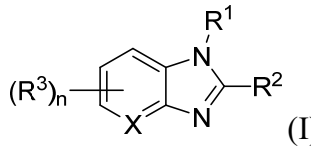
Claims:

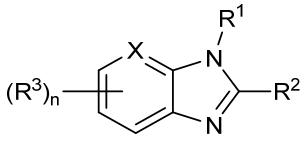
1. Use of a TRPC5 inhibitor or a calcineurin inhibitor; and a pharmaceutically acceptable carrier in the preparation of a pharmaceutical composition for treating a human subject suffering from a kidney disease, wherein the pharmaceutical composition is to be administered to a human subject selected to have a urinary level of one or more biomarkers selected from Rac1, Rac1-GTP, phospho-LIM kinase 1, and phospho-cofilin above a pre-determined threshold.

2. Use of a TRPC5 inhibitor or a calcineurin inhibitor; and a pharmaceutically acceptable carrier in the preparation of a pharmaceutical composition for treating a human subject suffering from a kidney disease wherein the pharmaceutical composition is to be administered to a subject 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 above a pre-determined threshold.

3. The 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-

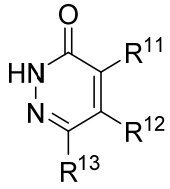
aryl; heterocycloalkyl; -N=C(R)-aryl; -N(R)-alkylene-heteroaryl; -N(R)-alkylene-OH; -S-alkylene-C(O)N(R)-aryl; -S-alkylene-C(O)N(R)-heteroaryl; alkylene-C(O)-heterocycloalkyl; alkylene-N(R)-alkyl; alkylene-N(R)-aryl; and -S-alkyl;

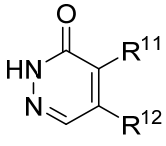
R^3 is independently selected from alkyl, halogen, -CN, -OMe, -OH, $-NO_2$, $-NH_2$, $-N(Me)_2$, $-CF_3$, $-OCF_3$, $-CHF_2$, $-OCHF_2$, and -O-alkylene-OH;

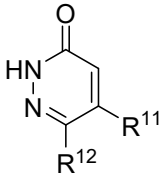
R is H, or Me; and

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;

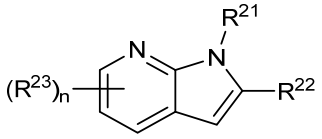
R^{15} is independently H or alkyl;

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

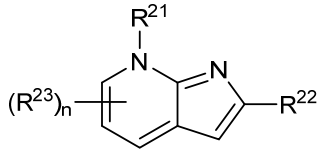
one and only one of R^{11}, R^{12}, and R^{13} is –heterocyclyl-L-R^{14} or -heteroaryl-L-R^{14};

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';

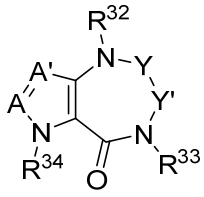
R^{23} is independently selected from alkyl, halogen, OMe, OH, $N(Me)_2$, CF_3, or OCF_3, -O- and alkylene-OH;

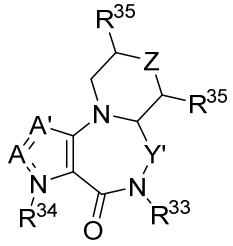
R is H, or Me;

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;

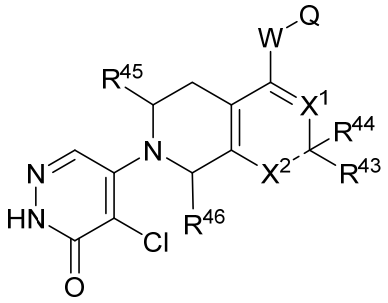
Y' is -C(O)-, CH_2, $CHR^{33'}$, $C(R^{33'})_2$, or Y' is taken together with R^{33} to form a 5- or 6-membered ring;

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 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 -$CH(CH_3)$-;

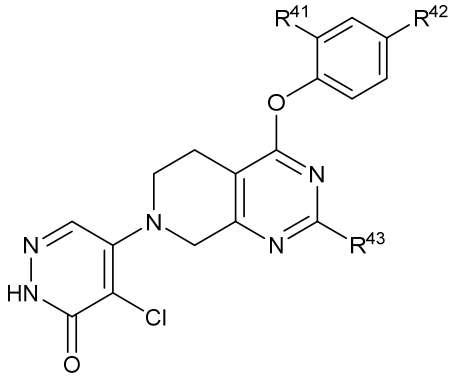
Q is 2-trifluoromethyl-4-fluorophenyl, 2-difluoromethyl-4-fluorophenyl, 2-trifluoromethylphenyl, 2-methyl-4-fluorophenyl, 2-chloro-4-fluorophenyl, 2-chlorophenyl, 1-(benzyl)-4-methylpiperidin-3-yl, 4-trifluoromethylpyridin-3-yl, 2-trifluoromethyl-6-fluorophenyl, 2-trifluoromethyl-3-cyanophenyl, 2-ethyl-3-fluorophenyl, 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 use of claim 4, wherein the TRPC5 inhibitor is a compound of Formula XI:



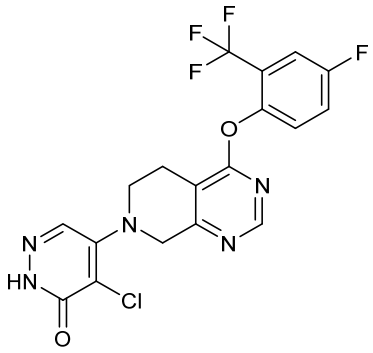
(XI), or a pharmaceutically acceptable salt thereof; wherein:

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

R^{42} is hydrogen or fluoro; and

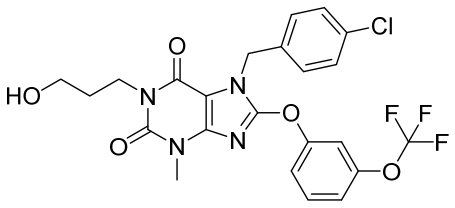
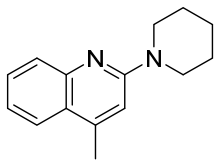
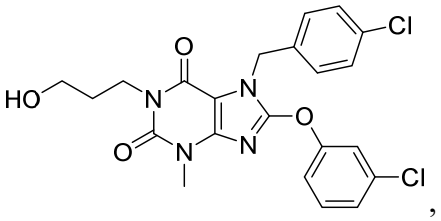
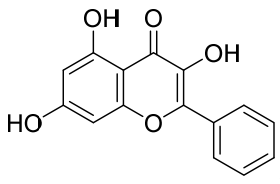
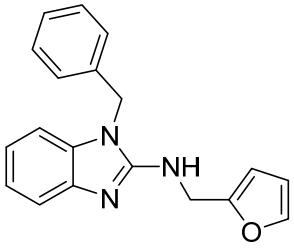
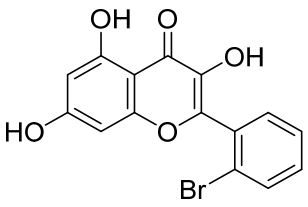
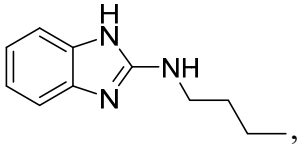
R^{43} is hydrogen, $-NH_2$, $-CH_2OH$, or $CH(OH)-CH_2OH$.

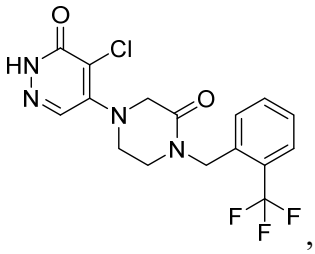
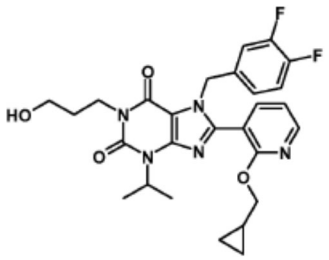
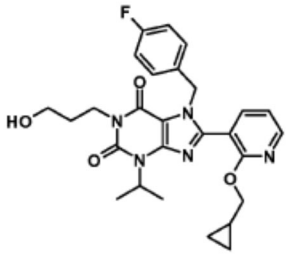
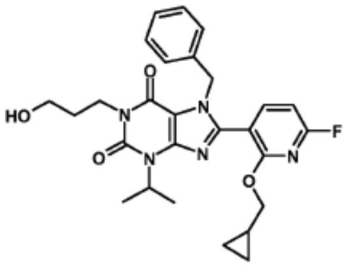
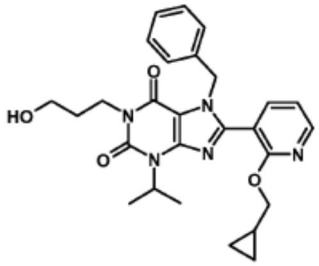
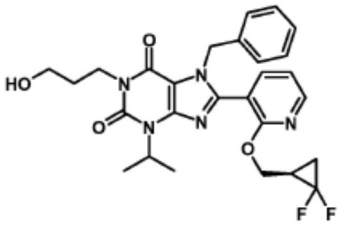
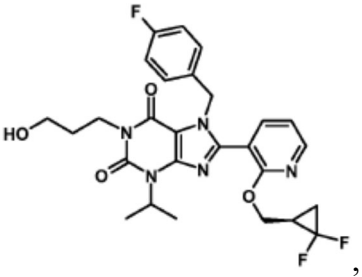
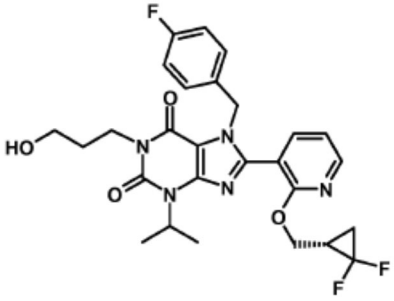
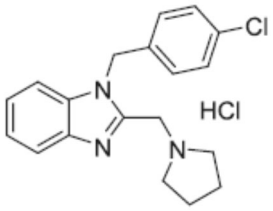
6. The use of claim 5, wherein the TRPC5 inhibitor is:



, or a pharmaceutically acceptable salt thereof.

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


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, or

, or a pharmaceutically acceptable salt thereof.

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

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

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

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

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

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

17. The 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 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 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.