oligonucleotide was detected and analyzed on an Oligo HTCS LC-MS system (Novatia). After the first-level scan, the molecular weight was calculated through a normalized method on the Promass software.

**Example 15. Preparation of GalNAc-modified oligonucleotides**

The amino-modified oligonucleotide (sense strand) prepared in **Example 14** was dissolved in a buffer solution. Various GalNAc-pentafluorophenol esters (GalNAc selected from GalNAc-1 to GalNAc-10) dissolved in acetonitrile were respectively added to the amino-modified oligonucleotide solution, mixed well, and then reacted at room temperature for at least 3 hours. After the reaction is completed, the acetyl protecting group was removed, and the reaction product was purified by ion exchange chromatography (WATERS) using a linear gradient DNAPAc PA-100 ion exchange column. The mobile phase A solution was 20 mM NaOH, and the mobile phase B soluition was 20 mM NaOH + 2 M NaCl mixture.

**Table 1.** GalNAc-modified oligonucleotides (sense strand)

| **Sample Number** | **Structure（5'-3'）** | **Measured Molecular Weight** |
|---|---|---|
| Sense strand -101 | (SEQ ID NO:3)5'-GalNAc-1-mGfUmAfUmGfUfUmGfCfCfCmGfUfUfUmGfUfCmA3' | 7497.93 |
| Sense strand -102 | (SEQ ID NO:4)5'-GalNAc-2-mGfUmAfUmGfUfUmGfCfCfCmGfUfUfUmGfUfCmA3' | 7669.08 |
| Sense strand -103 | (SEQ ID NO:5)5'-GalNAc-3-mGfUmAfUmGfUfUmGfCfCfCmGfUfUfUmGfUfCmA3' | 7611.08 |
| Sense strand -104 | (SEQ ID NO:6)5'-GalNAc-4-mGfUmAfUmGfUfUmGfCfCfCmGfUfUfUmGfUfCmA3' | 7782.24 |
| Sense strand -105 | (SEQ ID NO:7)5'-GalNAc-5-mGfUmAfUmGfUfUmGfCfCfCmGfUfUfUmGfUfCmA3' | 7750.16 |
| Sense strand -106 | (SEQ ID NO:8)5'-GalNAc-6-mGfUmAfUmGfUfUmGfCfCfCmGfUfUfUmGfUfCmA3' | 7579.00 |
| Sense strand -107 | (SEQ ID NO:9)5'-GalNAc-7-mGfUmAfUmGfUfUmGfCfCfCmGfUfUfUmGfUfCmA3' | 7692.16 |

| | | |
|---|---|---|
| Sense strand - 108 | (SEQ ID NO:10)5'-GalNAc-8-mGfUmAfUmGfUfUmGfCfCfCmGfUfUfUmGfUfCmA3' | 7863.31 |
| Sense strand - 109 | (SEQ ID NO:11)5'-GalNAc-9-mGfUmAfUmGfUfUmGfCfCfCmGfUfUfUmGfUfCmA3' | 7753.27 |
| Sense strand - 110 | (SEQ ID NO:12)5'-GalNAc-10-mGfUmAfUmGfUfUmGfCfCfCmGfUfUfUmGfUfCmA3' | 7810.32 |

Note: N=RNA; dN=DNA; mN=2'OMe modification; and fN=2'F modification.

Sequence of exemplary modified oligonucleotides and corresponding molecular weight (MW) detection results are shown in Table 1.

**Example 16. Preparation of double-stranded oligonucleotides**

The experiment was carried out as follows: The 5'-Cy5-antisense strand oligonucleotides synthesized in Example 13 were respectively mixed with the sense strand-GalNAc-1-10 oligonucleotides prepared in Example 15, according to the UV absorption ratio of 1:1. The mixture was incubated at 95°C for 3 minutes in a heated water bath, then cooled to room temperature to form double-stranded oligonucleotides.

**Table 2.** Double-stranded RNA structures

| Sample number | Double-stranded structure（5'-3'） |
|---|---|
| 101 | (SEQ ID NO:13)5'-GalNAc-1-mGfUmAfUmGfUfUmGfCfCfCmGfUfUfUmGfUfCmA-3'<br>(SEQ ID NO:14)3'-fCmAfUmAfCmAmAfCmGmGmGfCmAmAmAfCmAmGmU-Cy5-5' |
| 102 | (SEQ ID NO:15)5'-GalNAc-2-mGfUmAfUmGfUfUmGfCfCfCmGfUfUfUmGfUfCmA3'<br>(SEQ ID NO:16)3'-fCmAfUmAfCmAmAfCmGmGmGfCmAmAmAfCmAmGmU-Cy5-5' |
| 103 | (SEQ ID NO:17)5'-GalNAc-3-mGfUmAfUmGfUfUmGfCfCfCmGfUfUfUmGfUfCmA3'<br>(SEQ ID NO:18)3'-fCmAfUmAfCmAmAfCmGmGmGfCmAmAmAfCmAmGmU-Cy5-5' |
| 104 | (SEQ ID NO:19)5'-GalNAc-4-mGfUmAfUmGfUfUmGfCfCfCmGfUfUfUmGfUfCmA3'<br>(SEQ ID NO:20)3'-fCmAfUmAfCmAmAfCmGmGmGfCmAmAmAfCmAmGmU-Cy5-5' |
| 105 | (SEQ ID NO:21)5'-GalNAc-5-mGfUmAfUmGfUfUmGfCfCfCmGfUfUfUmGfUfCmA3'<br>(SEQ ID NO:22)3'-fCmAfUmAfCmAmAfCmGmGmGfCmAmAmAfCmAmGmU-Cy5-5' |
| 106 | (SEQ ID NO:23)5'-GalNAc-6-mGfUmAfUmGfUfUmGfCfCfCmGfUfUfUmGfUfCmA3'<br>(SEQ ID NO:24)3'-fCmAfUmAfCmAmAfCmGmGmGfCmAmAmAfCmAmGmU-Cy5-5' |
| 107 | (SEQ ID NO:25)5'-GalNAc-7-mGfUmAfUmGfUfUmGfCfCfCmGfUfUfUmGfUfCmA3'<br>(SEQ ID NO:26)3'-fCmAfUmAfCmAmAfCmGmGmGfCmAmAmAfCmAmGmU-Cy5-5' |

| | |
|---|---|
| 108 | (SEQ ID NO:27)5'-GalNAc-8-mGfUmAfUmGfUfUmGfCfCfCmGfUfUfUmGfUfCmA3'<br>(SEQ ID NO:28)3'-fCmAfUmAfCmAmAfCmGmGmGfCmAmAmAfCmAmGmU-Cy5-5' |
| 109 | (SEQ ID NO:29)5'-GalNAc-9-mGfUmAfUmGfUfUmGfCfCfCmGfUfUfUmGfUfCmA3'<br>(SEQ ID NO:30)3'-fCmAfUmAfCmAmAfCmGmGmGfCmAmAmAfCmAmGmU-Cy5-5' |
| 110 | (SEQ ID NO:31)5'-GalNAc-10-mGfUmAfUmGfUfUmGfCfCfCmGfUfUfUmGfUfCmA3'<br>(SEQ ID NO:32)3'-fCmAfUmAfCmAmAfCmGmGmGfCmAmAmAfCmAmGmU-Cy5-5' |

Note: N=RNA; dN=DNA; mN=2'OMe modification; and fN=2'F modification.

**Example 17. Detection of cell targeting capability of modified oligonucleotides**

Modified oligonucleotides for animal experiments were filtered through a 0.22 μm membrane before injection.

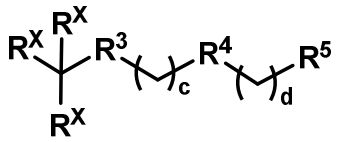
*1. Isolation of mouse primary hepatocytes*

Mice obtained from Beijing Vital River Laboratory Animal Technology Co., Ltd. were anesthetized. Mouse skin and muscle layer were cut open to expose the liver. Perfusion catheter was inserted into the portal vein, and a small opening was cut in the inferior vena cava to prepare the liver for perfusion. The perfusion Solution I (Hank's, 0.5 mM EGTA, pH 8) and perfusion Solution II (low-glucose DMEM, 100 U/mL Type IV, pH 7.4) were pre-warmed to 40°C. The perfusion solution I (at 37°C) was infused into the liver along the portal vein at a flow rate of 7 mL/min for 5 minutes until the liver turned gray. Then, the liver was perfused with 37°C perfusion Solution II at a flow rate of 7 mL/min for 7 minutes. After the perfusion is complete, the liver was isolated and placed in Solution III (10% FBS, low-glucose DMEM, 4°C) to terminate the digestion. The liver envelope was pierced with forceps, and gently shaken to release the hepatocytes. The hepatocytes were filtered with a 70 μm cell strainer, and then centrifuged at 50 g for 2 minutes. After centrifugation, supernatant was discarded. The hepatocytes were then resuspended in Solution IV (40% percoll low-glucose DMEM, 4°C), and centrifuged at 100 g for 2 minutes. Supernatant was discarded, and 2% FBS low-glucose DMEM was added to resuspend the cells for subsequence experiments. Trypan blue staining was used to measure cell viability.

*2. Determination of the GalNAc binding curve and Kd value*

**WHAT IS CLAIMED IS:**

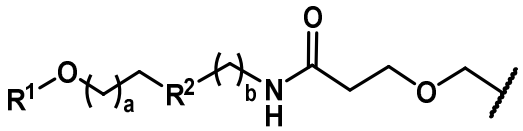
1. A compound of Formula **(I)**:



Formula **(I)**

or a pharmaceutically acceptable salt thereof, wherein:

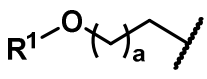
each $\mathbf{R^X}$ is independently selected from the group consisting of:

- H; and
- $-CH_2O\mathbf{R^{X2}}$, wherein $\mathbf{R^{X2}}$ is H, $C_{1\text{-}6}$ alkyl, or a hydroxyl protecting group;
-  **(A1)**,

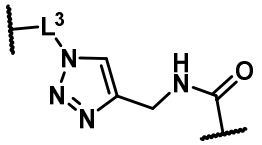
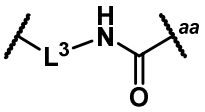
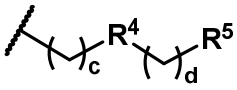
provided that at least one $\mathbf{R^X}$ is a group of Formula **(A1)**;

each $\mathbf{R^1}$ is an independently selected moiety capable of binding an asialoglycoproteinreceptor (ASGPR);

each $\mathbf{R^2}$ is independently selected from the group consisting of: $-C(\mathbf{R^6})_2-$; $-OC(\mathbf{R^6})_2C(\mathbf{R^6})_2O-$; $-C(\mathbf{R^6})(OH)-C(\mathbf{R^6})(OH)-$; *-C(=O)N$\mathbf{R^7}$-; *-N$\mathbf{R^7}$C(=O)-; $C_{6\text{-}10}$ arylene; $C_{2\text{-}6}$ alkenylene; and $C_{2\text{-}6}$ alkynylene,

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

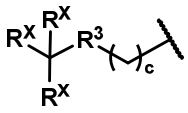
$\mathbf{R^3}$ is selected from the group consisting of:

- ; , wherein ***aa*** represents the point of attachment to ;
- -(C**R**$^{6}$**R**$^{6}$)$_{x}$-O-(C**R**$^{6}$**R**$^{6}$)$_{y}$-, wherein **x** and **y** are independently 0, 1, 2, or 3; and
- -**L**$^{3}$-**L**$^{3C}$-, wherein **L**$^{3C}$ 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**$^{a}$;

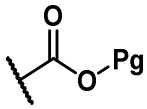
**L**$^{3}$ is –C(**R**$^{6}$)$_{2}$-,

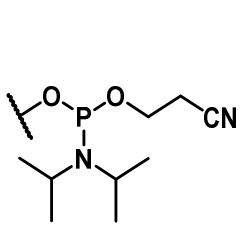
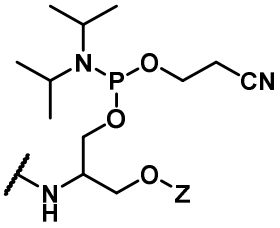
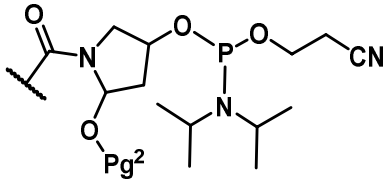
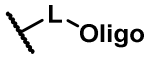
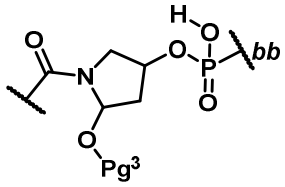
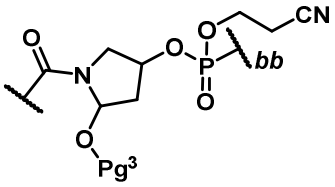
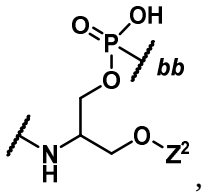
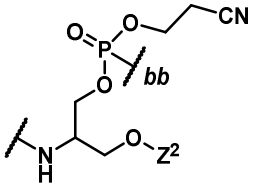
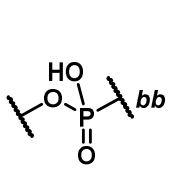
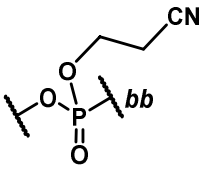
**R**$^{4}$ is selected from the group consisting of: -C(**R**$^{6}$)$_{2}$-; -OC(**R**$^{6}$)$_{2}$C(**R**$^{6}$)$_{2}$O-; -C(**R**$^{6}$)(OH)-C(**R**$^{6}$)(OH)-; *-C(=O)N**R**$^{7}$-; *-N**R**$^{7}$C(=O)-; $C_{6-10}$ arylene, $C_{3-10}$ cycloalkylene, 5-10 membered heteroarylene, and 4-10 membered 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 selected **R**$^{a}$, and

wherein the * represents the point of attachment to ;

**R**$^{5}$ is selected from the group consisting of:

- hydroxyl; C(O)OH;
-  wherein **Pg** is a carboxyl activating group or a carboxyl protecting group;

-  ;  wherein **Z** is a hydroxyl protecting group;
-  , wherein **Pg$^2$** is a hydroxyl protecting group; and
- , wherein: **L** is a bond or a divalent group selected from the group consisting of:
  - **-R$^2$-**, **-R$^3$-**, **-R$^4$-**, -O-, -C(=O)-, -C(=O)O-, -OC(=O)-,
  -  ,  , wherein **Pg$^3$** is H or **Pg$^2$**;
  -  ,  , wherein **Z$^2$** is H or a hydroxyl protecting group; and
  -  or  ;

    wherein ***bb*** represents the point of attachment to **Oligo**, and
  - **Oligo** is an oligonucleotide;

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

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

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

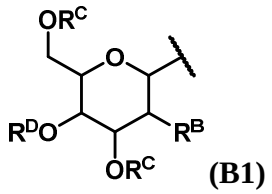
**c** and **d** are each independently selected integers from 0 to 10; and

each occurrence of $\mathbf{R^a}$ 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.

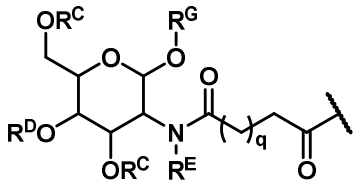
2. The compound of claim 1, wherein at least two $\mathbf{R^X}$ are each independently a group of Formula **(A1)**;~~.~~

preferably, ~~3. The compound of claims 1 or 2, wherein~~ each $\mathbf{R^X}$ is independently a group of Formula **(A1**).

3~~4~~. The compound of any one of claims 1-~~3~~2, wherein each $\mathbf{R^1}$ is independently a group of Formula **(B1)** or **(B2)**:

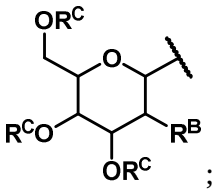



**(B1)**




**(B2)**

wherein:



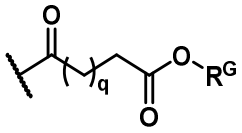
$\mathbf{R^D}$ is selected from the group consisting of: $\mathbf{R^C}$ and ;

each $\mathbf{R^B}$ is independently selected from the group consisting of: -N$\mathbf{R^E R^F}$ and -O$\mathbf{R^C}$;

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

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

each $\mathbf{R^F}$ is independently selected from the group consisting of: H and

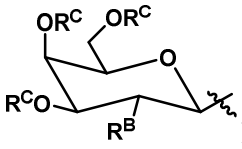


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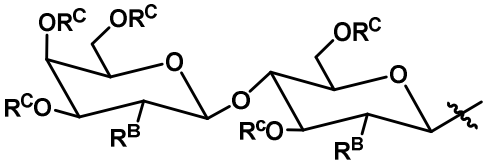
$\mathbf{R^G}$ is $C_{1\text{-}6}$ alkyl; and

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

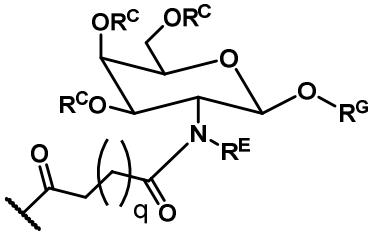
preferably, ~~5. The compound of claim 4, wherein~~ each $\mathbf{R^1}$ is independently a group having Formula **(B1-a)**, **(B1-b)**, or **(B2-a**):



Formula **(B1-a)**



Formula **(B1-b**)



Formula **(B2-a)**~~.~~;

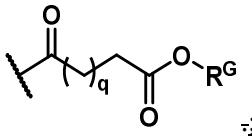
preferably,~~6. The compound of claims 4 or 5, wherein~~ each $\mathbf{R^B}$ is independently $N\mathbf{R^E}\mathbf{R^F}$~~.~~;

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

preferably,~~8. The compound of any one of claims 4-7, wherein~~ each $\mathbf{R^E}$ is -C(=O)$CH_3$~~.~~;

preferably,~~9. The compound of any one of claims 4-8, wherein~~ each $\mathbf{R^F}$ is H~~.~~;

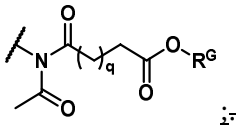
preferably,~~10. The compound of any one of claims 4-8, wherein~~ each $\mathbf{R^F}$ is



~~.~~;

preferably,~~11. The compound of any one of claims 4-6, wherein~~ each $\mathbf{R^B}$ is NHC(=O)$CH_3$~~.~~;

preferably,~~12. The compound of any one of claims 4-6, wherein~~ each $\mathbf{R^B}$ is



~~.~~;

preferably,~~13. The compound of claims 4 or 5, wherein~~ each $\mathbf{R^B}$ is independently –O$\mathbf{R^C}$~~.~~;

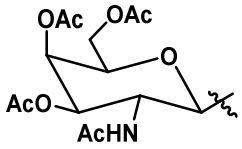
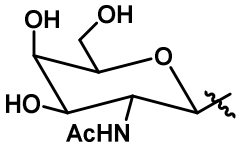
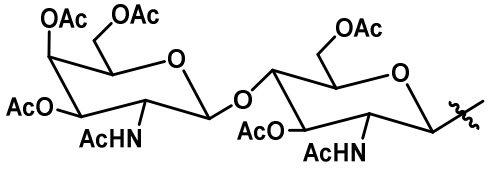
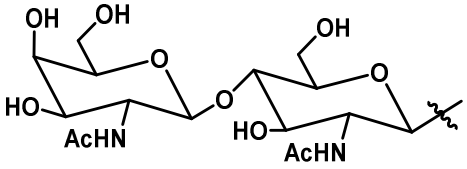
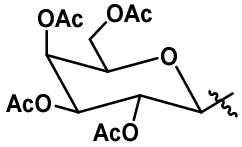
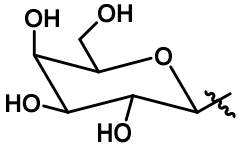
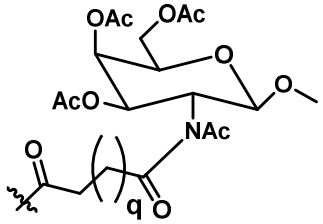
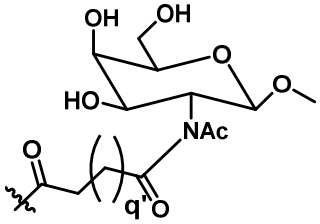
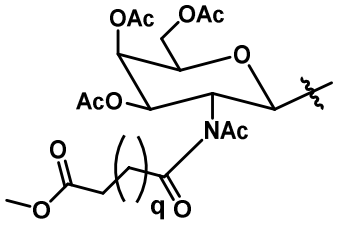
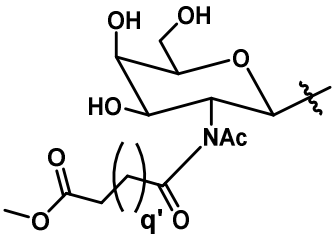
preferably,~~14. The compound of any one of claims 4-13, wherein~~ each $\mathbf{R^C}$ is independently C(=O)$C_{1\text{-}6}$ alkyl~~.~~;

preferably,~~15. The compound of any one of claims 4-14, wherein~~ each $\mathbf{R^C}$ is C(=O)$CH_3$~~.~~;

preferably, ~~16. The compound of any one of claims 4-14, wherein~~ each $\mathbf{R^C}$ is H~~.~~;

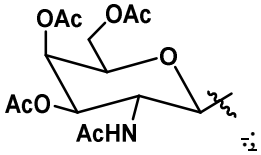
preferably,~~17. The compound of any one of claims 4-16, wherein~~ each $\mathbf{R^G}$ is $CH_3$.

~~184~~. The compound of any one of claims 1-~~5~~3, wherein each $\mathbf{R^1}$ is selected from the group consisting of the following:

| | |
|---|---|
|  |  |
|  |  |
|  |  |
| <br>wherein, **q** is an integer selected from 1 to 10; | <br>wherein, **q'** is an integer selected from 1 to 10; |
| <br>wherein, **q** is an integer selected from 1 to 10; | <br>wherein, **q'** is an integer selected from 1 to 10. |

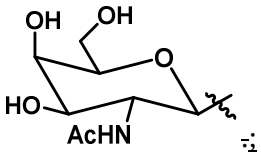
~~195~~. The compound of any one of claims 1-~~184~~, wherein each $\mathbf{R^1}$ is the same~~.~~;

preferably, ~~20. The compound of any one of claims 1-19, wherein~~ each $\mathbf{R^1}$ is




~~.~~;

preferably, ~~21. The compound of any one of claims 1-19, wherein~~ each $\mathbf{R^1}$ is




~~.~~;

preferably, ~~22. The compound of any one of claims 1-21, wherein~~ each $\mathbf{R^2}$ is independently *-C(=O)N$\mathbf{R^7}$- or *-N$\mathbf{R^7}$C(=O)-~~.~~;

preferably, ~~23. The compound of any one of claims 1-22, wherein~~ each $\mathbf{R^2}$ is independently *-C(=O)N$\mathbf{R^7}$-~~.~~;

preferably, ~~24. The compound of any one of claims 1-23, wherein~~ each $\mathbf{R^2}$ is *-C(=O)NH-~~.~~;

preferably, ~~25. The compound of any one of claims 1-21, wherein~~ each $\mathbf{R^2}$ is independently -C($\mathbf{R^6}$)$_2$-~~.~~;

preferably,~~26. The compound of any one of claims 1-21 or 25, wherein~~ each $\mathbf{R^2}$ is –$CH_2$-~~.~~;

preferably,~~27. The compound of any one of claims 1-26, wherein~~ each $\mathbf{R^2}$ is the same~~.~~;

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

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

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

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

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

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

~~34~~6. The compound of any one of claim 1-~~21~~5, wherein each **a** is the same; each **b** is the same; and each $\mathbf{R^2}$ is the same~~.~~;

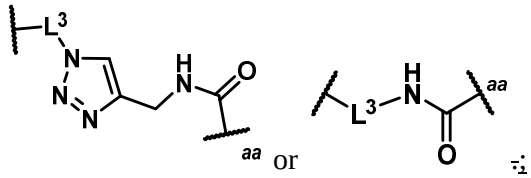
preferably,~~35. The compound of claim 34, wherein~~ **a** is an integer from 1 to 4; **b** is an integer from 1 to 4; and $\mathbf{R^2}$ is *-C(=O)N$\mathbf{R^7}$~~.~~;

preferably,~~36. The compound of claim 35, wherein~~ **a** is 3; **b** is 3; and $\mathbf{R^2}$ is *-C(=O)NH~~.~~;

preferably,~~37. The compound of claim 34, wherein~~ **a** is an integer from 1 to 4; **b** is an integer from 1 to 4; and $\mathbf{R^2}$ is –C($\mathbf{R^6}$)$_2$-~~.~~;

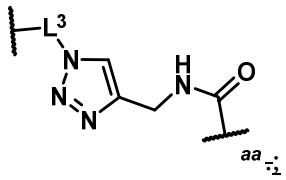
preferably,~~38. The compound of claim 37, wherein~~ $\mathbf{R^2}$ is –$CH_2$-; and $3 \leq (\mathbf{a}+\mathbf{b}) \leq 5$.

~~39~~7. The compound of any one of claims 1-~~38~~6, wherein $\mathbf{R^3}$ is



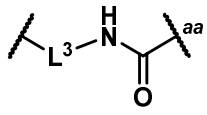

~~.~~;

preferably,~~40. The compound of any one of claims 1-39, wherein~~ **R³** is




~~.~~;

preferably,~~41. The compound of any one of claims 1-39, wherein~~ **R³** is




~~.~~;

preferably,~~42. The compound of any one of claims 1-41, wherein~~ **L³** is –C(**R⁶**)₂-~~.~~;

preferably,~~43. The compound of any one of claims 1-42, wherein~~ **L³** is –CH₂-~~.~~;

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

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

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

preferably,~~47. The compound of any one of claims 1-46, wherein~~ **R⁴** is *-C(=O)N**R⁷**-~~.~~;

preferably,~~48. The compound of any one of claims 1-47, wherein~~ **R⁴** is *-C(=O)NH-~~.~~;

preferably,~~49. The compound of any one of claims 1-46, wherein~~ **R⁴** is –C(**R⁶**)₂-~~.~~;

preferably,~~50. The compound of any one of claims 1-46 or 49, wherein~~ **R$^4$** is –$CH_2$-~~.~~;

preferably,~~51. The compound of any one of claims 1-50, wherein~~ **d** is an integer from 1 to 2~~.~~;

preferably,~~52. The compound of any one of claims 1-50, wherein~~ **d** is an integer from 3 to 7.

~~53~~8. The compound of any one of claims 1-~~43~~7, wherein **R$^4$** is –C(**R$^6$**)$_2$-; and each of **c** and **d** is independently 1 or 2~~.~~;

preferably,~~54. The compound of claim 53, wherein~~ **R$^4$** is –$CH_2$-; and each of **c** and **d** is 1~~.~~;

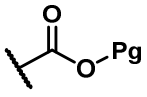
preferably,~~55. The compound of any one of claims 1-43, wherein~~ **R$^4$** is –C(**R$^6$**)$_2$-; and $4 \leq (\mathbf{c} + \mathbf{d}) \leq 12$~~.~~;

preferably,~~56. The compound of claim 55, wherein~~ **R$^4$** is –$CH_2$-; and $7 \leq (\mathbf{c} + \mathbf{d}) \leq 10$~~.~~;

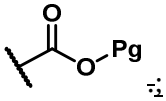
preferably,~~57. The compound of any one of claims 1-43, wherein~~ **R$^4$** is *–C(=O)N**R$^7$**-; and $5 \leq (\mathbf{c} + \mathbf{d}) \leq 10$~~.~~;

preferably,~~58. The compound of claim 57, wherein~~ **R$^4$** is *–C(=O)N**R$^7$**-; and $7 \leq (\mathbf{c} + \mathbf{d}) \leq 9$~~.~~;

preferably,~~59. The compound of claims 57 or 58, wherein~~ **c** is 3.

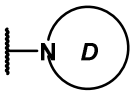
~~60~~9. The compound of any one of claims 1-~~59~~8, wherein $\mathbf{R^5}$ is C(O)OH or 

~~.~~;

preferably,~~61. The compound of any one of claims 1-59, wherein~~ $\mathbf{R^5}$ is 

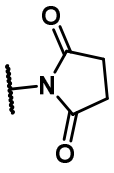
~~.~~;

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

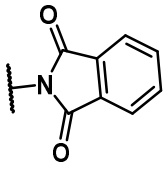
preferably,~~63. The compound of any one of claims 1-62, wherein~~ **Pg** is 

, 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~~.~~;

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

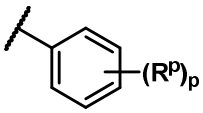
**(i)** 

; or

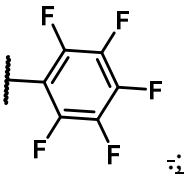
**(ii)** 

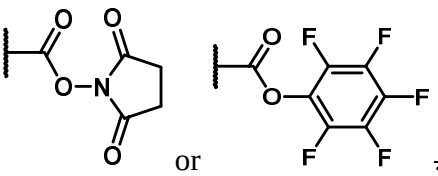
which is optionally substituted with 1-6 substituents each independently selected from the group consisting of: halo, $NO_2$, $C(O)C_{1-4}$ alkyl, $C(O)OC_{1-4}$ alkyl, $S(O)C_{1-4}$ alkyl, $C_{1-6}$ alkyl, $C_{1-6}$ haloalkyl, and –OH~~.~~;

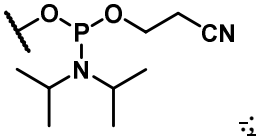
preferably,~~65. The compound of any one of claims 1-62, wherein~~ **Pg** is $C_{6-10}$ aryl or 5-10 membered heteroaryl substituted with 1-6 substituents each independently selected from the group consisting of: -F; -Cl; -$NO_2$; $C(O)C_{1-4}$ alkyl, $C(O)OC_{1-4}$ alkyl, and $S(O)C_{1-4}$ alkyl~~.~~;

preferably,~~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 $\mathbf{R^p}$ is –F, -Cl, or –$NO_2$~~.~~;

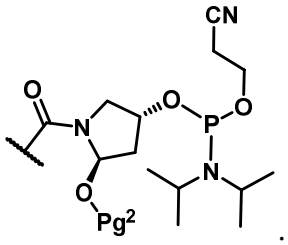
preferably,~~67. The compound of claim 66, wherein~~ each $\mathbf{R^p}$ is –F~~.~~;

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

preferably,~~69. The compound of any one of claims 1-62, wherein~~ $\mathbf{R^5}$ is ~~.~~;

preferably,~~70. The compound of any one of claims 1-59, wherein~~ $\mathbf{R^5}$ is ~~.~~;

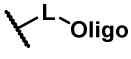
preferably,~~71. The compound of any one of claims 1-59, wherein~~ **R**$^{5}$ is




~~72~~10. The compound of any one of claims 1-~~71~~8, 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)~~.~~;

preferably,~~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).

~~74~~11. The compound of claim 1, wherein the compound is selected from the group consisting of compounds **GalNAc-1** through **GalNAc-12**.

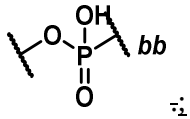
~~75~~12. The compound of any one of claims 1-~~59~~8, wherein **R**$^{5}$ is 

, 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~~.~~;

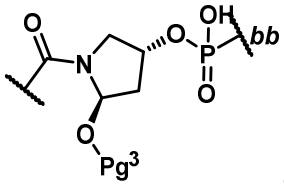
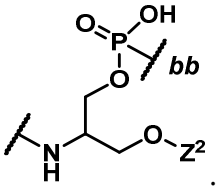
preferably,~~76. The compound of any one of claims 1-59 or 75, wherein~~ **L** is a bond~~.~~;

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

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



~~.~~;

preferably,~~79. The compound of any one of claims 1-59 or 75, wherein~~ **L** is selected from the group consisting of:  and .

~~80~~13. The compound of any one of claims 1-~~59~~ 7 or ~~75-79~~12, wherein the oligonucleotide comprises a single-stranded oligonucleotide and/or a double-stranded oligonucleotide~~.~~;

preferably,~~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, tracRNA, and sgRNA.

~~82~~14. The compound of any one of claims 1-~~59~~ 7 or ~~75~~12-~~81~~13, wherein the oligonucleotide comprises unmodified nucleotides and/or modified nucleotides~~.~~;

preferably,~~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~~.~~;

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

~~85~~15. The compound of any one of claims 1-~~59~~ 7 or ~~75-84~~12-14, 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~~.~~;

preferably,~~86. The compound of claim 85, wherein~~ the modifying group is a terminal modifying group~~.~~;

preferably,~~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~~.~~;

preferably,~~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,

preferably,~~89. The compound of claim 88, wherein~~ the thio modified phosphate is phosphorothioate~~.~~;

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

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

preferably,~~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.

~~93~~16. A compound of any one of claims 12-15; or a pharmaceutical composition comprising a compound of any one of claims 12-15, and a pharmaceutically acceptable excipient for use in the treatment or prevention of~~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 pharmaceutically acceptable excipient~~;

preferably, 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*, *AZINl*, *DEGSl*, *STXBP5L*, *TLR4*, *TRPM5*), genes related to non-alcoholic fatty liver disease (e.g., *PNPLA3*, *FDFTl*), and genes related to primary biliary cirrhosis (e.g., *HLA-DQB1*, *IL-12*, *IL-12RB2*).

17~~94~~. A method for detecting or localizing RNA in the liver of a subject, ~~comprising administering to the subject~~wherein a compound of any one of claims 12-15~~75-92~~; or a pharmaceutical composition comprising a compound of any one of claims12-15~~75-92~~, and a pharmaceutically acceptable excipient is to be administered to the subject.

~~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*, *AZINl*, *DEGSl*, *STXBP5L*, *TLR4*, *TRPM5*), genes related to non-alcoholic fatty liver disease (e.g., *PNPLA3*, *FDFTl*), and genes related to primary biliary cirrhosis (e.g., *HLA-DQB1*, *IL-12*, *IL-12RB2*).~~;

~~96~~18. The method of any one of claims ~~93~~16-~~95~~17, wherein the disease or 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, 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~~.~~;

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

preferably,~~98. The method of any one of claims 93-97, wherein~~ the subject is a mammal~~.~~;

preferably,~~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~~.~~;

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

~~101~~19. A pharmaceutical composition comprising a compound of any one of claims 12-15~~75-92~~ and a pharmaceutically acceptable excipient.

~~102~~20. The pharmaceutical composition of claim ~~101~~19, 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 patches~~.~~;

preferably,~~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, orally, via oral or nasal spray, or topically~~.~~;

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

preferably, ~~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~~.~~;

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