Claims:

1. A MAPT antisense oligonucleotide (MAPT ASO) 17-19 nucleotides in length and comprising the nucleobase sequence of any one of SEQ ID NOs: 5, 8, 4, 6, 7, 9, 21-24, 32-35, 19-21, 25-28, 29-31, 36-37, 41-43, 51-54, 38-40, 44-47, 48-50, and 55-56, wherein the MAPT ASO comprises at least one modified internucleoside linkage and/or at least one modified sugar.

2. The MAPT ASO of claim 1, wherein:

(a) the MAPT ASO comprises a nucleobase sequence consisting of the sequence of any one of SEQ ID NOs: 5, 8, 4, 6, 7, and 9; or

(b) the MAPT ASO is a gapmer having a gap segment consisting of the nucleobase sequence of any one of SEQ ID NOs:11, 14, 10, 12, 13, and 15.

3. A MAPT antisense oligonucleotide (MAPT ASO), wherein the MAPT ASO is a gapmer having a gap segment consisting of the nucleobase sequence of any one of SEQ ID NOs:11, 14, 10, 12, 13, and 15, wherein the MAPT ASO comprises at least one modified internucleoside linkage and at least one modified sugar.

4. The MAPT ASO of claim 3, wherein the MAPT ASO is:

(a) 15 to 25 linked nucleosides in length; or

(b) 16-19 nucleotides in length.

5. A MAPT antisense oligonucleotide (MAPT ASO), wherein the MAPT ASO is a gapmer 16 nucleotides in length and comprises a gap segment consisting of the nucleobase sequence of any one of SEQ ID NOs: 41-43, 51-54, 38-40, 44-47, 48-50, and 55-56, wherein the MAPT ASO comprises at least one modified internucleoside linkage and at least one modified sugar.

6. The MAPT ASO of claim 5, wherein the MAPT ASO comprises a nucleobase sequence consisting of the sequence of any one of SEQ ID NOs:21-24, 32-35, 19-21, 25-28, 29-31, 36-37.

7. The MAPT ASO of any one of claims 1-6, wherein the at least one modified internucleoside linkage is a phosphorothioate internucleoside linkage.

8. The MAPT ASO of any one of claims 1-7, wherein the MAPT ASO comprises:

(a) at least one modified sugar comprising a bicyclic sugar; or.

(b) 2-6 modified sugars each comprising a bicyclic sugar.

9. The MAPT ASO of claim 8, wherein each bicyclic sugar comprises:

(a) a chemical bridge between the 4′ and 2′ positions of the sugar, wherein each chemical bridge is independently selected from the group consisting of: 4′-CH(R)—O-2′ and 4′-$(CH_2)_2$—O-2′, wherein each R is independently selected from H, C_1-C_6 alkyl and C_1-C_6 alkoxy; or

(b) a chemical bridge between the 4′ and 2′ positions of the sugar, wherein each chemical bridge is 4′-CH(R)—O-2′, and wherein each R is independently H.

10. The MAPT ASO of any one of claims 1-9, further comprising a at least one modified nucleobase.

11. The MAPT ASO of claim 10, wherein the modified nucleobase comprises a 5-methyl cytosine.

12. The MAPT ASO of any one of claims 1-11, wherein the MAPT ASO comprises, from 5′ to 3′:

a 5′ wing segment having from 3 nucleosides, wherein each nucleoside of the 5′ wing segment comprises a modified sugar;

a gap segment having from 10-13 nucleosides, wherein each nucleoside of the gap segment is a deoxynucleoside; and

a 3′ wing segment having from 3 nucleosides, wherein each nucleoside of the 3′ wing segment comprises a modified sugar.

13. A MAPT ASO consisting of:

(a) 18 contiguous nucleobases complementary to nucleobases 78,441 to 78,458 of SEQ ID NO: 1;

(b) 17 contiguous nucleobases complementary to nucleobases 66,760 to 66,776 of SEQ ID NO: 1;

(c) 19 contiguous nucleobases complementary to nucleobases 78,631 to 78,649 of SEQ ID NO: 1;

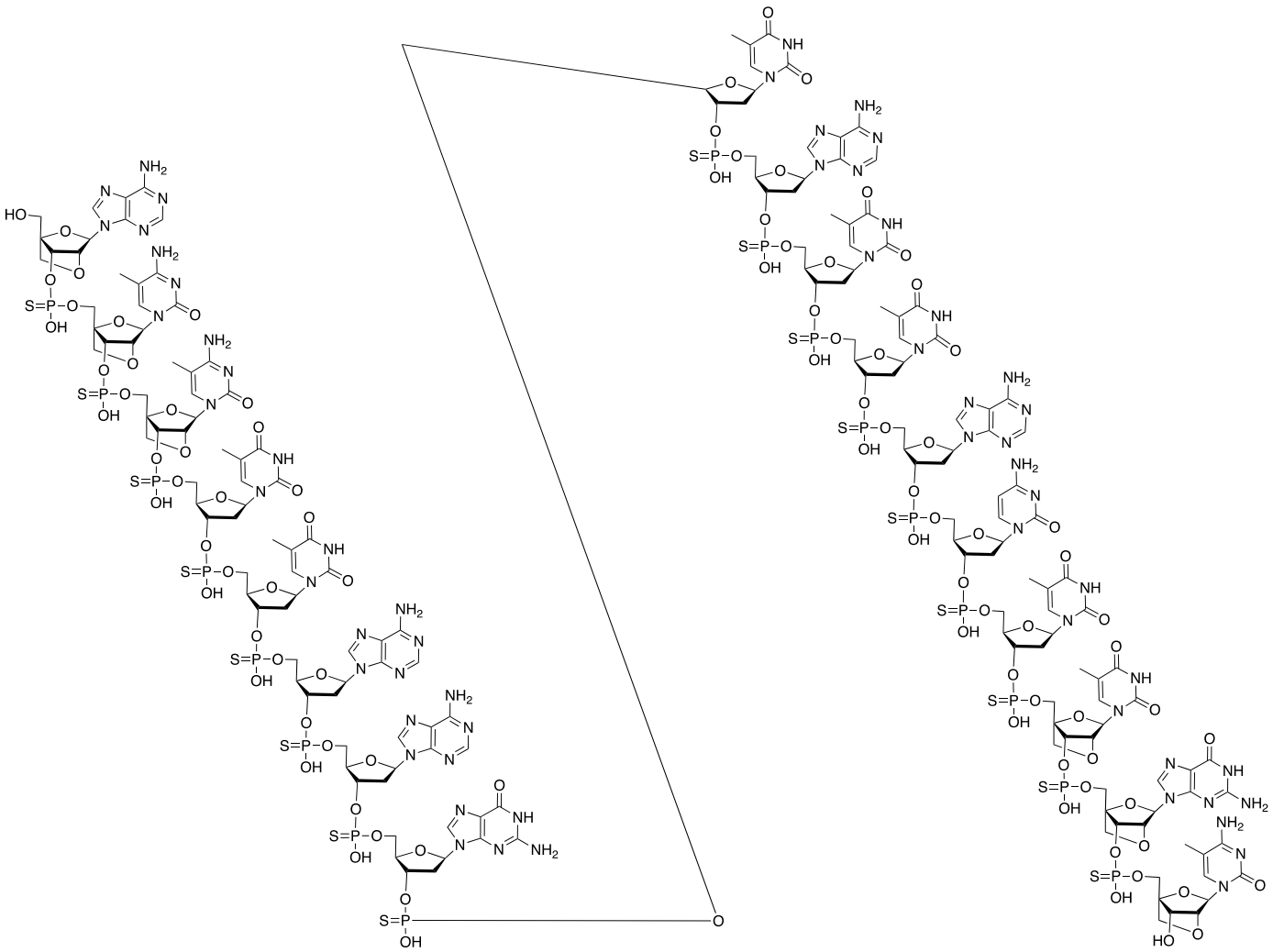
(d) 18 contiguous nucleobases complementary to nucleobases 78,828 to 78,845 of SEQ ID NO: 1; or

(e) 19 contiguous nucleobases complementary to nucleobases 90,215 to 90,233 of SEQ ID NO:1,

wherein the MAPT ASO comprises at least one modified internucleoside linkage and/or at least one modified sugar.

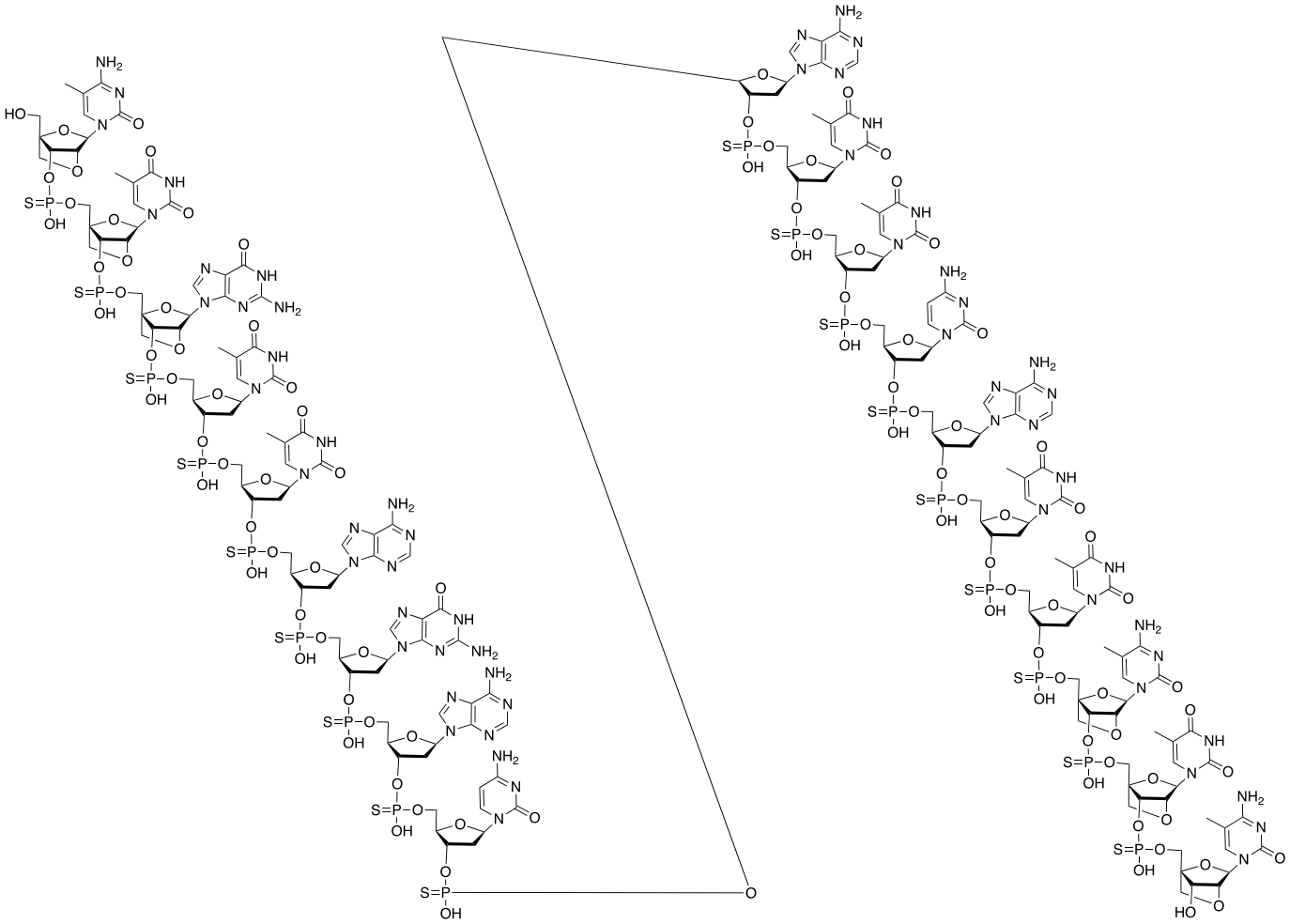
14. The MAPT ASO of claim 1, wherein the MAPT ASO has a chemical structure selected from the group consisting of:

(a)



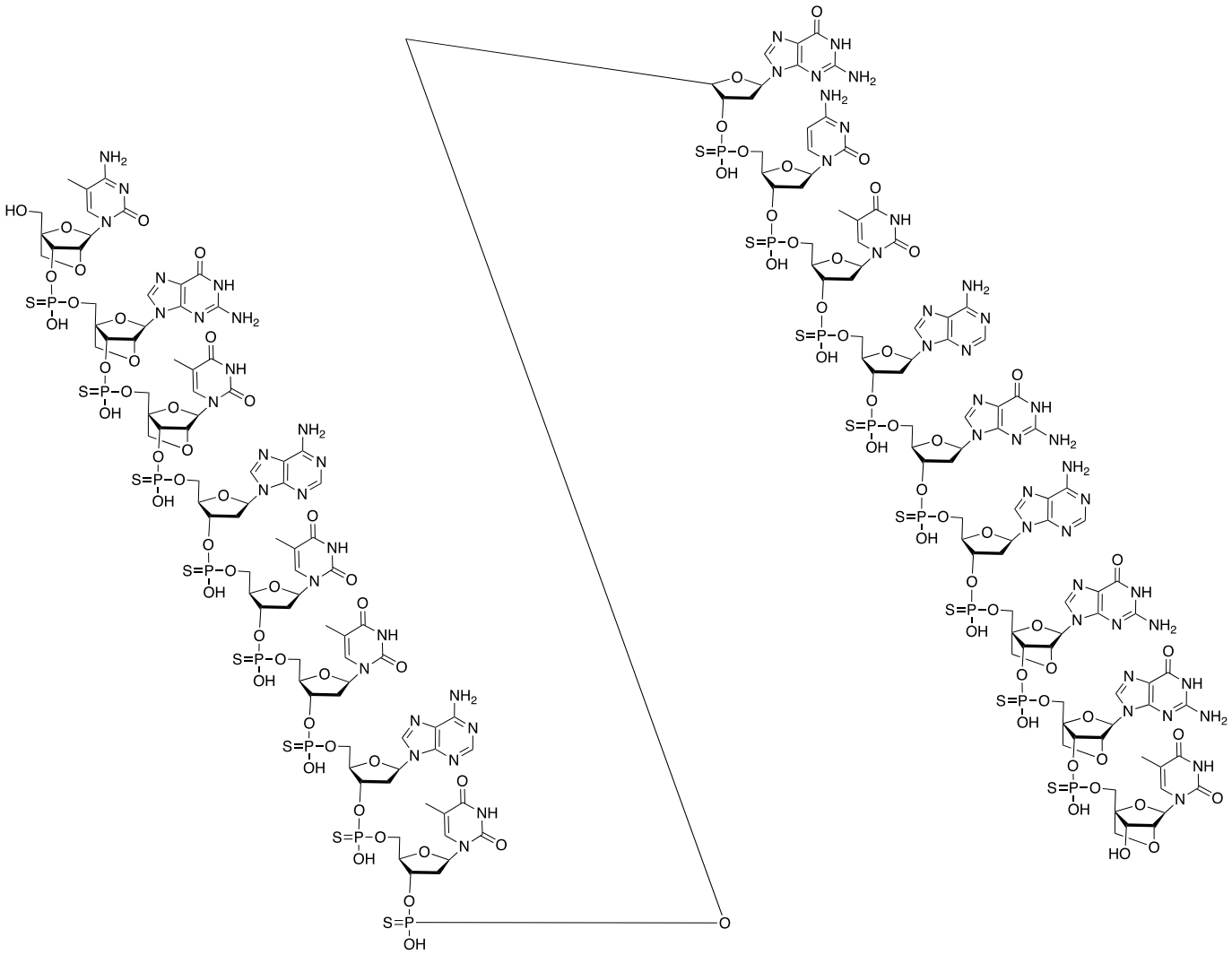
, or a salt thereof;

(b)



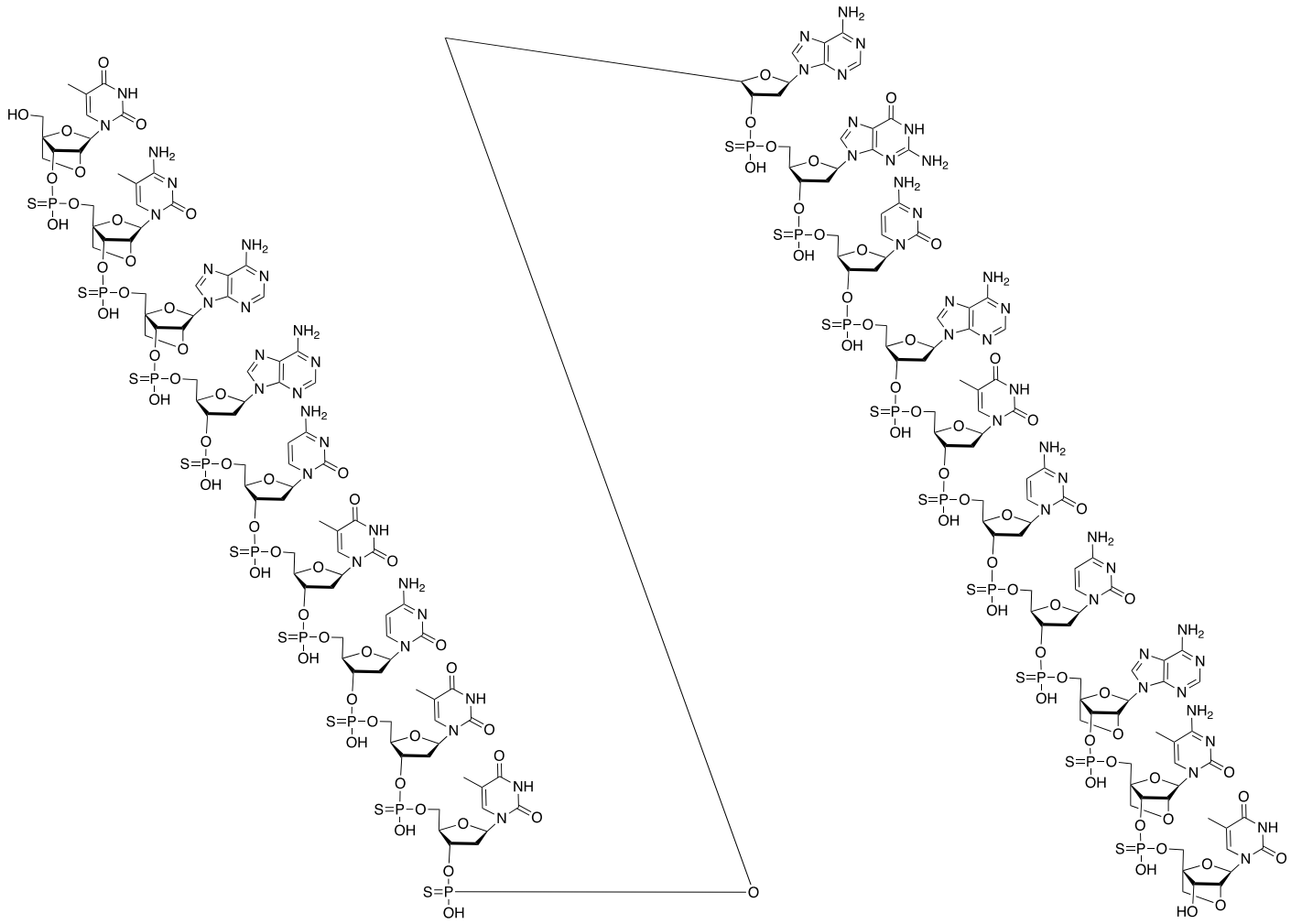
, or a salt thereof;

(c)



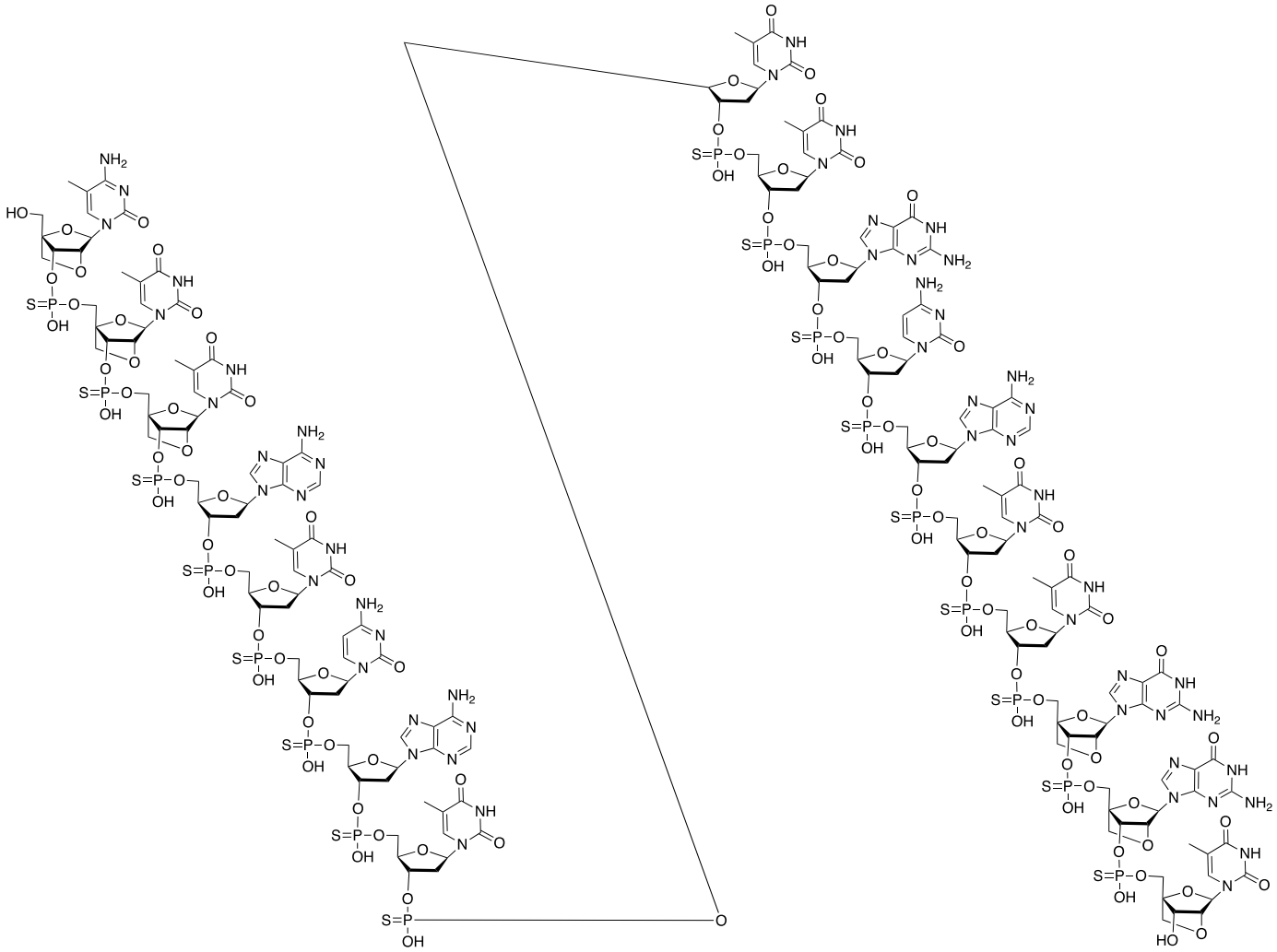
, or a salt thereof;

(d)



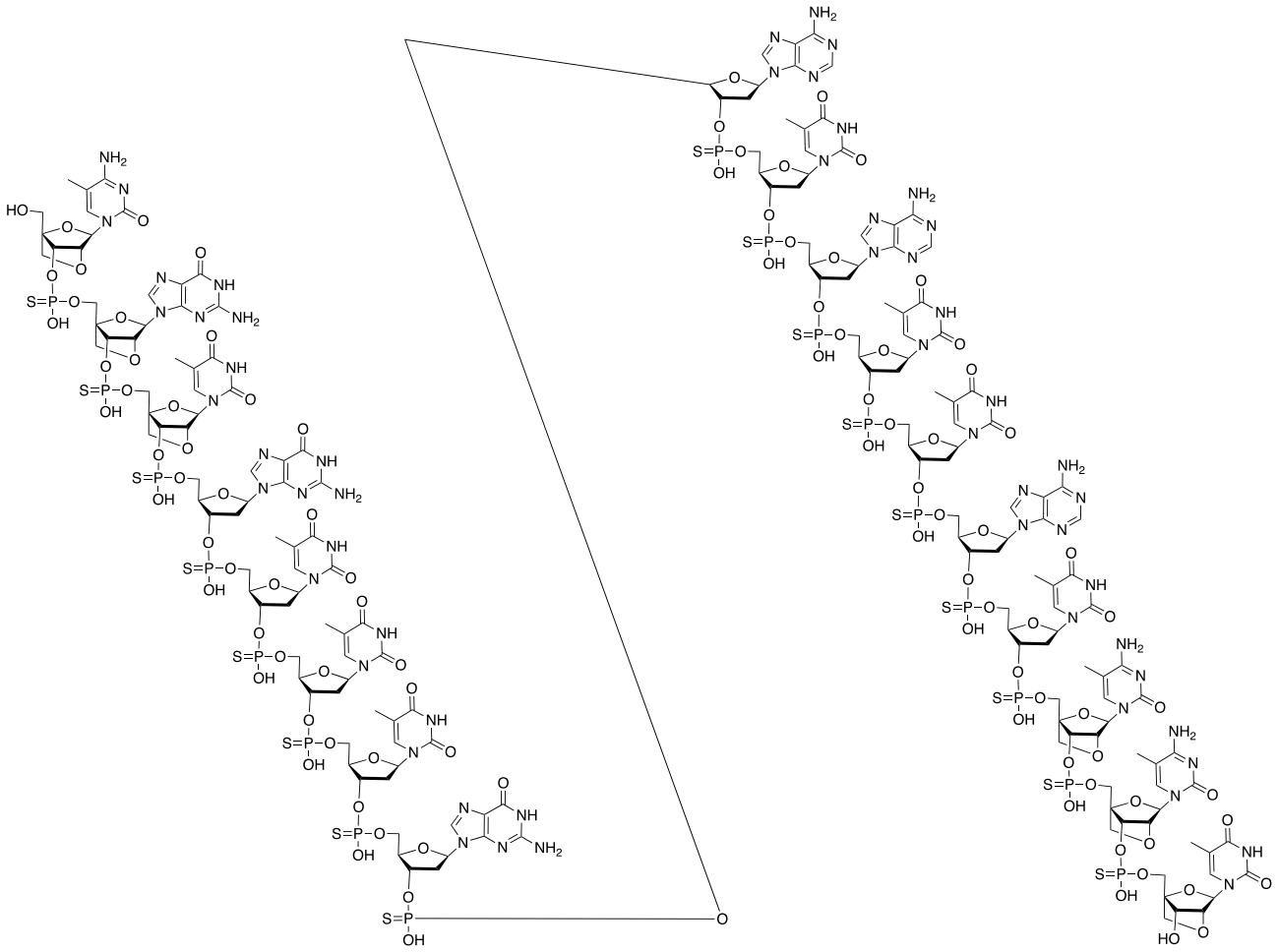
, or a salt thereof;

(e)



, or a salt thereof; or

(f)



, or a salt thereof.

15. The MAPT ASO of any one of claims 1-14, wherein the MAPT ASO is conjugated to a targeting ligand or a delivery vehicle.

16. The MAPT ASO of claim 15, wherein the targeting ligand specifically binds to the transferrin receptor (TfR) or a molecule expressed on the luminal surface of the blood brain barrier.

17. A pharmaceutical composition comprising the MAPT ASO of any one of claims 1-16 and a pharmaceutically acceptable carrier or diluent.

18. Use of the MAPT ASO of any one of claims 1-16 of the pharmaceutical composition of claim 17 in the manufacture of a medicament for:

(a) decreasing tau expression in a neuron, wherein the MAPT ASO decreases the expression level of an endogenous MAPT gene;

(b) modifying a neuron cell to decrease tau expression, wherein the MAPT ASO decreases the expression level of an endogenous MAPT gene or decreases the level of MAPT transcript in the neuron cell;

(c) reducing expression of tau in the spinal cord or a subject;

(d) reducing tau expression in a subject;

(e) reducing MAPT messenger ribonucleic acid (mRNA) expression in a human subject;

(f) the treatment of a tau-associated neurodegenerative disorder in a subject; or

(g) delivering a MAPT ASO to the CNS of a human subject, wherein said MAPT ASO decreases the expression level of an endogenous MAPT gene

19. The use according to claim 18, wherein the MAPT ASO or the pharmaceutical composition is formulated for intrathecal administration

20. The use according to claim 18, wherein tau expression is reduced in the CNS of the subject.

21. The use according to claim 18, wherein the MAPT ASO is to be administered to the subject by intrathecal administration or intravenous administration.

22. The use according to any one of claims 18-22, wherein the MAPT ASO decreases the expression level of an endogenous MAPT gene or reduces the level of a MAPT transcript by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or at least 95% as compared to the level without administering the MAPT ASO.

23. The use according to claim 18, wherein the tau-associated neurodegenerative syndrome is Alzheimer’s Disease.