~~What is c~~Claim~~ed i~~s:

1. Use of a TRPC5 inhibitor or a calcineurin inhibitor; and a pharmaceutically acceptable carrier in the preparation of a pharmaceutical composition for ~~A method of selecting and~~ treating a human subject suffering from a kidney disease, wherein the pharmaceutical composition is to be administered to ~~comprising the steps of:~~

~~a.~~ a ~~selecting the~~ human subject selected to have~~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. Use of a TRPC5 inhibitor or a calcineurin inhibitor; and a pharmaceutically acceptable carrier in the preparation of a pharmaceutical composition for ~~A method of~~ treating a human subject suffering from a kidney disease ~~comprising the step of~~wherein the pharmaceutical composition is to be administered~~ing~~ to ~~the subject a pharmaceutical composition comprising~~

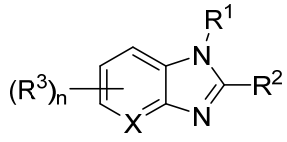
~~a TRPC5 inhibitor or a calcineurin inhibitor, and~~

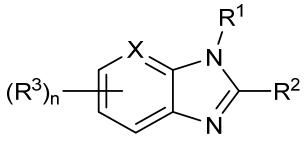
~~a pharmaceutically acceptable carrier;~~

~~only if the~~a 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~~use of claim 1 or 2, wherein the TRPC5 inhibitor is:

a. a compound of Formula (I) or Formula (II):


(I), or


(II),

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

X is CH, C(R^3), or N;

R^1 is selected from the group consisting of H; alkyl; cycloalkyl; heterocycloalkyl; alkenyl; aryl; heteroaryl; alkylene-aryl; alkylene-heteroaryl; -CH_2(O)N(R)-heteroaryl; -CH_2(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;

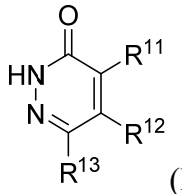
R^2 is selected from the group consisting of H; NH_2, alkyl; cycloalkyl; aryl; heteroaryl; alkylene-aryl, alkylene-N(alkyl)$_2$; alkylene-heterocycloalkyl; alkylene-cycloalkyl; –N(R)-alkyl; -N(R)-aryl; -N(R)-alkylene-aryl; -N(R)-cycloalkyl; -N(R)-heterocycloalkyl; -O-aryl; alkylene-O-aryl; heterocycloalkyl; -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;

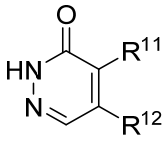
R^3 is independently selected from alkyl, halogen, -CN, -OMe, -OH, -NO_2, -NH_2, -N(Me)$_2$, -CF_3, -OCF_3, -CHF_2, -$OCHF_2$, and -O-alkylene-OH;

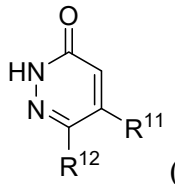
R is H, or Me; and

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

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


(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 $-CF_3$, $-C(H)F_2$, alkylene-CF_3, alkylene-$C(H)F_2$, $-SO_2$-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;

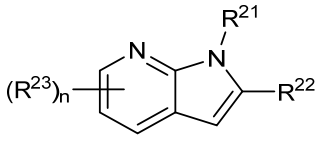
R^{15} is independently H or alkyl;

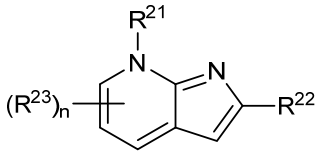
R^{16} is selected from the group consisting of alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, alkylene-aryl, $-C(O)N(R^{15})_2$, and CF_3;

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):


(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';

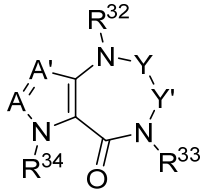
R^{23} is independently selected from alkyl, halogen, OMe, OH, $N(Me)_2$, CF_3, or OCF_3, -O- and alkylene-OH;

R is H, or Me;

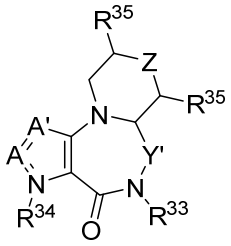
R' is H, methyl, ethyl, or isopropyl; and

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

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



(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-R^{31};

L is absent, CH_2, O, SO_2, or NR^{32};

R^{31} is selected from optionally substituted alkyl, optionally substituted aryl, and optionally substituted heteroaryl;

each R^{32} is independently H, or alkyl;

R^{33} is selected from optionally substituted alkyl, optionally substituted alkylene-OR^{32}, optionally substituted cycloalkylene-OR^{32}, optionally substituted alkylene-$N(R^{37})_2$, optionally substituted cycloalkylene-$N(R^{37})_2$, optionally substituted alkylene-$C(O)N(R^{32})_2$, optionally substituted cycloalkylene-$C(O)N(R^{32})_2$, optionally substituted alkylene-$S(O)_2N(R^{32})_2$, and optionally substituted cycloalkylene-$S(O)_2N(R^{32})_2$;

R^{34} is selected from alkyl, optionally substituted alkylene-aryl, and optionally substituted alkylene-heteroaryl;

each R^{35} is independently selected from H, $N(R^{32})_2$, OR^{32};

each R^{37} 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)-, CH_2, CHR^{36}, $C(R^{36})_2$;

each R^{36} is independently selected from H, alkyl, and optionally substituted alkylene-OH;

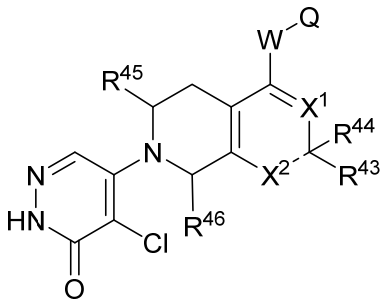
Y' is -C(O)-, CH_2, $CHR^{33'}$, $C(R^{33'})_2$, or Y' is taken together with R^{33} to form a 5- or 6-membered ring;

each $R^{33'}$ is independently selected from optionally substituted alkyl, optionally substituted alkylene-OR^{32}, optionally substituted cycloalkylene-OR^{32}, optionally substituted alkylene-$N(R^{37})_2$, optionally substituted cycloalkylene-$N(R^{37})_2$, optionally substituted alkylene-$C(O)N(R^{32})_2$, optionally substituted cycloalkylene-$C(O)N(R^{32})_2$, optionally substituted alkylene-$S(O)_2N(R^{32})_2$, and optionally substituted cycloalkylene-$S(O)_2N(R^{32})_2$; and

Z is absent, CH_2, CHR^{35}, O, -NR^{32}-, or -SO_2-;

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

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



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

"---" is a single bond or a double bond;

X^1 is CH or N;

when "---" is a double bond, X^2 is CH or N;

when "---" is a single bond, X^2 is $N(CH_3)$,

when X^1 is CH, X^2 is N or $N(CH_3)$;

W is -O-, -$N(CH_3)$-, -$N(CH_2CH_2OH)$-, cyclopropan-1,1-diyl, or -$CH(CH_3)$-;

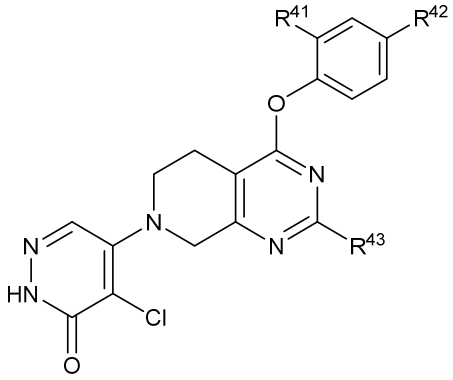
Q is 2-trifluoromethyl-4-fluorophenyl, 2-difluoromethyl-4-fluorophenyl, 2-trifluoromethylphenyl, 2-methyl-4-fluorophenyl, 2-chloro-4-fluorophenyl, 2-chlorophenyl, 1-(benzyl)-4-methylpiperidin-3-yl, 4-trifluoromethylpyridin-3-yl, 2-trifluoromethyl-6-fluorophenyl, 2-trifluoromethyl-3-cyanophenyl, 2-ethyl-3-fluorophenyl,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

R^{43} is hydrogen, -CH_2OH, -$CH(OH)$-CH_2OH, -NH_2, -$CH(OH)CH_3$, -OCH_3, or -NH-$(CH_2)_2OH$; and when "---" is a double bond, R^{44} is absent;

and when "---" is a single bond, R^{43} and R^{44} are taken together to form =O; and

each of R^{45} and R^{46} is independently hydrogen or $-CH_3$.

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



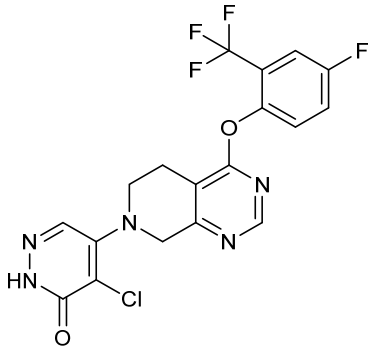
(XI), or a pharmaceutically acceptable salt thereof; wherein:

R^{41} is chloro, $-CF_3$, $-CHF_2$, or $-CH_3$;

R^{42} is hydrogen or fluoro; and

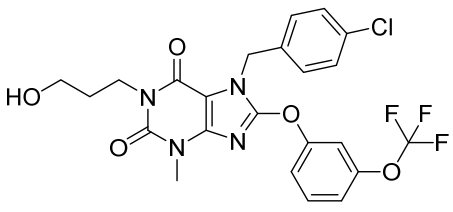
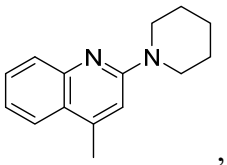
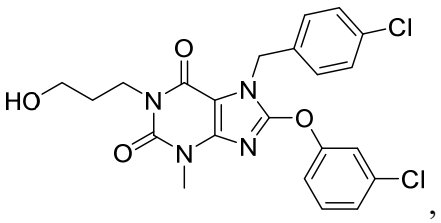
R^{43} is hydrogen, $-NH_2$, $-CH_2OH$, or $CH(OH)-CH_2OH$.

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



, or a pharmaceutically acceptable salt thereof.

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


, 
, 
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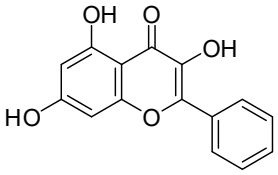
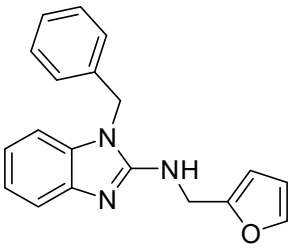
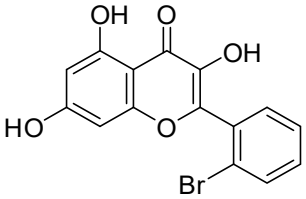
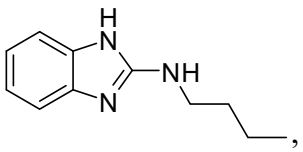
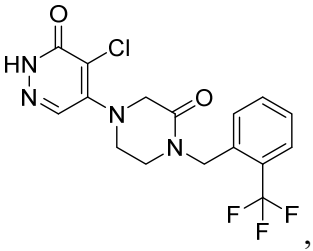
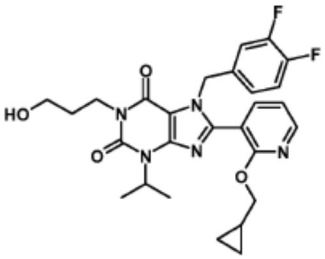
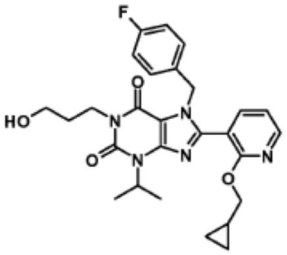
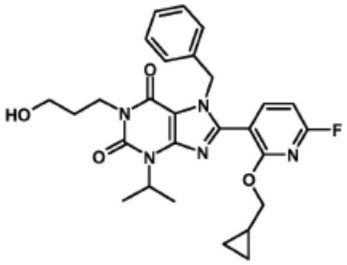
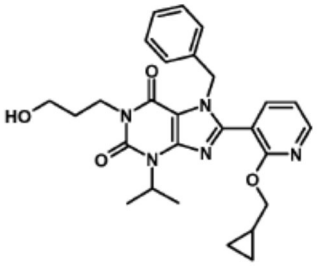
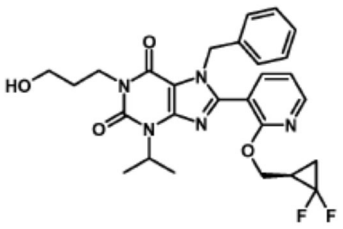
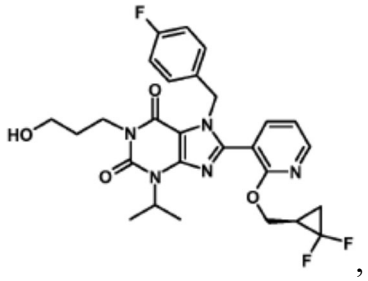
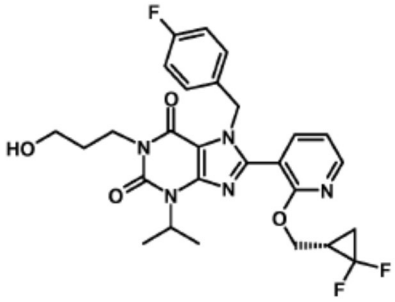
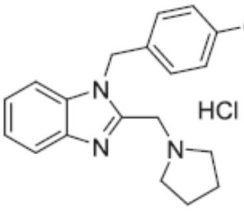
, , , , , , , , , , , , , , , or , or a pharmaceutically acceptable salt thereof.

8. The ~~method~~use of claim 1 or 2, wherein the calcineurin inhibitor is cyclosporin A, tacrolimus, or voclosporin, or a pharmaceutically acceptable salt thereof.

9. The ~~method~~use 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~~use of claim 9, wherein the kidney disease is diabetic nephropathy, or focal segmental glomerulosclerosis.

11. The ~~method~~use of claim 9, wherein the kidney disease is autosomal dominant polycystic kidney disease of autosomal recessive polycystic kidney disease.

12. The ~~method~~use 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~~use of claim 12, wherein the urinary Rac1 level in a subject is measured in a fraction of urine comprising extracellular vesicles.

14. The ~~method~~use 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~~use of claim 14, wherein the pre-determined threshold level at a level above the 90th percentile in the population.

16. The ~~method~~use of claim 15, wherein the pre-determined threshold level at a level above the 95th percentile in the population.

17. The ~~method~~use 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~~from an isolated urine sample from 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~~from an isolated urine sample from 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.