

What is claimed is:

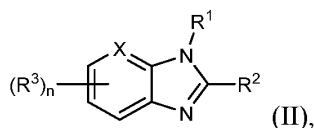
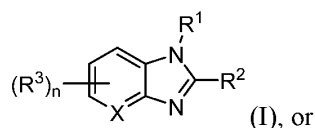
1. A method of selecting and treating a human subject suffering from a kidney disease comprising the steps of:
 - a. selecting the subject if a urinary level of one or more biomarkers selected from Rac1, Rac1-GTP, phospho-LIM kinase 1, and phospho-cofilin in the subject is above a pre-determined threshold; and
 - b. administering to the selected subject a pharmaceutical composition comprising a TRPC5 inhibitor or a calcineurin inhibitor; and a pharmaceutically acceptable carrier.
2. A method of treating a human subject suffering from a kidney disease comprising the step of

administering to the subject a pharmaceutical composition comprising

a TRPC5 inhibitor or a calcineurin inhibitor, and

a pharmaceutically acceptable carrier;

only if the subject is determined to have a pre-treatment urinary level of one or more biomarkers selected from Rac1, Rac1-GTP, phospho-LIM kinase 1, and phospho-cofilin that is above a pre-determined threshold.
3. The method of claim 1 or 2, wherein the TRPC5 inhibitor is:
 - a. a compound of Formula (I) or Formula (II):



or a pharmaceutically acceptable salt of either of the foregoing, wherein:

X is CH, C(R³), or N;

R¹ is selected from the group consisting of H; alkyl; cycloalkyl; heterocycloalkyl; alkenyl; aryl; heteroaryl; alkylene-aryl; alkylene-heteroaryl; -CH₂(O)N(R)-heteroaryl; -CH₂(O)N(R)-alkyl; alkylene-N(alkyl)₂; heterocycloalkyl; alkylene-O-alkyl; alkylene-O-aryl;

alkylene-N(R)-C(O)-aryl; alkylene-N(R)-C(O)-alkyl; alkylene-C(O)-N(R)-alkyl; alkylene-C(O)-N(R)-aryl; alkylene-C(O)-cycloalkyl; and alkylene-C(O)-N(R)-heteroaryl;

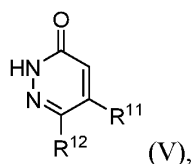
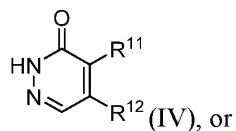
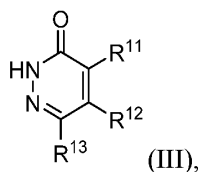
R^2 is selected from the group consisting of H; NH_2 , alkyl; cycloalkyl; aryl; heteroaryl; alkylene-aryl, alkylene-N(alkyl)₂; alkylene-heterocycloalkyl; alkylene-cycloalkyl; -N(R)-alkyl; -N(R)-aryl; -N(R)-alkylene-aryl; -N(R)-cycloalkyl; -N(R)-heterocycloalkyl; -O-aryl; alkylene-O-aryl; heterocycloalkyl; -N=C(R)-aryl; -N(R)-alkylene-heteroaryl; -N(R)-alkylene-OH; -S-alkylene-C(O)N(R)-aryl; -S-alkylene-C(O)N(R)-heteroaryl; alkylene-C(O)-heterocycloalkyl; alkylene-N(R)-alkyl; alkylene-N(R)-aryl; and -S-alkyl;

R^3 is independently selected from alkyl, halogen, -CN, -OMe, -OH, -NO₂, -NH₂, -N(Me)₂, -CF₃, -OCF₃, -CHF₂, -OCHF₂, and -O-alkylene-OH;

R is H, or Me; and

n is 0, 1, 2, 3, or 4;

b. a compound of Formula (III), (IV), or (V):



or a tautomer or a pharmaceutically acceptable salt of any of the foregoing, wherein:

R^{11} and R^{13} are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl, heterocyclyl, heteroaryl, halogen, -OH, -CN, -cycloalkyl, -O-alkyl, -O-cycloalkyl, -O-aryl, -aryl-O-aryl -CF₃, -C(H)F₂, alkylene-CF₃, alkylene-C(H)F₂, -SO₂-alkyl, and -O-alkylene-O-alkyl, -heterocyclyl-L- R^4 , and -heteroaryl-L- R^4 ;

R^{12} is -heterocyclyl-L- R^{14} ;

R^{14} is absent or selected from the group consisting of alkyl, cycloalkyl, aryl, alkylene-aryl, alkylene-heteroaryl, heteroaryl, heterocyclyl, $-C(O)N(R^{15})_2$, and CF_3 ;

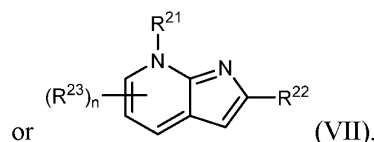
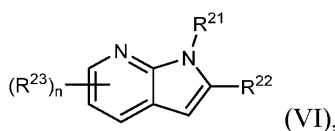
R^{15} is independently H or alkyl;

R^{16} is selected from the group consisting of alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, alkylene-aryl, $-C(O)N(R^{15})_2$, and CF_3 ;

L is absent or selected from the group consisting of methylene, $-C(O)-$, $-SO_2-$, $-CH_2N(Me)-$, $-N(R^{15})(R^{16})-$, $-C(R^{15})(R^{16})-$, and $-O-R^{16}$, and

one and only one of R^{11} , R^{12} , and R^{13} is $-heterocyclyl-L-R^{14}$ or $-heteroaryl-L-R^{14}$;

c. a compound of Formula (VI) or (VII):



or a pharmaceutically acceptable salt thereof, wherein:

R^{21} is selected from the group consisting of alkyl, cycloalkyl, heterocycloalkyl; aryl; heteroaryl; alkylene-aryl; alkylene-heteroaryl; alkylene-O-aryl; alkylene-N(alkyl)₂; alkylene-heterocycloalkyl; alkylene-cycloalkyl; $-N(alkyl)_2$; and $-C(O)-aryl$;

R^{22} is selected from the group consisting of alkyl; cycloalkyl; heterocycloalkyl; aryl; heteroaryl; alkylene-N(alkyl)₂; alkylene-heterocycloalkyl; alkylene-cycloalkyl; alkylene-heterocycloalkyl; and alkylene-OR';

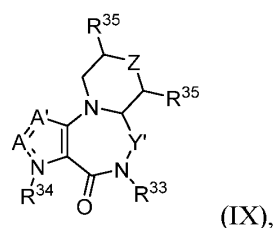
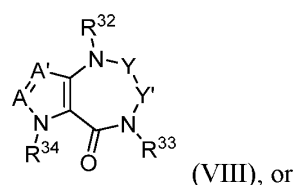
R^{23} is independently selected from alkyl, halogen, OMe, OH, $N(Me)_2$, CF_3 , or OCF_3 , $-O-$ and alkylene-OH;

R is H, or Me;

R' is H, methyl, ethyl, or isopropyl; and

n is 0, 1, 2, 3, or 4; or

d. a compound of Formula (VIII) or (IX):



or a pharmaceutically acceptable salt of either of the foregoing, wherein:

A and A' are independently selected from CR^a and N;

R^a is L-R³¹;

L is absent, CH₂, O, SO₂, or NR³²;

R³¹ is selected from optionally substituted alkyl, optionally substituted aryl, and optionally substituted heteroaryl;

each R³² is independently H, or alkyl;

R³³ is selected from optionally substituted alkyl, optionally substituted alkylene-OR³², optionally substituted cycloalkylene-OR³², optionally substituted alkylene-N(R³⁷)₂, optionally substituted cycloalkylene-N(R³⁷)₂, optionally substituted alkylene-C(O)N(R³²)₂, optionally substituted cycloalkylene-C(O)N(R³²)₂, optionally substituted alkylene-S(O)₂N(R³²)₂, and optionally substituted cycloalkylene-S(O)₂N(R³²)₂;

R³⁴ is selected from alkyl, optionally substituted alkylene-aryl, and optionally substituted alkylene-heteroaryl;

each R³⁵ is independently selected from H, N(R³²)₂, OR³²;

each R³⁷ is independently selected from H, alkyl, (alkyl)C(O)-, (aryl)C(O)-, (alkyl)S(O)₂-, and (aryl)S(O)₂-;

Y is -C(O)-, CH₂, CHR³⁶, C(R³⁶)₂;

each R³⁶ is independently selected from H, alkyl, and optionally substituted alkylene-OH;

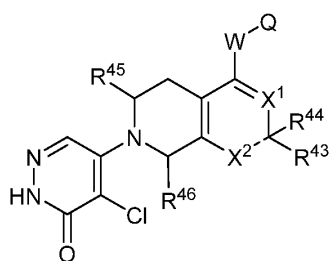
Y' is -C(O)-, CH₂, CHR^{33'}, C(R^{33'})₂, or Y' is taken together with R³³ to form a 5- or 6-membered ring;

each $R^{33'}$ is independently selected from optionally substituted alkyl, optionally substituted alkylene-OR³², optionally substituted cycloalkylene-OR³², optionally substituted alkylene-N(R³⁷)₂, optionally substituted cycloalkylene-N(R³⁷)₂, optionally substituted alkylene-C(O)N(R³²)₂, optionally substituted cycloalkylene-C(O)N(R³²)₂, optionally substituted alkylene-S(O)₂N(R³²)₂, and optionally substituted cycloalkylene-S(O)₂N(R³²)₂; and

Z is absent, CH₂, CHR³⁵, O, -NR³²-, or -SO₂-;

provided that Y and Y' are not both -C(O)-.

4. The method of claim 3, wherein the TRPC5 inhibitor is a compound of structural formula X:



(X), or a pharmaceutically acceptable salt thereof, wherein:

“---” is a single bond or a double bond;

X¹ is CH or N;

when “---” is a double bond, X² is CH or N;

when “---” is a single bond, X² is N(CH₃),

when X¹ is CH, X² is N or N(CH₃);

W is -O-, -N(CH₃)-, -N(CH₂CH₂OH)-, cyclopropan-1,1-diyl, or -CH(CH₃)-

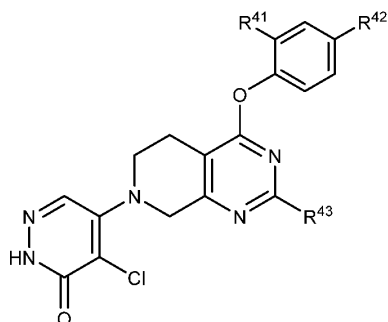
Q is 2-trifluoromethyl-4-fluorophenyl, 2-difluoromethyl-4-fluorophenyl, 2-trifluoromethylphenyl, 2-methyl-4-fluorophenyl, 2-chloro-4-fluorophenyl, 2-chlorophenyl, 1-(benzyl)-4-methylpiperidin-3-yl, 4-trifluoromethylpyridin-3-yl, 2-trifluoromethyl-6-fluorophenyl, 2-trifluoromethyl-3-cyanophenyl, 2-ethyl-3-fluorophenyl, 2-chloro-3-cyanophenyl, 2-trifluoromethyl-5-fluorophenyl, or 2-difluoromethylphenyl;

R⁴³ is hydrogen, -CH₂OH, -CH(OH)-CH₂OH, -NH₂, -CH(OH)CH₃, -OCH₃, or -NH-(CH₂)₂OH; and when “---” is a double bond, R⁴⁴ is absent;

and when “---” is a single bond, R⁴³ and R⁴⁴ are taken together to form =O; and

each of R⁴⁵ and R⁴⁶ is independently hydrogen or -CH₃.

5. The method of claim 4, wherein the TRPC5 inhibitor is a compound of Formula XI:



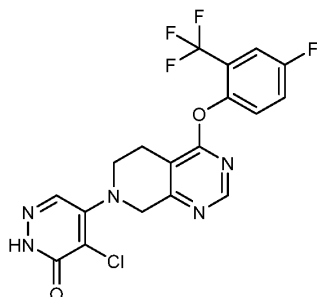
(XI), or a pharmaceutically acceptable salt thereof, wherein:

R⁴¹ is chloro, -CF₃, -CHF₂, or -CH₃;

R⁴² is hydrogen or fluoro; and

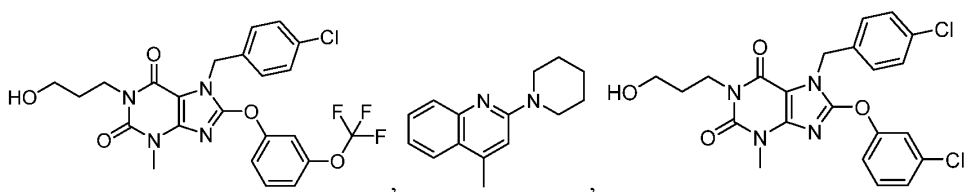
R⁴³ is hydrogen, -NH₂, -CH₂OH, or CH(OH)-CH₂OH.

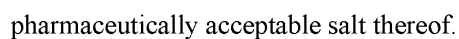
6. The method of claim 5, wherein the TRPC5 inhibitor is:



, or a pharmaceutically acceptable salt thereof.

7. The method of claim 1 or 2, wherein the TRPC5 inhibitor is





8. The method of claim 1 or 2, wherein the calcineurin inhibitor is cyclosporin A, tacrolimus, or voclosporin, or a pharmaceutically acceptable salt thereof.
9. The method of any one of claims 1-8, wherein the kidney disease is diabetic nephropathy, focal segmental glomerulosclerosis, minimal change disease, membranoproliferative glomerulonephritis (including post-streptococcal glomerulonephritis and bacterial endocarditis-associated glomerulonephritis), membranous nephropathy, other hepatitis C virus-associated

glomerulopathies, HIV-associated glomerulopathies, COVID-19-associated acute kidney injury, Alport syndrome, polycystic kidney disease (both autosomal dominant and autosomal recessive), IgA nephropathy, other genetic nephropathies or ciliopathies (e.g., HNF1beta, nephronophthisis, autosomal dominant cystic/tubular kidney disease), lupus nephritis, Goodpasture's syndrome (anti-GBM disease), and another complement- or immune-mediated kidney disease.

10. The method of claim 9, wherein the kidney disease is diabetic nephropathy, or focal segmental glomerulosclerosis.
11. The method of claim 9, wherein the kidney disease is autosomal dominant polycystic kidney disease or autosomal recessive polycystic kidney disease.
12. The method of any one of claims 1-11, wherein the subject is selected on the basis of having a urinary level of Rac1 above a pre-determined threshold.
13. The method of claim 12, wherein the urinary Rac1 level in a subject is measured in a fraction of urine comprising extracellular vesicles.
14. The method of claim 12 or 13, wherein the pre-determined threshold level is established by determining the range of urinary levels of the selected biomarker in a population of healthy humans; and establishing the pre-determined threshold level for the selected biomarker at a level above the 75th percentile in the population.
15. The method of claim 14, wherein the pre-determined threshold level is at a level above the 90th percentile in the population.
16. The method of claim 15, wherein the pre-determined threshold level is at a level above the 95th percentile in the population.

17. The method of claim 12 or 13, wherein the pre-determined threshold level for urinary Rac1 is between 100-500 pg/mL.

18. A method of determining the efficacy of a TRPC5 inhibitor therapy in a human subject suffering from a kidney disease, wherein prior to commencing the therapy the subject was determined to have a pre-treatment urinary level of one or more biomarkers selected from Rac1, Rac1-GTP, phospho-LIM kinase 1, and phospho-cofilin that is above a pre-determined threshold, the method comprising:

- a. obtaining the urinary level of the selected biomarker in the human subject at a time after initiation of TRPC5 therapy;
- b. comparing the level of the selected biomarker in step a. with the pre-treatment urinary level of the selected biomarker;
- c. determining that the TRPC5 inhibitor therapy is efficacious if the level of the selected biomarker in step a. is lower than the pre-treatment urinary level of the selected biomarker.

19. A method of determining the efficacy of a TRPC5 inhibitor therapy in a human subject suffering from a kidney disease, wherein prior to commencing the therapy the subject was determined to have a pre-treatment urinary level of one or more biomarkers selected from Rac1, Rac1-GTP, phospho-LIM kinase 1, and phospho-cofilin that is above a pre-determined threshold, the method comprising:

- a. obtaining the urinary level of the selected biomarker in the human subject at a time after initiation of TRPC5 therapy; and
- b. determining that the TRPC5 inhibitor therapy is efficacious if the level of the selected biomarker in step a. is lower than the pre-determined threshold for the selected biomarker.