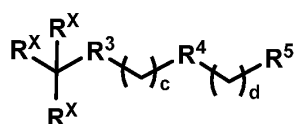


WHAT IS CLAIMED IS:

1. A compound of Formula (I):

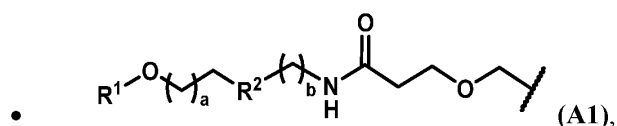


Formula (I)

or a pharmaceutically acceptable salt thereof, wherein:

each R^{X} is independently selected from the group consisting of:

- H; and
- $-\text{CH}_2\text{OR}^{\text{X}2}$, wherein $\text{R}^{\text{X}2}$ is H, C_{1-6} alkyl, or a hydroxyl protecting group;



provided that at least one R^{X} is a group of Formula (A1);

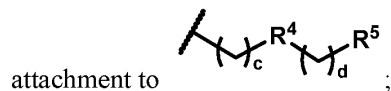
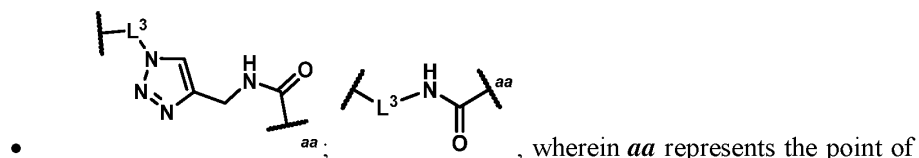
each R^1 is an independently selected moiety capable of binding an asialoglycoprotein receptor (ASGPR);

each R^2 is independently selected from the group consisting of: $-\text{C}(\text{R}^6)_2-$; $-\text{OC}(\text{R}^6)_2\text{C}(\text{R}^6)_2\text{O}-$; $-\text{C}(\text{R}^6)(\text{OH})-\text{C}(\text{R}^6)(\text{OH})-$; $^*\text{-C}(=\text{O})\text{NR}^7-$; $^*\text{-NR}^7\text{C}(=\text{O})-$; C_{6-10} arylene; C_{2-6} alkenylene; and C_{2-6} alkynylene,

wherein the C_{6-10} arylene, C_{2-6} alkenylene, and C_{2-6} alkynylene are each optionally substituted with 1-4 independently selected R^a , and the * represents the point of

attachment to $\text{R}^1 - \text{O} - \text{---} \text{---}$;

R^3 is selected from the group consisting of:

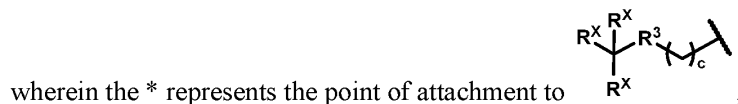


- $-(\text{CR}^6\text{R}^6)_x-\text{O}-(\text{CR}^6\text{R}^6)_y-$, wherein *x* and *y* are independently 0, 1, 2, or 3; and
- $-\text{L}^3-\text{L}^{3\text{C}}-$, wherein $\text{L}^{3\text{C}}$ is selected from the group consisting of: C_{3-10} cycloalkylene, C_{6-10} arylene, 5-10 membered heteroarylene, and 4-10 membered heterocyclylene, each of which is optionally substituted with 1-4 independently selected R^a ;

L^3 is $-\text{C}(\text{R}^6)_2-$,

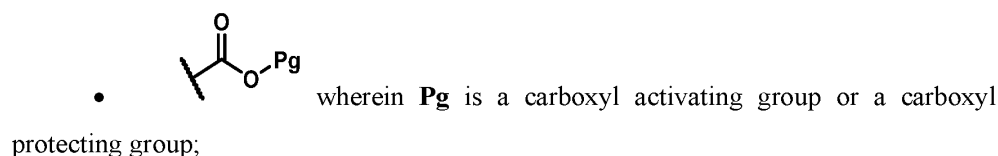
- 10 R^4 is selected from the group consisting of: $-\text{C}(\text{R}^6)_2-$; $-\text{OC}(\text{R}^6)_2\text{C}(\text{R}^6)_2\text{O}-$; $-\text{C}(\text{R}^6)(\text{OH})-\text{C}(\text{R}^6)(\text{OH})-$; $^*\text{-C}(=\text{O})\text{NR}^7-$; $^*\text{-NR}^7\text{C}(=\text{O})-$; C_{6-10} arylene, C_{3-10} cycloalkylene, 5-10 membered heteroarylene, and 4-10 membered heterocyclylene,

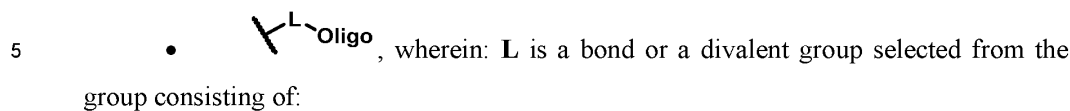
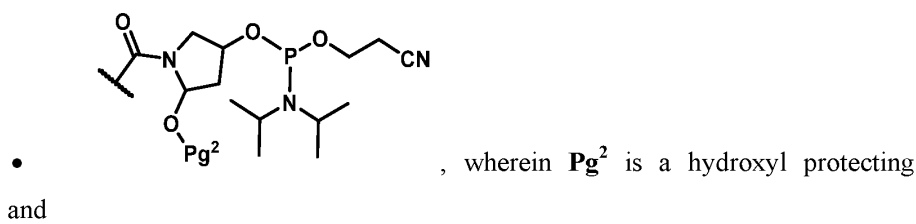
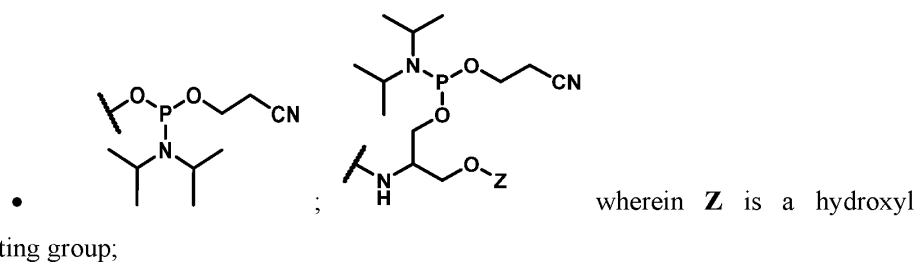
- wherein the C_{6-10} arylene, C_{3-10} cycloalkylene, 5-10 membered heteroarylene, and 4-10 membered heterocyclylene are each optionally substituted with 1-4 independently
15 selected R^a , and



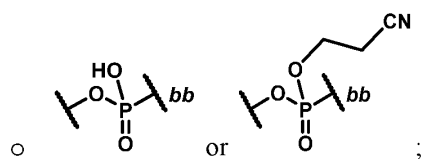
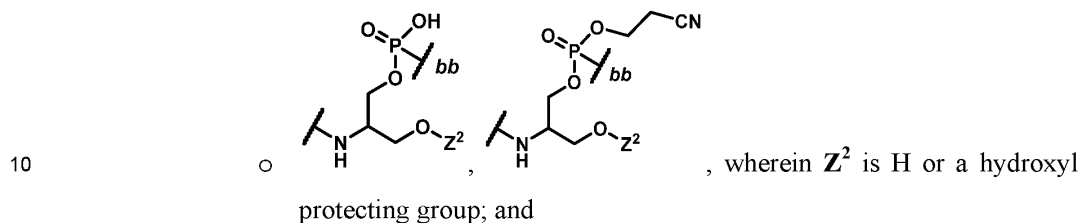
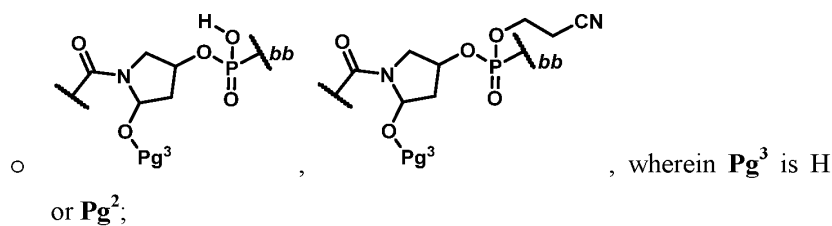
R^5 is selected from the group consisting of:

- 20 • hydroxyl; $\text{C}(\text{O})\text{OH}$;





- **-R²-, -R³-, -R⁴-, -O-, -C(=O)-, -C(=O)O-, -OC(=O)-,**



wherein **bb** represents the point of attachment to **Oligo**, and

- **Oligo** is an oligonucleotide;

each R^6 is independently selected from the group consisting of: H; C_{1-3} alkyl; C_{1-3} haloalkyl; and halo;

each R^7 is independently selected from the group consisting of: H; and C_{1-3} alkyl.

5

a and **b** are each independently selected integers from 1 to 10;

c and **d** are each independently selected integers from 0 to 10; and

each occurrence of R^a is independently selected from the group consisting of: halo, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

10

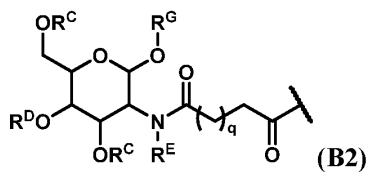
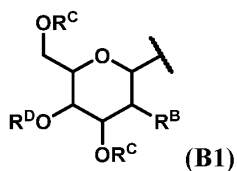
2. The compound of claim 1, wherein at least two R^x are each independently a group of Formula (A1).

15

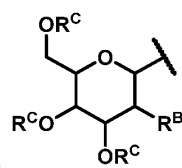
3. The compound of claims 1 or 2, wherein each R^x is independently a group of Formula (A1).

4. The compound of any one of claims 1-3, wherein each R^1 is independently a group of Formula (B1) or (B2):

20



wherein:



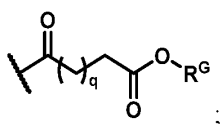
R^D is selected from the group consisting of: R^C and

each R^B is independently selected from the group consisting of: $-NR^E R^F$ and $-OR^C$;

each R^C is independently selected from the group consisting of: H and $-C(=O)C_{1-6}$ alkyl;

each R^E is independently $C(=O)C_{1-6}$ alkyl;

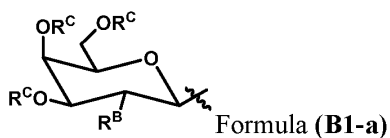
each R^F is independently selected from the group consisting of: H and



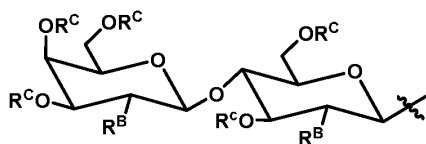
R^G is C_{1-6} alkyl; and

each q is independently an integer selected from 1 to 10.

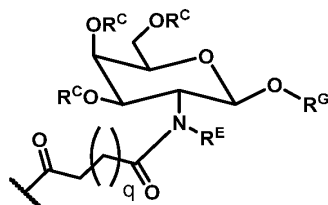
5. The compound of claim 4, wherein each R^1 is independently a group having Formula (B1-a), (B1-b), or (B2-a):



Formula (B1-a)



Formula (B1-b)



Formula (B2-a).

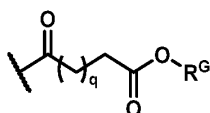
6. The compound of claims 4 or 5, wherein each R^B is independently $NR^E R^F$.

7. The compound of any one of claims 4-6, wherein each R^E is
 5 independently $-C(=O)C_{1-6}$ alkyl.

8. The compound of any one of claims 4-7, wherein each R^E is $-C(=O)CH_3$.

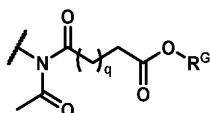
9. The compound of any one of claims 4-8, wherein each R^F is H.
 10

10. The compound of any one of claims 4-8, wherein each R^F is



11. The compound of any one of claims 4-6, wherein each R^B is
 15 $NHC(=O)CH_3$.

12. The compound of any one of claims 4-6, wherein each R^B is



13. The compound of claims 4 or 5, wherein each R^B is independently $-OR^C$.
 20

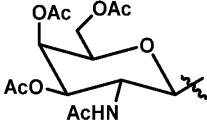
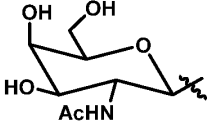
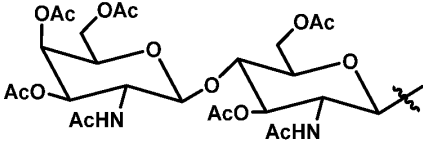
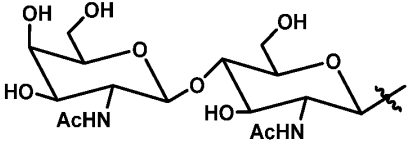
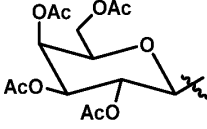
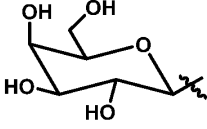
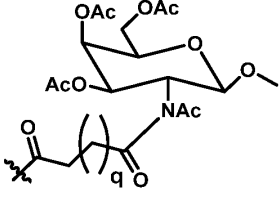
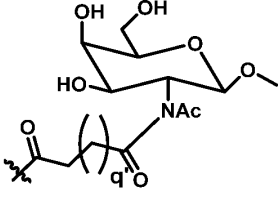
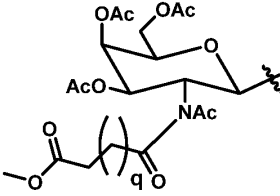
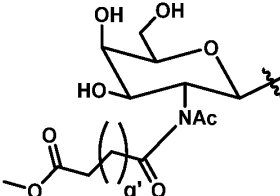
14. The compound of any one of claims 4-13, wherein each R^C is
 independently $C(=O)C_{1-6}$ alkyl.

15. The compound of any one of claims 4-14, wherein each R^C is $C(=O)CH_3$.
 25

16. The compound of any one of claims 4-14, wherein each R^C is H.

17. The compound of any one of claims 4-16, wherein each R^G is CH_3 .

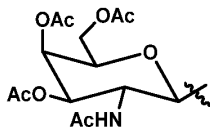
18. The compound of any one of claims 1-5, wherein each R^1 is selected from the group consisting of the following:

	
	
	
 wherein, q is an integer selected from 1 to 10;	 wherein, q' is an integer selected from 1 to 10;
 wherein, q is an integer selected from 1 to 10;	 wherein, q' is an integer selected from 1 to 10.

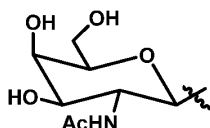
5

19. The compound of any one of claims 1-18, wherein each R^1 is the same.

20. The compound of any one of claims 1-19, wherein each R^1 is



21. The compound of any one of claims 1-19, wherein each R^1 is



5

22. The compound of any one of claims 1-21, wherein each R^2 is independently $^*-C(=O)NR^7$ - or $^*-NR^7C(=O)-$.

10 23. The compound of any one of claims 1-22, wherein each R^2 is independently $^*-C(=O)NR^7$ -.

24. The compound of any one of claims 1-23, wherein each R^2 is $^*-C(=O)NH-$.

15

25. The compound of any one of claims 1-21, wherein each R^2 is independently $-C(R^6)_2-$.

26. The compound of any one of claims 1-21 or 25, wherein each R^2 is $-CH_2-$.

20

27. The compound of any one of claims 1-26, wherein each R^2 is the same.

28. The compound of any one of claims 1-27, wherein each a is an independently selected integer from 1 to 4.

25

29. The compound of any one of claims 1-28, wherein each a is independently 2 or 3.

30. The compound of any one of claims 1-29, wherein each **a** is the same.

31. The compound of any one of claims 1-30, wherein each **b** is an
independently selected integer from 1 to 4.

32. The compound of any one of claims 1-31, wherein each **b** is independently
2 or 3.

33. The compound of any one of claims 1-32, wherein each **b** is the same.

34. The compound of any one of claim 1-21, wherein each **a** is the same; each
b is the same; and each **R**² is the same.

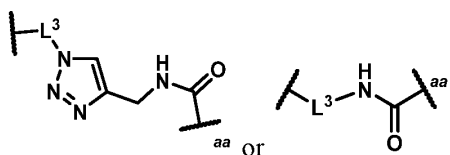
35. The compound of claim 34, wherein **a** is an integer from 1 to 4; **b** is an
integer from 1 to 4; and **R**² is *-C(=O)NR⁷.

36. The compound of claim 35, wherein **a** is 3; **b** is 3; and **R**² is *-C(=O)NH.

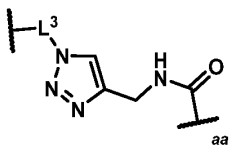
37. The compound of claim 34, wherein **a** is an integer from 1 to 4; **b** is an
integer from 1 to 4; and **R**² is -C(**R**⁶)₂-.

38. The compound of claim 37, wherein **R**² is -CH₂-; and 3≤(**a**+**b**)≤5.

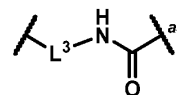
39. The compound of any one of claims 1-38, wherein **R**³ is



40. The compound of any one of claims 1-39, wherein R^3 is



41. The compound of any one of claims 1-39, wherein R^3 is



42. The compound of any one of claims 1-41, wherein L^3 is $-C(R^6)_2-$.

43. The compound of any one of claims 1-42, wherein L^3 is $-CH_2-$.

44. The compound of any one of claims 1-43, wherein c is an integer from 1 to 2.

45. The compound of any one of claims 1-43, wherein c is an integer from 2 to 5.

46. The compound of any one of claims 1-43, wherein c is an integer from 3 to 7.

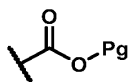
47. The compound of any one of claims 1-46, wherein R^4 is $^*-C(=O)NR^7-$.

48. The compound of any one of claims 1-47, wherein R^4 is $^*-C(=O)NH-$.

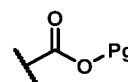
49. The compound of any one of claims 1-46, wherein R^4 is $-C(R^6)_2-$.

50. The compound of any one of claims 1-46 or 49, wherein R^4 is $-CH_2-$.
- 5 51. The compound of any one of claims 1-50, wherein d is an integer from 1 to 2.
52. The compound of any one of claims 1-50, wherein d is an integer from 3 to 7.
- 10 53. The compound of any one of claims 1-43, wherein R^4 is $-C(R^6)_2-$; and each of c and d is independently 1 or 2.
- 15 54. The compound of claim 53, wherein R^4 is $-CH_2-$; and each of c and d is 1.
- 20 55. The compound of any one of claims 1-43, wherein R^4 is $-C(R^6)_2-$; and $4 \leq (c + d) \leq 12$.
56. The compound of claim 55, wherein R^4 is $-CH_2-$; and $7 \leq (c + d) \leq 10$.
- 25 57. The compound of any one of claims 1-43, wherein R^4 is $*-C(=O)NR^7-$; and $5 \leq (c + d) \leq 10$.
58. The compound of claim 57, wherein R^4 is $*-C(=O)NR^7-$; and $7 \leq (c + d)$
- 30 ≤ 9 .
59. The compound of claims 57 or 58, wherein c is 3.

60. The compound of any one of claims 1-59, wherein R^5 is $C(O)OH$ or



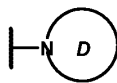
61. The compound of any one of claims 1-59, wherein R^5 is



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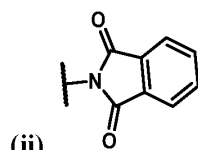
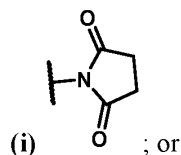
62. The compound of any one of claims 1-61, wherein **Pg** is a carboxyl activating group.

10

63. The compound of any one of claims 1-62, wherein **Pg** is , wherein **Ring D** is a 5-10 membered heteroaryl or 4-10 membered heterocyclyl, each optionally substituted with 1-6 substituents each independently selected from the group consisting of: halo, oxo, NO_2 , $C(O)C_{1-4}$ alkyl, $C(O)OC_{1-4}$ alkyl, $S(O)C_{1-4}$ alkyl, C_{1-6} alkyl, C_{1-6} haloalkyl, and $-OH$.

15

64. The compound of any one of claims 1-63, wherein **Pg** is:



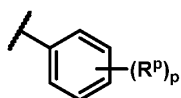
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which is optionally substituted with 1-6 substituents each independently selected from the group consisting of: halo, NO_2 , $C(O)C_{1-4}$ alkyl, $C(O)OC_{1-4}$ alkyl, $S(O)C_{1-4}$ alkyl, C_{1-6} alkyl, C_{1-6} haloalkyl, and $-OH$.

65. The compound of any one of claims 1-62, wherein **Pg** is C₆₋₁₀ aryl or 5-10 membered heteroaryl substituted with 1-6 substituents each independently selected from the group consisting of: -F; -Cl; -NO₂; C(O)C₁₋₄ alkyl, C(O)OC₁₋₄ alkyl, and S(O)C₁₋₄ alkyl.

5

66. The compound of any one of claims 1-62 or 65, wherein **Pg** is

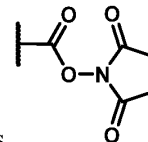
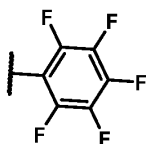


, wherein **p** is an integer from 1 to 5; and each **R^p** is -F, -Cl, or -NO₂.

10

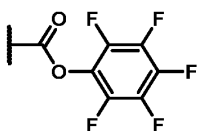
67. The compound of claim 66, wherein each **R^p** is -F.

68. The compound of any one of claims 1-62 or 65-66, wherein **Pg** is

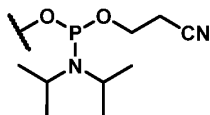


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69. The compound of any one of claims 1-62, wherein **R⁵** is

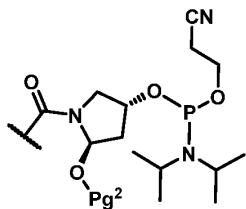


70. The compound of any one of claims 1-59, wherein **R⁵** is



20

71. The compound of any one of claims 1-59, wherein R^5 is



5 72. The compound of any one of claims 1-71, wherein each hydroxyl protecting group is independently selected from the group consisting of: a silyl protecting group; 4-monomethoxytrityl (MMTR); 4,4'-dimethoxytrityl (DMTR); and triphenylmethyl (trityl).

10 73. The compound of claim 72, wherein the silyl protecting group is selected from the group consisting of: *tert*-butyldimethylsilyl (TBMDS); *tert*-butyldiphenylsilyl (TBDPS), and triisopropylsilyl (TIPS).

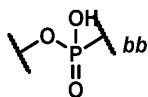
15 74. The compound of claim 1, wherein the compound is selected from the group consisting of compounds **GalNAc-1** through **GalNAc-12**.

20 75. The compound of any one of claims 1-59, wherein R^5 is $Y^L\text{-Oligo}$, wherein **Oligo** is an oligonucleotide that is attached to **L** via the 5'-end, 3'-end, or sequence middle of any strand via a phosphate group.

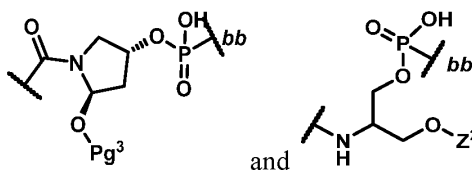
76. The compound of any one of claims 1-59 or 75, wherein **L** is a bond.

25 77. The compound of any one of claims 1-59 or 75, wherein **L** is C(=O) or -O-.

78. The compound of any one of claims 1-59 or 75, wherein **L** is



5 79. The compound of any one of claims 1-59 or 75, wherein **L** is selected



from the group consisting of:

and

10 80. The compound of any one of claims 1-59 or 75-79, wherein the oligonucleotide comprises a single-stranded oligonucleotide and/or a double-stranded oligonucleotide.

15 81. The compound of any one of claims 1-59 or 75-80, wherein the oligonucleotide is selected from the group consisting of: DNA, siRNA, miRNA, pre-miRNA, antagomir, mRNA, antisense oligonucleotide (ASO), aptamer, crRNA, tracrRNA, and sgRNA.

20 82. The compound of any one of claims 1-59 or 75-81, wherein the oligonucleotide comprises unmodified nucleotides and/or modified nucleotides.

25 83. The conjugate compound of claim 82, wherein the modified nucleotides are each independently selected from the group consisting of: 2'-O-(2-methoxyethyl)-modified nucleotides; 2'-O-alkyl modified nucleotides; 2'-O-allyl modified nucleotides; 2'-C-allyl modified nucleotides; 2'-fluoro modified nucleotides; 2'-deoxy modified nucleotides; 2'-hydroxy modified nucleotides; locked nucleic acids (LNAs) modified nucleotides, glycol nucleic acids (GNAs) modified nucleotides, and unlocked nucleic acids (UNAs) modified nucleotides.

84. The compound of claim 83, wherein the 2'-O-alkyl modified nucleotides are 2'-O-methyl nucleotides.

5 **85.** The compound of any one of claims 1-59 or 75-84, wherein the oligonucleotide comprises a modifying group, wherein the modifying group is selected from the group consisting of: cholesterol, polyethylene glycol, fluorescent probes, biotin, polypeptides, vitamins, tissue targeting molecules, and a combination thereof.

10 **86.** The compound of claim 85, wherein the modifying group is a terminal modifying group.

15 **87.** The compound of any one of claims 1-59 or 75-86, wherein the phosphate group is a phosphodiester or a modified phosphate group.

88. The conjugate compound of claim 87, wherein the modified phosphate group is selected from one or more of: thio modified phosphate, amino modified phosphate,

20 **89.** The compound of claim 88, wherein the thio modified phosphate is phosphorothioate.

90. The conjugate compound of any one of claims 1-59 or 75-89, wherein
25 the oligonucleotide comprises one or more peptide nucleic acids and/or morpholino nucleic acids.

91. The conjugate compound of any one of claims 1-59 or 75-90, wherein
30 the oligonucleotide is an oligonucleotide of from 5 to 100 base pairs.

92. The compound of any one of claims 1-59 or 75-91, wherein the oligonucleotide conjugate compound is synthesized via solid-phase synthesis or liquid-phase synthesis.

5 **93.** A method for treating and/or preventing pathological conditions or diseases in a subject, wherein the conditions or diseases are caused by the expression of one or more genes in liver cells, the method comprising administering to the subject a compound of any one of claims 75-92; or a pharmaceutical composition comprising a compound of any one of claims 75-92, and a
10 pharmaceutically acceptable excipient.

94. A method for detecting or localizing RNA in the liver of a subject, comprising administering to the subject a compound of any one of claims 75-92; or a pharmaceutical composition comprising a compound of any one of claims 75-92,
15 and a pharmaceutically acceptable excipient.

95. The method of claim 93, wherein the one or more genes are selected from: HBV genome, HCV genome, *PCSK9*, a gene expressing xanthine oxidase (e.g., *XDH*), *URAT1*, *APOB*, liver fibrosis-related genes (e.g., *AP3S2*, *AQP2*, *AZIN1*,
20 *DEGSI*, *STXBP5L*, *TLR4*, *TRPM5*), genes related to non-alcoholic fatty liver disease (e.g., *PNPLA3*, *FDFTI*), and genes related to primary biliary cirrhosis (e.g., *HLA-DQB1*, *IL-12*, *IL-12RB2*).

96. The method of any one of claims 93-95, wherein the disease or
25 condition is selected from the group consisting of: hereditary angioedema, familial tyrosinemia type I, Alagille syndrome, α -1-antitrypsin deficiency, bile acid synthesis and metabolic defects, biliary atresia, cystic fibrosis liver disease, idiopathic neonatal hepatitis, mitochondrial liver disease, progressive familial intrahepatic cholestasis, primary sclerosing cholangitis, transthyretin amyloidosis,
30 hemophilia, homozygous familial hypercholesterolemia, hyperlipidemia, hepatitis B virus infection (HBV), hepatitis C virus infection (HCV), steatohepatitis,

nonalcoholic steatohepatitis (NASH), nonalcoholic fatty liver disease (NAFLD), hyperglycemia and diseases involving abnormally increased hepatic glucose production similar to type II diabetes, hepatitis, and hepatic porphyrins.

5 **97.** The method of any one of claims 93-96, wherein the compound or pharmaceutical composition is administered intravenously, intramuscularly, subcutaneously, via microneedle patches, orally, via oral or nasal spray, or topically.

10 **98.** The method of any one of claims 93-97, wherein the subject is a mammal.

99. The method of any one of claims 93-98, wherein the subject is selected from the group consisting of: bovine, equine, sheep, swine, canine, feline, rodent, and primate.

15 **100.** The method of any one of claims 93-99, wherein the subject is human.

101. A pharmaceutical composition comprising a compound of any one of claims 75-92 and a pharmaceutically acceptable excipient.

20 **102.** The pharmaceutical composition of claim 101, wherein the pharmaceutical composition is formulated in a dosage form selected from the group consisting of: powders, tablets, granules, capsules, solutions, emulsions, suspensions, injections, sprays, aerosols, dry powder inhalations, and microneedle
25 patches.

103. The pharmaceutical composition of claims 101 or 102, wherein the pharmaceutical composition is suitable for administration to a subject in need thereof intravenously, intramuscularly, subcutaneously, via microneedle patches,
30 orally, via oral or nasal spray, or topically.

104. The pharmaceutical composition of claim 103, wherein the subject is a mammal.

5 **105.** The pharmaceutical composition of claim 104, wherein the mammal is selected from the group consisting of: bovine, equine, sheep, swine, canine, feline, rodent, and primate.

10 **106.** The pharmaceutical composition of any one of claims 103-105, wherein the subject is human.