METHODS AND COMPOSITIONS FOR TREATMENT OF POLYCYSTIC KIDNEY DISEASE

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority of US Provisional Application No. 63/253,933, filed October 8, 2021, which is incorporated by reference herein in its entirety for any purpose.

FIELD

[0002] Provided herein are compositions and methods for the treatment of polycystic kidney disease.

BACKGROUND

[0003] Polycystic kidney disease is characterized by the accumulation of numerous fluid-filled cysts in the kidney. These cysts are lined by a single layer of epithelial cells called the cyst epithelium. Over time, the cysts increase in size due to elevated cell proliferation and active secretion of fluid by the cyst epithelium. The enlarged cysts compress surrounding normal tissue, resulting in a decline of kidney function. The disease eventually progresses to end-stage renal disease, requiring dialysis or kidney transplant. At this stage, the cysts may be surrounded by areas of fibrosis containing atrophic tubules. Polycystic kidney disease can also cause cysts to develop in the liver and elsewhere in the body.

[0004] A number of genetic disorders can result in polycystic kidney disease (PKD). The various forms of PKD are distinguished by the manner of inheritance, for example, autosomal dominant or autosomal recessive inheritance; the involvement of organs and presentation of phenotypes outside of the kidney; the age of onset of end-stage renal disease, for example, at birth, in childhood or adulthood; and the underlying genetic mutation that is associated with the disease. *See*, for example, Kurschat et al., 2014, Nature Reviews Nephrology, 10: 687–699.

SUMMARY

[0004a] In one aspect, the disclosure provides a compound comprising a modified oligonucleotide, wherein the modified oligonucleotide has the following structure in the 5’ to 3’ orientation:

$$(N'')_p\text{-}(N)_r\text{-}(N')_q$$

wherein each N” is, independently, a modified or unmodified nucleoside;

p is from 0 to 14; wherein if p is not 0, the nucleobase sequence of $(N'')_p$ is complementary to an equal-length portion of the nucleobase sequence of miR-17;

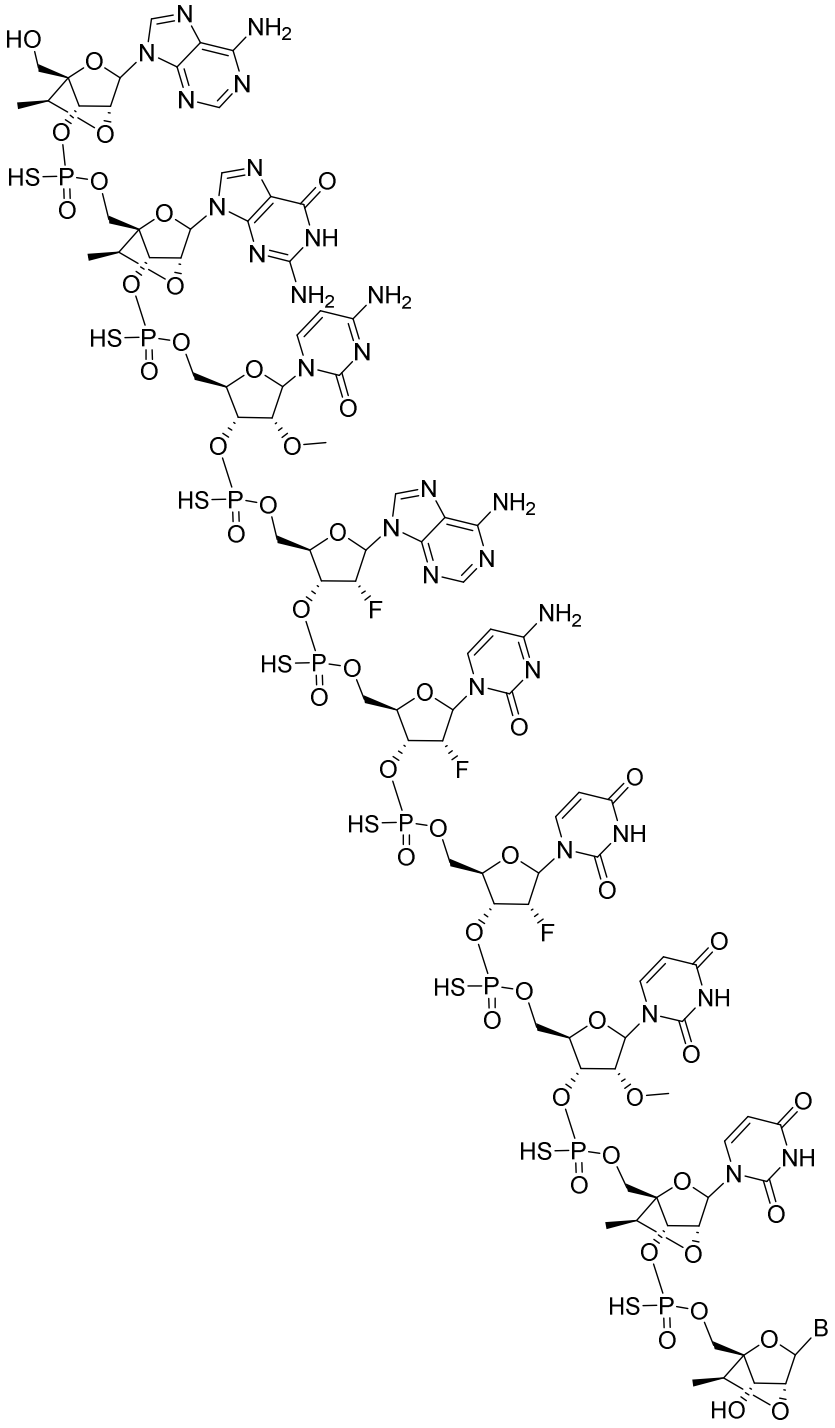
each N of $(N)_r$ is, independently, a modified or unmodified nucleotide, and the nucleobase sequence of $(N)_r$ is 5’-AGCACUUU-3’;

N’ is a nucleoside comprising a modified sugar moiety;

q is 0 or 1; wherein if q is 1, the nucleobase of N’ is a uracil nucleobase, a cytosine nucleobase, or a purine nucleobase, provided that the purine nucleobase does not have a hydrogen bond acceptor at position 6; and

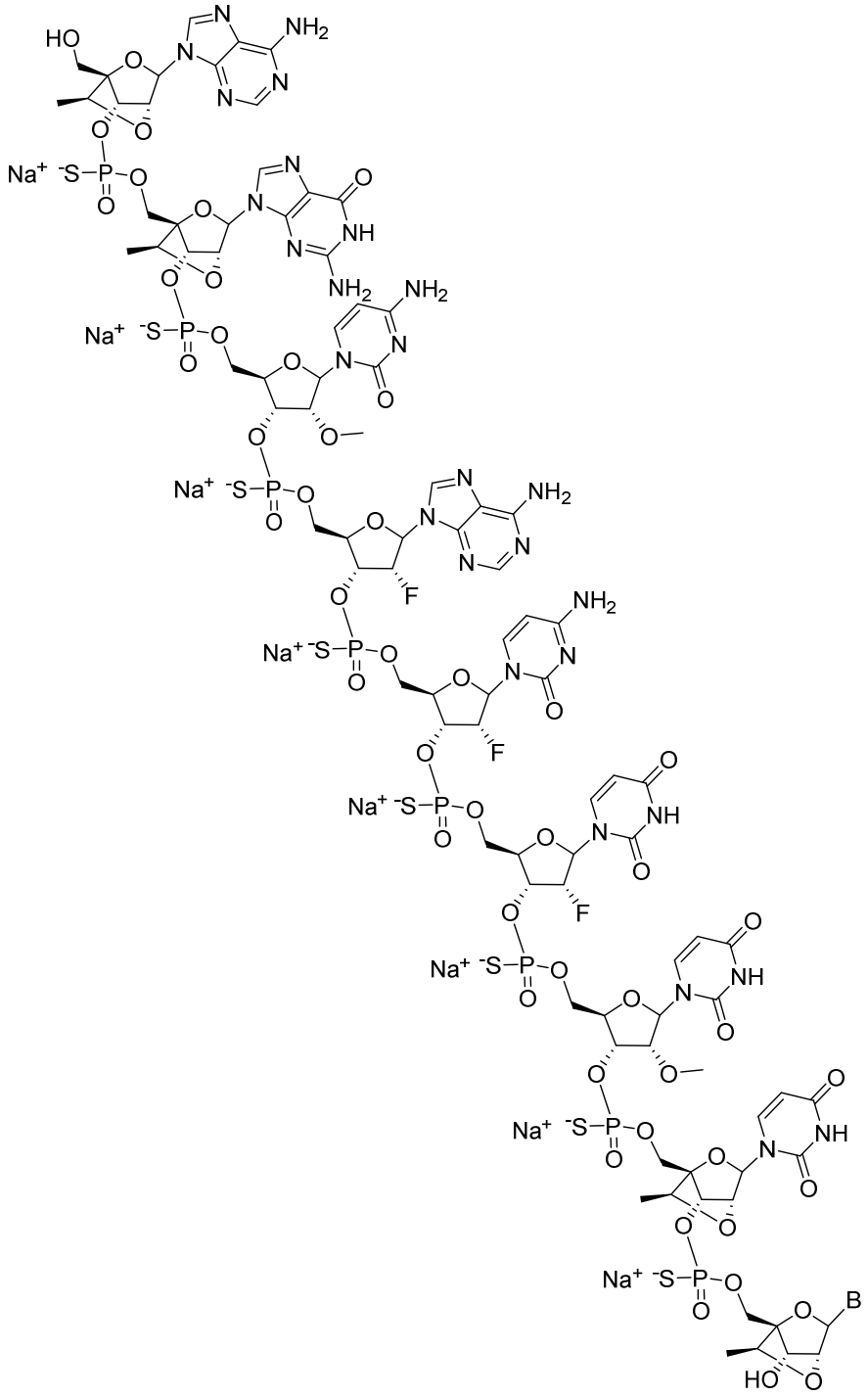
each cytosine is independently selected from a non-methylated cytosine and a 5-methylcytosine; or a pharmaceutically acceptable salt thereof.

[0004b] In one aspect, the disclosure provides a modified oligonucleotide having the structure:



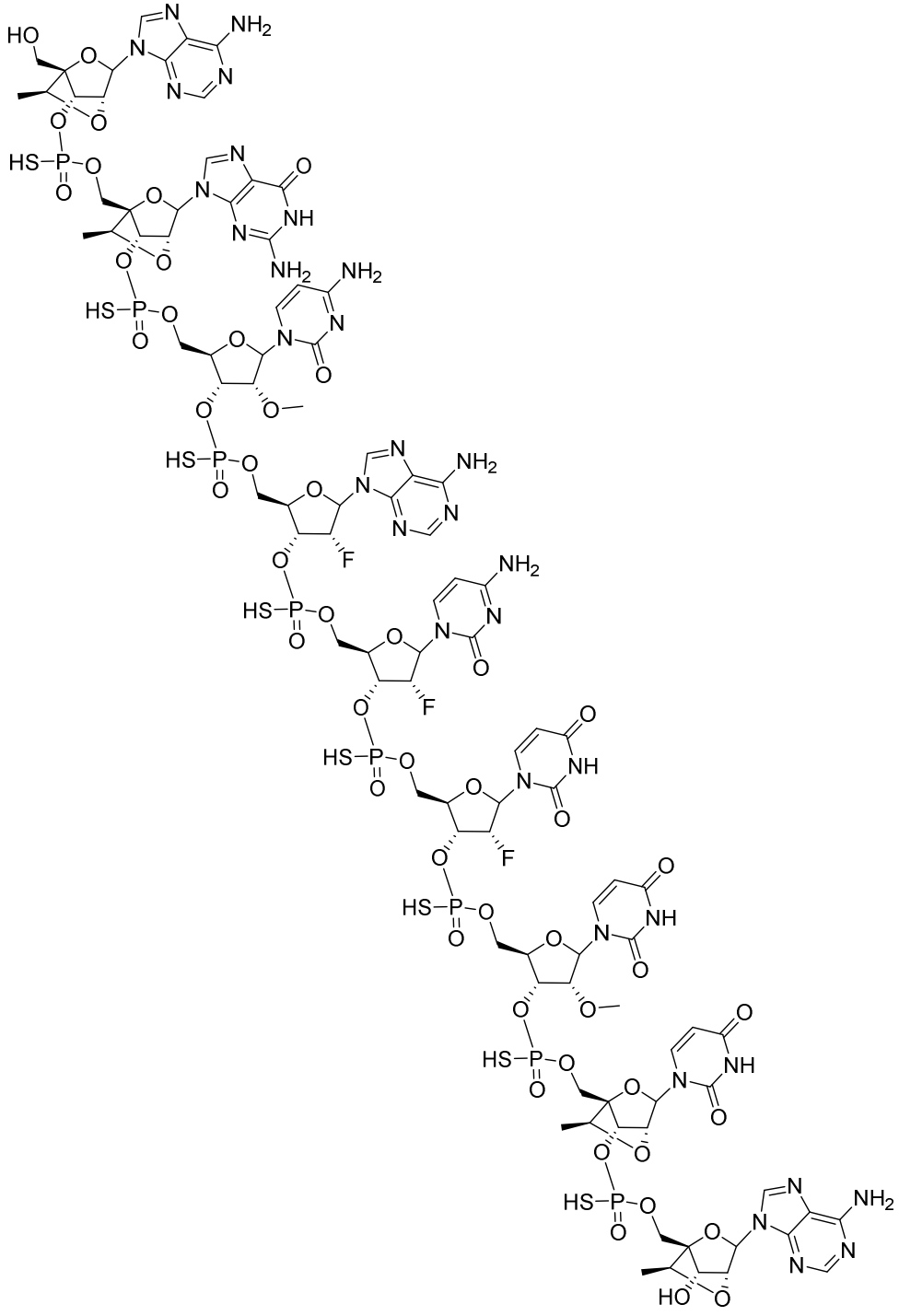
wherein B is a uridine nucleobase, a cytosine nucleobase, or a purine nucleobase, provided that the purine nucleobase does not have a hydrogen bond acceptor at position 6; or a pharmaceutically acceptable salt thereof, optionally wherein B is selected from adenosine, 2-aminopurine, 2,6-diaminopurine, and isoguanosine.

[0004c] In one aspect, the disclosure provides a modified oligonucleotide having the structure:



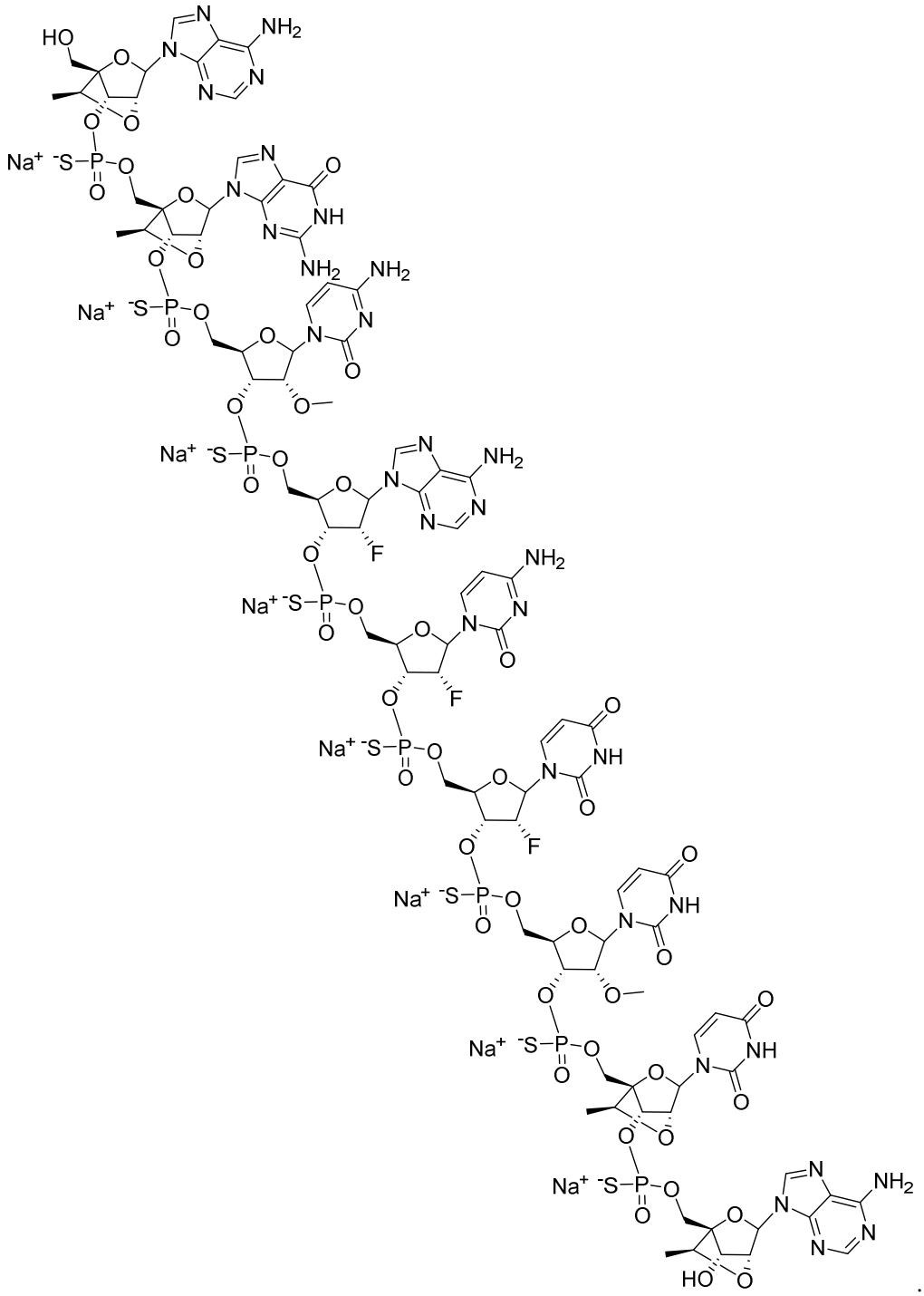
wherein B is a uridine nucleobase, a cytosine nucleobase, or a purine nucleobase, provided that the purine nucleobase does not have a hydrogen bond acceptor at position 6, optionally wherein B is selected from adenosine, 2-aminopurine, 2,6-diaminopurine, and isoguanosine.

[0004d] In one aspect, the disclosure provides a modified oligonucleotide having the structure:



or a pharmaceutically acceptable salt thereof.

[0004e] In one aspect, the disclosure provides a modified oligonucleotide having the structure:



[0004f] In one aspect, the disclosure provides a pharmaceutical composition comprising a compound as disclosed herein or a modified oligonucleotide as disclosed herein and a pharmaceutically acceptable diluent, optionally wherein the pharmaceutically acceptable diluent is an aqueous solution, optionally wherein the aqueous solution is a saline solution.

[0004g] In one aspect, the disclosure provides a pharmaceutical composition comprising a compound as disclosed herein or a modified oligonucleotide as disclosed herein, which is a lyophilized composition.

[0004h] In one aspect, the disclosure provides a pharmaceutical composition consisting essentially of a compound as disclosed herein or a modified oligonucleotide as disclosed herein in a saline solution.

[0004i] In one aspect, the disclosure provides an *in vitro* method for inhibiting the activity of one or more members of the miR-17 family in a cell, comprising contacting the cell with a compound as disclosed herein or a modified oligonucleotide as disclosed herein.

[0004j] In one aspect, the disclosure provides use of a compound as disclosed herein, a modified oligonucleotide as disclosed herein, or a pharmaceutical composition as disclosed herein in the manufacture of a medicament for inhibiting the activity of one or more members of the miR-17 family in a subject.

[0004k] In one aspect, the disclosure provides use of a compound as disclosed herein, a modified oligonucleotide as disclosed herein, or a pharmaceutical composition as disclosed herein in the manufacture of a medicament for treating polycystic kidney disease in a subject in need thereof.

Example 1. A compound comprising a modified oligonucleotide, wherein the modified oligonucleotide has the following structure in the 5' to 3' orientation:

$$(N'')_p\text{-}(N)_r\text{-}(N')_q$$

wherein each N" is, independently, a modified or unmodified nucleoside;

p is from 0 to 14; wherein if p is not 0, the nucleobase sequence of $(N'')_p$ is complementary to an equal-length portion of the nucleobase sequence of miR-17;

each N of $(N)_r$ is, independently, a modified or unmodified nucleotide, and the nucleobase sequence of $(N)_r$ is 5'-AGCACUUU-3';

N' is a nucleoside comprising a modified sugar moiety;

q is 0 or 1; wherein if q is 1, the nucleobase of N' is a uracil nucleobase, a cytosine nucleobase, or a purine nucleobase, provided that the purine nucleobase does not have a hydrogen bond acceptor at position 6; and

each cytosine is independently selected from a non-methylated cytosine and a 5-methylcytosine; or a pharmaceutically acceptable salt thereof.

Example 2. The compound of example 1, wherein the structure of $(N)_r$ is:

$A_SG_SC_MA_FC_FU_FU_MU_S$

wherein nucleosides followed by subscript "M" are 2'-O-methyl nucleosides;

nucleosides followed by subscript "F" are 2'-fluoro nucleosides; and

nucleosides followed by subscript "S" are S-cEt nucleosides.

Example 3. The compound of example 1 or example 2, wherein at least one internucleoside linkage is a phosphorothioate internucleoside linkage.

Example 4. The compound of any one of examples 1 to 3, wherein each internucleoside linkage is a phosphorothioate internucleoside linkage.

Example 5. The compound of any one of examples 1 to 4, wherein q is 1.

Example 6. The compound of any one of examples 1 to 4, wherein q is 0.

Example 7. The compound of any one of examples 1 to 6, wherein p is 0.

Example 8. The compound of any one of examples 1 to 6, wherein p is selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14.

Example 9. The compound of example 8, wherein the nucleobase sequence of $(N'')_p$ has no more than one mismatch to the nucleobase sequence of miR-17 (SEQ ID NO: 1).

Example 10. The compound of example 8, wherein the nucleobase sequence of $(N'')_p$ has no mismatches to the nucleobase sequence of miR-17 (SEQ ID NO: 1).

Example 11. The compound of any one of examples 8, 9, or 10, wherein the nucleobase sequence of $(N'')_p$ is selected from CUACCUGCACUGUA (SEQ ID NO: 7), CUACCUGCACUGU (SEQ ID NO: 8), CUACCUGCACUG (SEQ ID NO: 9), CUACCUGCACU (SEQ ID NO: 10), CUACCUGCAC (SEQ ID NO: 11), CUACCUGCA, CUACCUGC, CUACCUG, CUACCU, CUACC, CUAC, CUA, CU, and C.

Example 12. The compound of any one of examples 1 to 5 or 7 to 11, wherein the nucleobase of N' is a purine nucleobase that does not have a hydrogen bond acceptor at position 6.

Example 13. The compound of example 12, wherein the nucleobase of N' is selected from adenosine, 2-aminopurine, 2,6-diaminopurine, and isoguanosine.

Example 14. The compound of any one of examples 1 to 13, wherein the sugar moiety of N' is not a 2'-O-methyl sugar.

Example 15. The compound of any one of examples 1 to 14, wherein the sugar moiety of N' is a 2'-O-methoxyethyl sugar or an S-cEt sugar.

Example 16. The compound of example 2, wherein the structure of the modified oligonucleotide is 5'-$A_SG_SC_MA_FC_FU_FU_MU_SA_S$-3', wherein each cytosine is a non-methylated cytosine.

Example 17. The compound of example 2, wherein the structure of the modified oligonucleotide is 5'-$A_SG_SC_MA_FC_FU_FU_MU_SU_S$-3', wherein each cytosine is a non-methylated cytosine.

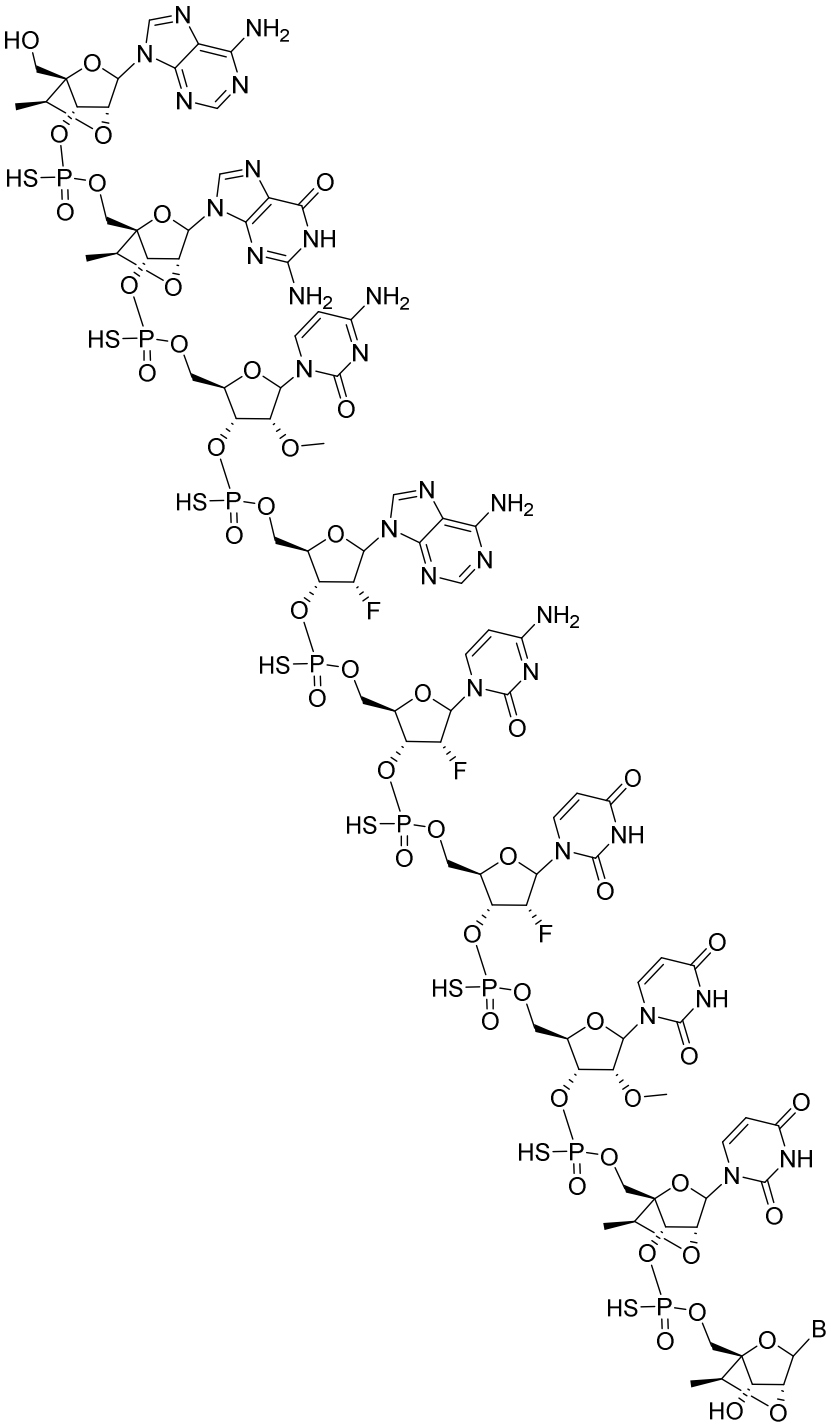
Example 18. The compound of example 2, wherein the structure of the modified oligonucleotide is 5'-$A_SG_SC_MA_FC_FU_FU_MU_SC_S$-3', wherein each cytosine is a non-methylated cytosine.

Example 19. The compound of example 2, wherein the structure of the modified oligonucleotide is 5'-$A_SG_SC_MA_FC_FU_FU_MU_S$-3', wherein each cytosine a non-methylated cytosine.

Example 20. The compound of any one of examples 1 to 19, wherein the compound consists of the modified oligonucleotide.

Example 21. The compound of any one of examples 1 to 20, wherein the pharmaceutically acceptable salt is a sodium salt.

Example 22. A modified oligonucleotide having the structure:

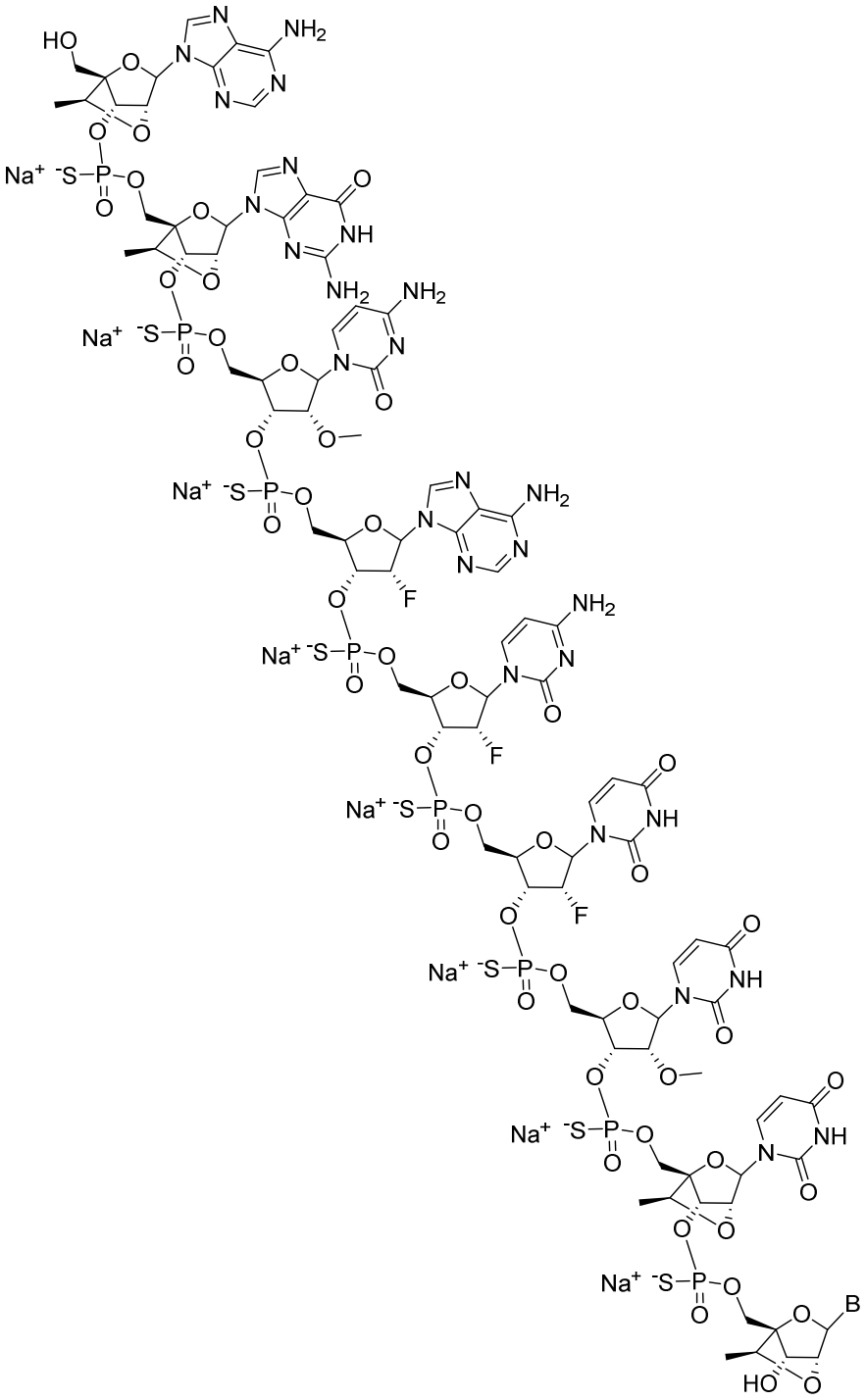


wherein B is a uridine nucleobase, a cytosine nucleobase, or a purine nucleobase, provided that the purine nucleobase does not have a hydrogen bond acceptor at position 6; or a pharmaceutically acceptable salt thereof.

Example 23. The modified oligonucleotide of example 22, wherein B is selected from adenosine, 2-aminopurine, 2,6-diaminopurine, and isoguanosine.

Example 24. The modified oligonucleotide of example 22 or example 23, wherein the pharmaceutically acceptable salt is a sodium salt.

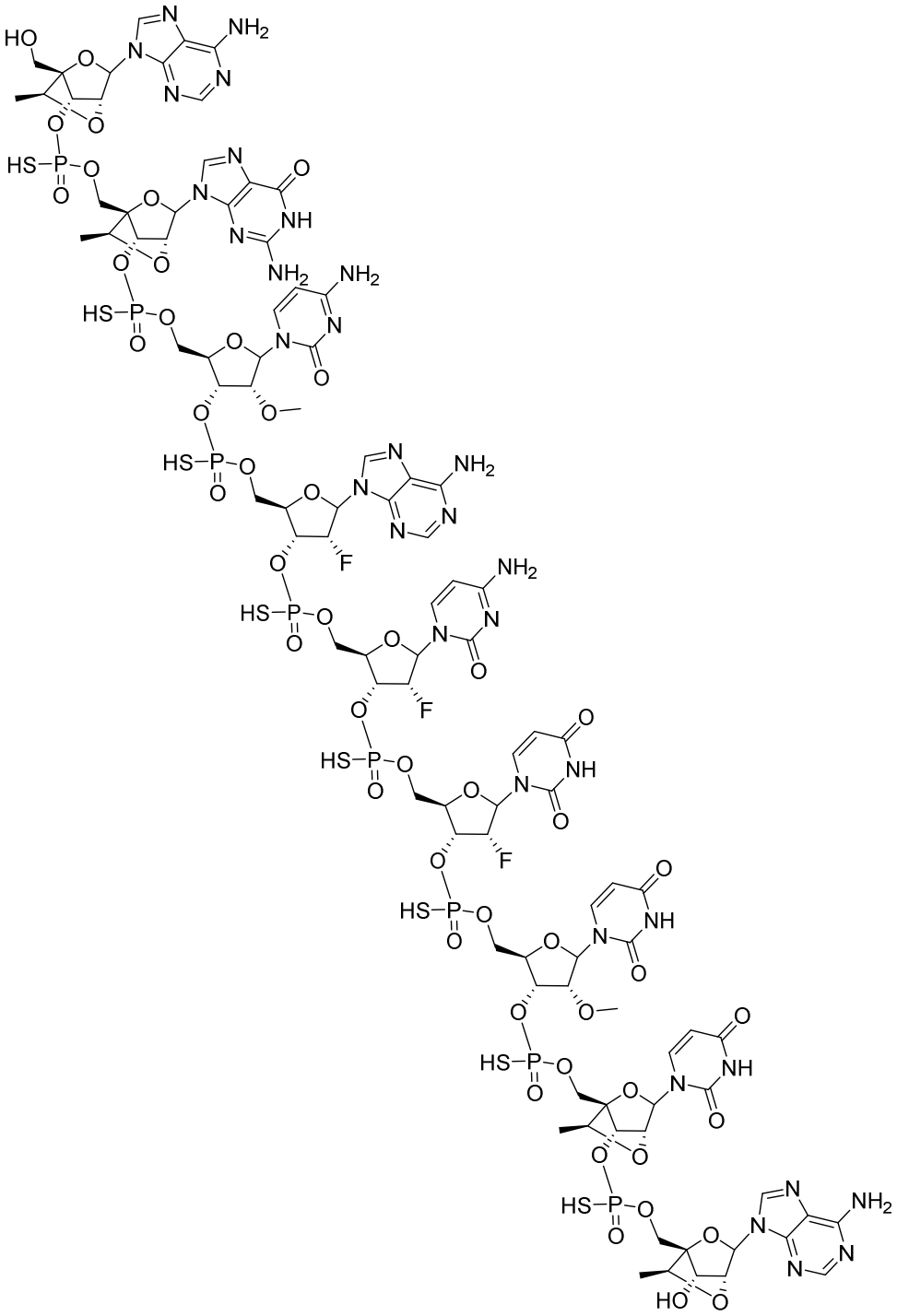
Example 25. A modified oligonucleotide having the structure:



wherein B is a uridine nucleobase, a cytosine nucleobase, or a purine nucleobase, provided that the purine nucleobase does not have a hydrogen bond acceptor at position 6.

Example 26. The modified oligonucleotide of example 25, wherein B is selected from adenosine, 2-aminopurine, 2,6-diaminopurine, and isoguanosine.

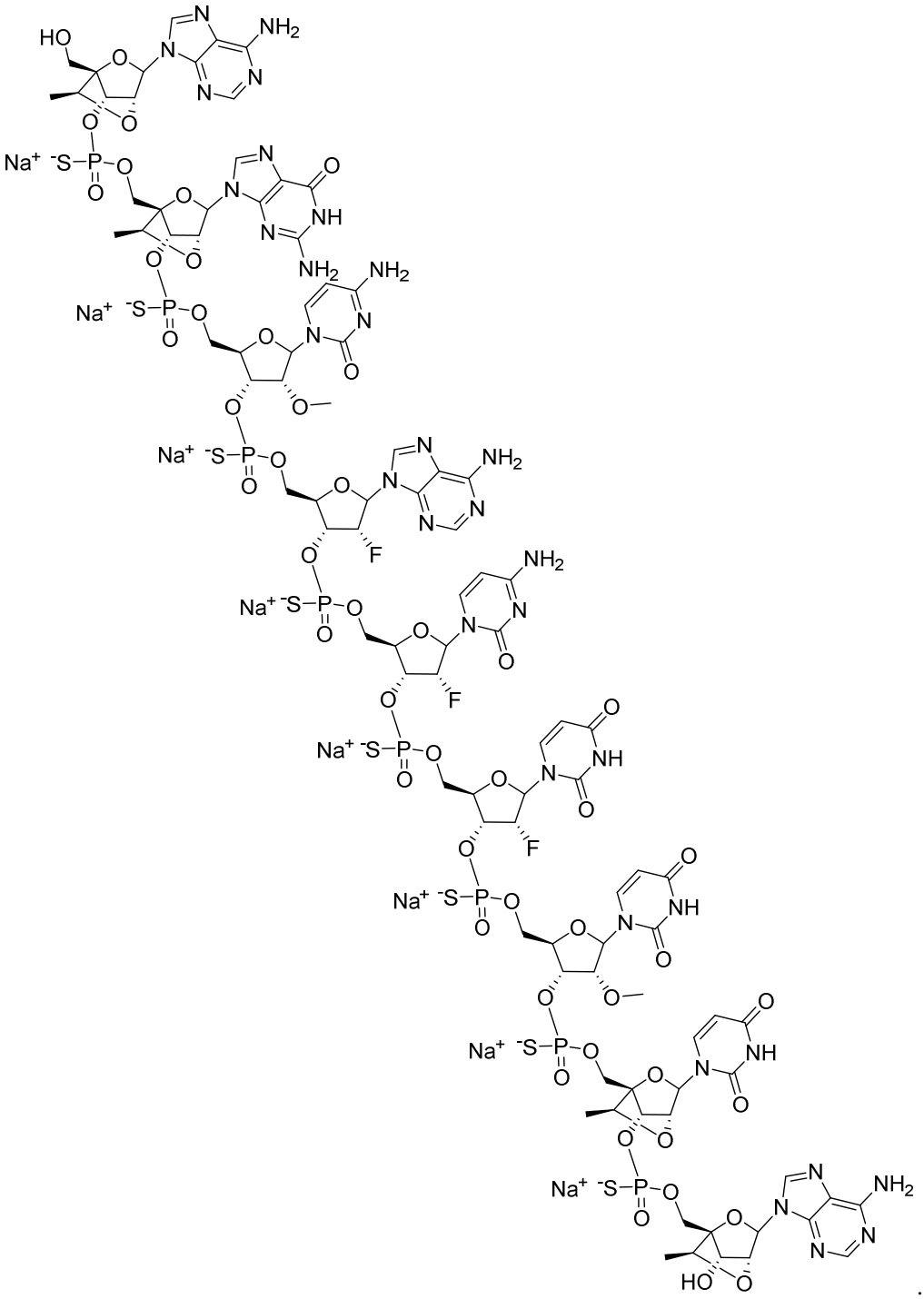
Example 27. A modified oligonucleotide having the structure:



or a pharmaceutically acceptable salt thereof.

Example 28. The modified oligonucleotide of example 27, wherein the pharmaceutically acceptable salt is a sodium salt.

Example 29. A modified oligonucleotide having the structure:



Example 30. A pharmaceutical composition comprising a compound of any one of examples 1 to 21 or a modified oligonucleotide of any one of examples 22 to 29 and a pharmaceutically acceptable diluent.

Example 31. The pharmaceutical composition of example 30, wherein the pharmaceutically acceptable diluent is an aqueous solution.

Example 32. The pharmaceutical composition of example 31, wherein the aqueous solution is a saline solution.

Example 33. A pharmaceutical composition comprising a compound of any one of examples 1 to 21 or a modified oligonucleotide of any one of examples 22 to 29, which is a lyophilized composition.

Example 34. A pharmaceutical composition consisting essentially of a compound of any one of examples 1 to 21 or a modified oligonucleotide of any one of examples 22 to 29 in a saline solution.

Example 35. A method for inhibiting the activity of one or more members of the miR-17 family in a cell, comprising contacting the cell with a compound of any one of examples 1 to 21 or a modified oligonucleotide of any one of examples 22 to 29.

Example 36. A method for inhibiting the activity of one or more members of the miR-17 family in a subject, comprising administering to the subject a compound of any one of examples 1 to 21, a modified oligonucleotide of any one of examples 22 to 29, or a pharmaceutical composition of any one of examples 30 to 34.

Example 37. The method of example 36, wherein the subject has a disease associated with miR-17.

Example 38. A method of treating polycystic kidney disease comprising administering to a subject in need thereof a compound comprising a modified oligonucleotide, wherein the modified oligonucleotide has the following structure in the 5' to 3' orientation:

$$(N'')_p\text{-}(N)_r\text{-}(N')_q$$

wherein each N" is, independently, a modified or unmodified nucleoside;

p is from 0 to 14; wherein if p is not 0, the nucleobase sequence of $(N'')_p$ is complementary to an equal-length portion of the nucleobase sequence of miR-17;

each N of $(N)_r$ is, independently, a modified or unmodified nucleotide, and the nucleobase sequence of $(N)_r$ is 5'-AGCACUUU-3';

N' is a nucleoside comprising a modified sugar moiety;

q is 0 or 1; wherein if q is 1, the nucleobase of N' is a uridine nucleobase, a cytosine nucleobase, or a purine nucleobase, provided that the purine nucleobase does not have an H-bond acceptor at position 6; and

each cytosine is independently selected from a non-methylated cytosine and a 5-methylcytosine;

or a pharmaceutically acceptable salt thereof.

Example 39. The method of example 38, wherein the structure of $(N)_r$ is:

$A_SG_SC_MA_FC_FU_FU_MU_S$

wherein nucleosides followed by subscript "M" are 2'-O-methyl nucleosides; nucleosides followed by subscript "F" are 2'-fluoro nucleosides; and nucleosides followed by subscript "S" are S-cEt nucleosides.

Example 40. The method of example 38 or example 39, wherein at least one internucleoside linkage is a phosphorothioate internucleoside linkage.

Example 41. The method of any one of examples 38 to 40, wherein each internucleoside linkage is a phosphorothioate internucleoside linkage.

Example 42. The method of any one of examples 38 to 41, wherein q is 1.

Example 43. The method of any one of examples 38 to 41, wherein q is 0.

Example 44. The method of any one of examples 38 to 43, wherein p is 0.

Example 45. The method of any one of examples 38 to 43, wherein p is selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14.

Example 46. The method of example 45, wherein the nucleobase sequence of $(N'')_p$ has no more than one mismatch to the nucleobase sequence of miR-17 (SEQ ID NO: 1).

Example 47. The compound of example 45, wherein the nucleobase sequence of $(N'')_p$ has no mismatches to the nucleobase sequence of miR-17 (SEQ ID NO: 1).

Example 48. The compound of example 47, wherein the nucleobase sequence of $(N'')_p$ is selected from CUACCUGCACUGUA (SEQ ID NO: 7), CUACCUGCACUGU (SEQ ID NO: 8), CUACCUGCACUG (SEQ ID NO: 9), CUACCUGCACU (SEQ ID NO: 10), CUACCUGCAC (SEQ ID NO: 11), CUACCUGCA, CUACCUGC, CUACCUG, CUACCU, CUACC, CUAC, CUA, CU, and C.

Example 49. The method of any one of examples 38 to 42 or 44 to 48, wherein the nucleobase of N' is a purine nucleobase that does not have a hydrogen-bond acceptor at position 6.

Example 50. The method of example 49, wherein the nucleobase of N' is selected from adenosine, 2-aminopurine, 2,6-diaminopurine, and isoguanosine.

Example 51. The method of any one of examples 38 to 50, wherein the sugar moiety of N' is not a 2'-O-methyl sugar.

Example 52. The compound of any one of examples 38 to 51, wherein the sugar moiety of N' is a 2'-O-methoxyethyl sugar or an S-cEt sugar.

Example 53. The method of example 39, wherein the structure of the modified oligonucleotide is 5'-$A_SG_SC_MA_FC_FU_FU_MU_SA_S$-3', and each cytosine is a non-methylated cytosine.

Example 54. The method of example 39, wherein the structure of the modified oligonucleotide is 5'-$A_SG_SC_MA_FC_FU_FU_MU_SU_S$-3', wherein each cytosine is a non-methylated cytosine.

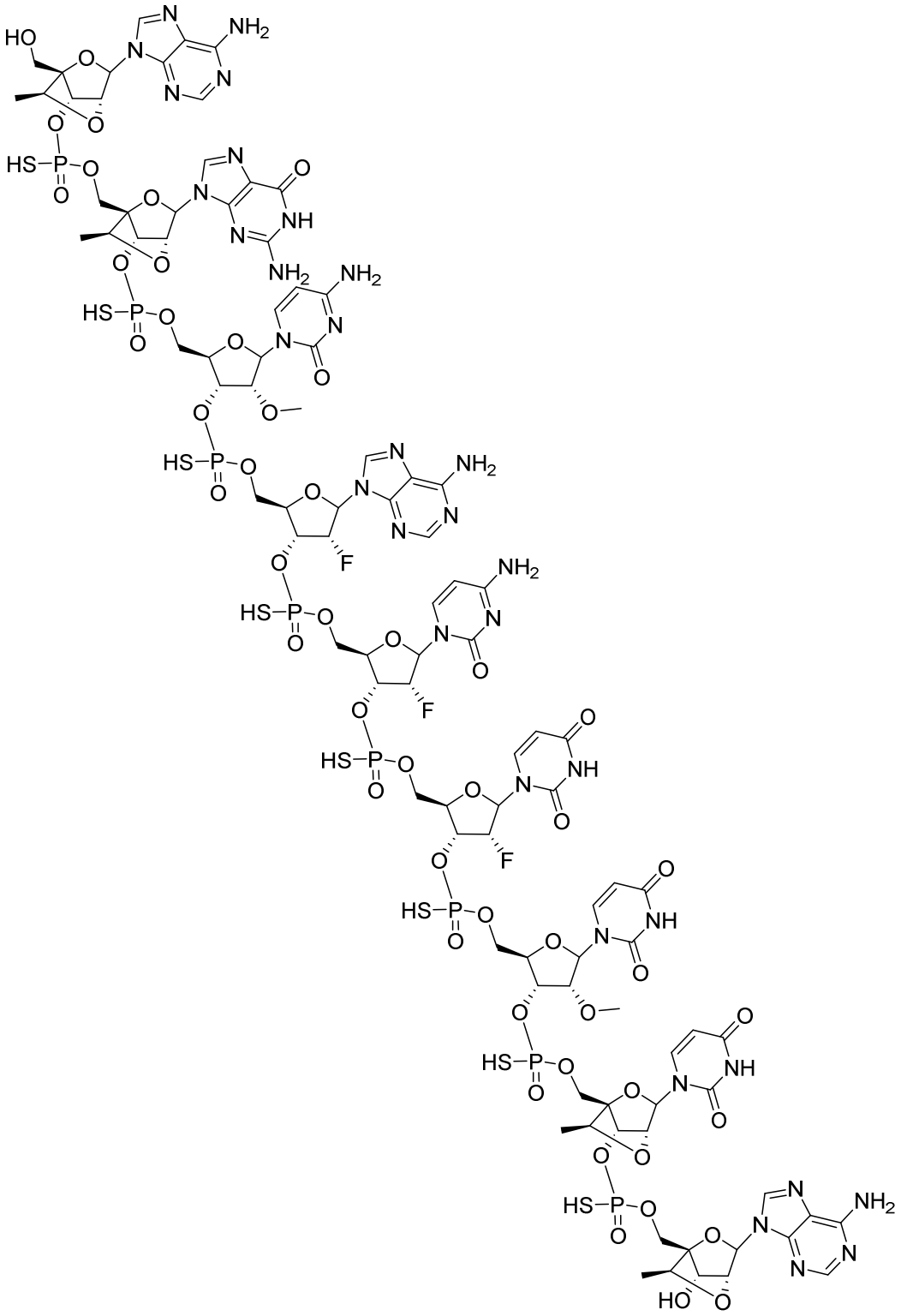
Example 55. The method of example 39, wherein the structure of the modified oligonucleotide is 5'-$A_SG_SC_MA_FC_FU_FU_MU_SC_S$-3', wherein each cytosine is a non-methylated cytosine.

Example 56. The method of example 39, wherein the structure of the modified oligonucleotide is 5'-$A_SG_SC_MA_FC_FU_FU_MU_S$-3', wherein each cytosine a non-methylated cytosine.

Example 57. The method of any one of examples 38 to 56, wherein the compound consists of the modified oligonucleotide.

Example 58. The method of any one of examples 38 to 57, wherein the pharmaceutically acceptable salt is a sodium salt.

Example 59. A method of treating polycystic kidney disease comprising administering to a subject in need thereof a modified oligonucleotide having the structure:



or a pharmaceutically acceptable salt thereof.

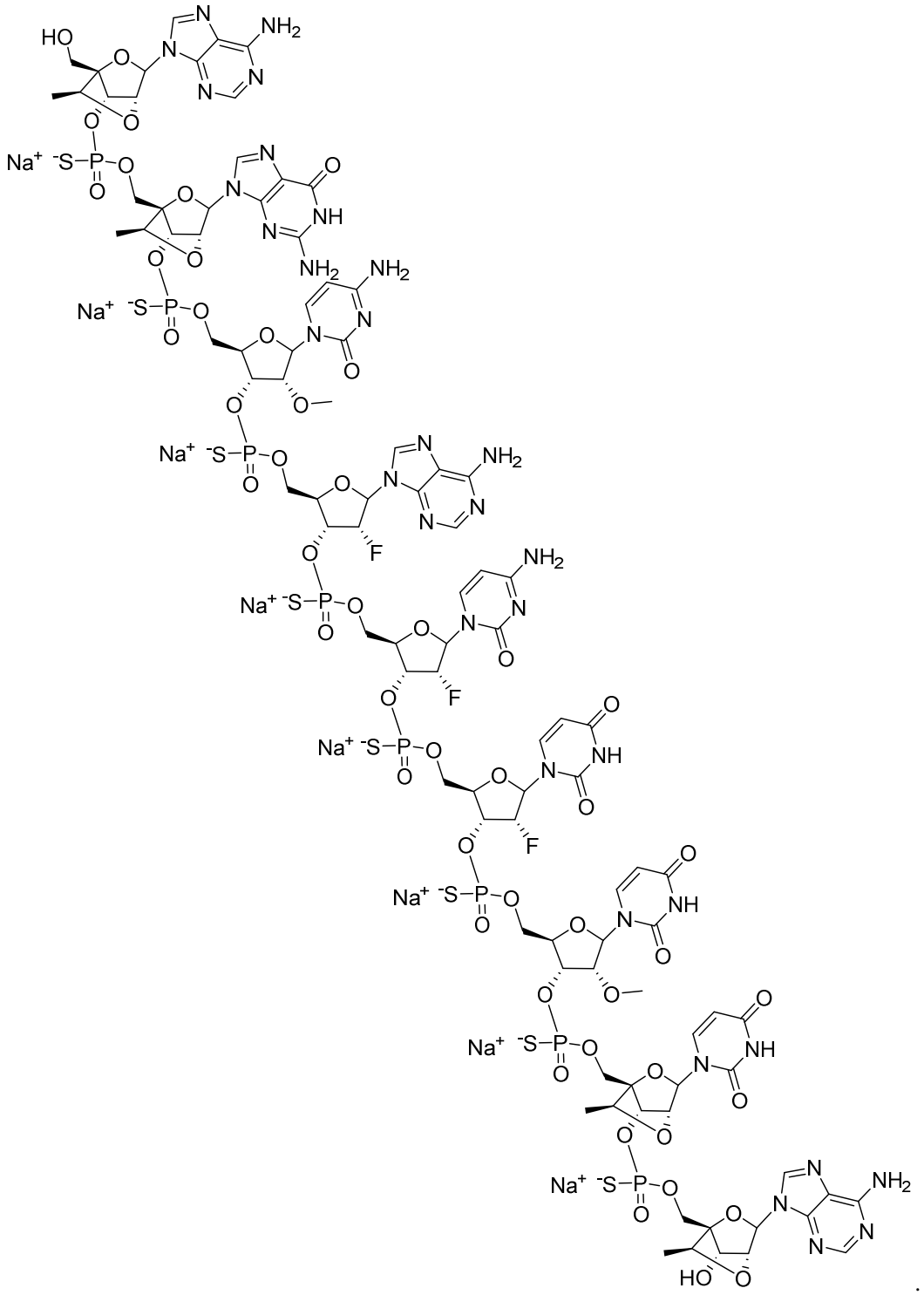
Example 60. The method of example 59, wherein pharmaceutically acceptable salt is a sodium salt.

Example 61. The method of example 60, wherein the modified oligonucleotide is present in a pharmaceutical composition comprising a pharmaceutically acceptable diluent.

Example 62. The method of example 61, wherein the pharmaceutically acceptable diluent is a sterile aqueous solution.

Example 63. The method of example 62, wherein the sterile aqueous solution is a saline solution.

Example 64. A method of treating polycystic kidney disease comprising administering to a subject in need thereof a modified oligonucleotide having the structure:



Example 65. The method of example 64, wherein the modified oligonucleotide is present in a pharmaceutical composition comprising a pharmaceutically acceptable diluent.

Example 66. The method of example 65, wherein the pharmaceutically acceptable diluent is a sterile aqueous solution.

Example 67. The method of example 66, wherein the sterile aqueous solution is a saline solution.

Example 68. The method of any one of examples 38 to 67, wherein the subject has polycystic kidney disease.

Example 69. The method of any one of examples 38 to 67, wherein the subject is suspected of having polycystic kidney disease.

Example 70. The method of any one of examples 38 to 68, wherein the subject has been diagnosed as having polycystic kidney disease using clinical, histopathologic, and/or genetic criteria.

Example 71. The method of any one of examples 38 to 70, wherein the subject, prior to administration of the compound, modified oligonucleotide, or pharmaceutical composition, was determined to have a decreased level of polycystin-1 (PC1) and/or polycystin-2 (PC2) in the kidney, urine or blood of the subject.

Example 72. The method of any one of examples 38 to 71, wherein the polycystic kidney disease is autosomal recessive polycystic kidney disease.

Example 73. The method of any one of examples 38 to 71, wherein the polycystic kidney disease is autosomal dominant polycystic kidney disease.

Example 74. The method of any one of examples 38 to 73, wherein the subject has a mutation selected from a mutation in the PKD1 gene or a mutation in the PKD2 gene.

Example 75. The method of any one of examples 38 to 74, wherein the subject has increased total kidney volume.

Example 76. The method of any one of examples 38 to 75, wherein the subject has hypertension.

Example 77. The method of any one of examples 38 to 76, wherein the subject has impaired kidney function.

Example 78. The method of any one of examples 38 to 77, wherein the administering reduces total kidney volume in the subject.

Example 79. The method of any one of examples 38 to 78, wherein the administering slows the rate of increase of total kidney volume in the subject.

Example 80. The method of example 78 or example 79, wherein the total kidney volume is height-adjusted total kidney volume.

Example 81. The method of any one of examples 38 to 80, wherein the administering slows the rate of decline of glomerular filtration rate in the subject.

Example 82. The method of any one of examples 38 to 81, wherein the administering increases glomerular filtration rate in the subject.

Example 83. The method of example 81 or example 82, wherein the glomerular filtration rate is estimated glomerular filtration rate.

Example 84. The method of any one of examples 38 to 83, wherein the administering slows the increase in the growth of cysts in the kidney and/or liver of the subject.

Example 85. The method of any one of examples 38 to 84, wherein the administering:

a) improves kidney function in the subject;
b) delays the worsening of kidney function in the subject;
c) reduces kidney pain in the subject;
d) slows the increase in kidney pain in the subject;
e) delays the onset of kidney pain in the subject;
f) reduces hypertension in the subject;
g) slows the worsening of hypertension in the subject;
h) delays the onset of hypertension in the subject;
i) reduces fibrosis in the kidney of the subject;
j) slows the worsening of fibrosis in the kidney of the subject;
k) delays the onset of end stage renal disease in the subject;
l) delays time to dialysis for the subject;
m) delays time to renal transplant for the subject; and/or
n) improves life expectancy of the subject.

Example 86. The method of any one of examples 38 to 85, wherein the administering:

a) reduces albuminuria in the subject;
b) slows the worsening of albuminuria in the subject;
c) delays the onset of albuminuria in the subject;
d) reduces hematuria in the subject;
e) slows the worsening of hematuria in the subject;
f) delays the onset of hematuria in the subject;
g) reduces blood urea nitrogen level in the subject;

h) reduces serum creatinine level in the subject;
i) improves creatinine clearance in the subject;
j) reduces albumin:creatinine ratio in the subject;
k) increases polycystin-1 (PC1) in the urine of the subject;
l) increases polycystin-2 (PC2) in the urine of the subject;
m) reduces neutrophil gelatinase-associated lipocalin (NGAL) protein in the urine of the subject; and/or
n) reduces kidney injury molecule-1 (KIM-1) protein in the urine of the subject.

Example 87. The method of one of examples 38 to 86, comprising:

a) measuring total kidney volume in the subject;
b) measuring hypertension in the subject;
c) measuring kidney pain in the subject;
d) measuring polycystin-1 (PC1) in the urine of the subject;
e) measuring polycystin-2 (PC2) in the urine of the subject;
f) measuring fibrosis in the kidney of the subject;
g) measuring blood urea nitrogen level in the subject;
h) measuring serum creatinine level in the subject;
i) measuring creatinine clearance in the subject;
j) measuring albuminuria in the subject;
k) measuring albumin:creatinine ratio in the subject;
l) measuring glomerular filtration rate in the subject;
m) measuring neutrophil gelatinase-associated lipocalin (NGAL) protein in the urine of the subject; and/or
n) measuring kidney injury molecule-1 (KIM-1) protein in the urine of the subject.

Example 88. The method of any one of examples 38 to 87, comprising administering at least one additional therapy, wherein at least one additional therapy is an anti-hypertensive agent.

Example 89. The method of any one of examples 38 to 87, comprising administering at least one additional therapy selected from an angiotensin II converting enzyme (ACE) inhibitor, an angiotensin II receptor blocker (ARB), a diuretic, a calcium channel blocker, a kinase inhibitor, an adrenergic receptor antagonist, a vasodilator, a benzodiazepine, a renin inhibitor, an aldosterone receptor antagonist, an endothelin receptor blocker, an mammalian target of rapamycin (mTOR) inhibitor, a hormone analogue, a vasopressin receptor 2 antagonist, an aldosterone receptor antagonist, a glucosylceramide synthase inhibitor, an antihyperglycermic agent, dialysis, and kidney transplant.

Example 90. The method of example 89, wherein the angiotensin II converting enzyme (ACE) inhibitor is selected from captopril, enalapril, lisinopril, benazepril, quinapril, fosinopril, and ramipril.

Example 91. The method of example 89, wherein the angiotensin II receptor blocker (ARB) is selected from candesartan, irbesartan, olmesartan, losartan, valsartan, telmisartan, and eprosartan.

Example 92. The method of example 89, wherein the vasopressin receptor 2 antagonist is tolvaptan.

Example 93. The method of example 89, wherein the aldosterone receptor antagonist is spironolactone.

Example 94. The method of example 89, wherein the kinase inhibitor is selected from bosutinib and KD019.

Example 95. The method of example 89, wherein the mTOR inhibitor is selected from everolimus, rapamycin, and sirolimus.

Example 96. The method of example 89, wherein the hormone analogue is selected from somatostatin and adrenocorticotrophic hormone.

Example 97. The method of example 89, wherein the glucosylceramide synthase inhibitor is venglustat.

Example 98. The method of example 89, wherein the antihyperglycemic agent is metformin.

Example 99. The method of any one of examples 38 to 96, comprising administering a therapeutically effective amount of the compound.

Example 100. The method of any one of examples 38 to 99, wherein the subject is a human subject.

Example 101. A compound comprising a modified oligonucleotide, wherein the modified oligonucleotide has the following structure in the 5' to 3' orientation:

$(N'')_p$-$(N)_r$-$(N')_q$

wherein each N" is, independently, a modified or unmodified nucleoside;

p is from 0 to 14; wherein if p is not 0, the nucleobase sequence of $(N'')_p$ is complementary to an equal-length portion of the nucleobase sequence of miR-17;

each N of $(N)_r$ is, independently, a modified or unmodified nucleotide, and the nucleobase sequence of $(N)_r$ is 5'-AGCACUUU-3';
N' is a nucleoside comprising a modified sugar moiety;
q is 0 or 1; wherein if q is 1, the nucleobase of N' is a uridine nucleobase, a cytosine nucleobase, or a purine nucleobase, provided that the purine nucleobase does not have an H-bond acceptor at position 6; and
each cytosine is independently selected from a non-methylated cytosine and a 5-methylcytosine; or a pharmaceutically acceptable salt thereof, for use in therapy.

Example 102. The compound of example 101, wherein the therapy is the treatment of polycystic kidney disease.
Example 103. The compound of example 102, wherein the polycystic kidney disease is autosomal dominant polycystic kidney disease (ADPKD).
Example 104. The compound of example 102, wherein the polycystic kidney disease is autosomal recessive polycystic kidney disease (ARPKD).
Example 105. A compound of any one of examples 1 to 22, a modified oligonucleotide of any one of examples 23 to 29, or a pharmaceutical composition of any one of examples 30 to 33, for use in therapy.

BRIEF DESCRIPTION OF FIGURES

[0005] **Figure 1.** Purine nucleobase structures.

[0006] **Figure 2A-2C**. Efficacy of RG-NG-1015 in the *Pkd1*-F/RC model of PKD. Effects of treatment on (2A) kidney-to-body weight ratio, (2B) blood urea nitrogen (BUN) level, and (2C) blood creatinine level.

[0007] **Figure 3**. Maximum Tolerated Dose (MTD) study and Comparative Dose Assessment of RG-NG-1001, RGLS4326, and RG-NG-1017. 6–7-week-old male C57BL/6J mice were dosed with a single intracerebroventricular (ICV) injection of RG-NG-1001 and RGLS4326 (anti-miR-17 oligos that inhibit AMPA-R) and RG-NG-1017 (anti-miR-17 oligos that does not inhibit AMPA-R; RG-NG-1017) at different dose levels in 4 µLvolume and monitored for 7 days. Mortality of the mice is indicated for the three different compounds at different dosages.

[0008] **Figure 4A-4F**. Assessment of activity of RG-NG-1015 and RGLS4326 against miR-17 (4A), miR-20a (4B), miR-93 (4C), and miR106(a) (4D) luciferase sensors activity in HeLa cells in vitro is set forth. Assessment of activity of RG-NG-1015 and RGLS4326 against luciferase sensors containing full length 3' untranslated region (UTR) of the miR-17 direct target genes PKD1 (4E) and PKD2 (4F) is set forth.

What is claimed is:

1. A compound comprising a modified oligonucleotide, wherein the modified oligonucleotide has the following structure in the 5' to 3' orientation:

$$(N'')_p\text{-}(N)_r\text{-}(N')_q$$

wherein each N" is, independently, a modified or unmodified nucleoside;
p is from 0 to 14; wherein if p is not 0, the nucleobase sequence of $(N'')_p$ is complementary to an equal-length portion of the nucleobase sequence of miR-17;
each N of $(N)_r$ is, independently, a modified or unmodified nucleotide, and the nucleobase sequence of $(N)_r$ is 5'-AGCACUUU-3';
N' is a nucleoside comprising a modified sugar moiety;
q is 0 or 1; wherein if q is 1, the nucleobase of N' is a uracil nucleobase, a cytosine nucleobase, or a purine nucleobase, provided that the purine nucleobase does not have a hydrogen bond acceptor at position 6; and
each cytosine is independently selected from a non-methylated cytosine and a 5-methylcytosine; or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, wherein the structure of $(N)_r$ is:

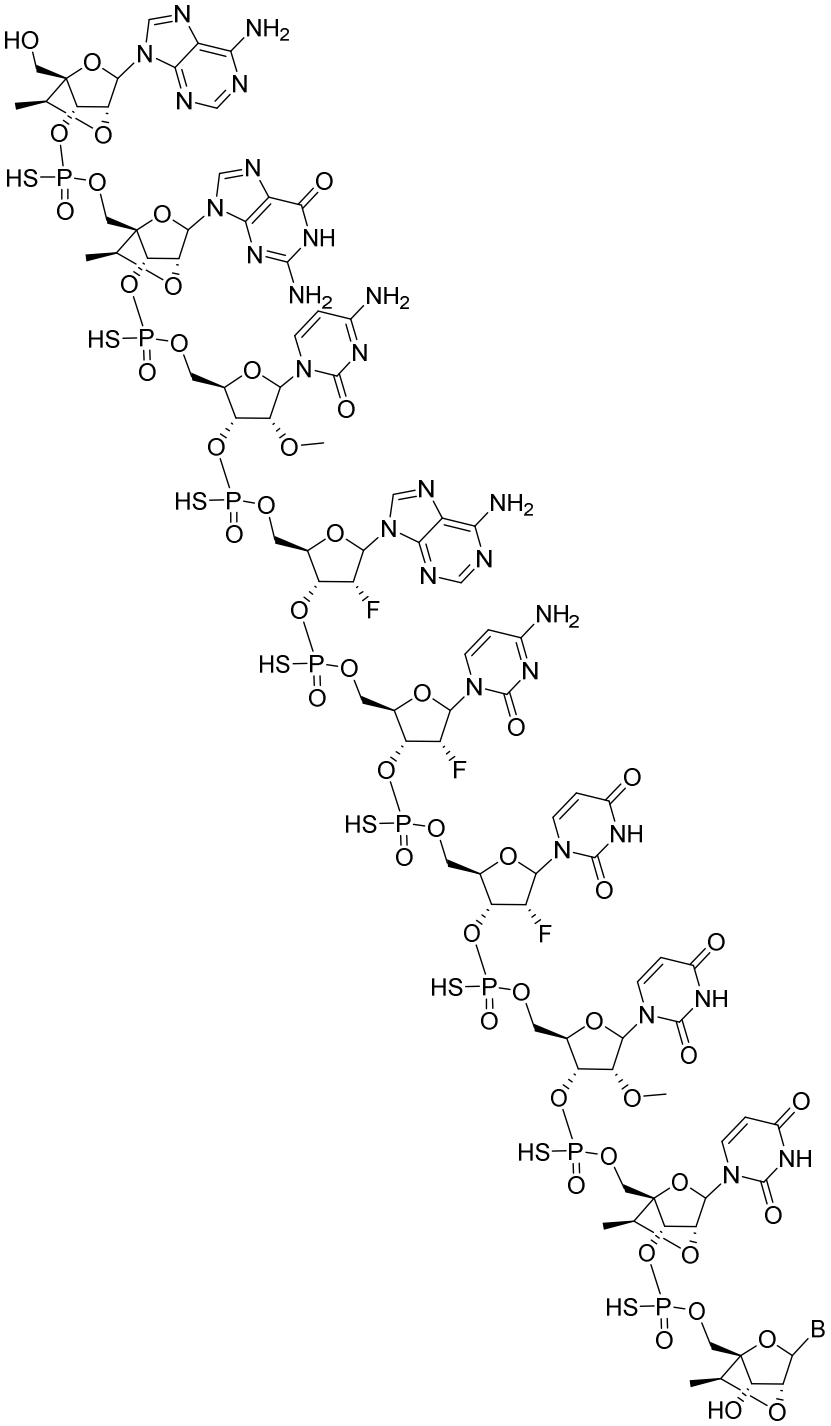
$$A_SG_SC_MA_FC_FU_FU_MU_S$$

wherein nucleosides followed by subscript "M" are 2'-O-methyl nucleosides;
nucleosides followed by subscript "F" are 2'-fluoro nucleosides; and
nucleosides followed by subscript "S" are S-cEt nucleosides.

3. The compound of claim 1 or 2, wherein at least one internucleoside linkage is a phosphorothioate internucleoside linkage, optionally wherein each internucleoside linkage is a phosphorothioate internucleoside linkage.
4. The compound of claim 1, wherein p is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14, and
(a) the nucleobase sequence of $(N'')_p$ has no more than one mismatch to the nucleobase sequence of miR-17 (SEQ ID NO: 1); or
(b) the nucleobase sequence of $(N'')_p$ has no mismatches to the nucleobase sequence of miR-17 (SEQ ID NO: 1); or
(c) the nucleobase sequence of $(N'')_p$ is selected from CUACCUGCACUGUA (SEQ ID NO: 7), CUACCUGCACUGU (SEQ ID NO: 8), CUACCUGCACUG (SEQ ID NO: 9), CUACCUGCACU (SEQ ID NO: 10), CUACCUGCAC (SEQ ID NO: 11), CUACCUGCA, CUACCUGC, CUACCUG, CUACCU, CUACC, CUAC, CUA, CU, and C.
5. The compound of any one of claims 1 to 4, wherein the nucleobase of N' is a purine nucleobase that does not have a hydrogen bond acceptor at position 6, optionally wherein the nucleobase of N' is selected from adenosine, 2-aminopurine, 2,6-diaminopurine, and isoguanosine.

6. The compound of any one of claims 1 to 5, wherein the sugar moiety of N' is not a 2'-O-methyl sugar, or the sugar moiety of N' is a 2'-O-methoxyethyl sugar or an S-cEt sugar.
7. The compound of claim 1, wherein the structure of the modified oligonucleotide is 5'-$A_SG_SC_MA_FC_FU_FU_MU_SA_S$-3', or 5'-$A_SG_SC_MA_FC_FU_FU_MU_SU_S$-3', or 5'-$A_SG_SC_MA_FC_FU_FU_MU_SC_S$-3', or 5'-$A_SG_SC_MA_FC_FU_FU_MU_S$-3', wherein each cytosine is a non-methylated cytosine.
8. The compound of any one of claims 1 to 7, wherein the compound consists of the modified oligonucleotide.
9. The compound of any one of claims 1 to 8, wherein the pharmaceutically acceptable salt is a sodium salt.

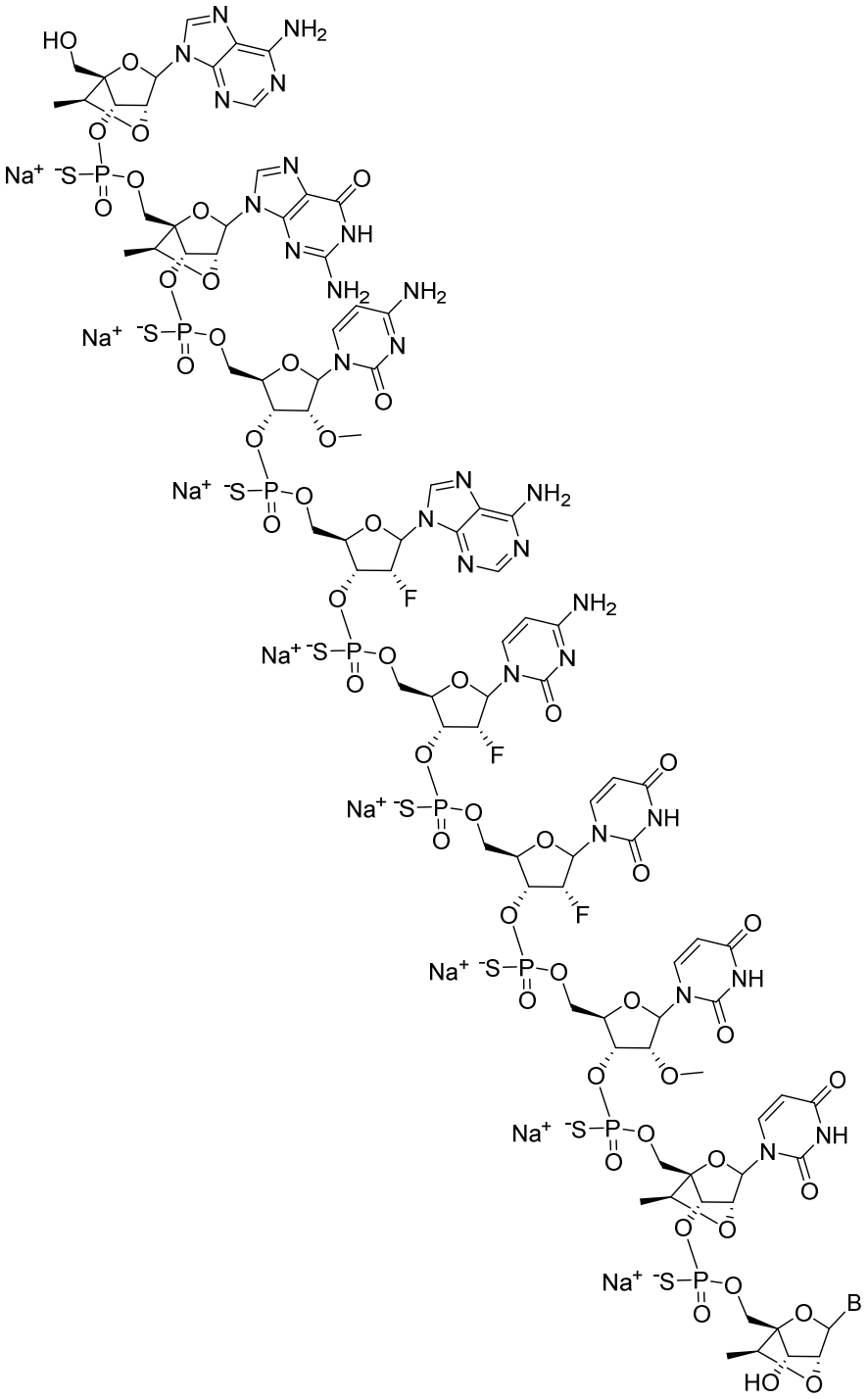
10. A modified oligonucleotide having the structure:



wherein B is a uridine nucleobase, a cytosine nucleobase, or a purine nucleobase, provided that the purine nucleobase does not have a hydrogen bond acceptor at position 6; or a pharmaceutically acceptable salt thereof, optionally wherein B is selected from adenosine, 2-aminopurine, 2,6-diaminopurine, and isoguanosine.

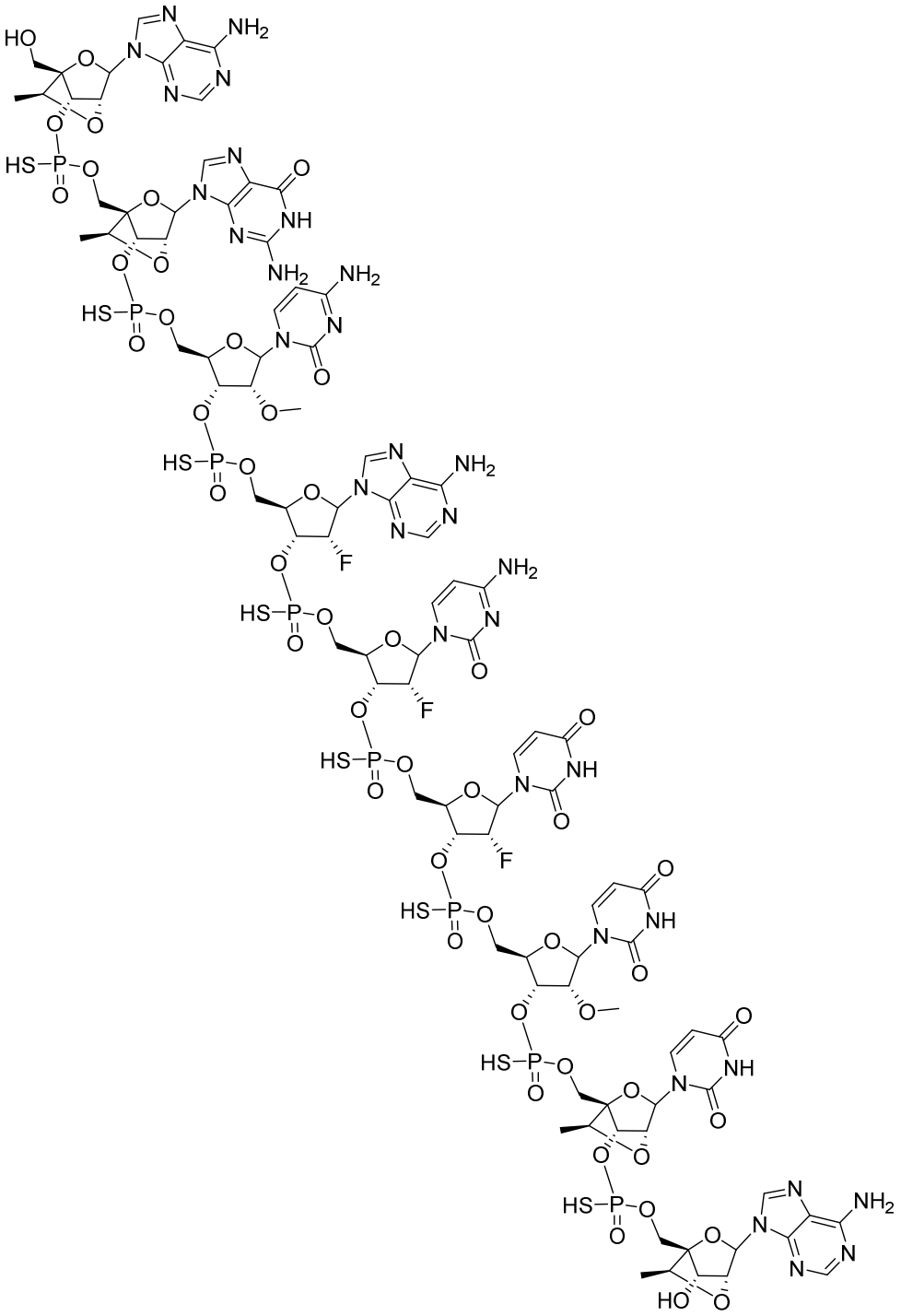
11. The modified oligonucleotide of claim 10, wherein the pharmaceutically acceptable salt is a sodium salt.

12. A modified oligonucleotide having the structure:



wherein B is a uridine nucleobase, a cytosine nucleobase, or a purine nucleobase, provided that the purine nucleobase does not have a hydrogen bond acceptor at position 6, optionally wherein B is selected from adenosine, 2-aminopurine, 2,6-diaminopurine, and isoguanosine.

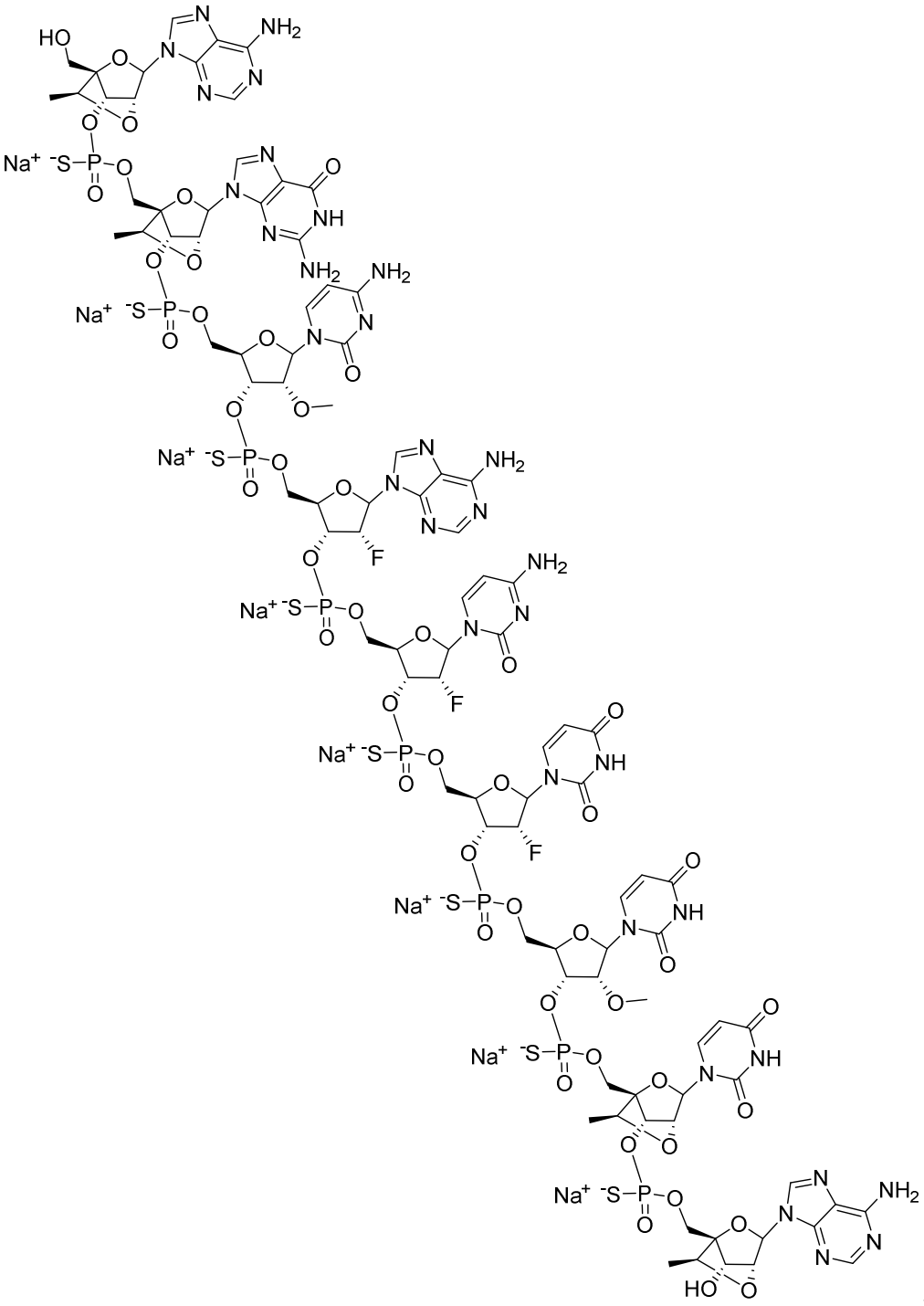
13. A modified oligonucleotide having the structure:



or a pharmaceutically acceptable salt thereof.

14. The modified oligonucleotide of claim 13, wherein the pharmaceutically acceptable salt is a sodium salt.

15. A modified oligonucleotide having the structure:



16. A pharmaceutical composition comprising a compound of any one of claims 1 to 9 or a modified oligonucleotide of any one of claims 10 to 15 and a pharmaceutically acceptable diluent, optionally wherein the pharmaceutically acceptable diluent is an aqueous solution, optionally wherein the aqueous solution is a saline solution.
17. A pharmaceutical composition comprising a compound of any one of claims 1 to 9 or a modified oligonucleotide of any one of claims 10 to 15, which is a lyophilized composition.

18. A pharmaceutical composition consisting essentially of a compound of any one of claims 1 to 9 or a modified oligonucleotide of any one of claims 10 to 15 in a saline solution.
19. An *in vitro* method for inhibiting the activity of one or more members of the miR-17 family in a cell, comprising contacting the cell with a compound of any one of claims 1 to 9 or a modified oligonucleotide of any one of claims 10 to 15.
20. Use of a compound of any one of claims 1 to 9, a modified oligonucleotide of any one of claims 10 to 15, or a pharmaceutical composition of any one of claims 16 to 18 in the manufacture of a medicament for inhibiting the activity of one or more members of the miR-17 family in a subject.
21. The use of claim 20, wherein the subject has a disease associated with miR-17.
22. Use of a compound of any one of claims 1 to 9, a modified oligonucleotide of any one of claims 10 to 15, or a pharmaceutical composition of any one of claims 16 to 18 in the manufacture of a medicament for treating polycystic kidney disease in a subject in need thereof.
23. The use of claim 22, wherein (a) the subject has polycystic kidney disease; (b) the subject is suspected of having polycystic kidney disease; (c) the subject has been diagnosed as having polycystic kidney disease using clinical, histopathologic, and/or genetic criteria; and/or (d) the subject, prior to administration of the compound, modified oligonucleotide, or pharmaceutical composition, was determined to have a decreased level of polycystin-1 (PC1) and/or polycystin-2 (PC2) in the kidney, urine or blood of the subject.
24. The use of claim 22 or 23, wherein the polycystic kidney disease is autosomal recessive polycystic kidney disease, or wherein the polycystic kidney disease is autosomal dominant polycystic kidney disease.
25. The use of any one of claims 22 to 24, wherein (a) the subject has a mutation selected from a mutation in the *PKD1* gene or a mutation in the *PKD2* gene; (b) the subject has increased total kidney volume; (c) the subject has hypertension; and/or (d) the subject has impaired kidney function.
26. The use of any one of claims 22 to 25, wherein (a) the medicament reduces total kidney volume in the subject; (b) the medicament slows the rate of increase of total kidney volume in the subject, optionally wherein the total kidney volume is height-adjusted total kidney volume; (c) the medicament slows the rate of decline of glomerular filtration rate in the subject; (d) the medicament increases glomerular filtration rate in the subject, optionally wherein the glomerular filtration rate is estimated glomerular filtration rate; and/or (e) the medicament slows the increase in the growth of cysts in the kidney and/or liver of the subject.
27. The use of any one of claims 22 to 26, wherein the medicament:
    a) improves kidney function in the subject;
    b) delays the worsening of kidney function in the subject;

c) reduces kidney pain in the subject;

d) slows the increase in kidney pain in the subject;

e) delays the onset of kidney pain in the subject;

f) reduces hypertension in the subject;

g) slows the worsening of hypertension in the subject;

h) delays the onset of hypertension in the subject;

i) reduces fibrosis in the kidney of the subject;

j) slows the worsening of fibrosis in the kidney of the subject;

k) delays the onset of end stage renal disease in the subject;

l) delays time to dialysis for the subject;

m) delays time to renal transplant for the subject;

n) improves life expectancy of the subject

o) reduces albuminuria in the subject;

p) slows the worsening of albuminuria in the subject;

q) delays the onset of albuminuria in the subject;

r) reduces hematuria in the subject;

s) slows the worsening of hematuria in the subject;

t) delays the onset of hematuria in the subject;

u) reduces blood urea nitrogen level in the subject;

v) reduces serum creatinine level in the subject;

w) improves creatinine clearance in the subject;

x) reduces albumin:creatinine ratio in the subject;

y) increases polycystin-1 (PC1) in the urine of the subject;

z) increases polycystin-2 (PC2) in the urine of the subject;

aa) reduces neutrophil gelatinase-associated lipocalin (NGAL) protein in the urine of the subject; and/or

bb) reduces kidney injury molecule-1 (KIM-1) protein in the urine of the subject.

28. The use of any one of claims 22 to 27, comprising:

a) measuring total kidney volume in the subject;

b) measuring hypertension in the subject;

c) measuring kidney pain in the subject;

d) measuring polycystin-1 (PC1) in the urine of the subject;

e) measuring polycystin-2 (PC2) in the urine of the subject;

f) measuring fibrosis in the kidney of the subject;

g) measuring blood urea nitrogen level in the subject;

h) measuring serum creatinine level in the subject;

i) measuring creatinine clearance in the subject;

j) measuring albuminuria in the subject;

k) measuring albumin:creatinine ratio in the subject;

l) measuring glomerular filtration rate in the subject;

m) measuring neutrophil gelatinase-associated lipocalin (NGAL) protein in the urine of the subject; and/or

n) measuring kidney injury molecule-1 (KIM-1) protein in the urine of the subject.

29. The use of any one of claims 22 to 28, wherein the medicament is for administration with at least one additional therapy, wherein at least one additional therapy is an anti-hypertensive agent;

or wherein at least one additional therapy is selected from an angiotensin II converting enzyme (ACE) inhibitor, an angiotensin II receptor blocker (ARB), a diuretic, a calcium channel blocker, a kinase inhibitor, an adrenergic receptor antagonist, a vasodilator, a benzodiazepine, a renin inhibitor, an aldosterone receptor antagonist, an endothelin receptor blocker, an mammalian target of rapamycin (mTOR) inhibitor, a hormone analogue, a vasopressin receptor 2 antagonist, an aldosterone receptor antagonist, a glucosylceramide synthase inhibitor, an antihyperglycermic agent, dialysis, and kidney transplant.

30. The use of claim 29, wherein the angiotensin II converting enzyme (ACE) inhibitor is selected from captopril, enalapril, lisinopril, benazepril, quinapril, fosinopril, and ramipril; the angiotensin II receptor blocker (ARB) is selected from candesartan, irbesartan, olmesartan, losartan, valsartan, telmisartan, and eprosartan; the vasopressin receptor 2 antagonist is tolvaptan; the aldosterone receptor antagonist is spironolactone; the kinase inhibitor is selected from bosutinib and KD019; the mTOR inhibitor is selected from everolimus, rapamycin, and sirolimus; the hormone analogue is selected from somatostatin and adrenocorticotrophic hormone; the glucosylceramide synthase inhibitor is venglustat; and the antihyperglycemic agent is metformin.

31. The use of any one of claims 22 to 30, wherein the subject is a human subject.