

Claims

1. A double-stranded ribonucleic acid (dsRNA) agent for inhibiting expression of Hepatitis B virus (HBV) in a cell, wherein the dsRNA agent comprises a sense strand and an antisense strand, and optionally a targeting ligand, wherein the nucleotide positions 2 to 18 in the antisense strand comprises a region substantially complementary to an HBV RNA transcript, and wherein the antisense strand comprises a region of complementarity to the HBV RNA transcript which comprises at least 15, 16, 17, 18, or 19 contiguous nucleotides that differ by 0, 1, 2, or 3 nucleotides from one of the antisense sequences listed in one of Tables 1-4.
2. The dsRNA agent of claim 1, wherein the dsRNA agent comprises a sense strand sequence set forth in any one of Tables 1-4, wherein the sense strand sequence is at least substantially or fully complementary to the antisense strand sequence in the dsRNA agent.
3. The dsRNA agent of claim 1, wherein the dsRNA agent comprises an antisense strand sequence set forth in any one of Tables 1-4.
4. The dsRNA agent of claim 1, wherein the dsRNA agent comprises the sequences set forth as a duplex sequence in any of Tables 1-4.
5. The dsRNA of claim 1, wherein the dsRNA agent comprises at least one modified nucleotide, and optionally wherein
all or substantially all of the nucleotides of the antisense strand are modified nucleotides, and optionally all or substantially all of the nucleotides of the sense strand and the antisense strand are modified nucleotides, and preferably the at least one modified nucleotide is independently selected from the group consisting of: 2'-O-methyl nucleotide, 2'-Fluoro nucleotide, 2'-deoxy nucleotide, 2'3'-seco nucleotide mimic, locked nucleotide, unlocked nucleic acid nucleotide (UNA), glycol nucleic acid nucleotide (GNA), 2'-F-Arabino nucleotide, 2'-methoxyethyl nucleotide, abasic nucleotide, ribitol, inverted nucleotide, inverted abasic nucleotide, inverted 2'-OMe nucleotide, inverted 2'-deoxy nucleotide, 2'-amino-modified nucleotide, 2'-alkyl-modified nucleotide, morpholino nucleotide, 3'-OMe nucleotide, a nucleotide comprising a 5'-phosphorothioate group, a terminal nucleotide linked to a cholesteryl derivative or dodecanoic acid bisdecylamide group, a 2'-amino-modified nucleotide, a phosphoramidate, a non-natural base comprising nucleotide, or an E-vinylphosphonate nucleotide at the 5' end of the antisense strand, or

the sense strand is a modified sense strand sequence set forth in one of Tables 2-4, and optionally the antisense strand is a modified antisense strand sequence set forth in one of Tables 2-4.

6. The dsRNA agent of claim 1, wherein the dsRNA agent comprises at least one phosphorothioate internucleoside linkage, and optionally wherein

the sense strand comprises at least one phosphorothioate internucleoside linkage, preferably, the sense strand comprises 1, 2, 3, 4, 5, or 6, phosphorothioate internucleoside linkages; or

the antisense strand comprises at least one phosphorothioate internucleoside linkage, preferably, the antisense strand comprises 1, 2, 3, 4, 5, or 6, phosphorothioate internucleoside linkage.

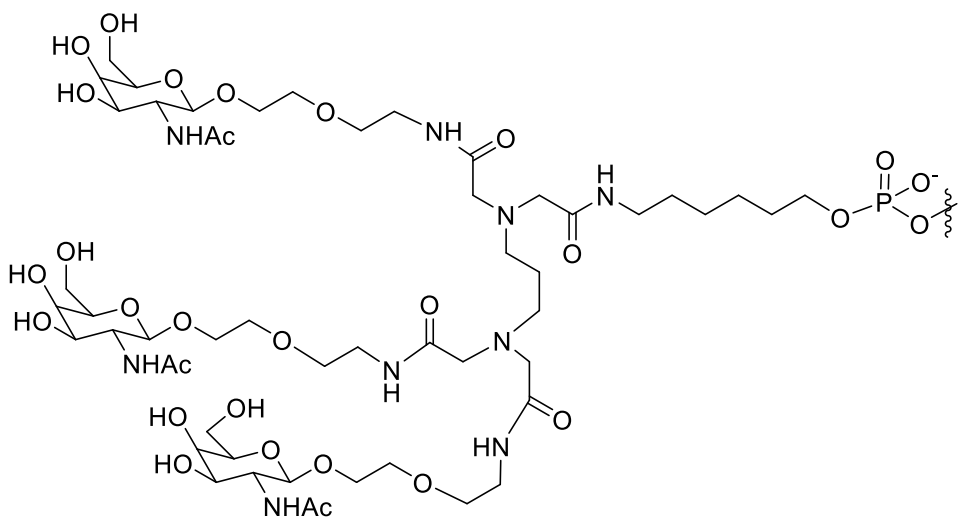
7. The dsRNA agent of claim 1, wherein the sense strand is complementary or substantially complementary to the antisense strand for a region of 16-23 or 19-21 nucleotides in length.

8. The dsRNA agent of claim 1, wherein each strand is no more than 30, 25 or 23 nucleotides in length.

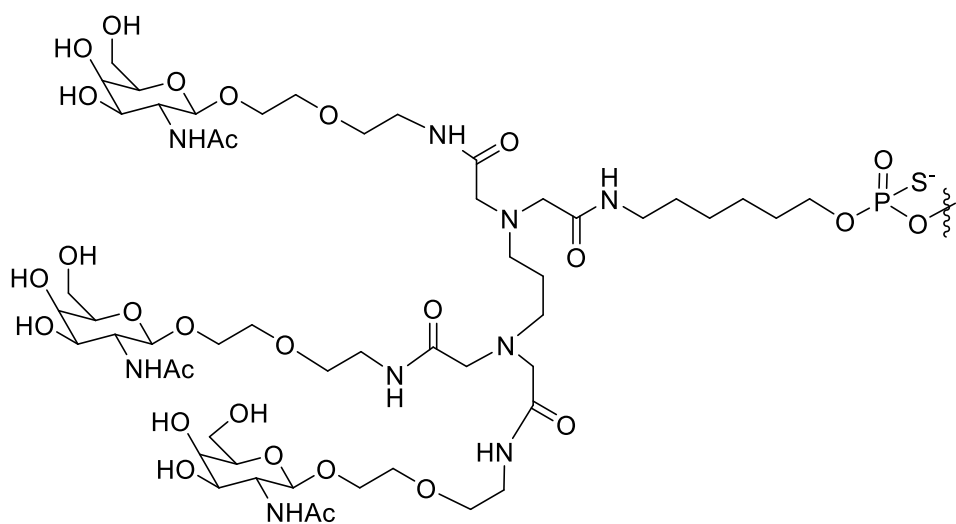
9. The dsRNA agent of claim 1, wherein the dsRNA agent comprises at least one modified nucleotide and further comprises one or more targeting groups or linking groups, and optionally the one or more targeting groups or linking groups are conjugated to the sense strand, preferably,

wherein the targeting group or linking group comprises N-acetyl-galactosamine (GalNAc),

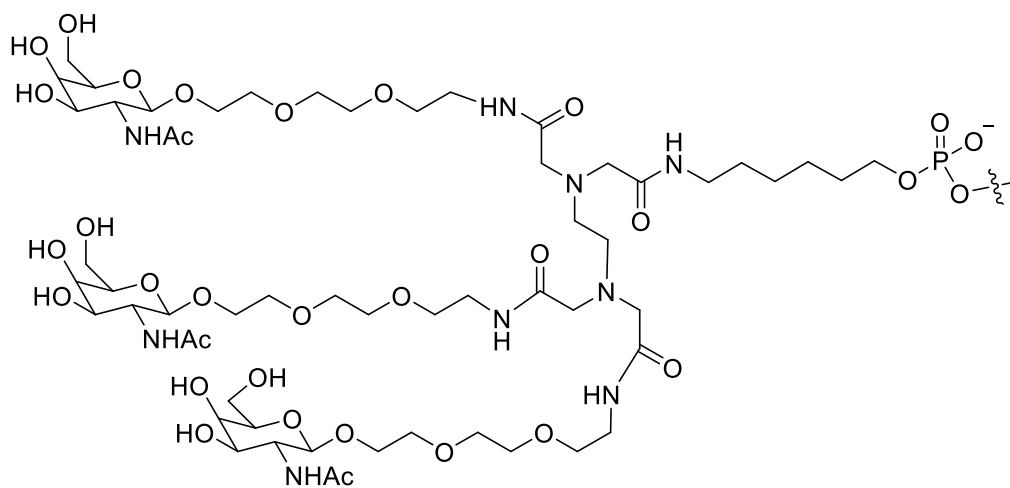
wherein the targeting group has a structure:



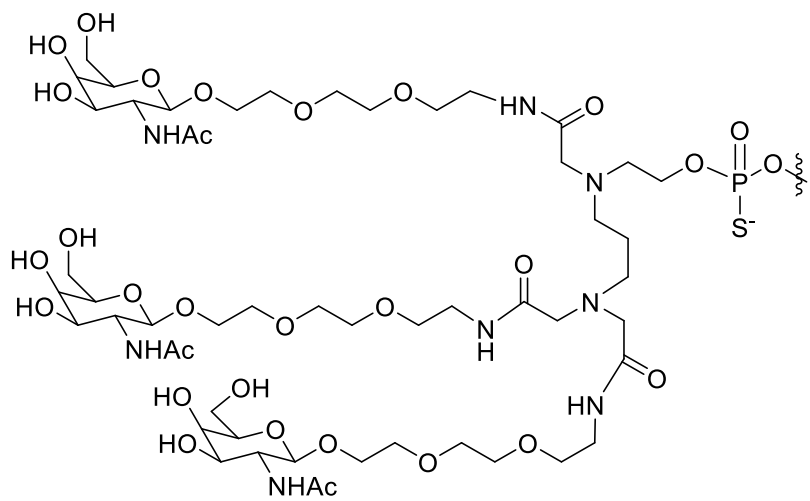
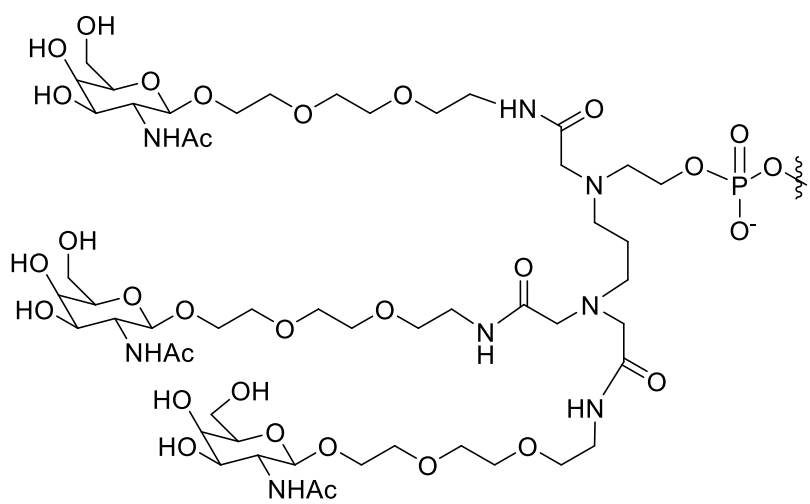
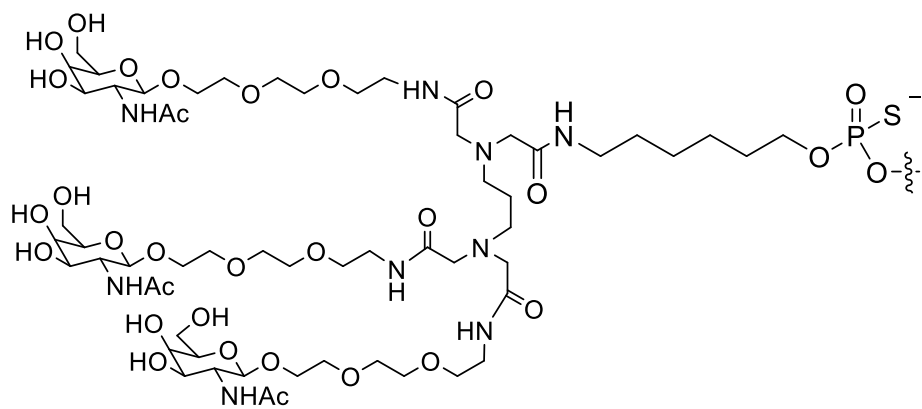
GLO-1,

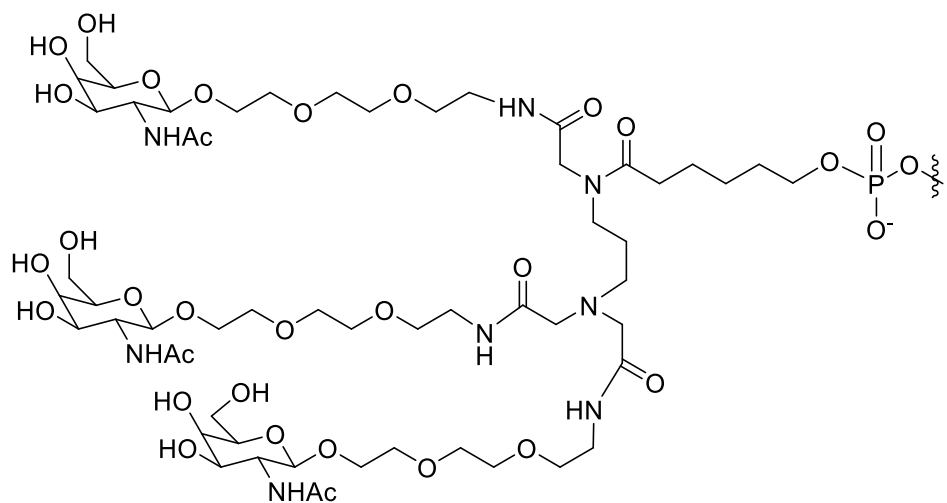


GLS-1,

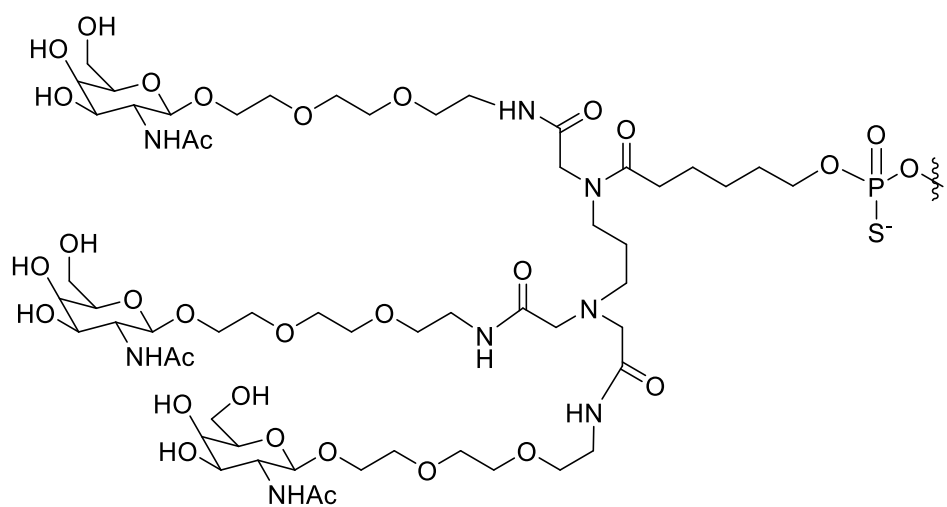


GLO-2,

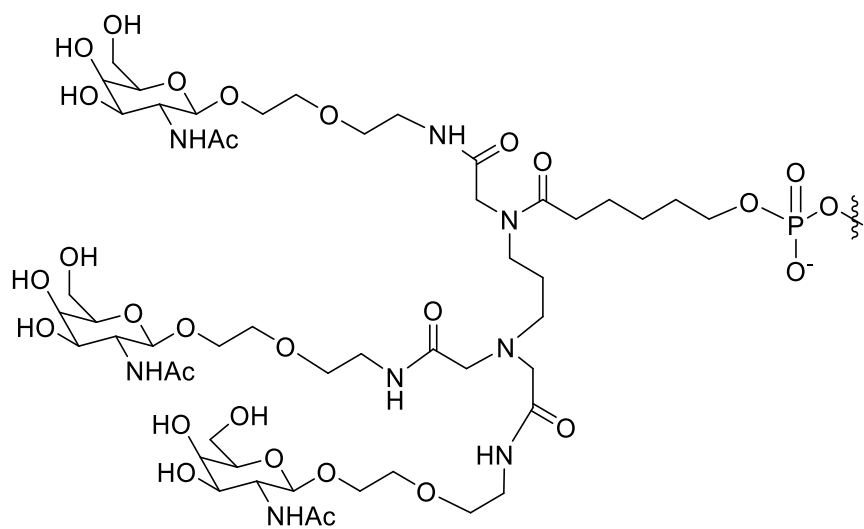




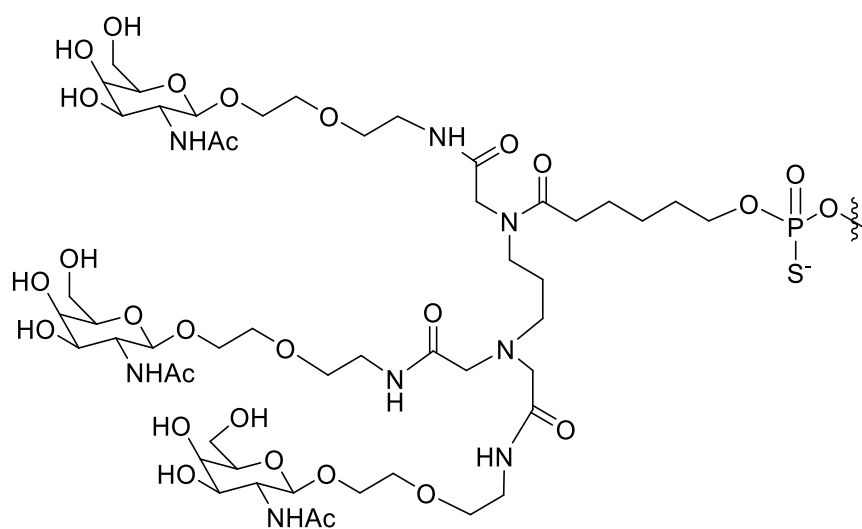
GLO-4,



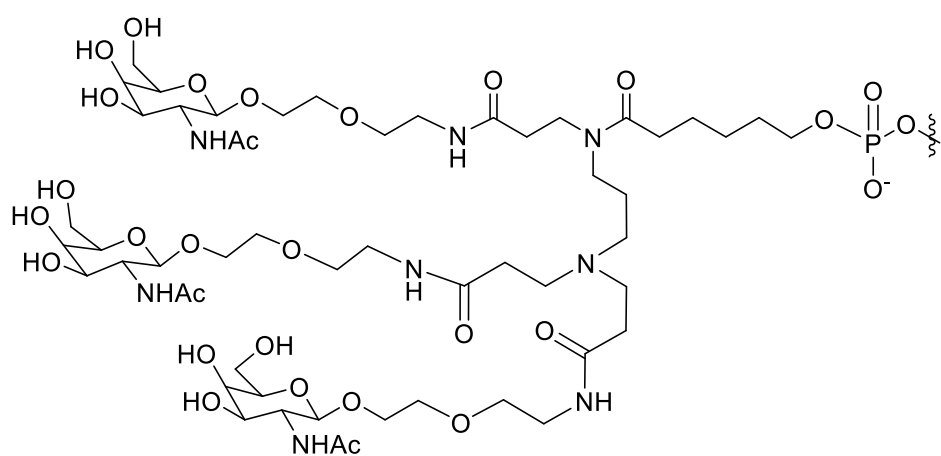
GLS-4,



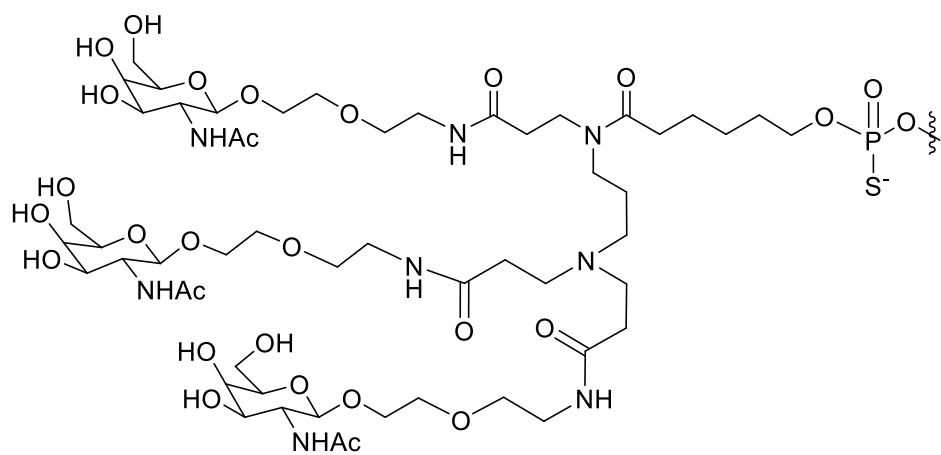
GLO-5,



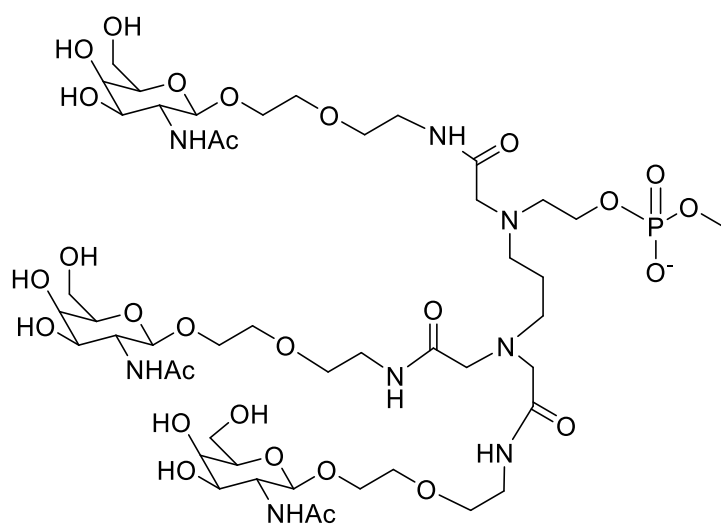
GLS-5,



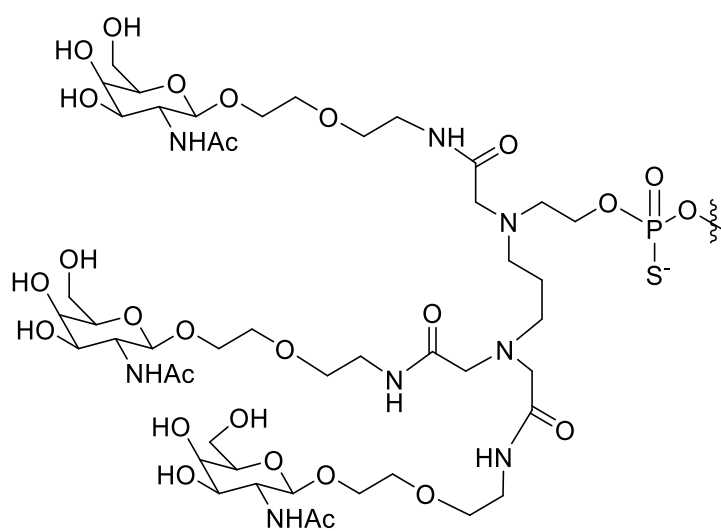
GLO-6,



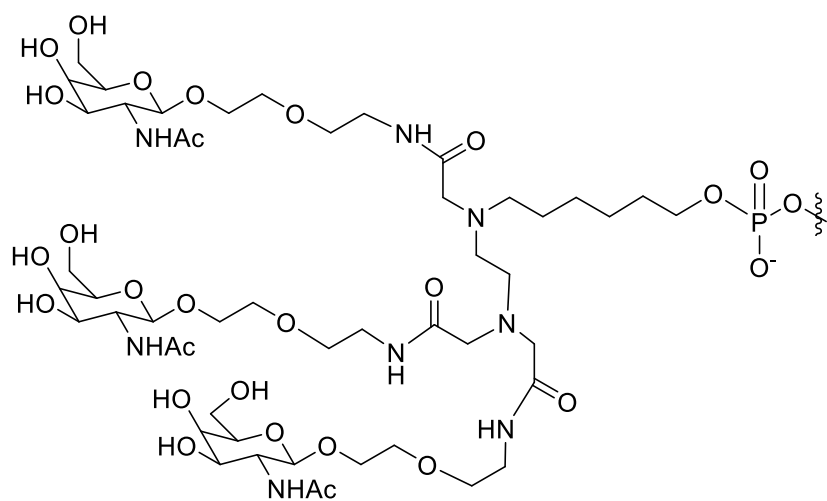
GLS-6,



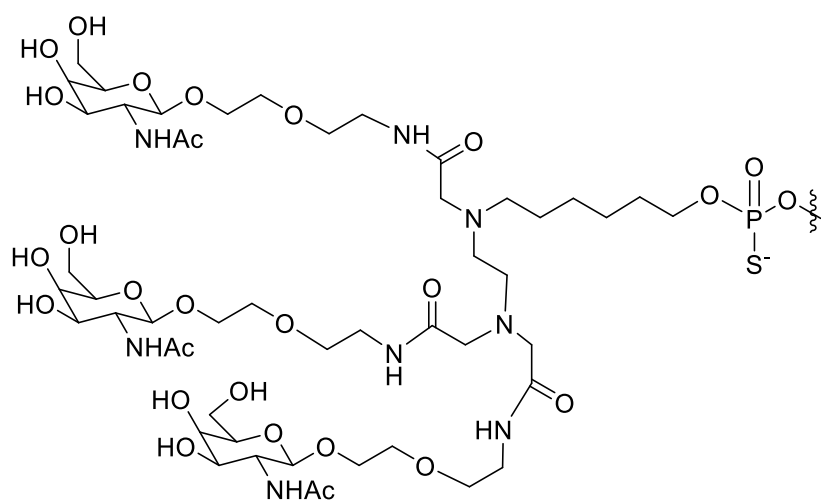
GLO-7,



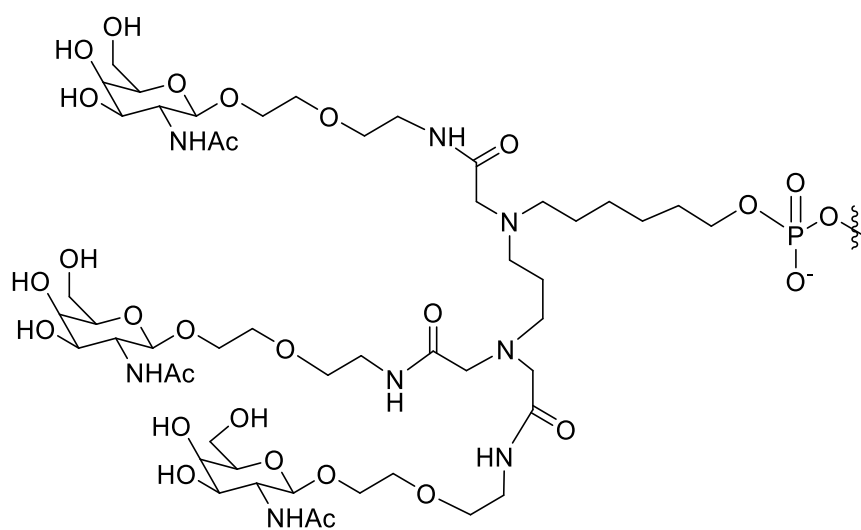
GLS-7,



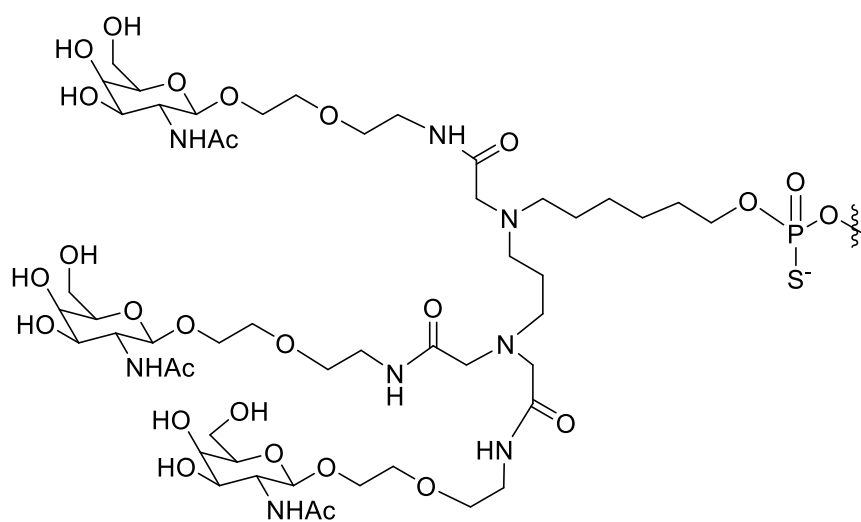
GLO-8,



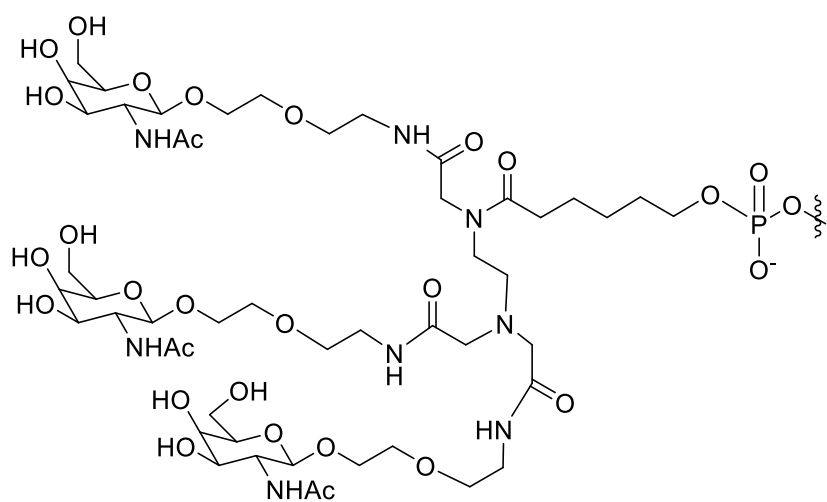
GLS-8,



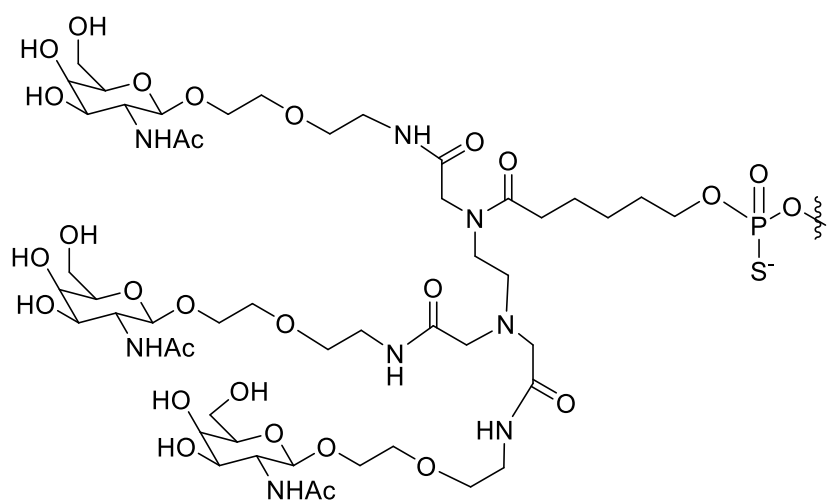
GLO-9,



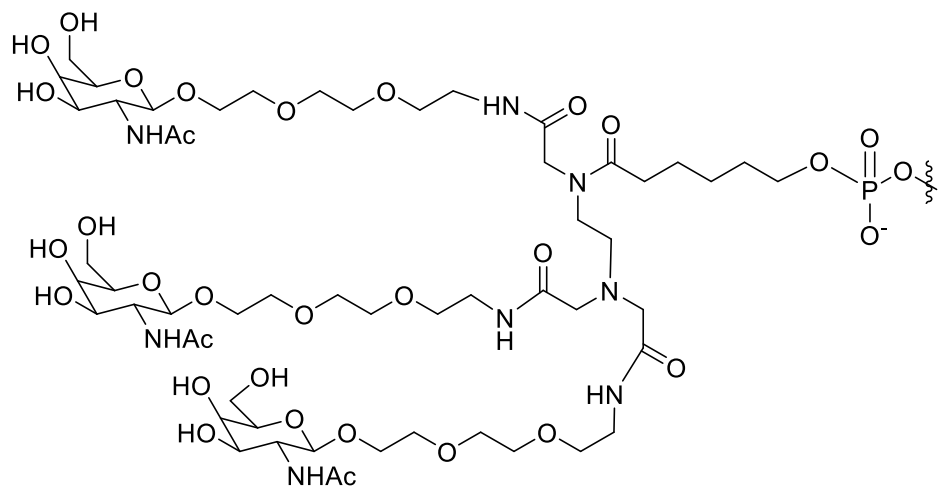
GLS-9,



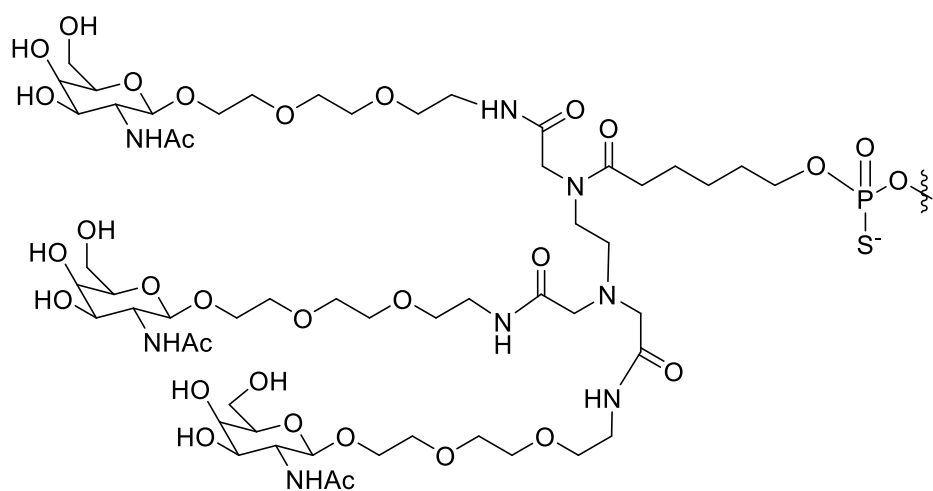
GLO-10,



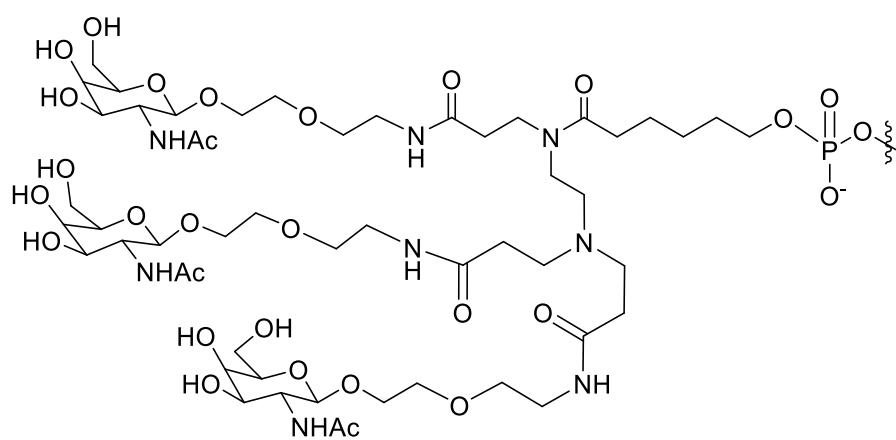
GLS-10,



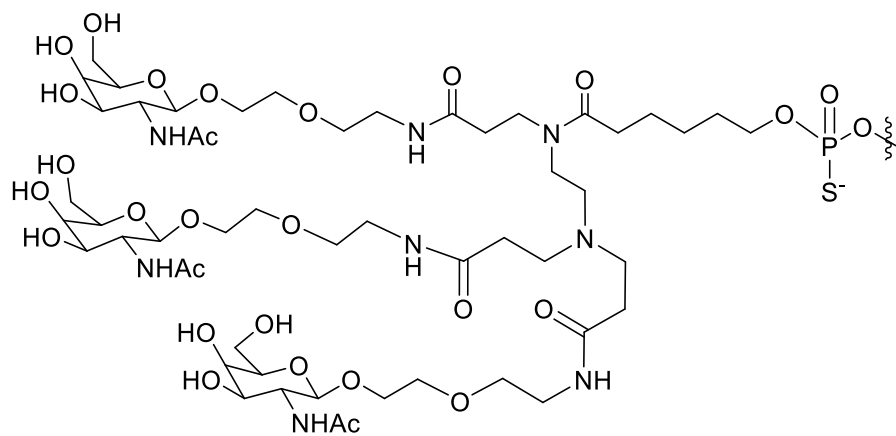
GLO-11,



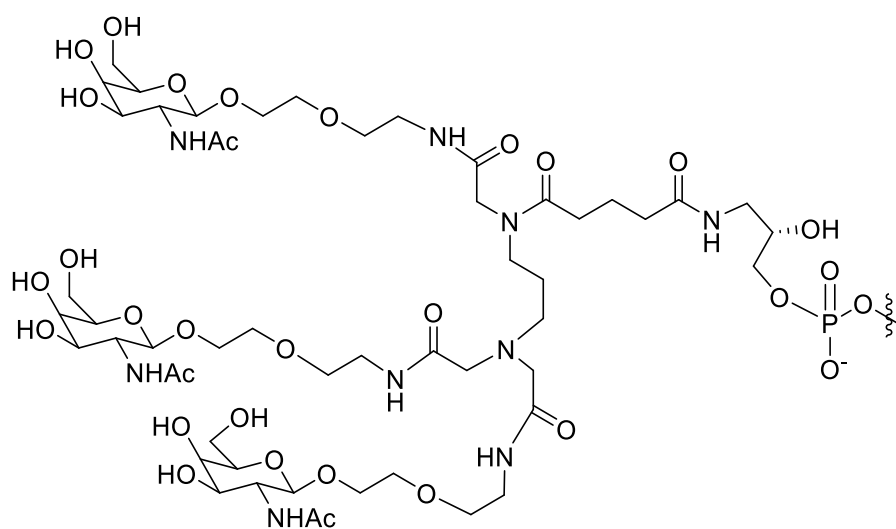
GLS-11,



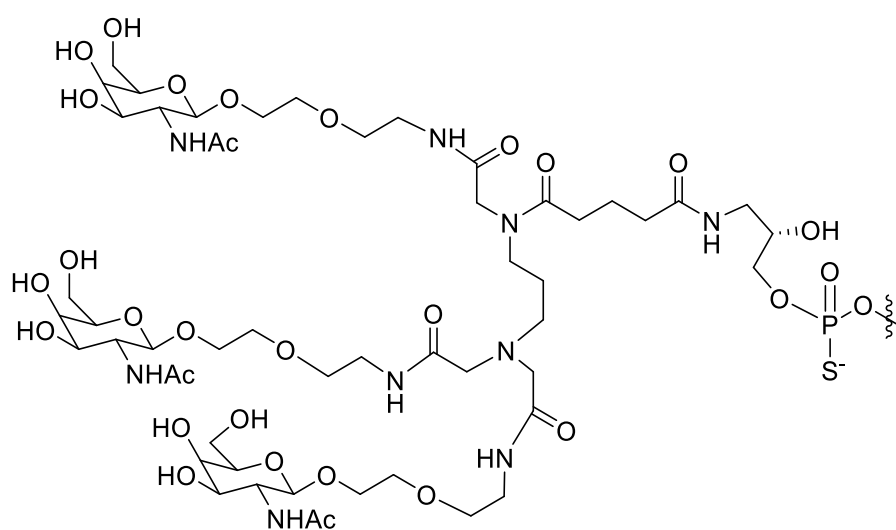
GLO-12,



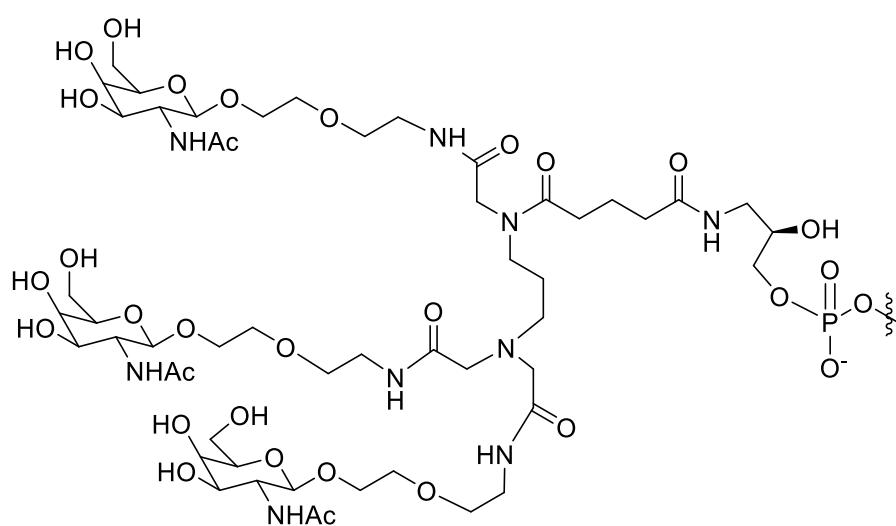
GLS-12,



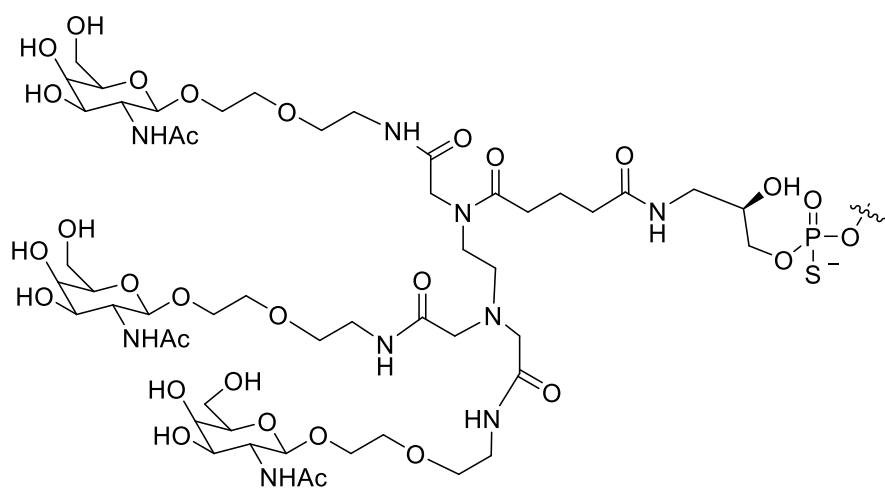
GLO-13,



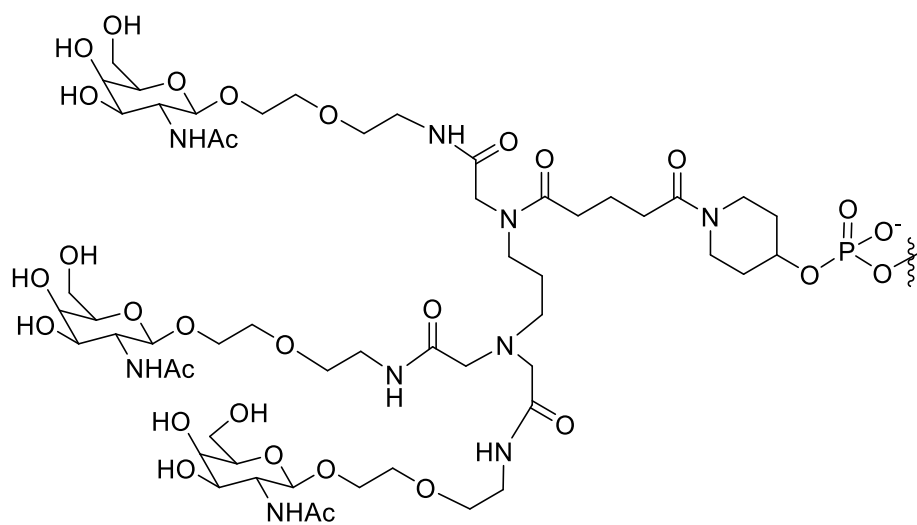
GLS-13,



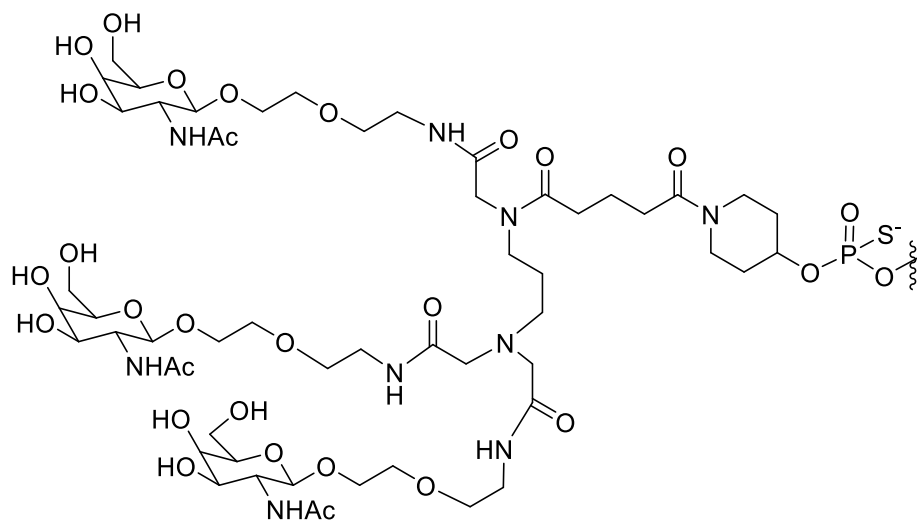
GLO-14,



GLS-14,



GLO-15,



GLS-15,

14. The dsRNA agent of claim 1, wherein the antisense strand comprises one of: SEQ ID NO: 419, 428, 433, 438, 442, 444, 445, 469, 582, 592, 594, 596, 597, 598, 585, 588, 642, 663-672 or 922-925, preferably, SEQ ID NO: 582, 642, 666, 922, 923 or 925.

15. The dsRNA agent of claim 1, wherein the dsRNA agent comprises SEQ ID NO: 281 and SEQ ID NO: 419; SEQ ID NO: 290 and SEQ ID NO: 428; SEQ ID NO: 295 and SEQ ID NO: 433; SEQ ID NO: 300 and SEQ ID NO: 438; SEQ ID NO: 304 and SEQ ID NO: 442; SEQ ID NO: 306 and SEQ ID NO: 444; SEQ ID NO: 307 and SEQ ID NO: 445; SEQ ID NO: 331 and SEQ ID NO: 469; SEQ ID NO: 557 and SEQ ID NO: 582; SEQ ID NO: 567 and SEQ ID NO: 592; SEQ ID NO: 569 and SEQ ID NO: 594; SEQ ID NO: 571 and SEQ ID NO: 596; SEQ ID NO: 572 and SEQ ID NO: 597; SEQ ID NO: 573 and SEQ ID NO: 598; SEQ ID NO: 560 and SEQ ID NO: 585; SEQ ID NO: 563 and SEQ ID NO: 588; SEQ ID NO: 607 and SEQ ID NO: 642; SEQ ID NO: 628 and SEQ ID NO: 663; SEQ ID NO: 629 and SEQ ID NO: 664; SEQ ID NO: 630 and SEQ ID NO: 665; SEQ ID NO: 631 and SEQ ID NO: 666; SEQ ID NO: 632 and SEQ ID NO: 667; SEQ ID NO: 633 and SEQ ID NO: 668; SEQ ID NO: 634 and SEQ ID NO: 669; SEQ ID NO: 635 and SEQ ID NO: 670; SEQ ID NO: 636 and SEQ ID NO: 671; or SEQ ID NO: 637 and SEQ ID NO: 672, SEQ ID NO: 918 and SEQ ID NO: 922, SEQ ID NO: 919 and SEQ ID NO: 923, SEQ ID NO: 920 and SEQ ID NO: 924, or SEQ ID NO: 921 and SEQ ID NO: 925; preferably, SEQ ID NO: 557 and SEQ ID NO: 582; SEQ ID NO: 607 and SEQ ID NO: 642, SEQ ID NO: 631 and SEQ ID NO: 666, SEQ ID NO: 918 and SEQ ID NO: 922, SEQ ID NO: 919 and SEQ ID NO: 923, or SEQ ID NO: 921 and SEQ ID NO: 925.

16. A composition comprising one, two, three, or more dsRNA agents of any one of claims 1-15.

17. A cell comprising the dsRNA agent of any one of claims 1-15.

18. The cell of claim 17, wherein the cell is a mammalian cell, optionally a human cell.

19. The double-stranded ribonucleic acid (dsRNA) agents of any one of claims 1-15 or a composition of claim 16 for use in inhibiting the expression of a hepatitis B virus (HBV) gene in a cell, comprising:

(i) preparing a cell comprising an effective amount of one or more double-stranded ribonucleic acid (dsRNA) agents of any one of claims 1-15 or a composition of claim 16;

and optionally comprising (ii) maintaining the cell of (i) for a time sufficient to obtain degradation of the mRNA transcript of an HBV gene, thereby inhibiting expression of the HBV gene in the cell, inhibiting replication of the HBV in the cell, and reducing a level of the HBV antigens in the cell; and preferably, the cell is in a subject and the dsRNA agent is administered to the subject subcutaneously or by IV administration, and optionally, following the administration of the dsRNA agent(s) to the subject, further comprises assessing inhibition of the HBV gene in a way of

(a) determining one or more physiological characteristics of an HBV-associated disease or condition in the subject, and

(b) comparing the determined physiological characteristic(s) to a baseline pre-treatment physiological characteristic of the HBV-associated disease or condition and/or to a control physiological characteristic of the HBV-associated disease or condition, wherein the comparison indicates one or more of a presence or absence of inhibition of expression of the HBV gene in the subject, and preferably the determined physiological characteristic in the subject is one or more of: a level of alanine aminotransferase (ALT) in the subject, a level of aspartate aminotransferase (AST) in the subject; an HBV viral load in the subject; HBV covalently closed circular DNA (cccDNA) level in the subject; a level of one or more HBV antigens in the subject; a level of one or more of HBcAg, HBsAg and HBeAg in the subject; presence, absence, and/or a level of one or more anti-Hepatitis B virus antibodies in the subject.

20. The double-stranded ribonucleic acid (dsRNA) agents of any one of claims 1-15 or a composition of claim 16 for use in inhibiting expression of an HBV gene in a subject, comprising administering to the subject an effective amount of one or more double-stranded ribonucleic acid (dsRNA) agents of any one of claims 1-15 or a composition of claim 16, and optionally, the dsRNA agent is administered to the subject subcutaneously or by IV administration,

and optionally further comprises assessing inhibition of the HBV gene, following the administration of the one or more dsRNA agents, wherein a means for the assessing comprises:

(i) determining one or more physiological characteristics of an HBV-associated disease or condition in the subject, and

(ii) comparing the determined physiological characteristic(s) to a baseline pre-treatment physiological characteristic of the HBV-associated disease or condition and/or to a control physiological characteristic of the HBV-associated disease or condition, wherein the comparison indicates one or more of a presence or absence of inhibition of expression of the HBV gene in the subject, and preferably the determined physiological characteristic in the subject is one or more of: a level of alanine aminotransferase (ALT) in the subject, a level of aspartate aminotransferase (AST) in the subject; an HBV viral load in the subject; HBV covalently closed circular DNA (cccDNA) level in the subject; a level of one or more HBV antigens in the subject; a level of one or more of: HBcAg, HBsAg and HBeAg in the subject; presence, absence, and/or a level of one or more anti-Hepatitis B virus antibodies in the subject.

21. The double-stranded ribonucleic acid (dsRNA) agents of any one of claims 1-15 or a composition of claim 16 for use in treating a disease or condition associated with the presence of a hepatitis B virus (HBV) protein, comprising administering to a subject an effective amount of one or more double-stranded ribonucleic acid (dsRNA) agents of any one of claims 1-15, or a composition of claim 16, to inhibit expression of the HBV gene encoding the HBV protein, preferably wherein the disease or condition is one or more of: hepatitis B, chronic hepatitis B, hepatitis D virus infection (delta hepatitis or HDV), liver injury, cirrhosis, acute hepatitis B, acute fulminant hepatitis, liver inflammation, liver fibrosis, and hepatocellular carcinoma, and optionally further comprises administering an additional therapeutic regimen to the subject, and preferably wherein the additional therapeutic regimen comprises: administering to the subject one or more: HBV antisense polynucleotides, additional HBV dsRNA therapeutic agent, a non-HBV dsRNA therapeutic agent, a HBV non-dsRNA therapeutic agent, and a behavioral modification.