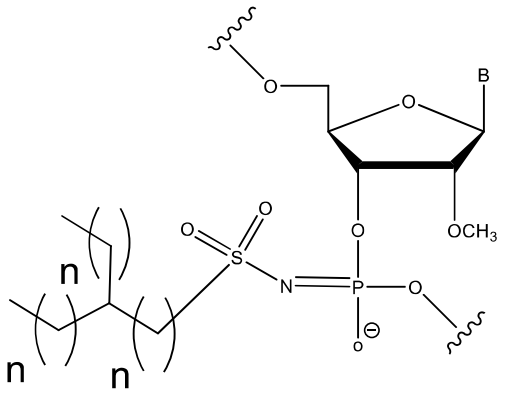
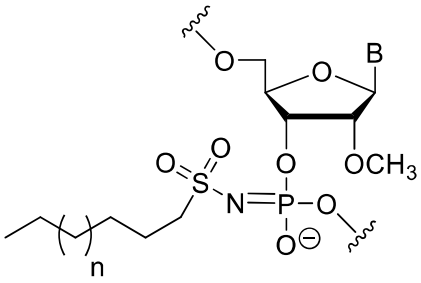
strand which is complementary to said antisense strand; and one or more lipophilic monomers, containing one or more lipophilic moieties, conjugated to one or more positions on at least one strand, optionally via a linker or carrier.

[0005a] In one aspect, the present disclosure refers to a compound comprising: an antisense strand which is complementary to a target gene; a sense strand which is complementary to said antisense strand; and one or more lipophilic monomers, wherein the lipophilic monomer comprises

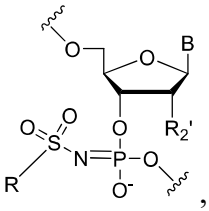


or



, wherein: n is an integer of 1-21; and B is a modified or unmodified nucleobase.

[0005b] In another aspect, the present disclosure refers to a compound comprising: an antisense strand which is complementary to a target gene; a sense strand which is complementary to said antisense strand; and one or more lipophilic monomers containing a lipophilic moiety conjugated to the sense strand and/or antisense strand, wherein the lipophilic monomer has a formula of



, wherein: R is the lipophilic moiety and wherein the lipophilic moiety contains a C_4-C_{30} hydrocarbon chain; n is an integer of 1-21; R_2' is H, OH, F, OMe, O-methoxyalkyl, O-allyl, O-N-methylacetamido, O-dimethylaminoethoxyethyl, or O-aminopropyl; and B is a modified or unmodified nucleobase.

[0005c] In another aspect, the present disclosure refers to use of a composition comprising the compound as described herein in the manufacture of a medicament for reducing the expression of a target gene in a subject.

[0005d] In another aspect, the present disclosure refers to use of a composition comprising the compound as described herein in the manufacture of a medicament for the treatment of a subject having a CNS disorder.

[0005e] In another aspect, the present disclosure refers to a composition comprising the compound as described herein for use in therapy.

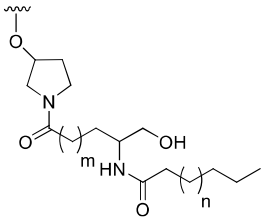
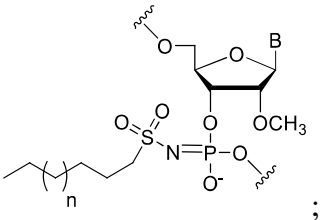
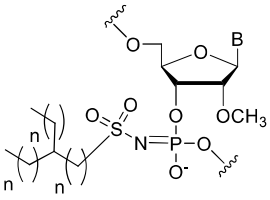
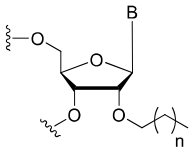
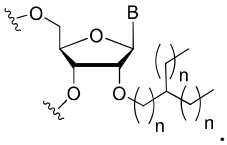
[0006] In some examples, the lipophilicity of the lipophilic moiety, measured by octanol-water partition coefficient, $\log K_{ow}$, exceeds 0. The lipophilic moiety may possess a $\log K_{ow}$ exceeding 1, exceeding 1.5, exceeding 2, exceeding 3, exceeding 4, exceeding 5, or exceeding 10.

[0007] In some examples, the hydrophobicity of the compound, measured by the unbound fraction in the plasma protein binding assay of the compound, exceeds 0.2. In one example, the plasma protein binding assay determined is an electrophoretic mobility shift assay (EMSA) using human serum albumin protein. The hydrophobicity of the compound, measured by fraction of unbound siRNA in the binding assay, exceeds 0.15, exceeds 0.2, exceeds 0.25, exceeds 0.3, exceeds 0.35, exceeds 0.4, exceeds 0.45, or exceeds 0.5 for an enhanced *in vivo* delivery of siRNA.

[0008] In some examples, the lipophilic moiety is an aliphatic, cyclic such as alicyclic, or polycyclic such as polyalicyclic compound, such as a steroid (e.g., sterol) or a linear or branched aliphatic hydrocarbon. Exemplary lipophilic moieties are lipid, cholesterol, retinoic acid, cholic acid, adamantane acetic acid, 1-pyrene butyric acid, dihydrotestosterone, 1,3-bis-O(hexadecyl)glycerol, geranyloxyhexyanol, hexadecylglycerol, borneol, menthol, 1,3-propanediol, heptadecyl group, palmitic acid, myristic acid, O3-(oleoyl)lithocholic acid, O3-(oleoyl)cholenic acid, ibuprofen, naproxen, dimethoxytrityl, or phenoxazine.

[0009] Suitable lipophilic moieties also include those containing a saturated or unsaturated C_4-C_{30} hydrocarbon chain (e.g., C_4-C_{30} alkyl or alkenyl), and an optional functional group selected from the group consisting of hydroxyl, amine, carboxylic acid, sulfonate, phosphate, thiol, azide, and alkyne. The functional groups are useful to attach the lipophilic moiety to the iRNA agent. In some examples, the lipophilic moiety contains a saturated or unsaturated C_6-C_{18} hydrocarbon chain (e.g., a linear C_6-C_{18} alkyl or alkenyl). In one example, the lipophilic moiety contains a saturated or unsaturated C_{16} hydrocarbon chain (e.g., a linear C_{16} alkyl or alkenyl). In some examples, the lipophilic moiety contains two or more carbon-carbon double bonds.

[0010] In some examples, the lipophilic moiety is a C_6-C_{30} moiety having a free terminal carboxylic acid functionality (e.g., hexanoic acid, heptanoic acid, octanoic acid,

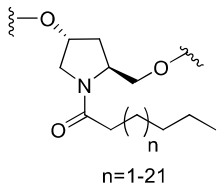

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; or

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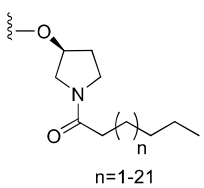
[0027] In the above structures for the lipophilic monomers, the monomers may also contain one or more asymmetric centers and thus occur as racemates and racemic mixtures, single enantiomers, individual diastereomers and diastereomeric mixtures. All such isomeric forms of the monomers are expressly included.

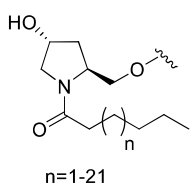
[0028] In the above structures for the lipophilic monomers, the alkylene chain can contain one or more unsaturated bonds.

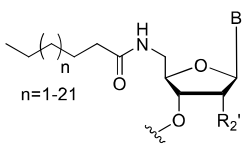
[0029] Integer m is 0-8. Integer n is 1-21. R_2' may be any functional group that is an acceptable 2'-modification for a ribose sugar, such as a 2'-O-methoxyalkyl (*e.g.*, 2'-O-methoxymethyl, 2'-O-methoxyethyl, or 2'-O-2-methoxypropanyl) modification, 2'-O-allyl modification, 2'-C-allyl modification, 2'-fluoro modification, 2'-O-N-methylacetamido (2'-O-NMA) modification, 2'-O-dimethylaminoethoxyethyl (2'-O-DMAEOE) modification, 2'-O-aminopropyl (2'-O-AP) modification, or 2'-ara-F modification. For instance, R_2' may be H, OH, F, OMe, O-methoxyalkyl, O-allyl, O-N-methylacetamido, O-dimethylaminoethoxyethyl, or O-aminopropyl. B is a modified or unmodified nucleobase. W is an alkyl group such as a C_1-C_4 alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl). R, R', and R'' are each independently H or an alkyl group such as a C_1-C_4 alkyl (e.g., methyl, ethyl, propyl, isopropyl, t-butyl).

[0030] In some examples, the lipophilic monomer conjugated to one or more positions of a strand of the compound has a structure of:

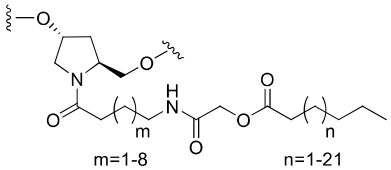


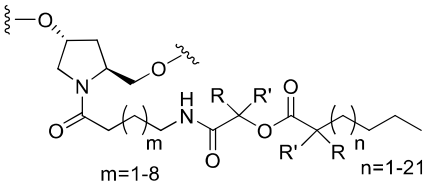
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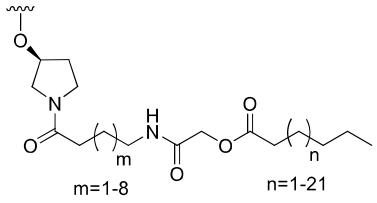
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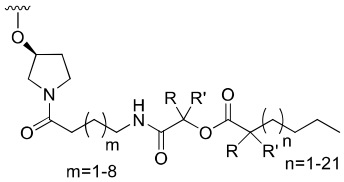
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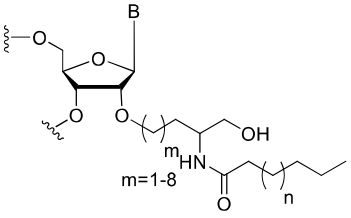
(R$_2$' is 2'-F, 2'-OMe,

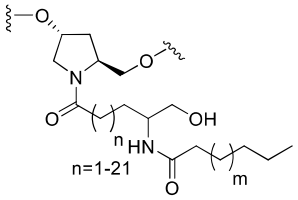


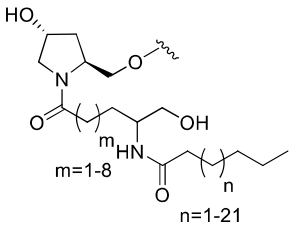
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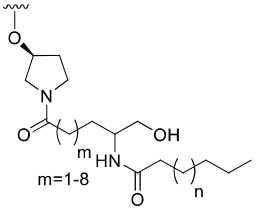
R, R'= H or CH_3, Ethyl, isopropyl, tButyl ;


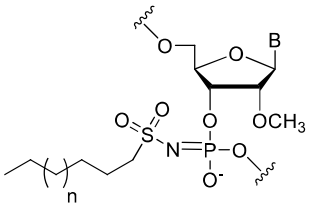
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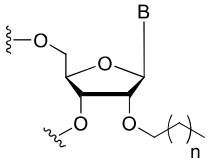
R, R'= H or CH_3, Ethyl, isopropyl, tButyl ;


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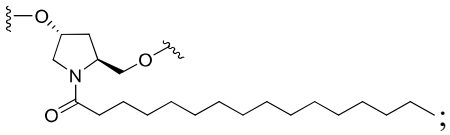
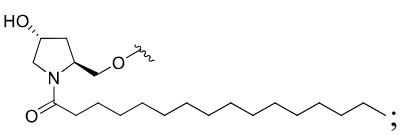
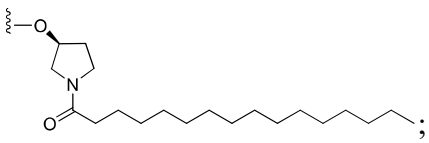
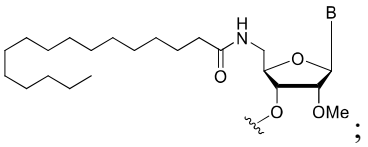
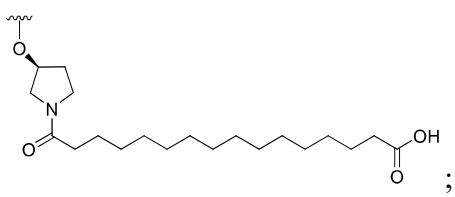
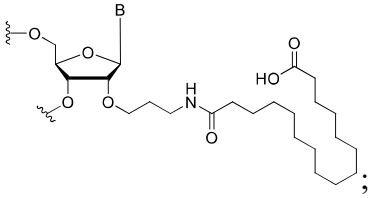
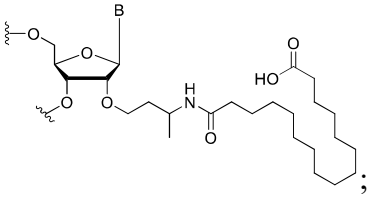
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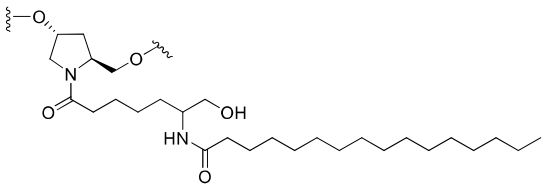
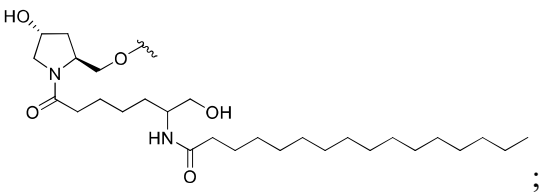
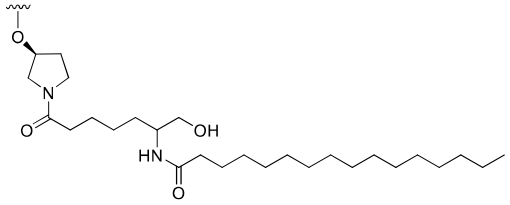
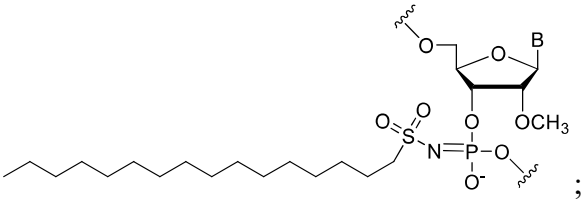
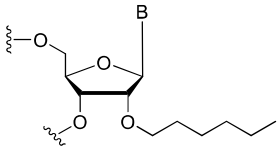
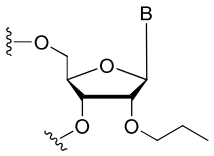
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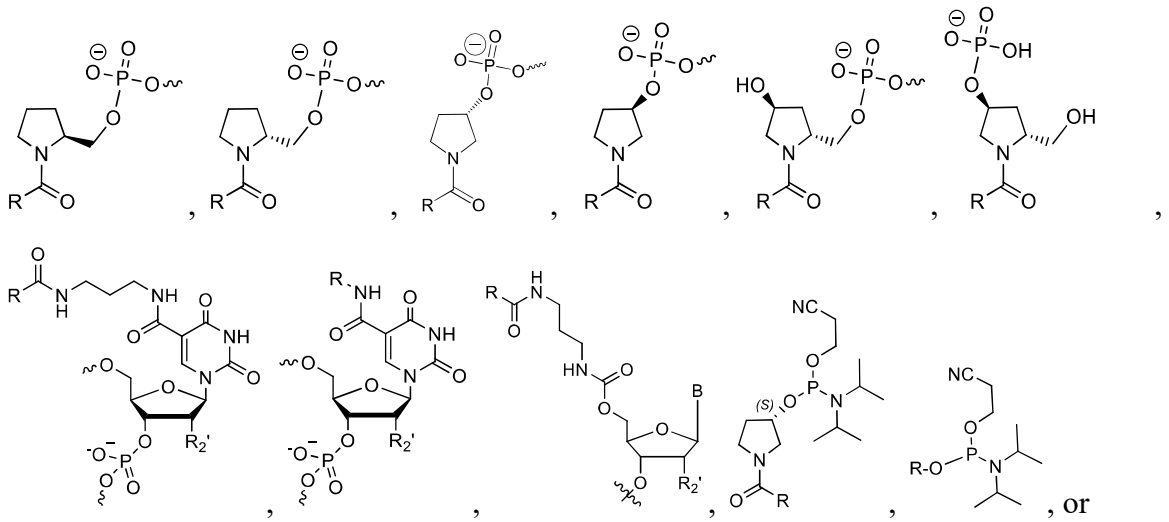
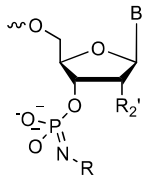
. In these structures, B is a modified or unmodified nucleobase.

[0031] Specific examples of the lipophilic monomers include:


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. In these structures, B is a modified or unmodified nucleobase; and R and R' are each independently H, methyl, ethyl, isopropyl, or t-butyl.

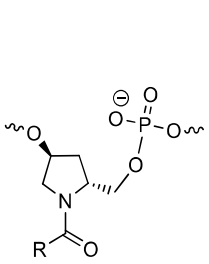
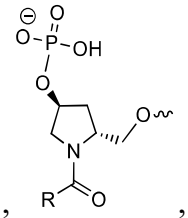
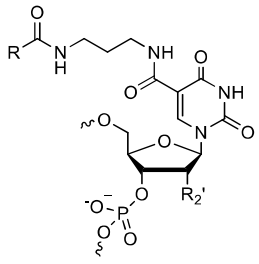
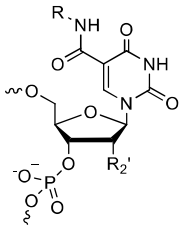
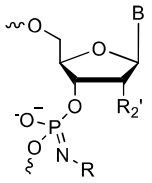
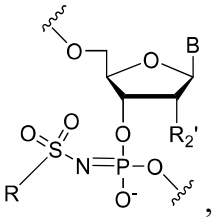
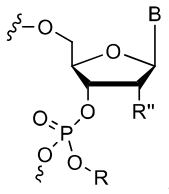
[0032] In some examples, the lipophilic monomer contains a lipophilic moiety conjugated to a strand of the compound (a single strand of a single-stranded oligonucleotide; or sense strand and/or antisense strand of a double-stranded oligonucleotide) via a carrier of:


, or

. In these examples, R is the lipophilic moiety as defined herein. R_2' is H, OH,

F, OMe, O-methoxyalkyl, O-allyl, O-N-methylacetamido, O-dimethylaminoethoxyethyl, or O-aminopropyl. B is a modified or unmodified nucleobase.

[0033] In some examples, the lipophilic monomer contains a lipophilic moiety conjugated to an internal position of a strand of the compound (a single strand of a single-

stranded oligonucleotide; or sense strand and/or antisense strand of a double-stranded oligonucleotide) via a carrier of:


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, or

, In these examples, R is the lipophilic moiety as defined herein. n is an integer of 1-21. R_2' is H, OH, F, OMe, O-methoxyalkyl, O-allyl, O-N-methylacetamido, O-dimethylaminoethoxyethyl, or O-aminopropyl. B is a modified or unmodified nucleobase.

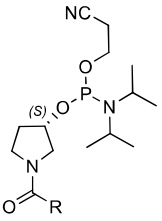
[0034] Additional examples of the lipophilic monomers can be found in the Examples.

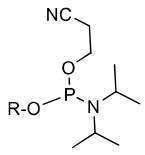
[0035] In some examples, the sense and antisense strands of the compound are each 15 to 30 nucleotides in length.

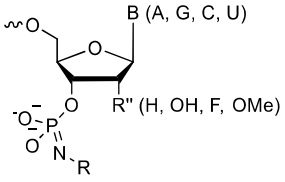
[0036] In one example, the sense and antisense strands of a compound are each 19 to 25 nucleotides in length.

[0037] In one example, the sense and antisense strands of the compound are each 21 to 23 nucleotides in length.

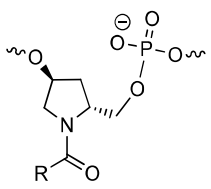
[0038] In some examples, the compound comprises a single-stranded overhang on at least one of the termini, e.g., 3' and/or 5' overhang(s) of 1-10 nucleotides in length, for instance, an overhang of 1, 2, 3, 4, 5, or 6 nucleotides. In some examples, both strands have at least one stretch of 1-5 (e.g., 1, 2, 3, 4, or 5) single-stranded nucleotides in the double stranded region. In one example, the single-stranded overhang is 1, 2, or 3 nucleotides in length. In some examples, the compound may also have a blunt end, located at the 5'-end of the antisense strand (or the 3'-end of the sense strand), or vice versa. In one example, the compound comprises a 3' overhang at the 3'-end of the antisense strand, and optionally a blunt end at the 5'-end of the antisense strand. In one example, the compound has a 5' overhang at the 5'-end of the sense strand, and optionally a blunt end at the 5'-end of the antisense strand. In one example, the compound has two blunt ends at both ends of the iRNA duplex.

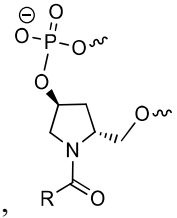


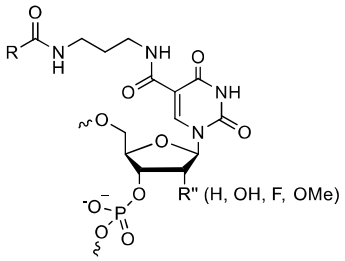
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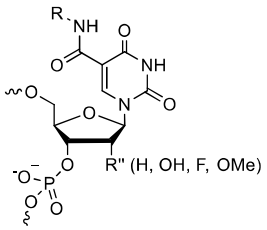
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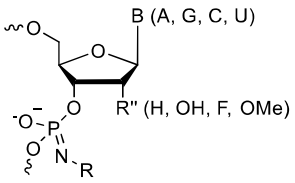
, wherein R is a ligand such as the lipophilic moiety.

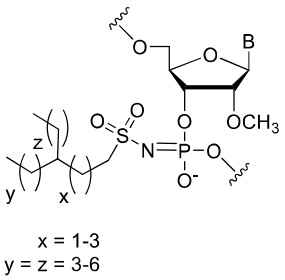
[0195] In certain embodiments, the lipophilic monomer contains a lipophilic moiety conjugated to the internal position of a strand via a carrier and/or linker. In one embodiment, the lipophilic monomer contains a lipophilic moiety conjugated to the internal position of a strand via a carrier of a formula:


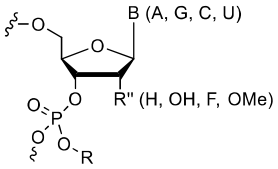
,


,


,


,


,


, or


, wherein R is a ligand such as the lipophilic moiety.

[0196] In some embodiments, the compound comprises one or more lipophilic monomers containing one or more lipophilic moieties conjugated to both ends of the sense strand.

[0197] In some embodiments, the compound comprises one or more lipophilic monomers containing one or more lipophilic moieties conjugated to both ends of the antisense strand.

[0198] In some embodiments, the compound comprises one or more lipophilic monomers containing one or more lipophilic moieties conjugated to internal position of the sense or antisense strand. In some embodiments, one or more lipophilic moieties are conjugated to the ribose, nucleobase, and/or at the internucleotide linkages. In some embodiments, one or more lipophilic moieties are conjugated to the ribose at the 2' position, 3' position, 4' position, and/or 5' position of the ribose. In some embodiments, one or more lipophilic moieties are conjugated at the nucleobase of natural (such as A, T, G, C, or U) or modified as defined herein. In some embodiments, one or more lipophilic moieties are conjugated at the phosphate or modified phosphate groups as defined herein.

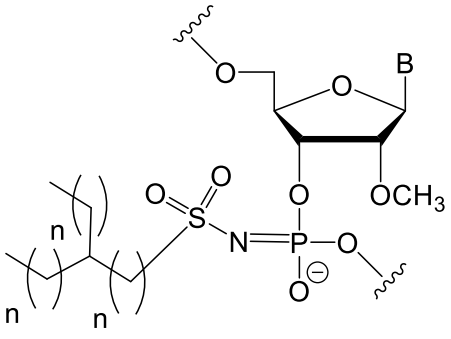
We Claim:

1. A compound comprising:

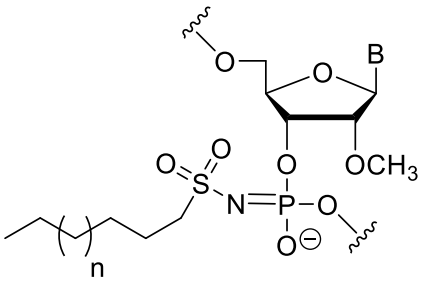
an antisense strand which is complementary to a target gene;

a sense strand which is complementary to said antisense strand; and

one or more lipophilic monomers, wherein the lipophilic monomer comprises



or



, wherein:

n is an integer of 1-21; and

B is a modified or unmodified nucleobase.

2. The compound of claim 1, wherein said sense and antisense strands are each 15 to 30 nucleotides in length.

3. The compound of claim 1, wherein said sense and antisense strands are each 19 to 25 nucleotides in length.

4. The compound of claim 1, wherein said sense and antisense strands are each 21 to 23 nucleotides in length.

5. The compound of claim 4, wherein the sense strand is 21 nucleotides in length, and the antisense strand is 23 nucleotides in length, wherein the strands form a double-stranded region of 21 consecutive base pairs having a 2-nucleotide long single-stranded overhangs at the 3’-end.

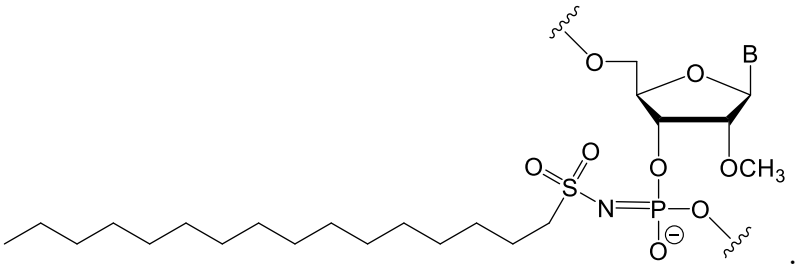
6. The compound of claim 1, wherein said compound comprises a single-stranded overhang on at least one of the termini.

7. The compound of claim 6, wherein said single-stranded overhang is 1, 2 or 3 nucleotides in length.

8. The compound of any one of claims 1-7, wherein the sense and the antisense strands comprise less than ten 2'-fluoro modified nucleotides.

9. The compound of any one of claims 1-7, wherein the sense and antisense strands comprise at least 50%, at least 60%, or least 70% of 2'-OMe modified nucleotides.

10. The compound of claim 1, wherein the lipophilic monomer is



wherein B is a modified or unmodified nucleobase.

11. The compound of any one of claims 1-10, wherein the sense strand comprises at least one phosphorothioate linkage at the 3'-end.

12. The compound of any one of claims 1-10, wherein the sense strand comprises at least two phosphorothioate linkages at the 3'-end.

13. The compound of claim 11 or 12, wherein one of the phosphorothioate linkages is located between the lipophilic monomer and the first nucleotide from the 3'-end of the sense strand.

14. The compound of any one of claims 1-13, further comprising a phosphate or phosphate mimic at the 5'-end of the antisense strand.

15. The compound of claim 14, wherein the phosphate mimic is a 5'-vinyl phosphonate (VP).

16. The compound of any one of claims 1-15, wherein the antisense strand comprises at least one GNA in the seed region.

17. The compound of claim 16, wherein the seed region is at position 5-7 from the 5'-end of the antisense strand.

18. The compound of any one of claims 1-17, further comprising a targeting ligand that targets a receptor which mediates delivery to a CNS tissue.

19. The compound of claim 18, wherein the targeting ligand is selected from the group consisting of Angiopep-2, lipoprotein receptor related protein (LRP) ligand, bEnd.3 cell binding ligand, transferrin receptor (TfR) ligand, manose receptor ligand, glucose transporter protein, and LDL receptor ligand.

20. The compound of any one of claims 1-17, further comprising a targeting ligand that targets a receptor which mediates delivery to an ocular tissue.

21. The compound of claim 20, wherein the targeting ligand is selected from the group consisting of trans-retinol, RGD peptide, LDL receptor ligand, and carbohydrate based ligands.

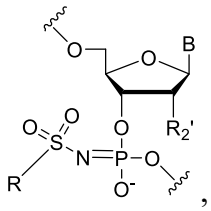
22. The compound of claim 21, wherein the targeting ligand is a RGD peptide and the RGD peptide is H-Gly-Arg-Gly-Asp-Ser-Pro-Lys-Cys-OH or Cyclo(-Arg-Gly-Asp-D-Phe-Cys).

23. A compound comprising:

an antisense strand which is complementary to a target gene;

a sense strand which is complementary to said antisense strand; and

one or more lipophilic monomers containing a lipophilic moiety conjugated to the sense strand and/or antisense strand, wherein the lipophilic monomer has a formula of



,

wherein:

R is the lipophilic moiety and wherein the lipophilic moiety contains a C_4-C_{30} hydrocarbon chain;

n is an integer of 1-21;

R_2' is H, OH, F, OMe, O-methoxyalkyl, O-allyl, O-N-methylacetamido, O-dimethylaminoethoxyethyl, or O-aminopropyl; and

B is a modified or unmodified nucleobase.

24. The compound of claim 23, wherein:

R is C_4-C_{30} alkyl; and/or

R_2' is H, F, OMe, O-N-methylacetamido, or OH.

25. The compound of any one of claims 1-24, wherein at least one lipophilic monomer is conjugated to one or more internal positions on at least one strand, wherein the internal positions include all positions, except the terminal position from each of the 3' end and 5' end of the strand, or except the terminal two positions from each of the 3' end and 5' end of the strand, or except the terminal three positions from each of the 3' end and 5' end of the strand.

26. The compound of claim 25, wherein the internal positions exclude positions 9-12, counting from the 5'-end of the sense strand, or exclude positions 11-13, counting from the 3'-end of the sense strand; and/or the internal positions exclude positions 12-14, counting from the 5'-end of the antisense strand.

27. The compound of claim 25, wherein the internal positions exclude positions 11-13 on the sense strand, counting from the 3'-end, and positions 12-14 on the antisense strand, counting from the 5'-end.

28. The compound of any one of claims 1-24, wherein at least one lipophilic monomer is located on the sense strand within the first five base pairs, first four base pairs, first three base pairs, first two base pairs, or first base pairs at the 5'-end of the antisense strand of the duplex region.

29. The compound of any one of claims 1-24, wherein one or more lipophilic monomers are located on one or more of the following internal positions: positions 4-8 and 13-18 on the sense strand, and positions 6-10 and 15-18 on the antisense strand, counting from the 5' end of each strand.

30. The compound of any one of claims 1-24, wherein one or more lipophilic monomers are located on one or more of the following internal positions: positions 5, 6, 7, 15, and 17 on the sense strand, and positions 15 and 17 on the antisense strand, counting from the 5' end of each strand.

31. The compound of claim 25, wherein the compound contains only one lipophilic monomer.

32. The compound of claim 31, wherein the one lipophilic monomer is located at position 5, 6, or 7 on the sense strand, counting from the 5' end of the strand.

33. Use of a composition comprising the compound according to any one of claims 1-32 in the manufacture of a medicament for reducing the expression of a target gene in a subject.

34. The use of claim 33, wherein the compound is to be administered extrahepatically, intrathecally, or intracerebroventricularly.

35. The use of claim 33, wherein composition is to be administered extrahepatically and reduces the expression of a target gene in a brain or spine tissue.

36. The use of claim 35, wherein:

the brain or spine tissue is selected from the group consisting of cortex, cerebellum,

cervical spine, lumbar spine, and thoracic spine; and/or

the target gene is selected from the group consisting of APP, ATXN2, C9orf72, TARDBP, MAPT(Tau), HTT, SNCA, FUS, ATXN3, ATXN1, SCA1, SCA7, SCA8, MeCP2, PRNP, SOD1, DMPK, and TTR.

37. The use of claim 33, wherein composition is to be administered extrahepatically and reduces the expression of a target gene in an ocular tissue.

38. Use of a composition comprising the compound according to any one of claims 1-32 in the manufacture of a medicament for the treatment of a subject having a CNS disorder.

39. The use of claim 38, wherein the CNS disorder is selected from the group of Alzheimer, amyotrophic lateral sclerosis (ALS), frontotemporal dementia, Huntington, Parkinson, spinocerebellar, prion, and lafora.

40. A composition comprising the compound according to any one of claims 1-32 for use in therapy.