

CLAIMS

1. An siRNA, comprising a sense strand and an antisense strand forming a double-stranded region, wherein:

the sense strand comprises at least 15 contiguous nucleotides and differs from SEQ ID NO: 24 by no more than 3 nucleotides;

the antisense strand comprises at least 15 contiguous nucleotides and differs from SEQ ID NO: 46 by no more than 3 nucleotides.

2. The siRNA according to claim 1, wherein:

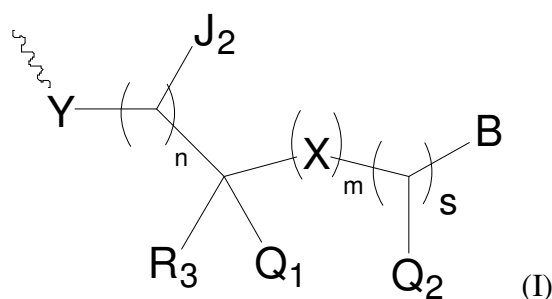
the sense strand comprises at least 17 contiguous nucleotides of SEQ ID NO: 24;

the antisense strand comprises at least 19 contiguous nucleotides of SEQ ID NO: 46.

3. The siRNA according to claim 1 or 2, comprising a sense strand set forth in SEQ ID NO: 24 and an antisense strand set forth in SEQ ID NO: 46.

4. The siRNA according to any one of the preceding claims, wherein at least one nucleotide in the sense and/or antisense strand is a modified nucleotide.

5. The siRNA according to any one of the preceding claims, wherein the antisense strand comprises a chemical modification of formula (I) or a tautomeric modification thereof in at least one nucleotide at positions 2 to 8 of the 5' region thereof:



wherein: Y is selected from the group consisting of O, NH, and S;

each X is independently selected from the group consisting of CR₄(R₄'), S, NR₅, and NH-CO, wherein R₄, R₄', and R₅ are each independently H or C₁-C₆ alkyl;

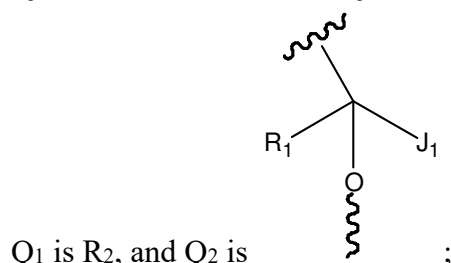
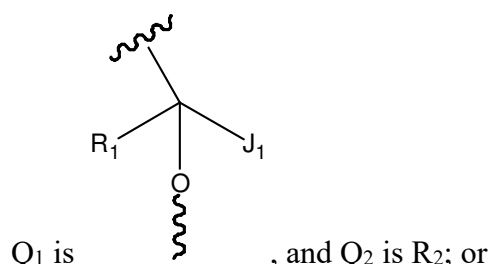
J₂ is H or C₁-C₆ alkyl;

n = 0, 1, or 2;

m = 0, 1, or 2;

s = 0 or 1;

R₃ is selected from the group consisting of H, OH, halogen, NH₂, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₂-C₆ alkenyl, C₂-C₆ alkynyl, S-CH₃, NCH₃(CH₃), OCH₂CH₂OCH₃, -O-alkylamino, and (CH₂)_pR₆, wherein R₆ is selected from the group consisting of OH, halogen, methoxy, ethoxy, N₃, C₂-C₆ alkenyl, and C₂-C₆ alkynyl, and p = 1, 2, or 3;



wherein:

R₁ is selected from the group consisting of H, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₂-C₆ alkenyl, C₂-C₆ alkynyl, and (CH₂)_qR₇, wherein R₇ is selected from the group consisting of OH, halogen, methoxy, ethoxy, N₃, C₂-C₆ alkenyl, and C₂-C₆ alkynyl, and q = 1, 2, or 3;

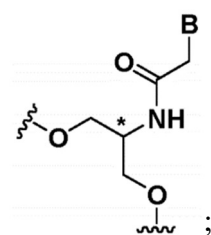
J₁ is H or C₁-C₆ alkyl;

R₂ is selected from the group consisting of H, OH, halogen, NH₂, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₂-C₆ alkenyl, C₂-C₆ alkynyl, S-CH₃, NCH₃(CH₃), OCH₂CH₂OCH₃, -O-alkylamino, and (CH₂)_rR₈, wherein R₈ is selected from the group consisting of OH, halogen, methoxy, ethoxy, N₃, C₂-C₆ alkenyl, and C₂-C₆ alkynyl, and r = 1, 2, or 3;

optionally, R₁ and R₂ are directly connected to form a ring;

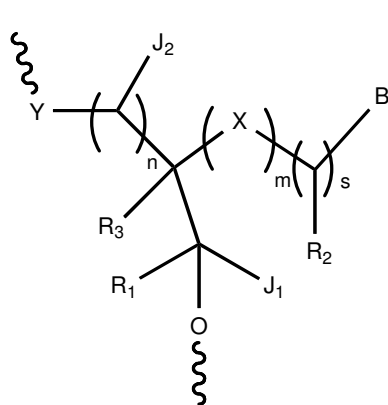
B is a base;

wherein: the chemical modification of formula (I) or the tautomeric modification thereof is not

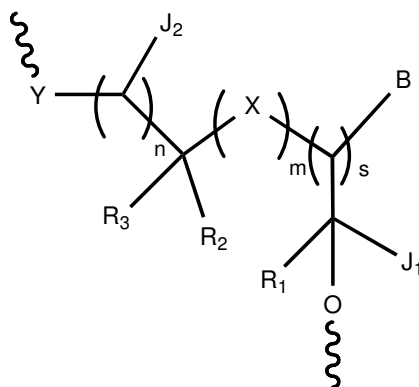


preferably, when X is NH-CO, R₁ is not H.

6. The siRNA according to any one of the preceding claims, wherein the antisense strand comprises a chemical modification of formula (I-1) or formula (I-2) or a tautomeric modification thereof in at least one of nucleotide positions 2 to 8 of the 5' region thereof:



formula (I-1)



formula (I-2).

7. The siRNA according to claim 6, wherein in formula (I-1) and formula (I-2),

Y is O or NH;

each X is independently selected from the group consisting of NH-CO, CH₂, and NH;

n = 0 or 1;

m = 0 or 1;

s = 0 or 1;

J₁ and J₂ are each independently H;

R₁ is selected from the group consisting of H, methyl, and CH₂OH;

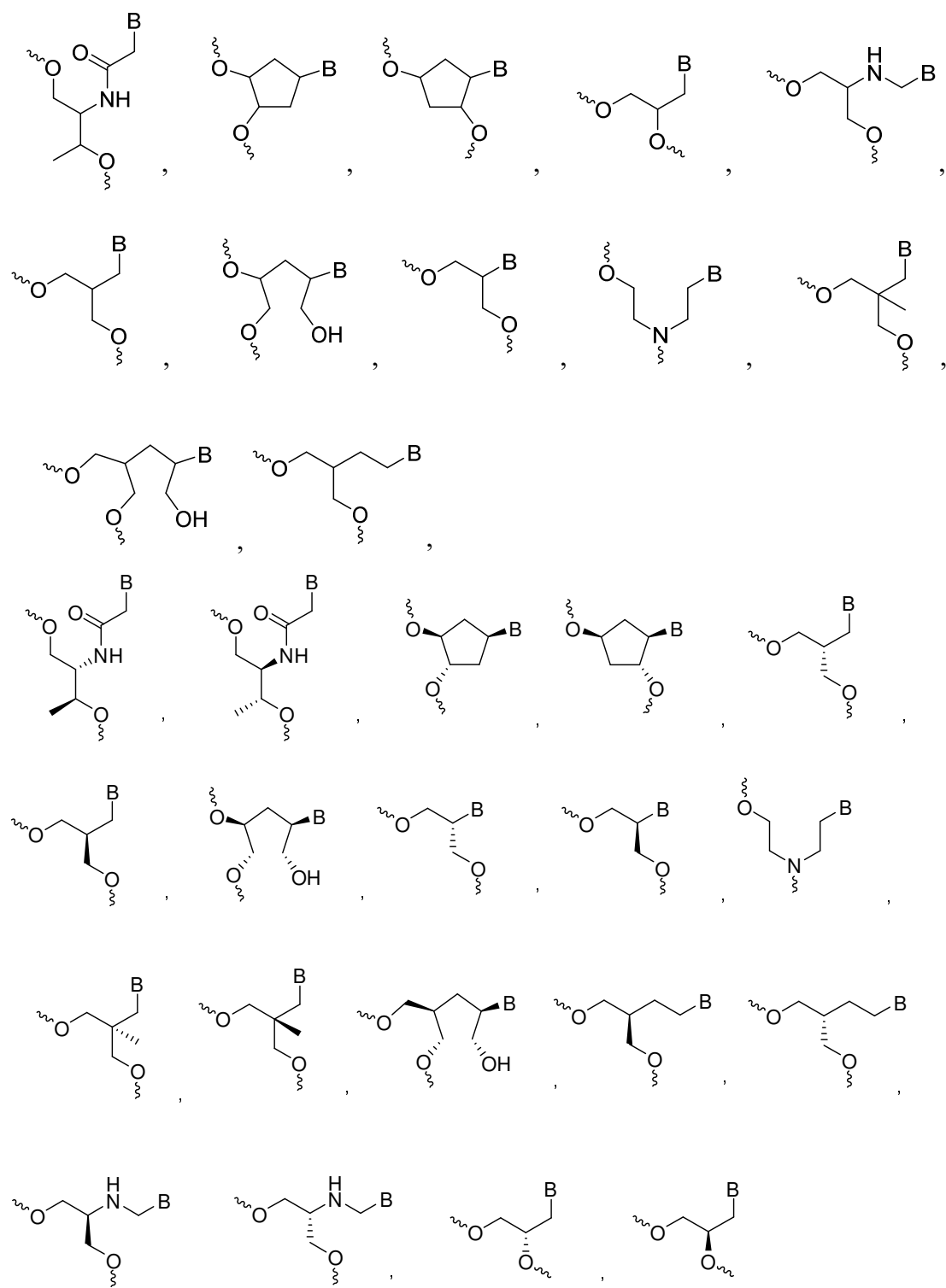
R₂ is selected from the group consisting of H, OH, NH₂, methyl, and CH₂OH;

R₃ is selected from the group consisting of H, OH, NH₂, methyl, and CH₂OH;

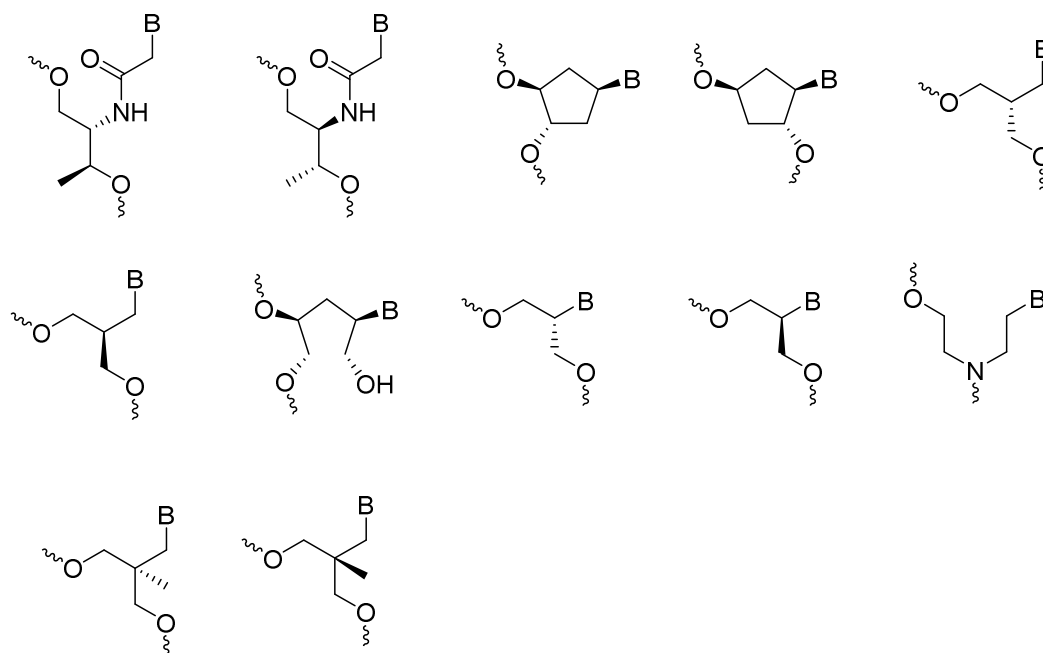
optionally, R₁ and R₂ are directly connected to form a ring;

preferably, each B is independently selected from the group consisting of bases at nucleotide positions 2 to 8 of the 5' region of the antisense strand containing the chemical modification of formula (I-1).

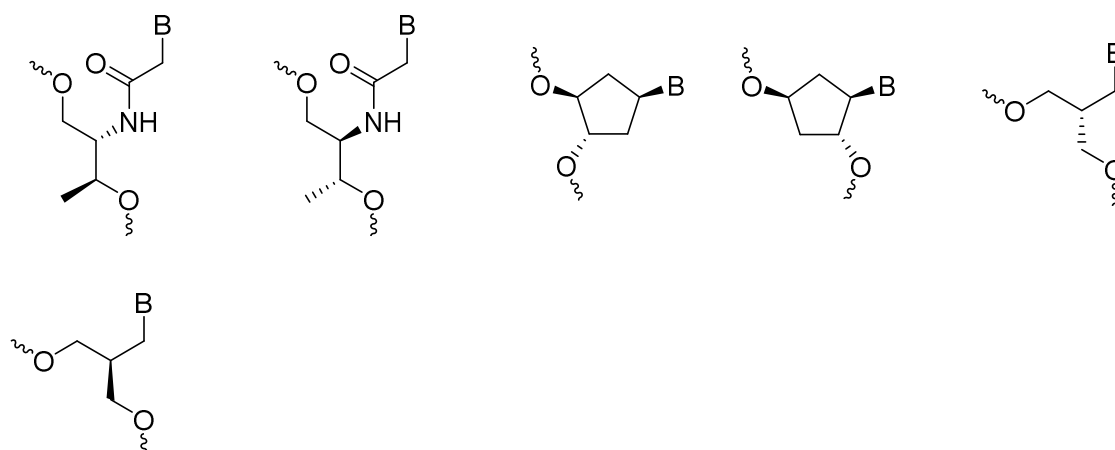
8. The siRNA according to any one of claims 5 to 7, wherein the chemical modification of formula (I) is selected from the group consisting of:



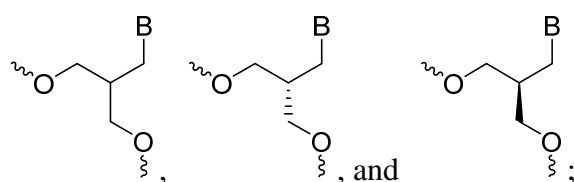
preferably, the chemical modification of formula (I) is selected from the group consisting of:



more preferably, the chemical modification of formula (I) is selected from the group consisting of:



further preferably, the chemical modification of formula (I) is selected from the group consisting of:



preferably, each B is independently selected from the group consisting of bases at nucleotide positions 2 to 8 of the 5' region of the antisense strand containing the chemical modification of formula (I-1).

9. The siRNA according to any one of the preceding claims, wherein the antisense strand comprises the chemical modification of formula (I) or the tautomeric modification thereof as defined in any one of claims 5 to 8 at position 5, 6, or 7 of the 5' region thereof;

when the chemical modification of formula (I) or the tautomeric modification thereof is at position 5 of the 5' region, B is a base at position 5 of the 5' region of the antisense strand;
when the chemical modification of formula (I) or the tautomeric modification thereof is at position 6 of the 5' region, B is a base at position 6 of the 5' region of the antisense strand;
when the chemical modification of formula (I) or the tautomeric modification thereof is at position 7 of the 5' region, B is a base at position 7 of the 5' region of the antisense strand.

10. The siRNA according to any one of the preceding claims, wherein the nucleotide sequence of the antisense strand comprises or is SEQ ID NO: 68.

11. The siRNA according to any one of the preceding claims, wherein at least one phosphoester group in the sense strand and/or the antisense strand is a modified phosphoester group, preferably a phosphorothioate group.

12. An siRNA conjugate, comprising:
the siRNA according to any one of claims 1 to 11, and
a targeting ligand linked to the end of the siRNA;
wherein preferably, the targeting ligand is linked to the 3' end of the sense strand of the siRNA.

13. The siRNA conjugate according to claim 12, wherein:
the targeting ligand comprises at least one targeting moiety, and
the targeting moieties are each independently selected from the group consisting of: galactose, galactosamine, *N*-formyl-galactosamine, *N*-acetyl-galactosamine, *N*-propionyl-galactosamine, *N*-*n*-butyryl-galactosamine, and *N*-isobutyryl-galactosamine;
preferably, the targeting moiety is *N*-acetyl-galactosamine;
more preferably, the targeting ligand comprises three targeting moieties.

14. A pharmaceutical composition, comprising:
the siRNA according to any one of claims 1 to 11 or the siRNA conjugate according to any one of claims 12 to 13, and
a pharmaceutically acceptable carrier.

15. Use of the siRNA according to any one of claims 1 to 11 or the siRNA conjugate according to any one of claims 12 to 13, or the pharmaceutical composition according to claim 14 in the manufacture of a medicament for treating or preventing a disease related to 17 β -hydroxysteroid dehydrogenase type 13 (HSD17B13) gene expression in a subject.

16. The use according to claim 15, wherein the medicament causes inhibition of the HSD17B13 gene expression.

17. The use according to claim 15 or 16, wherein the disease related to HSD17B13 gene expression is chronic fibro-inflammatory liver disease.

18. The use according to claim 17, wherein the chronic fibro-inflammatory liver disease is related to the accumulation and/or expansion of lipid droplets in the liver.

19. Use of the siRNA according to any one of claims 1 to 11 or the siRNA conjugate according to any one of claims 12 to 13, or the pharmaceutical composition according to claim 14 in the manufacture of a medicament for treating or preventing a disease, wherein the disease is selected from the group consisting of hepatitis, liver fibrosis, nonalcoholic steatohepatitis, nonalcoholic fatty liver disease, cirrhosis, alcoholic steatohepatitis, alcoholic fatty liver disease, HCV-associated cirrhosis, drug-induced liver injury, and hepatic necrosis.

20. Use of the siRNA according to any one of claims 1 to 11 or the siRNA conjugate according to any one of claims 12 to 13, or the pharmaceutical composition according to claim 14 in the manufacture of a medicament for reducing the risk of developing chronic liver disease in an individual suffering from steatosis, for inhibiting the progression of steatosis to steatohepatitis in an individual with steatosis, or for inhibiting the accumulation of lipid droplets in the liver.

21. Use of the siRNA according to any one of claims 1 to 11 or the siRNA conjugate according to any one of claims 12 to 13, or the pharmaceutical composition according to claim 14 in the manufacture of a medicament for treating or preventing a disease defined in any one of claims 15 to 20, wherein the siRNA is to be delivered to a liver of a subject *in vivo*.

22. A method for preparing an siRNA or siRNA conjugate, comprising:
synthesizing the siRNA according to any one of claims 1 to 11 or the siRNA conjugate according to any one of claims 12 to 13.