

Claims

1. A double-stranded ribonucleic acid (dsRNA) agent, wherein the dsRNA agent comprises: a sense strand and an antisense strand, wherein

(i) the sense strand differs from Formula (A) (5'-Z₁AGCUUGUUUGUGAAACZ₂-3') (SEQ ID NO: 656) by 0, 1, 2 or 3 nucleotides, wherein Z₁ is a nucleotide sequence comprising 0-15 nucleotide motifs, and Z₂ is selected from one of A, U, C, G or is absent, and

(ii) the antisense strand that differs from Formula (B) (5'-Z₃GUUUCACAAACAAGCUZ₄-3') (SEQ ID NO: 663) by 0, 1, 2 or 3 nucleotides, wherein Z₃ is selected from one of A, U, C, G or is absent, and Z₄ is a nucleotide sequence comprising 0-15 nucleotides,

wherein nucleotide positions 2 to 18 in the antisense strand comprise a region of complementarity to an Angiotensinogen (AGT) RNA transcript,

2. The dsRNA agent of claim 1, further comprising a targeting group.

3. The dsRNA agent as claimed in claim 1 or 2, wherein the dsRNA agent comprises at least one modified nucleotide,

optionally wherein all or substantially all nucleotides in the antisense strand are modified nucleotides, or wherein all or substantially all nucleotides of the sense and antisense strands are modified nucleotides,

optionally wherein the at least one modified nucleotide comprises: a 2'-O-methyl nucleotide, a 2'-Fluoro nucleotide, a 2'-deoxy nucleotide, a 2'3'-seco nucleotide mimic, a locked nucleotide, an unlocked nucleic acid nucleotide (UNA), a glycol nucleic acid nucleotide (GNA), a 2'-F-Arabino nucleotide, a 2'-methoxyethyl nucleotide, an abasic nucleotide, a ribitol, an inverted nucleotide, an inverted abasic nucleotide, an inverted 2'-OMe nucleotide, an inverted 2'-deoxy nucleotide, a 2'-amino-modified nucleotide, a 2'-alkyl-modified nucleotide, a morpholino nucleotide, a 3'-OMe nucleotide, a nucleotide including a 5'-phosphorothioate group, a terminal nucleotide linked to a cholesteryl derivative, a terminal nucleotide linked to a dodecanoic acid bisdecylamide group, a phosphoramidite, and a non-natural base including nucleotide, or a combination thereof,

optionally wherein the at least one modified nucleotide is selected from the group consisting of: a 2'-O-methyl nucleotide and a 2'-Fluoro nucleotide, or a combination thereof.

4. The dsRNA agent as claimed in any one of claims 1 to 3, wherein the dsRNA agent comprises at least one phosphorothioate internucleoside linkage,

optionally wherein the sense strand and/or the antisense strand comprises at least one (*e.g.*, 1, 2, 3, 4, 5, or 6) phosphorothioate internucleoside linkage.

5. The dsRNA agent as claimed in any one of claims 1-4, wherein the sense strand is complementary or substantially complementary to the antisense strand, and the region of complementarity between the sense strand and the antisense strand is 16 to 23 nucleotides, *e.g.*, 19-21 nucleotides, in length.

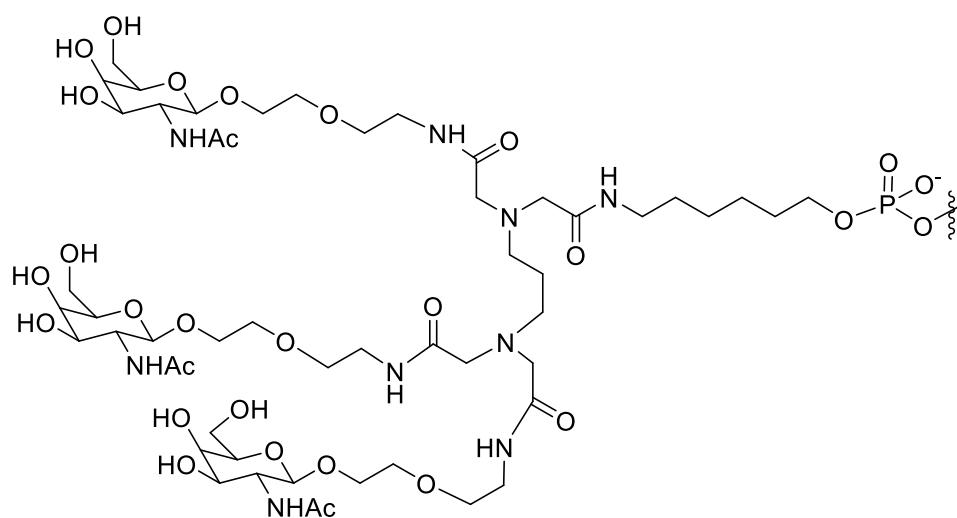
6. The dsRNA agent as claimed in any one of claims 1 to 5, wherein each strand is no more than 30, 25, or 23 nucleotides in length, optionally wherein each strand is 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides in length.

7. The dsRNA agent as claimed in any one of claims 1 to 6, wherein the dsRNA agent comprises at least one modified nucleotide and further comprises one or more targeting groups,

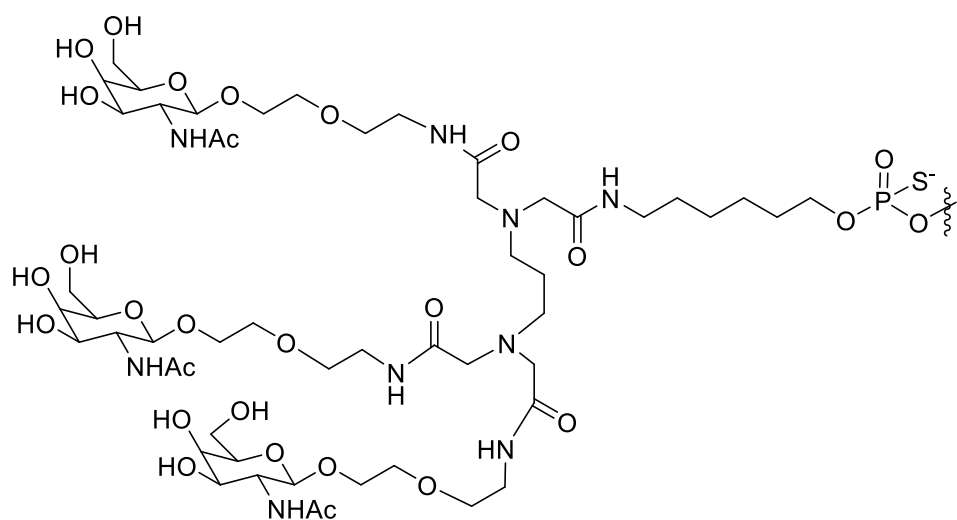
wherein the one or more targeting groups are conjugated to the sense strand,

optionally wherein the one or more targeting groups comprise(s) a N-acetyl-galactosamine (GalNAc),

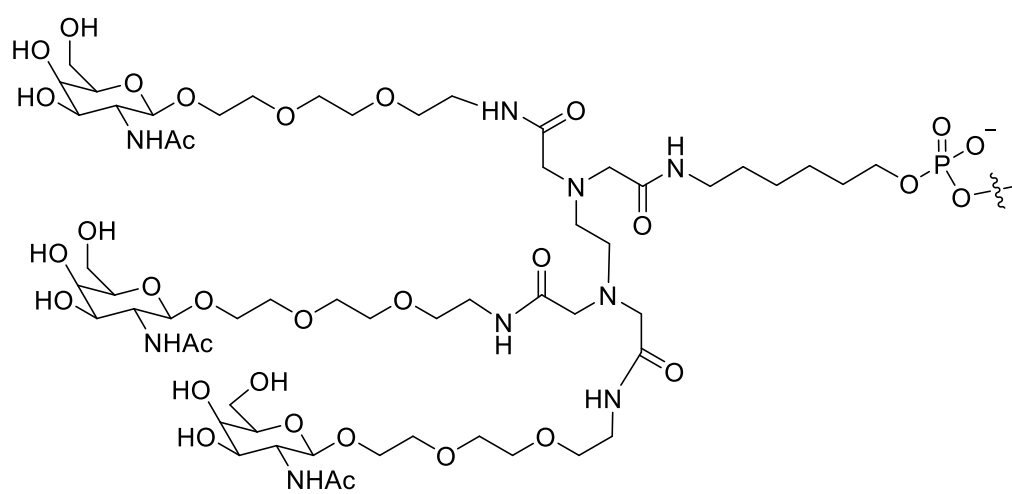
optionally wherein the one or more targeting groups is selected from the group consisting of:



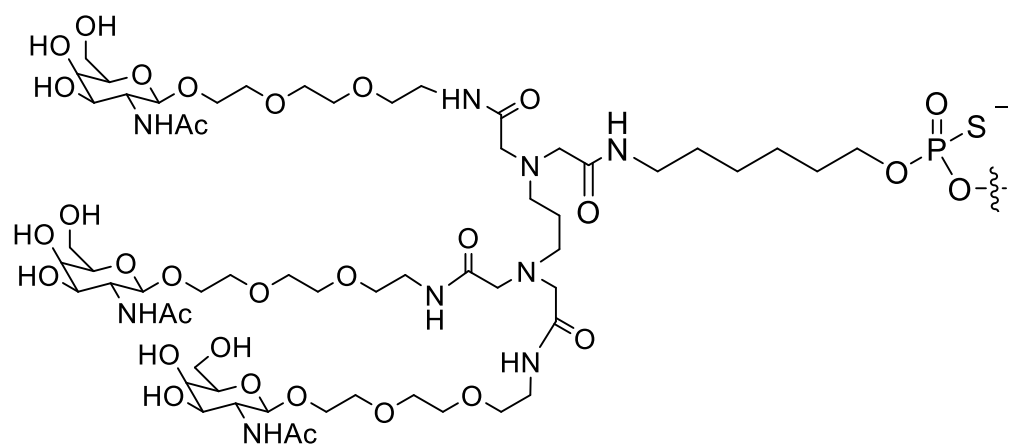
GLO-1,



GLS-1,



GLO-2,

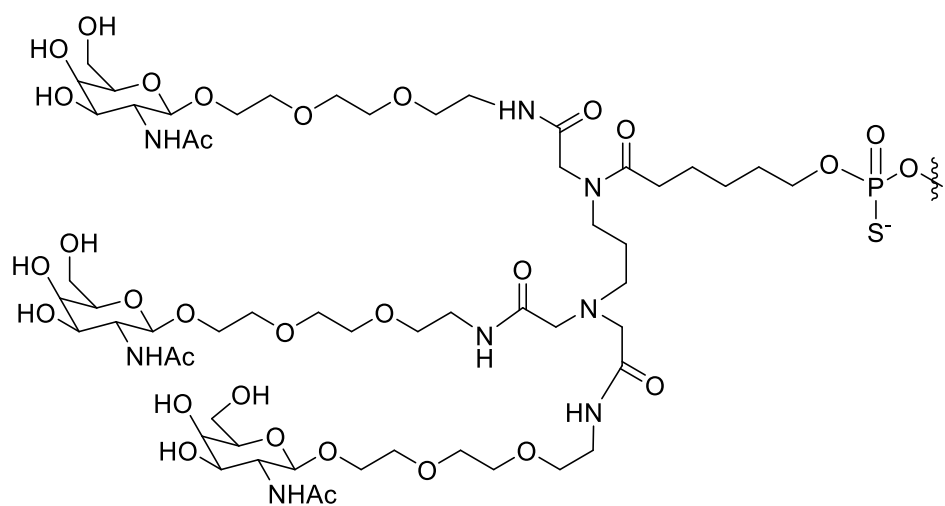


GLS-2,

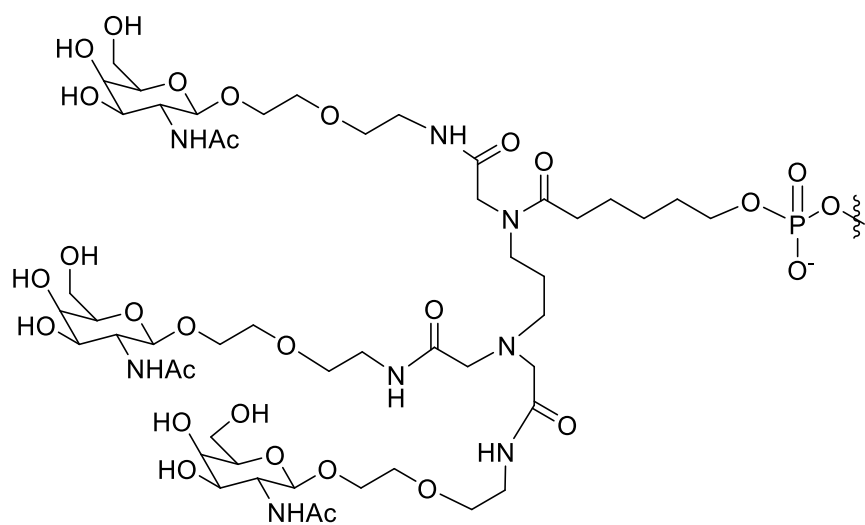
The chemical structure shows a cyclic peptide with three N-acetylglucosamine (GlcNAc) units. Each GlcNAc unit is a six-membered pyranose ring with hydroxyl groups at the 2, 3, and 6 positions and an N-acetyl group at the 1 position. The units are linked by a repeating sequence of three ether linkages and one amide linkage. The amide linkage is part of a cyclic peptide backbone that includes a phosphate group. The phosphate group is shown as a phosphorus atom double-bonded to an oxygen atom and single-bonded to three other oxygen atoms, one of which is negatively charged (S⁻). The structure is labeled with 'NHAc' for the N-acetyl group and 'S⁻' for the negatively charged sulfur atom.

CC(=O)N[C@@H]1[C@H](O[C@H]2[C@@H](CO)O[C@H](CO)[C@H](O)[C@H]2O)[C@H](O)[C@H](O)[C@H]1O.CC(=O)N[C@@H]3[C@H](O[C@H]4[C@@H](CO)O[C@H](CO)[C@H](O)[C@H]4O)[C@H](O)[C@H](O)[C@H]3O>>CC(=O)N[C@@H]1[C@H](O[C@H]2[C@@H](CO)O[C@H](CO)[C@H](O)[C@H]2O)[C@H](O)[C@H](O)[C@H]1O.CC(=O)N[C@@H]3[C@H](O[C@H]4[C@@H](CO)O[C@H](CO)[C@H](O)[C@H]4O)[C@H](O)[C@H](O)[C@H]3O

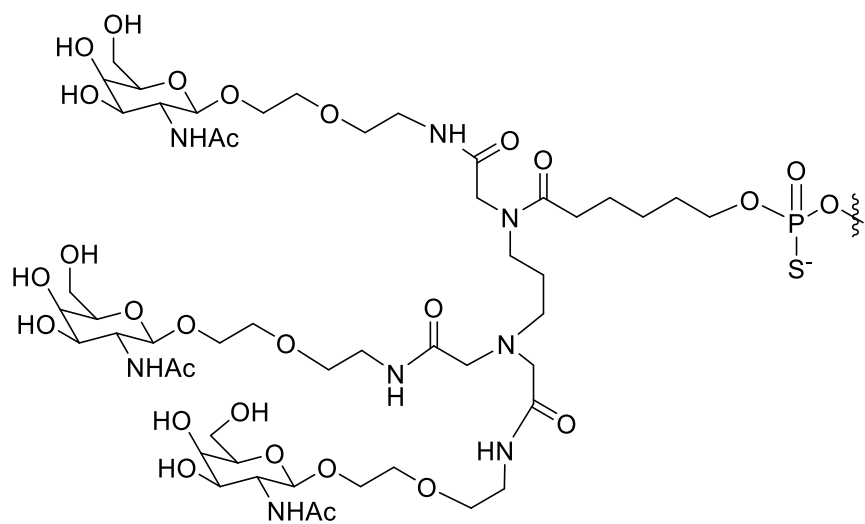
GLO-4,



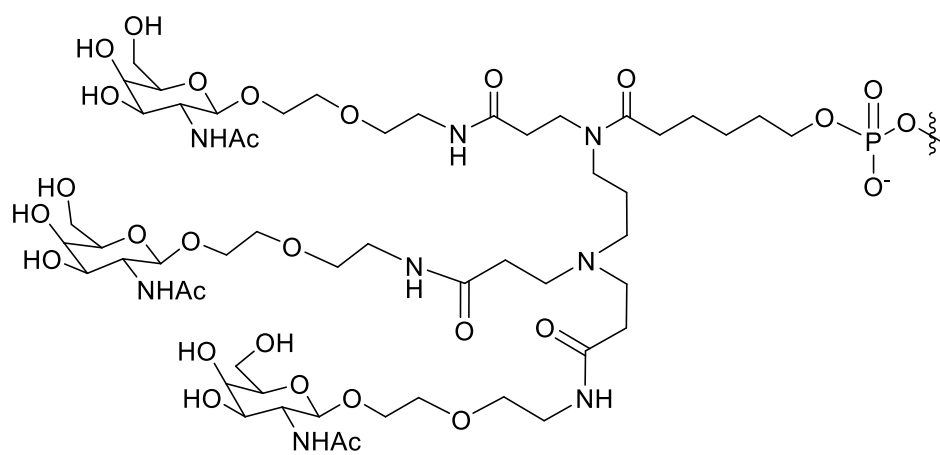
GLS-4,



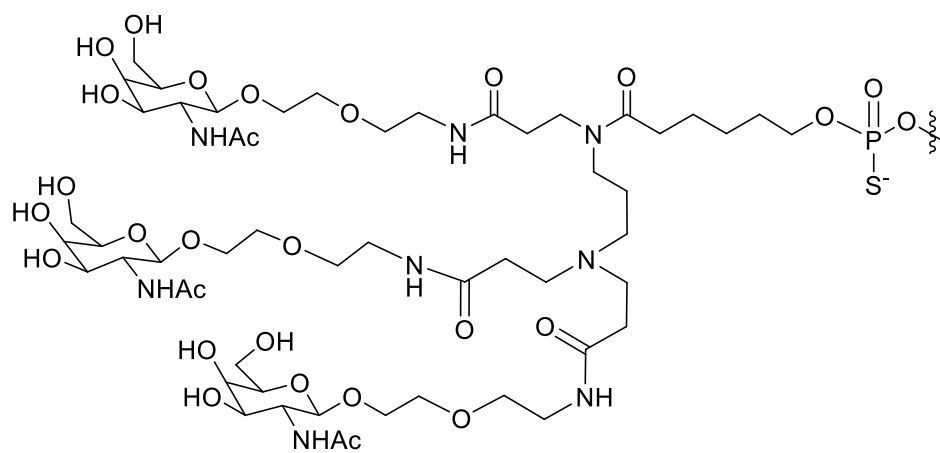
GLO-5,



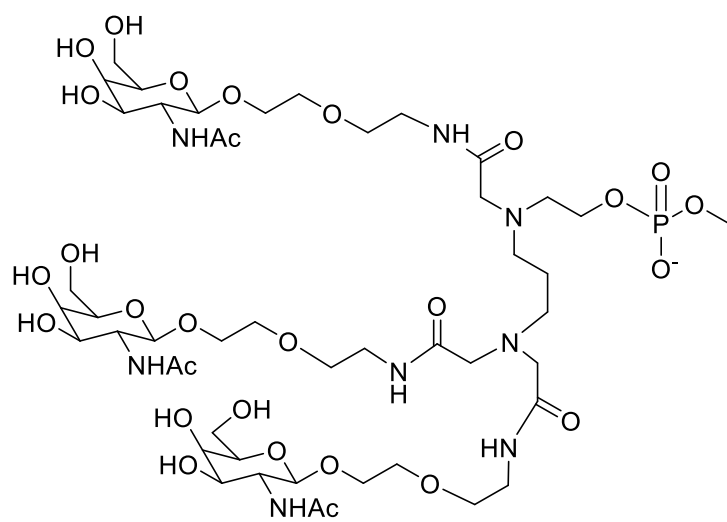
GLS-5,



GLO-6,



GLS-6,



GLO-7,

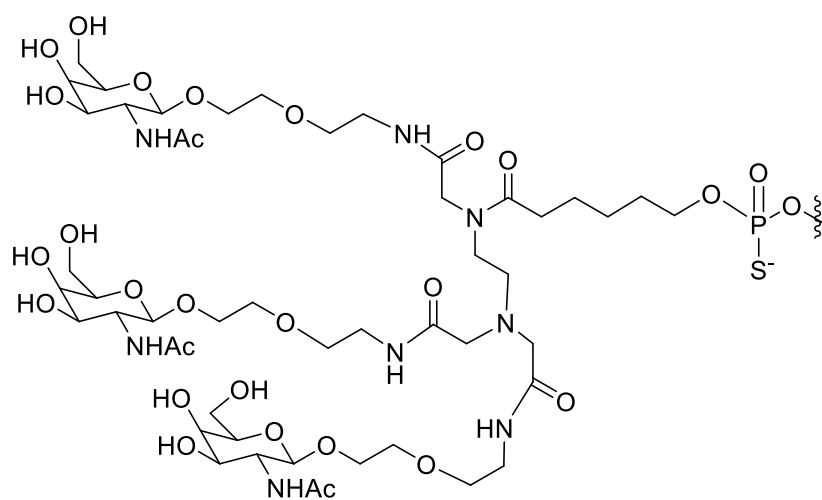
CC(=O)NCCOP(=O)([O-])[O-][illegible]

GLS-8,

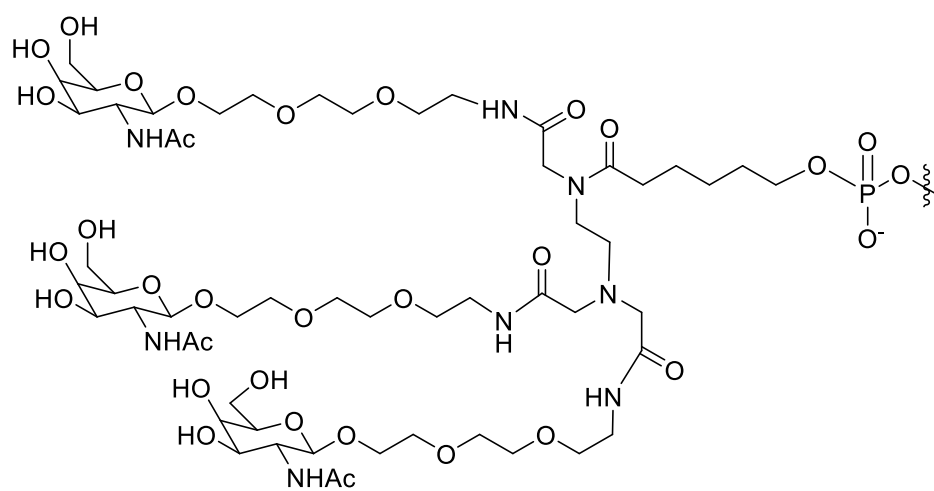
The chemical structure shows a cyclic peptide with three N-acetylglucosamine (GlcNAc) units. Each GlcNAc unit is a six-membered pyranose ring with hydroxyl groups at the 2, 3, and 6 positions and an N-acetyl group at the 1 position. The units are linked by amide bonds. A phosphate group is attached to the side chain of one of the units, consisting of a phosphorus atom double-bonded to an oxygen and single-bonded to a negatively charged sulfur atom and two other oxygen atoms, one of which is part of the side chain. The structure is drawn in a perspective view, with the rings and bonds clearly visible.

The chemical structure shows a branched dendritic molecule. It consists of three glucose units, each in its cyclic pyranose form and substituted with an acetamido group (NHAc) at the C2 position. The glucose units are linked via ether bonds at their C4 positions. The top and middle glucose units are connected to a central nitrogen atom through a chain of ether linkages and amide bonds. The bottom glucose unit is connected to a central nitrogen atom through a chain of ether linkages and an amide bond. The central nitrogen atom is also connected to a terminal phosphate group (O=P(O-)(O-)) via a chain of ether linkages and amide bonds. The molecule is highly branched and contains multiple amide and ether functional groups.

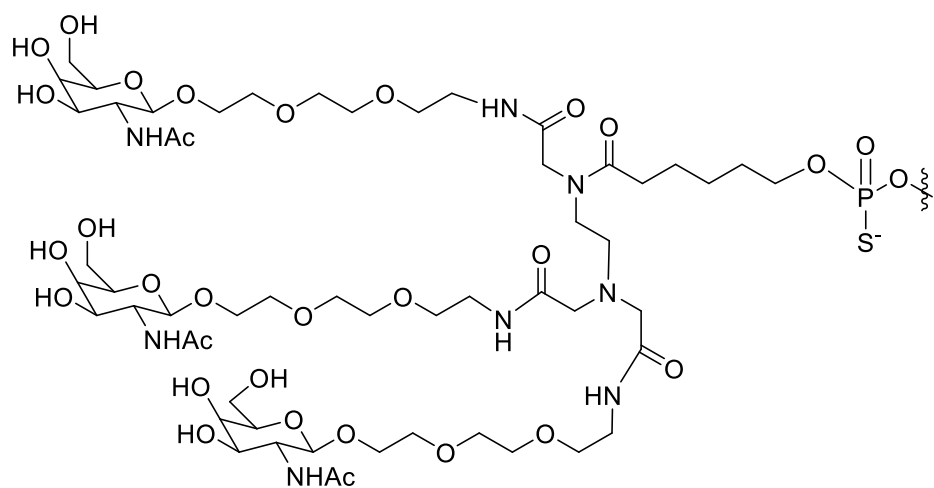
GLO-10,



GLS-10,



GLO-11,

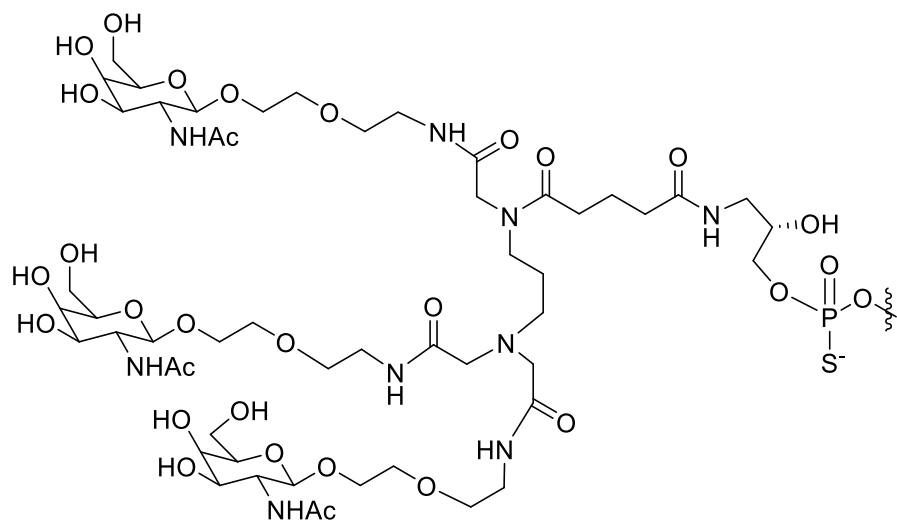


GLS-11,

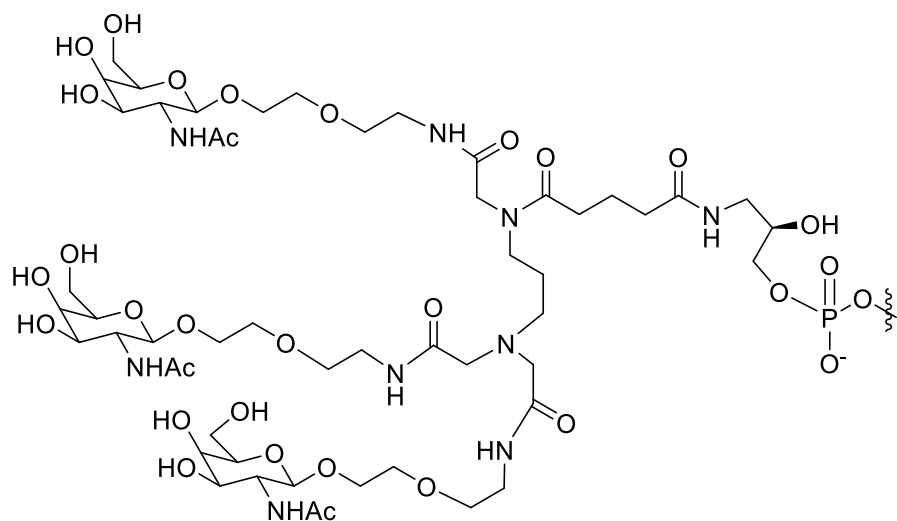
The chemical structure shows a branched dendritic molecule. It consists of three sugar units, each with an acetamido group (NHAc) at the C2 position. The sugar units are linked via ether bonds to a central chain. This chain includes two amide bonds and a phosphonate group (P=O, P-S⁻) at the end. The structure is drawn in a 2D representation with stereochemistry indicated by wedges and dashes.

The chemical structure shows a cyclic peptide derivative. It consists of a central peptide backbone with three N-acetylglucosamine (GlcNAc) units attached via their C6 hydroxyl groups. The GlcNAc units are linked to the peptide backbone through their C1 hydroxyl groups. The peptide backbone includes an amide bond (NH-CO) and a phosphate group (P=O, O⁻) attached to the side chain of one of the amino acid residues. The structure is drawn in a perspective view, showing the spatial arrangement of the atoms and bonds.

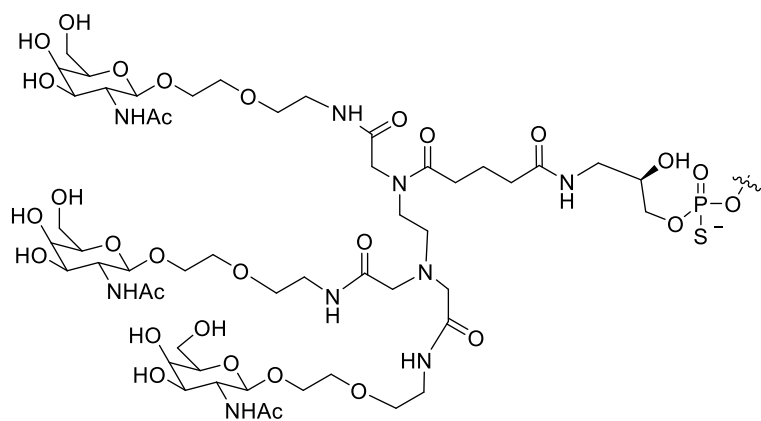
GLO-13,



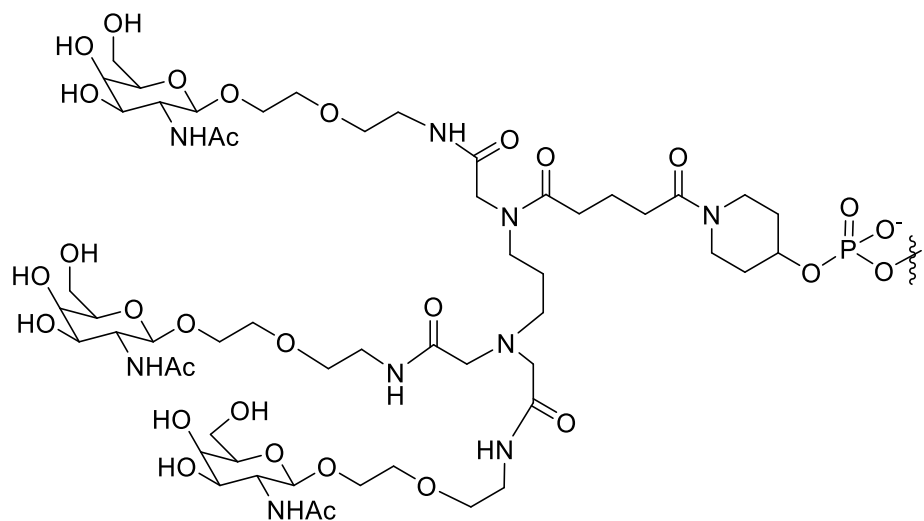
GLS-13,



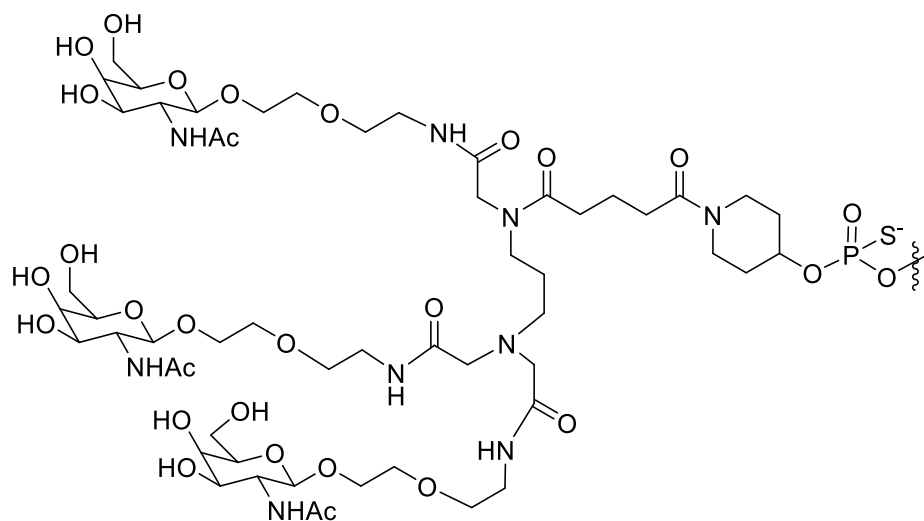
GLO-14,



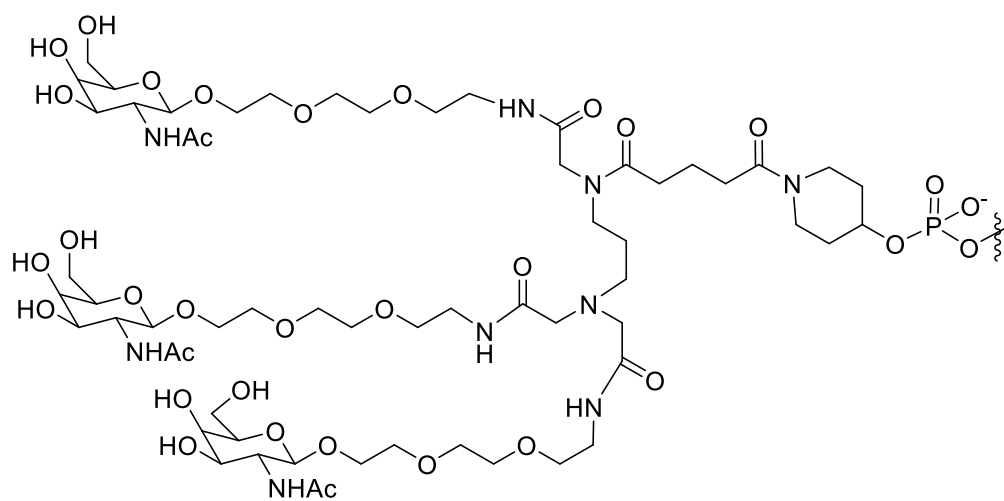
GLS-14,



GLO-15,

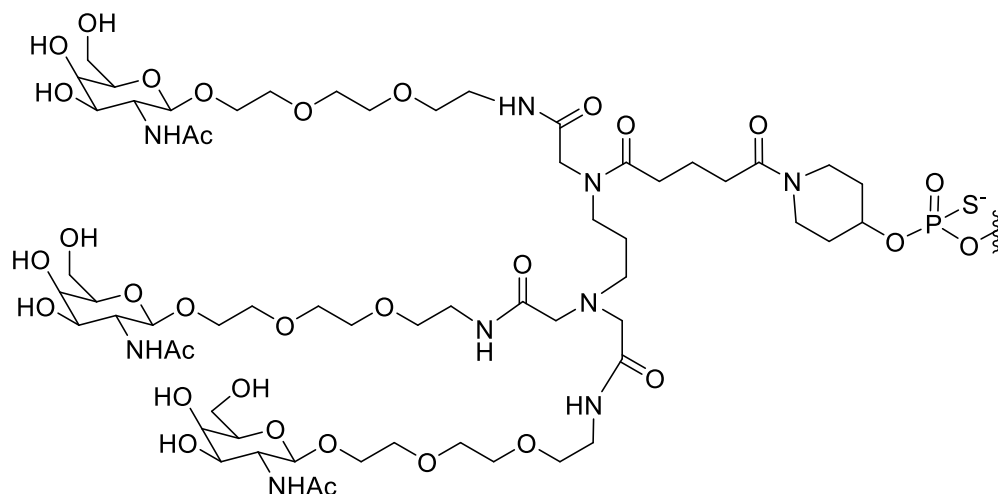


GLS-15,



GLO-16,

and



GLS-16.

8. The dsRNA agent as claimed in any one of claims 1 to 7, wherein the dsRNA agent comprises a targeting group conjugated to the 5'-terminal end or the 3'-terminal end of the sense strand,

optionally wherein the dsRNA agent comprises a targeting group conjugated to the 5'-terminal end of the sense strand.

9. The dsRNA agent as claimed in any one of claims 1 to 8, wherein the antisense strand comprises an inverted abasic residue at the 3'-terminal end, and/or the sense strand comprises one or two inverted abasic residues at the 3'-terminal end or/and the 5'-terminal end(s).

10. The dsRNA agent as claimed in any one of claims 1 to 9, wherein the dsRNA agent has two blunt ends or at least one of the sense strand or the antisense strand comprises a 3' overhang of at least 1 or at least 2 nucleotides.

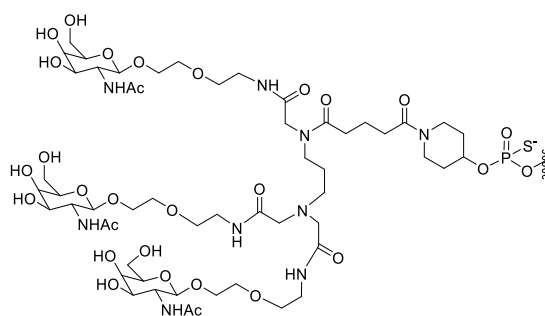
11. The dsRNA agent of claim 1, wherein the sense strand comprises the nucleotide sequence of SEQ ID NO:522 and the antisense strand comprises the nucleotide sequence of SEQ ID NO:523,

optionally wherein the sense strand and/or the antisense strand comprises one or more modified nucleotides, optionally wherein the one or more modified nucleotides are selected from the group consisting of a 2'-O-methyl nucleotide, a 2'-Fluoro nucleotide, or a combination thereof;

optionally wherein the sense strand comprises 1, 2, 3, 4, 5, or 6 phosphorothioate internucleoside linkages and/or the antisense strand comprises 1, 2, 3, 4, 5, or 6 phosphorothioate internucleoside linkages;

optionally wherein the sense strand comprises one or more inverted abasic residues, optionally wherein the sense strand comprises an inverted abasic residue at each of the 3'-terminal end and the 5'-terminal end; and

optionally, wherein the dsRNA agent comprises a targeting group, optionally wherein the targeting group comprises a N-acetyl-galactosamine (GalNAc), optionally, wherein the targeting group is conjugated to the 5'-end of the sense strand, optionally wherein the targeting group is



GLS-15.

12. The dsRNA agent of claim 11, wherein the sense strand comprises the nucleotide sequence of SEQ ID NO:526 and the antisense strand comprises the nucleotide sequence of SEQ ID NO:527.

13. The dsRNA agent of claim 11 or 12, wherein the sense strand comprises 3 phosphorothioate internucleoside linkages and/ or the antisense strand comprises 3 phosphorothioate internucleoside linkages.

14. The dsRNA agent of any one of claims 11 to 13, wherein the sense strand comprises an inverted abasic residue at each of the 3'-terminal end and the 5'-terminal end of the sense strand.

15. The dsRNA agent of any one of claims 11 to 14, wherein the dsRNA agent comprises a GalNAc targeting group.

16. The dsRNA agent of any one of claims 11 to 14, wherein the dsRNA agent comprises a GalNAc targeting group, wherein the GalNAc targeting group is

17. A composition comprising the dsRNA agent as claimed in any one of claims 1 to 16.

18. The composition as claimed in claim 17, further comprising (i) a pharmaceutically acceptable carrier and/or (ii) one or more additional therapeutic agents, optionally wherein the composition is packaged in a kit, container, pack, dispenser, prefilled syringe or vial and/or is formulated for subcutaneous or intravenous (IV) administration.

19. Use of the double-stranded ribonucleic acid (dsRNA) agent as claimed in any one of claims 1 to 16 or the composition as claimed in any one of claims 17 or 18 in the manufacture of a medicament for use in a method for inhibiting AGT gene expression in a cell, wherein cells comprising an effective amount of the double-stranded ribonucleic acid (dsRNA) agent as claimed in any one of claims 1 to 16 or the composition as claimed in any one of claims 17 or 18 are to be prepared.

20. Use of the double-stranded ribonucleic acid (dsRNA) agent as claimed in any one of claims 1 to 16 or the composition as claimed in any one of claims 17 or 18 in the manufacture of a medicament for use in a method of inhibiting AGT gene expression in a subject, wherein an effective amount of the double-stranded ribonucleic acid (dsRNA) agent as claimed in any one of claims 1 to 16 or the composition as claimed in any one of claims 17 or 18 is to be administered to the subject.

21. Use of the double-stranded ribonucleic acid (dsRNA) agent as claimed in any one of claims 1 to 16 or the composition as claimed in any one of claims 17 or 18 in the manufacture of a medicament for the treatment of a disease or condition associated with an AGT protein, wherein an effective amount of the double-stranded ribonucleic acid (dsRNA) agent as claimed in any one of claims 1 to 16 or the composition as claimed in any one of claims 17 or 18 is to be administered to a subject, so as to inhibit AGT gene expression.

22. The use as claimed in claim 21, wherein the disease or condition is caused by or associated with: activation of the renin-angiotensin-aldosterone system (RAAS) or symptoms or progression thereof in response to activation of the RAAS, hypertension, hypertensive disease, hypertension, borderline hypertension, essential hypertension, secondary hypertension, isolated hypertension, systolic hypertension, diastolic hypertension, pregnancy-related hypertension, diabetic hypertension, resistant hypertension, refractory hypertension, paroxysmal hypertension, renovascular hypertension, Goldblatt hypertension, ocular hypertension, glaucoma, pulmonary hypertension, portal hypertension, systemic venous hypertension, unstable hypertension, hypertensive heart disease, hypertensive nephropathy, atherosclerosis, arteriosclerosis, vasculopathy, diabetic nephropathy, diabetic retinopathy, chronic heart failure, cardiomyopathy, diabetic cardiomyopathy, glomerulosclerosis, aortic stenosis, aortic aneurysm, ventricular fibrosis, heart failure, myocardial infarction, angina, stroke, renal disease, renal failure, systemic sclerosis, intrauterine growth retardation (IUGR), and fetal growth restriction.

23. The use as claimed in claim 21, further comprising an additional treatment regimen to be administered to the subject,

optionally wherein the additional treatment regimen comprises a non-AGT dsRNA therapeutic agent to be administered to the subject,

optionally wherein the non-AGT dsRNA therapeutic agent is selected from the group consisting of: a diuretic, an angiotensin converting enzyme (ACE) inhibitor, a vascular Tensin II receptor antagonist, a beta-blocker, a vasodilator, a calcium channel blocker, an aldosterone antagonist, an alpha2-agonist, a renin inhibitor, an alpha-blocker, a peripherally acting adrenergic agent, a selective D1 receptor partial agonist, a non-selective alpha-adrenergic antagonist, a synthetic, a steroidal antimineralocorticoid, and therapeutic agents for hypertension formulated as a combinations of agents, or a combination of any of the foregoing.

24. The use as claimed in any one of claims 21 to 23, wherein the dsRNA agent or composition is to be administered subcutaneously or by IV administration to the subject.

25. The use as claimed in any one of claims 21 to 24, further comprising determining the efficacy of the administered double-stranded ribonucleic acid (dsRNA) agent or composition in the subject,

optionally wherein the means for determining the efficacy of treatment in the subject comprises:

- (i) determining one or more physiological characteristics of an AGT-associated disease or condition in a subject, and
- (ii) comparing the one or more physiological characteristic(s) to one or more baseline pre-treatment physiological characteristics of the AGT-associated disease or condition, wherein the comparing indicates one or more of the presence, absence, and level of efficacy of the double-stranded ribonucleic acid (dsRNA) agent or composition administered to the subject,

optionally wherein the one or more physiological characteristics is selected from the group consisting of hypertension, essential hypertension, secondary hypertension, a hypertensive emergency, malignant hypertension, accelerated hypertension, acute hypertension, pregnancy-related hypertension, and resistant hypertension,

optionally wherein a reduction in hypertension indicates the efficacy of the double-stranded ribonucleic acid (dsRNA) agent or composition.

26. Use of the double-stranded ribonucleic acid (dsRNA) agent as claimed in any one of claims 1 to 16 or the composition as claimed in any one of claims 17 or 18 in the manufacture of a medicament for use in a method of reducing the level of AGT protein in a subject as compared to a baseline pre-treatment level of AGT protein in the subject, wherein an effective amount of the double-stranded ribonucleic acid (dsRNA) agent as claimed in any one of claims 1 to 16 or the composition as claimed in any one of claims 17 or 18 is to be administered to a subject to reduce the level of AGT gene expression.

27. Use of the double-stranded ribonucleic acid (dsRNA) agent as claimed in any one of claims 1 to 16 or the composition as claimed in any one of claims 17 or 18 in the manufacture of a medicament for use in a method of altering one or more physiological characteristics of an AGT-associated disease or condition in a subject as compared to one or more baseline pre-treatment physiological characteristics of the AGT-associated disease or condition in the subject, wherein an effective amount of a double-stranded ribonucleic acid (dsRNA) agent as claimed in any one of claims 1 to 16 or a composition as claimed in any one of claims 17 or 18 is to be administered to a subject, to change the one or more physiological characteristics of an AGT-associated disease or condition in the subject.

28. The double-stranded ribonucleic acid (dsRNA) agent as claimed in any one of claims 1 to 16 or the composition as claimed in any one of claims 17 or 18 for use in therapy.