10511, 10522-10548, 10530-10549, 10531-10551, 10533-10553, 10645-10669, 10651-10670, 10653-10673, 10655-10674, 10656-10675, 10657-10676, 10658-10680, 10662-10681, 10663-

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10. A compound comprising a modified oligonucleotide 8 to 80 linked nucleosides in length having a nucleobase sequence comprising a portion of at least 8 contiguous nucleobases 100% complementary to an equal length portion of nucleobases 26711-26802, 26778-26797, 9930-9949, 9953-9973, 9959-9978, 9961-9981, 9970-9992, 9975-9994, 9984-10003, 10040-10059, 10043-10063, 10045-10064, 10046-10065, 10049-10068, 10054-10073, 10160-10179, 10209-10229, 10212-10231, 10214-10235, 10217-10236, 10218-10238, 10327-10346, 10389-10413, 10490-10511, 10522-10548, 10530-10549, 10531-10551, 10533-10553, 10645-10669, 10651-10670, 10653-10673, 10655-10674, 10656-10675, 10657-10676, 10658-10680, 10662-10681, 10663-10684, 10666-10685, 10667-10684, 10670-10689, 10702-10721, 10727-10747, 10729-10748, 10730-10750, 10733-10755, 10737-10756, 10742-10761, 10763-10782, 10814-10835, 10817-10836, 10818-10837, 10940-10964, 11008-11027, 11074-11097, 11123-11150, 11158-11182, 11168-11187, 11170-11190, 11171-11197, 11199-11218, 11200-11220, 11209-11228, 11318-11342, 11413-11432, 11559-11578, 11594-11618, 11707-11731, 11872-11891, 11920-11939, 12247-12266, 12285-12304, 12549-12573, 12671-12695, 12806-12826, 12839-12863, 12890-12909, 12927-12961, 13098-13117, 13212-13231, 13239-13258, 13441-13461, 13921-13945, 13962-13996, 14177-14201, 14194-14218, 14239-14258, 14385-14404, 14457-14522, 14504-14527, 14537-14556, 14648-14697, 14715-14790, 14715-14739, 14735-14764, 14746-14765, 14749-14774, 14756-14779, 14765-14789, 14771-14790, 14807-14831, 14852-14871, 14882-14901, 14953-15015, 14997-15065, 15041-15107, 15041-15092, 15083-15107, 15178-15197, 15214-15243, 15219-15243, 15248-15276, 15255-15276, 15292-15311, 15318-15338, 15321-15342, 15353-15372, 15368-

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11. A compound comprising a modified oligonucleotide complementary to nucleotides 10040-10059, 10044-10063, 10045-10064, 10054-10073, 10210-10229, 10214-10234, 10217-10236, 10490-10509, 10492-10511, 10522-10541, 10530-10549, 10531-10550, 10532-10551, 10533-10552, 10535-10554, 10536-10555, 10645-10664, 10650-10669, 10655-10674, 10656-10675, 10657-10676, 10659-10678, 10660-10679, 10661-10680, 10663-10682, 10664-10683, 10665-10684, 10666-10685, 10667-10686, 10670-10689, 10727-10746, 10730-10749, 10731-10750, 10732-10752, 10734-10753, 10735-10754, 10737-10756, 10816-10835, 10818-10837, 10819-10840, 10940-10961, 10944-10963, 11074-11094, 11127-11149, 11131-11178, 11170-11190, 11172-11193, 11175-11196, 11178-11197, 11199-11219, 11201-11221, 11203-11222, 11559-11578, 11599-11618, 12285-12304, 13442-13461, 14462-14522, 14504-14523, 14505-14527, 14648-14669, 14651-14670, 14658-14682, 14666-14686, 14673-14697, 14741-14765, 14750-14774, 14757-14777, 14759-14779, 14769-14789, 14772-14792, 14773-14793, 14807-14901, 14993-15015, 14999-15020, 15248-15273, 15321-15342, 15573-15665, 15881-15952, 16830-16852, 16900-16921, 17450-17470, 18155-18176, 18173-18193, 18310-18331, 18323-18344, 18379-18436, 20300-20321, 20837-20857, 22439-22463, 22771-22792, 23242-23262, 25033-25092, 25075-25104, 25246-25291, 25782-25860, 25900-25934, 25950-26030, 26165-26185, 26169-26219, 26300-26372, 26520-26550, 26629-26650, 26721-26799, 27050-27075, 27236-27256, 27382-27402, 27775-27799, 27782-27809, 27853-27877, 28026-28048, 28128-28152, 28468-28488, 28476-28500, 29010-29031, 29143-29164, 29245-29265, 29548-29589, 29827-29847, 29838-29858, 29844-29873, 30483-30503, 32431-32450, 32432-32452, 32446-32468, 32455-32475, 32459-32479, 32462-32487, 32591-32639, 33179-33199, 33412-33433, 33729-33749, 34211-34231, 35436-35457, 36251-36272, or 36354-36428 of a DGAT2 nucleic acid having the nucleobase sequence of SEQ ID NO: 2.

12. A compound comprising a modified oligonucleotide 8 to 80 linked nucleoside in length having a nucleobase sequence comprising a portion of at least 8 contiguous nucleobases complementary to an equal length portion of nucleobases 10040-10059, 10044-10063, 10045-10064, 10054-10073, 10210-10229, 10214-10234, 10217-10236, 10490-10509, 10492-10511, 10522-10541, 10530-10549, 10531-10550, 10532-10551, 10533-10552, 10535-10554, 10536-10555, 10645-10664, 10650-10669, 10655-10674, 10656-10675, 10657-10676, 10659-10678, 10660-10679, 10661-10680, 10663-10682, 10664-10683, 10665-10684, 10666-10685, 10667-10686, 10670-10689, 10727-10746, 10730-10749, 10731-10750, 10732-10752, 10734-10753,

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13. A compound comprising a modified oligonucleotide 8 to 80 linked nucleosides in length complementary within nucleotides 26778-26797, 23242-23261, 26630-26649, 15251-15270, 28026-28045, 35436-35455, 10820-10836, 23246-23262 of SEQ ID NO: 2.

14. A compound comprising a modified oligonucleotide 8 to 80 linked nucleosides in length and having a nucleobase sequence comprising any one of SEQ ID NO: 1423, 1371, 1415, 1849, 2959, 3292, 4198, and 4373.

15. A compound comprising a modified oligonucleotide having a nucleobase sequence consisting of any one of SEQ ID NO: 1423, 1371, 1415, 1849, 2959, 3292, 4198, and 4373.

16. A compound comprising a modified oligonucleotide 8 to 80 linked nucleosides in length having a nucleobase sequence comprising any one of SEQ ID NO: 1423, 1371, 1415, 1849, 2959, 3292, 4198, and 4373, wherein the modified oligonucleotide comprises

a gap segment consisting of linked deoxynucleosides;

a 5' wing segment consisting of linked nucleosides; and

a 3' wing segment consisting of linked nucleosides;

wherein the gap segment is positioned between the 5' wing segment and the 3' wing segment and wherein each nucleoside of each wing segment comprises a modified sugar.

17. A compound comprising a modified oligonucleotide 20 linked nucleosides in length having a nucleobase sequence consisting of any one of the sequence recited in SEQ ID Nos: 1423, 1371, 1415, 1849, 2959, and 3292, wherein the modified oligonucleotide comprises

a gap segment consisting of ten linked deoxynucleosides;

a 5' wing segment consisting of five linked nucleosides; and

a 3' wing segment consisting of five linked nucleosides;

wherein the gap segment is positioned between the 5' wing segment and the 3' wing segment, wherein each nucleoside of each wing segment comprises a 2'-O-methoxyethyl sugar; wherein each internucleoside linkage is a phosphorothioate linkage and wherein each cytosine is a 5-methylcytosine.

18. A compound comprising a modified oligonucleotide 17 linked nucleosides in length having a nucleobase sequence consisting of any one of the sequence recited in SEQ ID Nos: 4198, and 4373, wherein the modified oligonucleotide comprises

a gap segment consisting of ten linked deoxynucleosides;

a 5' wing segment consisting of three linked nucleosides; and

a 3' wing segment consisting of four linked nucleosides;

wherein the gap segment is positioned between the 5' wing segment and the 3' wing segment, wherein each nucleoside of each wing segment comprises a 2'-O-methoxyethyl sugar; wherein each internucleoside linkage is a phosphorothioate linkage and wherein each cytosine is a 5-methylcytosine.

19. The compound of any one of the claims 1-18, wherein the oligonucleotide is at least 80%, 85%, 90%, 95%, or 100% complementary to SEQ ID Nos: 1 or 2.

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

21. The compound of claim 20, wherein the modified internucleoside linkage is a phosphorothioate internucleoside linkage.

22. The compound of claim 20 or 21, wherein the modified sugar is a bicyclic sugar.

23. The compound of claim 22, wherein the bicyclic sugar is selected from the group consisting of: 4'-(CH₂)-O-2' (LNA); 4'-(CH₂)₂-O-2' (ENA); and 4'-CH(CH₃)-O-2' (cEt).

24. The compound of claim 20 or 21, wherein the modified sugar is 2'-O-methoxyethyl.

25. The compound of any one of claims 20-24, wherein the modified nucleobase is a 5-methylcytosine.

26. The compound of any one of claims 1-25, wherein the modified oligonucleotide comprises:

a gap segment consisting of linked deoxynucleosides;
a 5' wing segment consisting of linked nucleosides; and
a 3' wing segment consisting of linked nucleosides;

wherein the gap segment is positioned immediately adjacent to and between the 5' wing segment and the 3' wing segment and wherein each nucleoside of each wing segment comprises a modified sugar.

27. The compound of any one of claims 1-26, wherein the compound is single-stranded.

28. The compound of any one of claims 1-26, wherein the compound is double-stranded.

29. The compound of any one of claims 1-28, wherein the compound comprises ribonucleotides.

30. The compound of any one of claims 1-28, wherein the compound comprises deoxyribonucleotides.

31. The compound of any one of claims 1-30, wherein the modified oligonucleotide consists of 10 to 30 linked nucleosides.

32. The compound of any one of claims 1-30, wherein the modified oligonucleotide consists of 12 to 30 linked nucleosides.

33. The compound of any one of claims 1-30, wherein the modified oligonucleotide consists of 15 to 30 linked nucleosides.

34. A compound comprising a modified oligonucleotide consisting of 20 linked nucleosides having a nucleobase sequence consisting of the sequence recited in SEQ ID NO: 1423, wherein the modified oligonucleotide comprises

a gap segment consisting of ten linked 2'-deoxynucleosides;
a 5' wing segment consisting of five linked nucleosides; and
a 3' wing segment consisting of five linked nucleosides;

wherein the gap segment is positioned between the 5' wing segment and the 3' wing segment, wherein each nucleoside of each wing segment comprises a 2'-O-methoxyethyl sugar; wherein each internucleoside linkage is a phosphorothioate linkage and wherein each cytosine is a 5-methylcytosine.

35. A compound consisting of a modified oligonucleotide having a nucleobase sequence consisting of the sequence recited in SEQ ID NO: 1423, wherein the modified oligonucleotide comprises

a gap segment consisting of ten linked 2'-deoxynucleosides;
a 5' wing segment consisting of five linked nucleosides; and
a 3' wing segment consisting of five linked nucleosides;

wherein the gap segment is positioned between the 5' wing segment and the 3' wing segment, wherein each nucleoside of each wing segment comprises a 2'-O-methoxyethyl sugar; wherein each internucleoside linkage is a phosphorothioate linkage and wherein each cytosine is a 5-methylcytosine.

36. A compound comprising a modified oligonucleotide according to the following formula:
Tes Ges mCes mCes Aes Tds Tds Tds Ads Ads Tds Gds Ads Gds mCds Tes Tes mCes Aes mCe (SEQ ID NO: 1423); wherein,

A = an adenine,

mC = a 5'-methylcytosine

G = a guanine,

T = a thymine,

e = a 2'-O-methoxyethyl modified nucleoside,

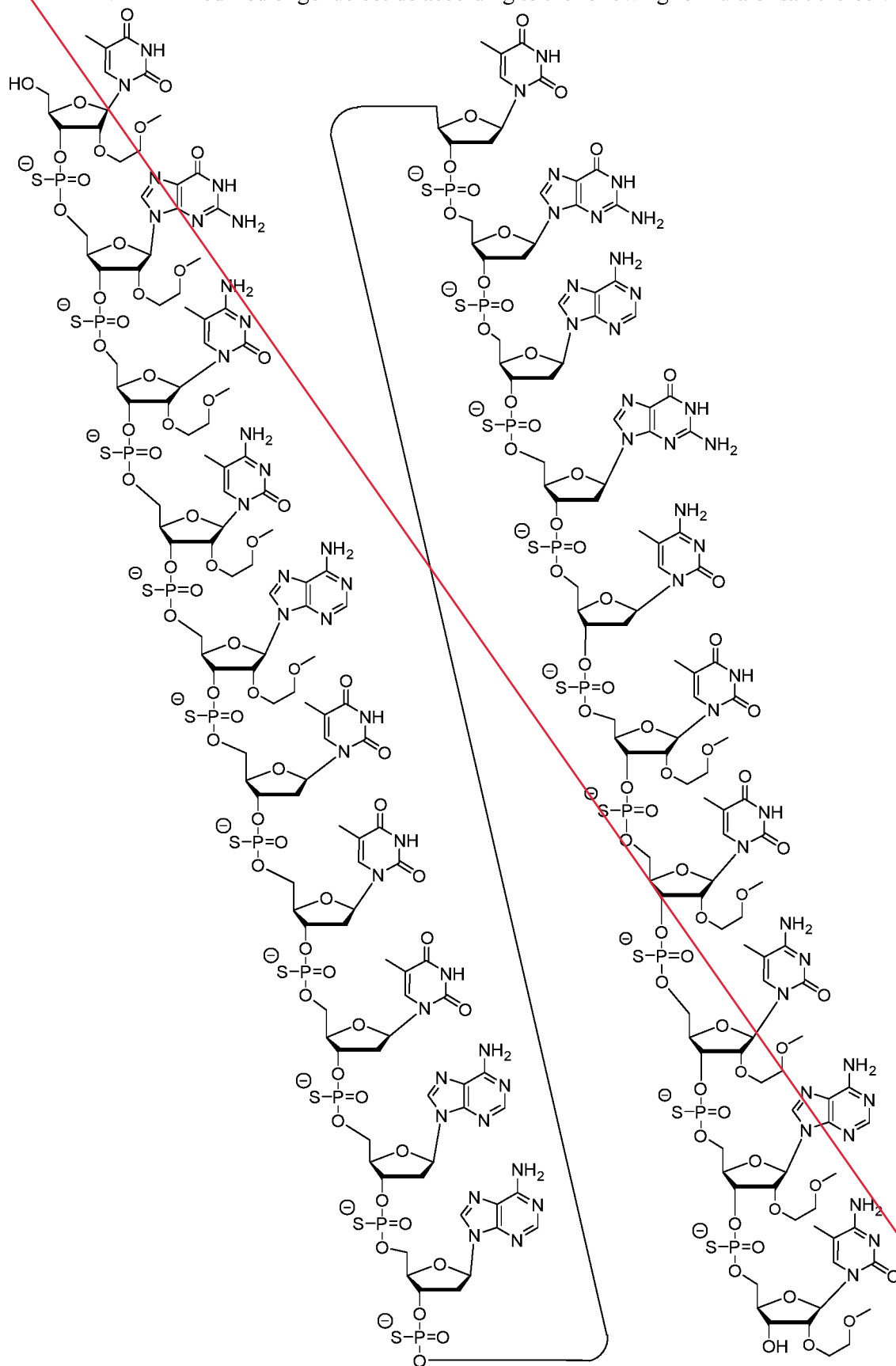
d = a 2'-deoxynucleoside, and

s = a phosphorothioate internucleoside linkage.

37. The compound of any one of the preceding claim, further comprising a conjugated group.

38. The compound of any one of the preceding claim, further comprising a conjugated GalNAc moiety.

39. A modified oligonucleotide according to the following formula or salt thereof:



40. A compound consisting of a pharmaceutically acceptable salt of any of the compounds of claims 1-39.

41. The compound of claim 40, wherein the pharmaceutically acceptable salt is a sodium salt.

42. The compound of claim 40, wherein the pharmaceutically acceptable salt is a potassium salt.

43. A composition comprising the compound or modified oligonucleotide of any one of claims 1-42 or salt thereof and a pharmaceutically acceptable carrier.

44. A composition comprising a compound or modified oligonucleotide of any preceding claim for use in therapy.

45. A method of treating, preventing, or ameliorating a disease associated with DGAT2 in an individual comprising administering to the individual the compound or composition of any one of claims 1-44 or salt thereof, thereby treating, preventing, or ameliorating the disease.

46. The method of claim 45, wherein the disease is NAFLD, NASH, lipodystrophy, or partial lipodystrophy.

47. The method of any one of claims 45 and 46, wherein administering the compound or composition reduces, inhibits or improves triglyceride synthesis, lipid synthesis, insulin resistance, insulin signaling, insulin sensitivity and cardiovascular risk profile.

48. A method of inhibiting expression of DGAT2 in a cell comprising contacting the cell with the compound or composition of any one of claims 1-44, thereby inhibiting expression of DGAT2 in the cell.

49. The method of claim 48, wherein the cell is in the liver or white adipose tissue of any individual.

50. The method of claim 49, wherein the individual has, or is at risk of having, NAFLD, NASH, lipodystrophy, or partial lipodystrophy.

51. A method of reducing or inhibiting triglyceride synthesis, lipid synthesis and insulin resistance in the liver or white adipose tissue of an individual having, or at risk of having, a disease associated with DGAT2 comprising administering the compound or composition of claims 1-44 to the individual, thereby reducing or inhibiting triglyceride synthesis, lipid synthesis and insulin resistance in the liver or white adipose tissue of the individual.

52. The method of claim 51, wherein the individual has, or is at risk of having NAFLD, NASH, lipodystrophy, or partial lipodystrophy.

53. The method of any of claims 51 or 52, wherein the compound or composition is administered to the individual parenterally.

54. Use of a compound or composition of any one of claims 1-44 for treating, preventing, or ameliorating a disease associated with DGAT2.

55. The use of claim 54, wherein the disease is NAFLD, NASH, lipodystrophy, or partial lipodystrophy.

56. Use of the compound or composition of any one of claims 1-44 in the manufacture or preparation of a medicament for treating, preventing or ameliorating a disease associated with DGAT2.

57. The use of claim 56, wherein the disease is NAFLD, NASH, lipodystrophy, or partial lipodystrophy.

WHAT IS CLAIMED:

1. An oligomeric compound comprising or consisting of a modified oligonucleotide according to the following formula: Tes Ges mCes mCes Aes Tds Tds Tds Ads Ads Tds Gds Ads Gds mCds Tes Tes mCes Aes mCe (SEQ ID NO: 1423); wherein,

A = an adenine nucleobase,

mC = a 5-methylcytosine nucleobase,

G = a guanine nucleobase,

T = a thymine nucleobase,

e = a 2'-O(CH₂)₂-OCH₃ furanosyl modified sugar moiety,

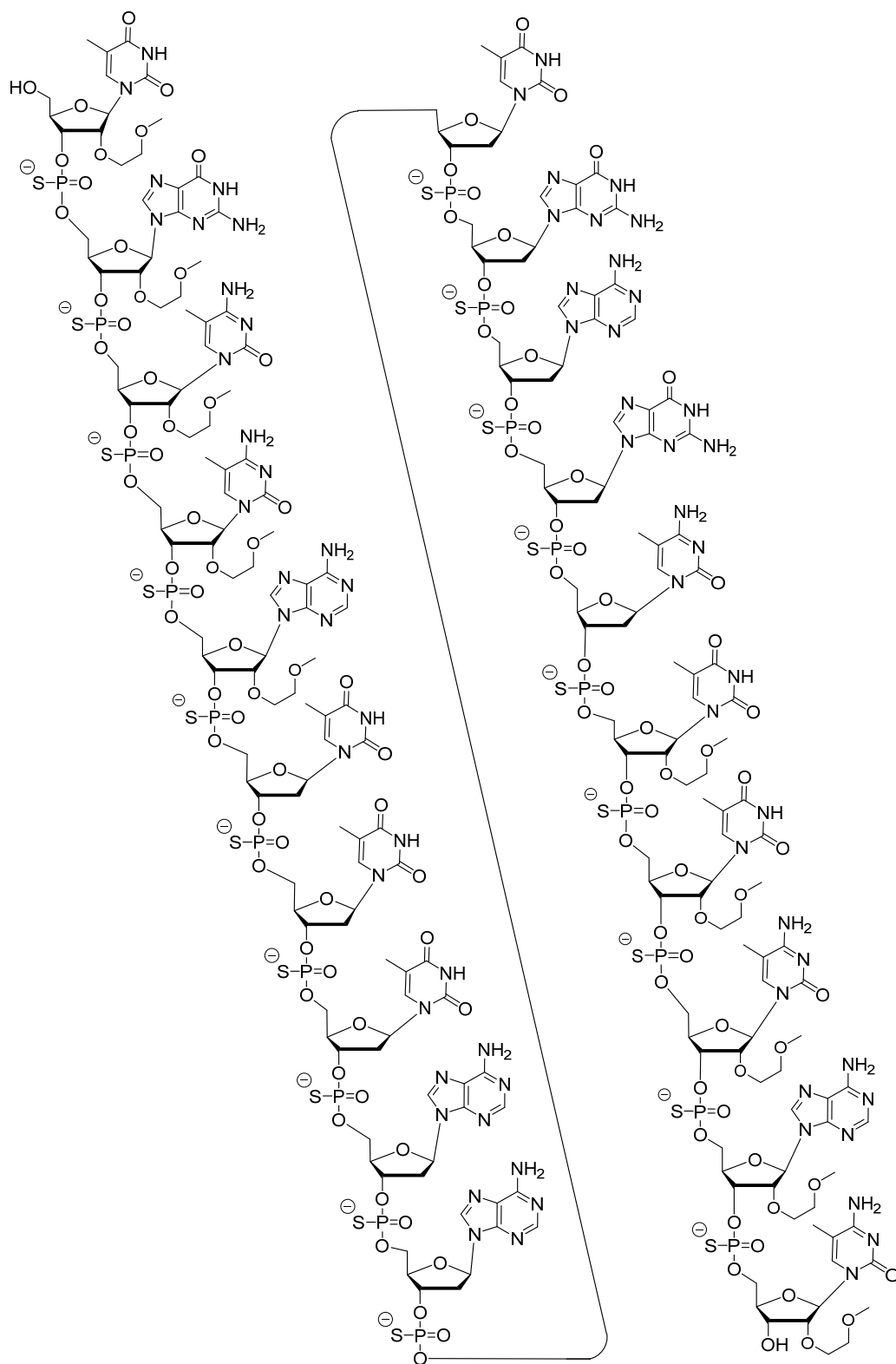
d = a 2'-deoxyfuranosyl sugar moiety, and

s = a phosphorothioate internucleoside linkage.

2. The oligomeric compound of claim 1, further comprising a conjugate group.

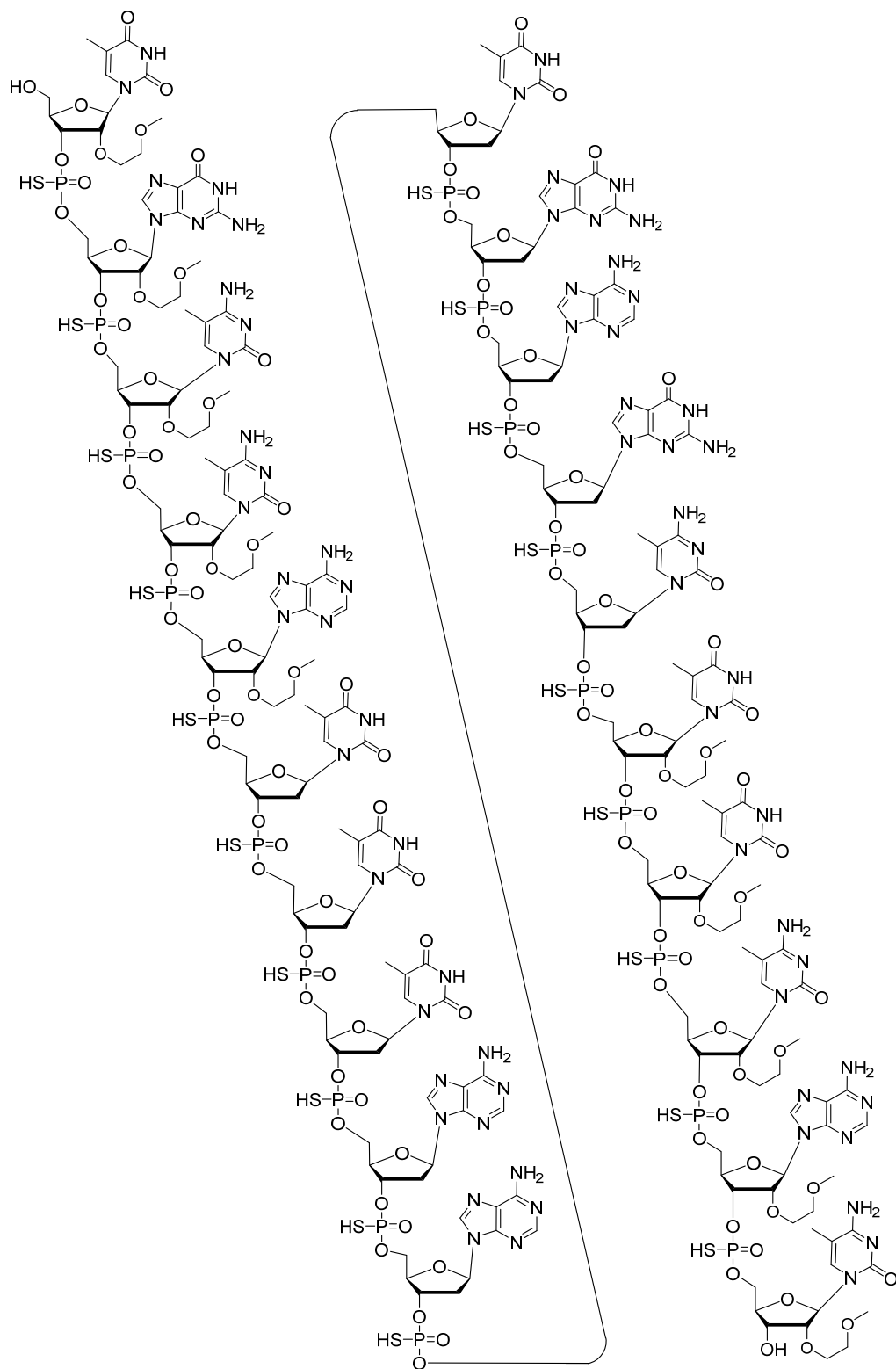
3. The oligomeric compound of claim 2, wherein the conjugate group is a GalNAc moiety.

4. A modified oligonucleotide, wherein the anion form of the modified oligonucleotide has the following chemical structure:



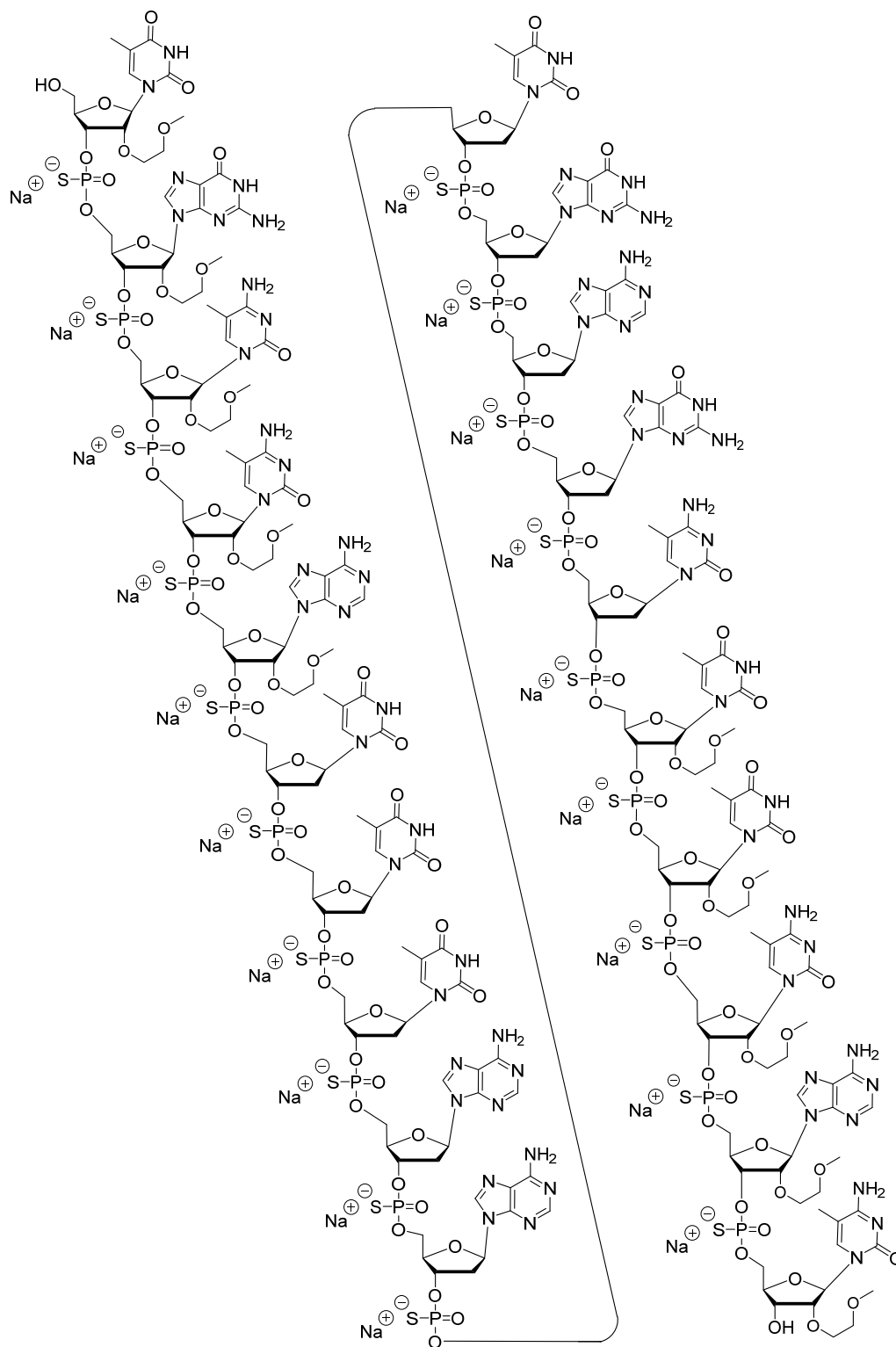
(SEQ ID NO: 1423).

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



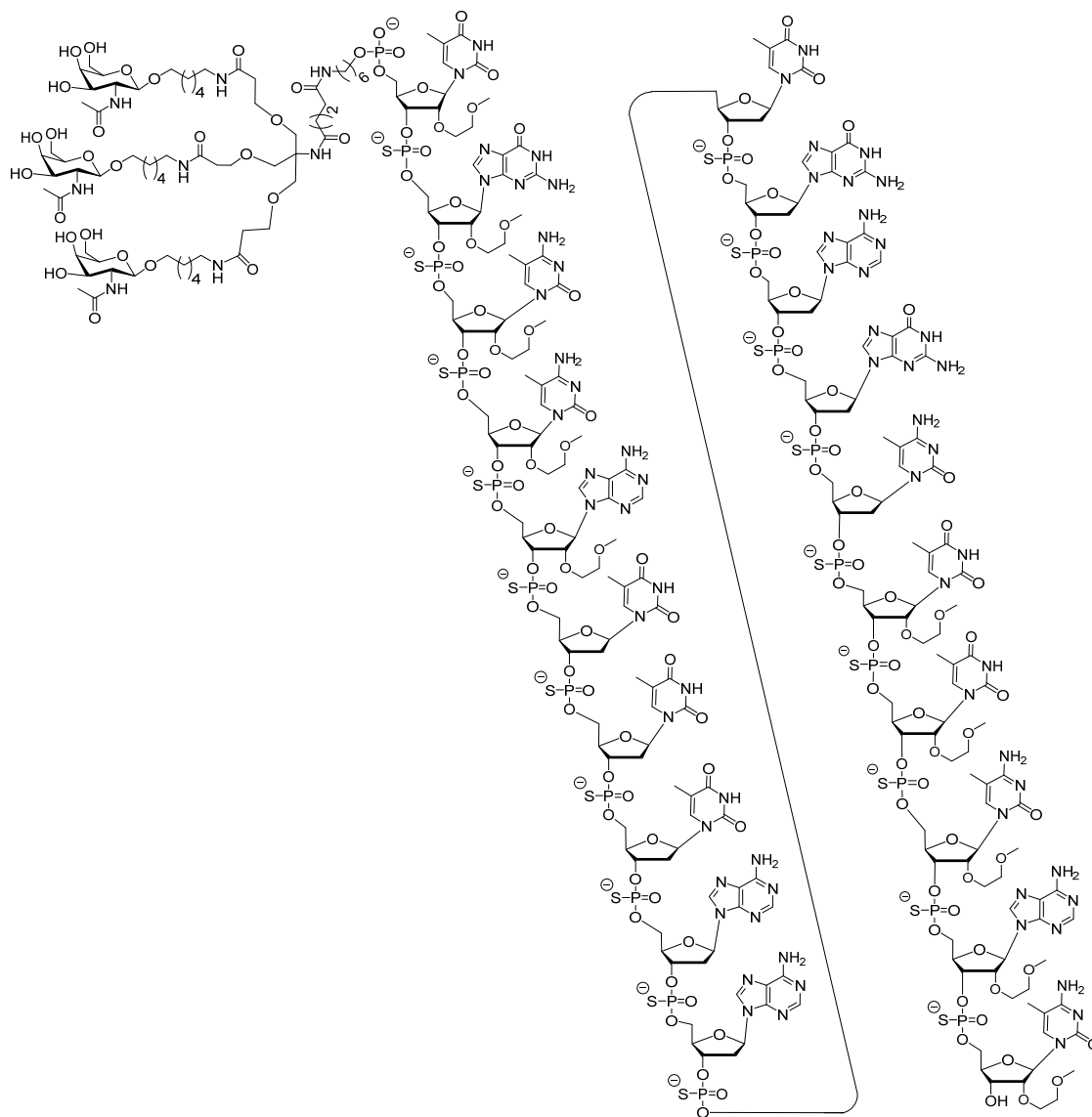
(SEQ ID NO: 1423), or a salt thereof.

6. The modified oligonucleotide of claim 5, which is the sodium salt or the potassium salt.
7. A modified oligonucleotide according to the following chemical structure:



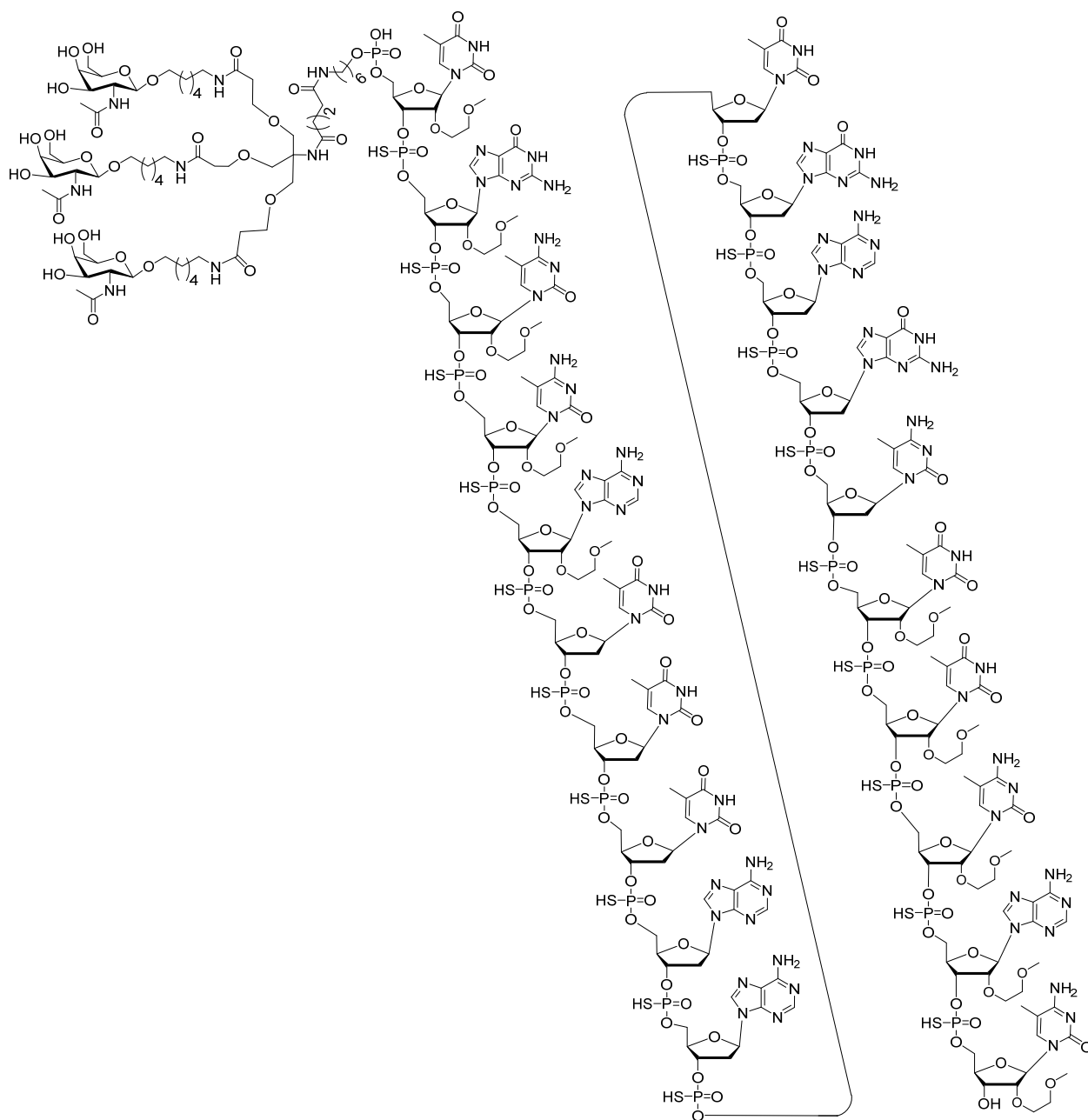
(SEQ ID NO: 1423).

8. An oligomeric compound, wherein the anion form of the oligomeric compound has the following chemical structure:



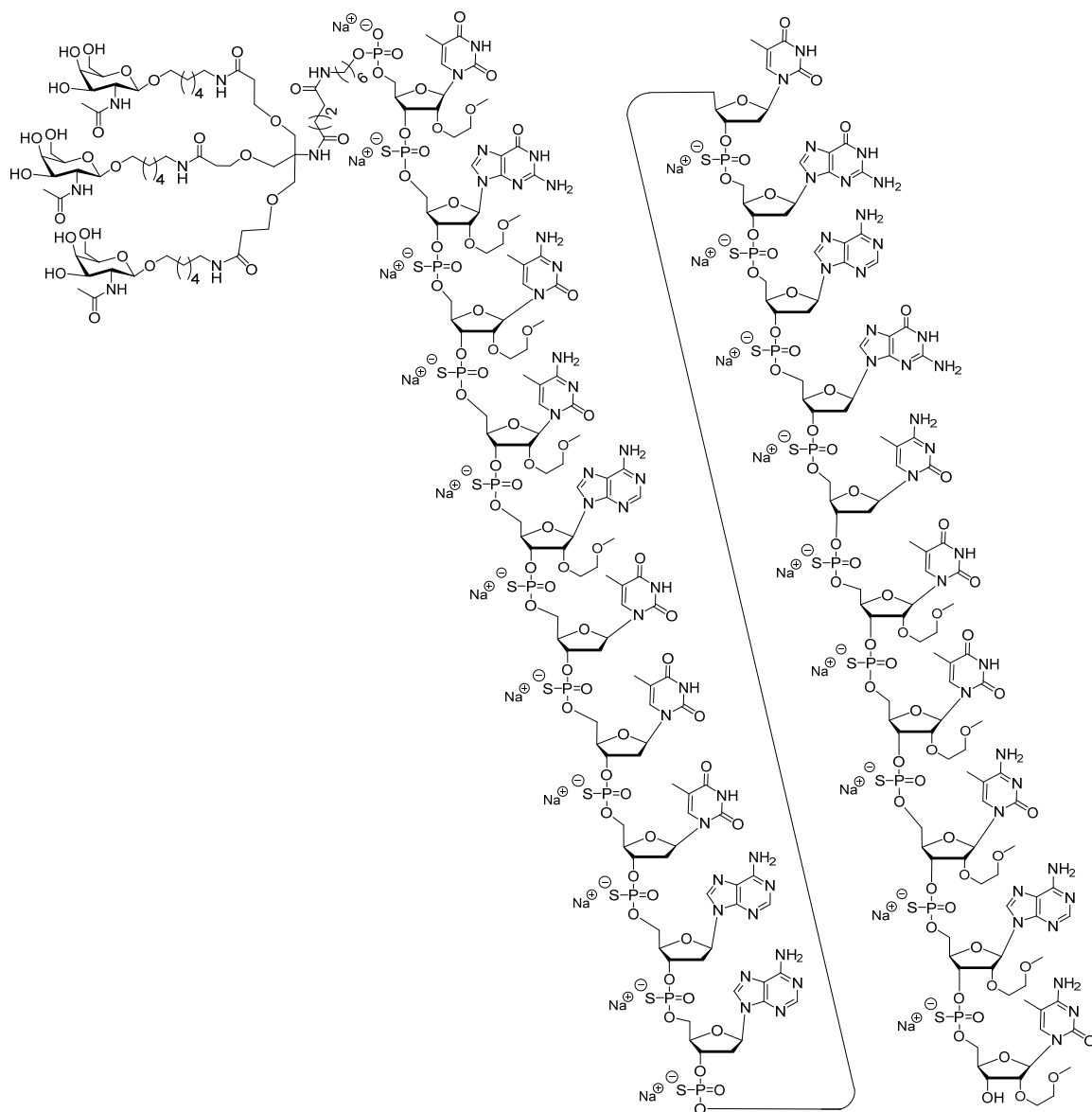
(SEQ ID NO: 1423).

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



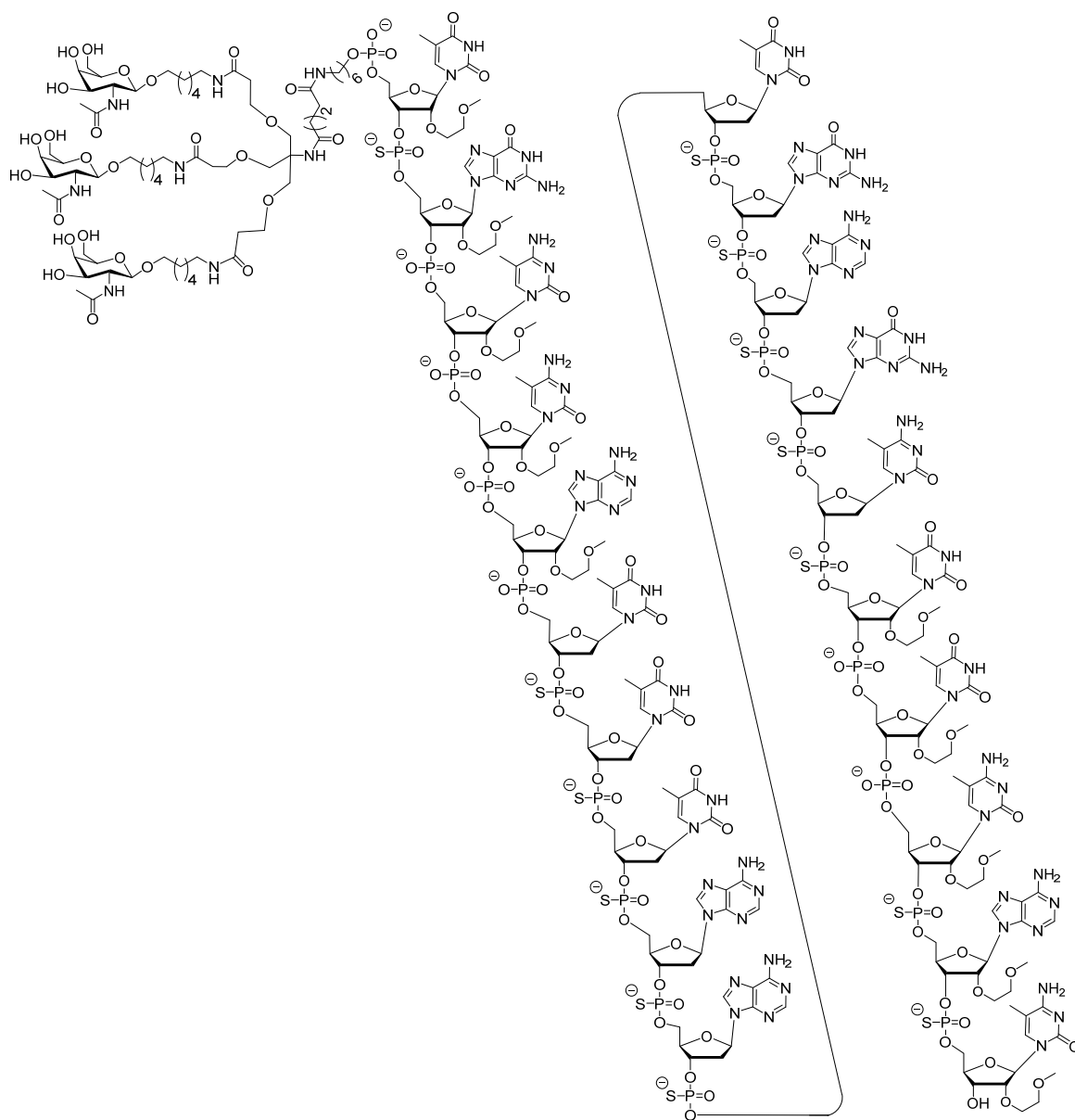
(SEQ ID NO: 1423), or a salt thereof.

10. The oligomeric compound of claim 9, which is the sodium salt or the potassium salt.
11. An oligomeric compound according to the following chemical structure:



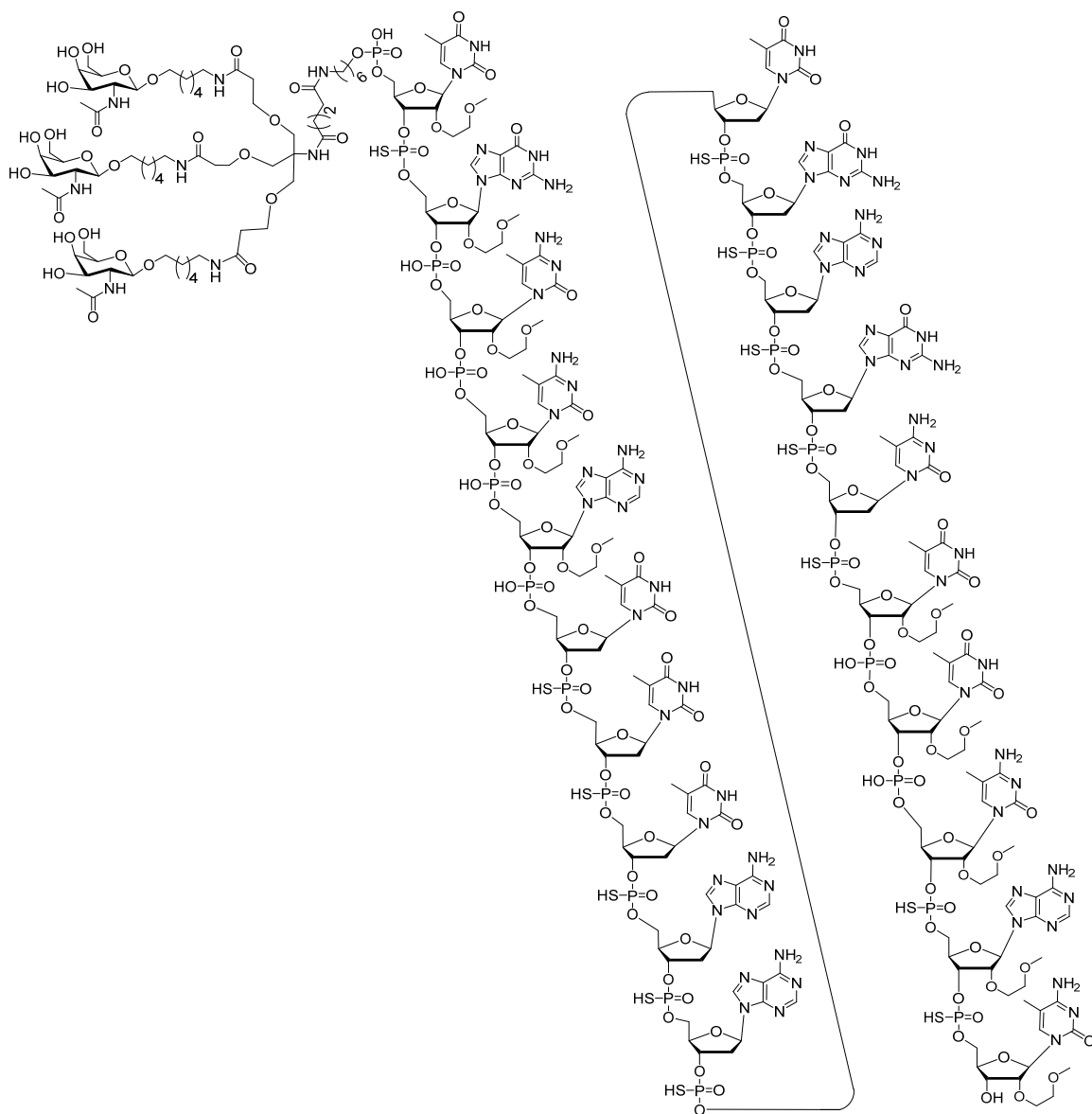
(SEQ ID NO: 1423).

12. An oligomeric compound, wherein the anion form of the oligomeric compound has the following chemical structure:



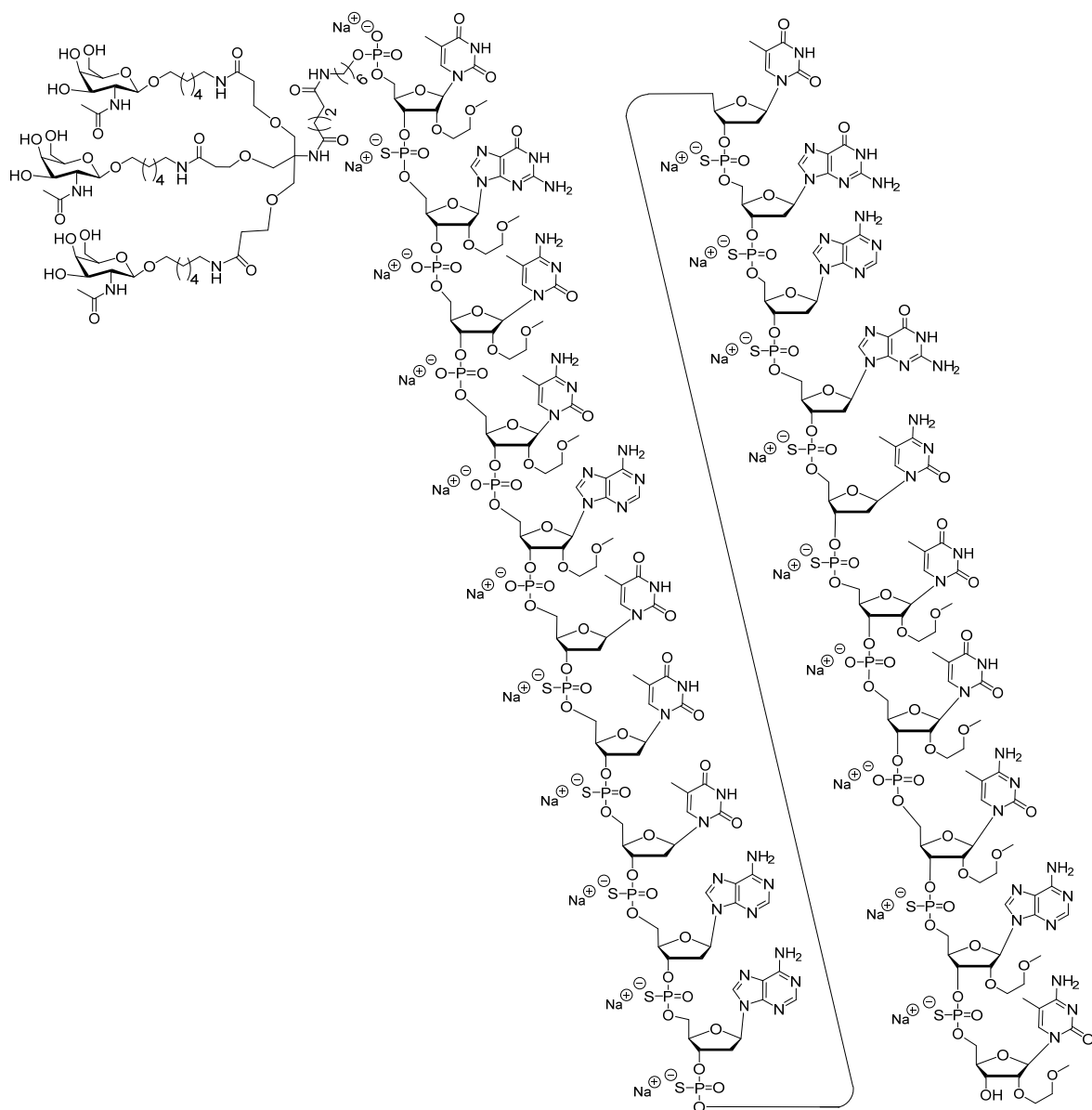
(SEQ ID NO: 1423).

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



(SEQ ID NO: 1423), or a salt thereof.

14. The oligomeric compound of claim 13, which is the sodium salt or the potassium salt.
15. An oligomeric compound according to the following chemical structure:



(SEQ ID NO: 1423).

16. A composition comprising the oligomeric compound or modified oligonucleotide of any one of the preceding claims and a pharmaceutically acceptable carrier or diluent.
17. The composition of claim 16, wherein the pharmaceutically acceptable carrier or diluent is phosphate-buffered saline (PBS) or water.
18. A composition comprising the oligomeric compound or modified oligonucleotide of any one of claims 1-15, or the composition of claim 16 or claim 17, for use in therapy.

19. The oligomeric compound or modified oligonucleotide of any one of claims 1-15, or the composition of claim 16 or claim 17, for use as a medicament.

20. Use of the oligomeric compound or modified oligonucleotide of any one of claims 1-15, or the composition of claim 16 or claim 17, in the manufacture of a medicament for treating NAFLD, NASH, lipodystrophy, or partial lipodystrophy.

21. Use of the oligomeric compound or modified oligonucleotide of any one of claims 1-15, or the composition of claim 16 or claim 17, in the manufacture of a medicament for treating NASH.