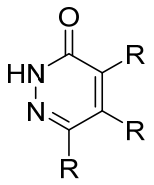
Claims

1. Use of

a. a TRPC5 inhibitory compound of structural Formula (A), or a tautomer or a pharmaceutically acceptable salt thereof:



(A)

wherein

each R is 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, -O-alkylene-O-alkyl, –heterocyclyl-L-R^4, and heteroaryl-L-R^4;

R^4 is absent or selected from the group consisting of alkyl, cycloalkyl, polycyclyl, aryl, heterocyclyl, heteroaryl, $-C(O)N(R^5)_2$, and CF_3;

R^5 is independently H or alkyl;

R^6 is selected from the group consisting of alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, alkylene-aryl, $-C(O)N(R^5)_2$, and CF_3;

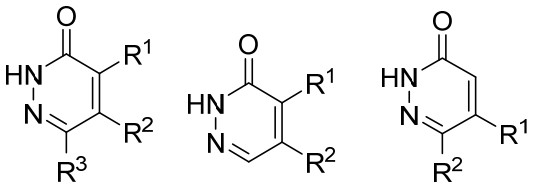
L is absent or selected from the group consisting of methylene, -C(O)-, $-SO_2$-, $-CH_2N(Me)$-, $-N(R^5)(R^6)$-, $-C(R^5)(R^6)$-, and -O-R^6; and

one and only one R is -heterocyclyl-L-R^4 or -heteroaryl-L-R^4; and

b. a second therapeutic agent selected from an immunomodulator, a calcineurin inhibitor, a renin angiotensin aldosterone system inhibitor, an antiproliferative agent, an alkylating agent, a corticosteroid, an angiotensin converting enzyme inhibitor, an adrenocorticotropic hormone stimulant, an angiotensin receptor blocker, a sodium-glucose transport protein 2 inhibitor, a dual sodium-glucose transport protein 1/2 inhibitor, a nuclear Factor-1 (erythroid-derived 2)-like 2 agonist, a chemokine receptor 2 inhibitor, a chemokine receptor 5 inhibitor, an endothelin 1 receptor antagonist, a beta blocker, a mineralocorticoid receptor antagonist, a loop or thiazide diuretic, a calcium channel blocker, a statin, a short- intermediate or long-acting insulin, a dipeptidyl

peptidase 4 inhibitor, a glucagon-like peptide 1 receptor agonist, a sulfonylurea, an apoptosis signal-regulating kinase-1, a chymase inhibitor, a selective glycation inhibitor, a renin inhibitor, an interleukin-33 inhibitor, a farnesoid X receptor agonist, a soluble guanylate cyclase stimulator, a thromboxane receptor antagonist, a xanthine oxidase inhibitor, an erythropoietin receptor agonist, a cannabinoid receptor type 1 inverse agonist, a NADPH oxidase inhibitor, an anti-vascular endothelial growth factor B, an anti-fibrotic agent, a neprilysin inhibitor, a dual CD80/CD86 inhibitor, a CD40 antagonist, a cellular cholesterol and lipid blocker, a PDGFR antagonist, a Slit guidance ligand 2, an APOL1 inhibitor, an Nrl2 activator/NF-κB inhibitor, a somatostatin receptor agonist, a PPAR gamma agonist, a AMP activated protein kinase stimulator, a tyrosine kinase inhibitor, a glucosylceramide synthase inhibitor, an arginine vasopressin receptor 2 antagonist, a xanthine oxidase inhibitor, and a vasopressin receptor 2 antagonist; in the preparation of a medicament for treating a disease or disorder selected from kidney disease, anxiety, depression, pain, or cancer; wherein the TRPC5 inhibitory compound of structural Formula (A), or a tautomer or a pharmaceutically acceptable salt thereof is to be co-administered with the second therapeutic agent.

2. The use of claim 1, wherein the TRPC5 inhibitory compound is represented by structural Formula (A-I), (A-II), or (A-III), or a tautomer or a pharmaceutically acceptable salt thereof;



wherein

R^1 and R^3 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^2 is –heterocyclyl-L-R^4;

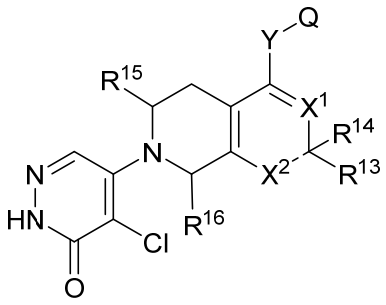
R^4 is absent or selected from the group consisting of alkyl, cycloalkyl, aryl, alkylene-aryl, alkylene-heteroaryl, heteroaryl, heterocyclyl, -C(O)N(R^5)$_2$, and CF_3;

R^5 is independently H or alkyl;

R^6 is selected from the group consisting of alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, alkylene-aryl, -C(O)N(R^5)$_2$, and CF_3;

L is absent or selected from the group consisting of methylene, -C(O)-, -SO_2-, -CH_2N(Me)-, -N(R^5)(R^6)-, -C(R^5)(R^6)-, and -O-R^6; and

one and only one of R^1, R^2, and R^3 is –heterocyclyl-L-R^4 or -heteroaryl-L-R^4.

3. The use of claim 1, wherein the TRPC5 inhibitory compound has structural formula (I):  (I), 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);

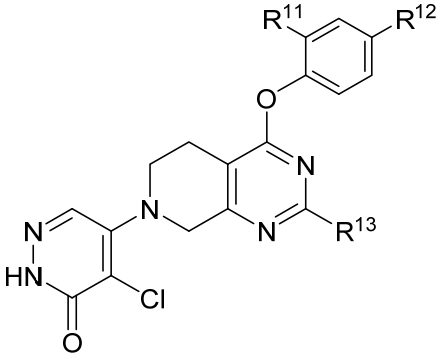
Y is -O-, -N(CH_3)-, -N(CH_2CH_2OH)-, cyclopropan-1,1-diyl, or -CH(CH_3)-;

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;

when "---" is a double bond, R^{13} is hydrogen, -CH_2OH, -CH(OH)-CH_2OH, -NH_2, -CH(OH)CH_3, -OCH_3, or -NH-(CH_2)$_2$OH; and R^{14} is absent; or

when "---" is a single bond, R^{13} and R^{14} are taken together to form =O; and

each of R^{15} and R^{16} is independently hydrogen or $-CH_3$.

4. The use of claim 2, wherein the TRPC5 inhibitory compound has the structural formula (II):  (II), or a pharmaceutically acceptable salt thereof; wherein:

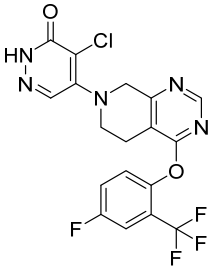
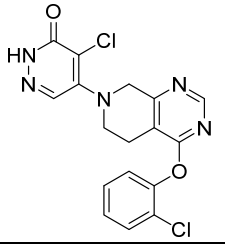
R^{11} is chloro, $-CF_3$, $-CHF_2$, or $-CH_3$;

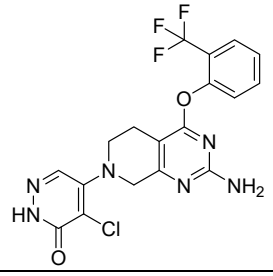
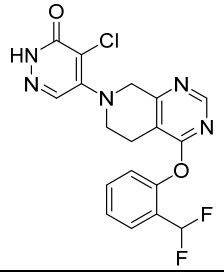
R^{12} is hydrogen or fluoro; and

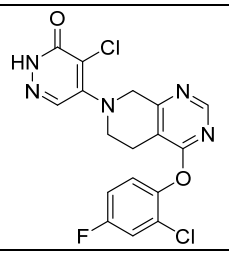
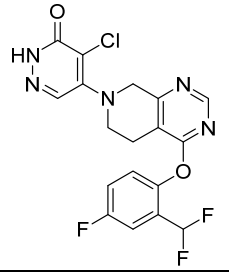
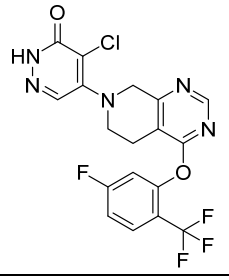
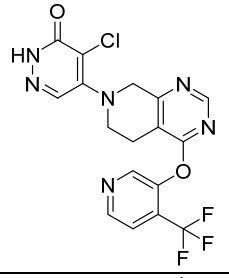
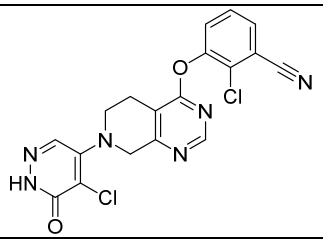
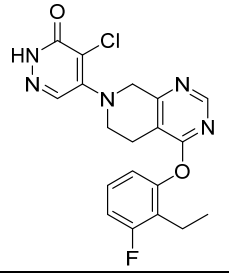
R^{13} is hydrogen, $-NH_2$, $-CH_2OH$, or $CH(OH)-CH_2OH$.

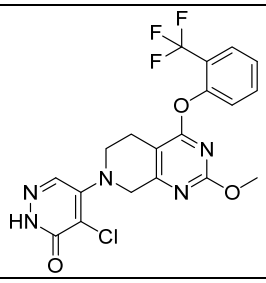
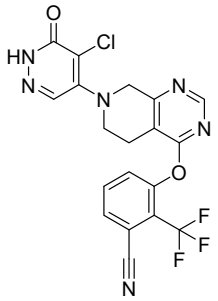
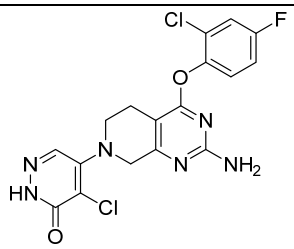
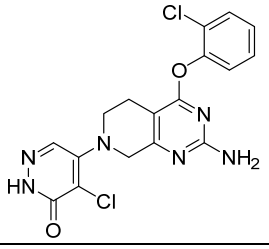
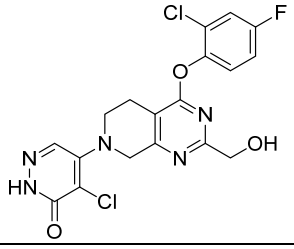
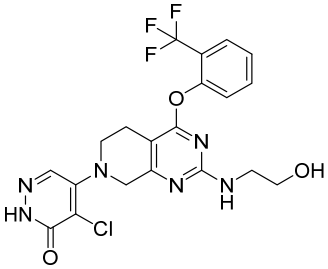
5. The use of claim 4, wherein R^{11} is $-CHF_2$; and R^{12} is fluoro.

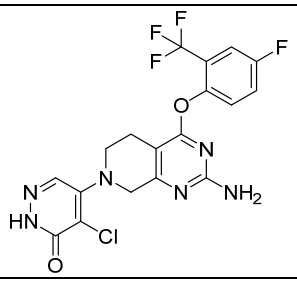
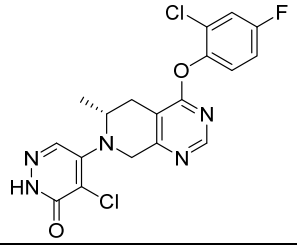
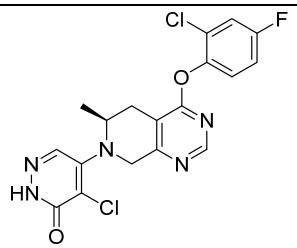
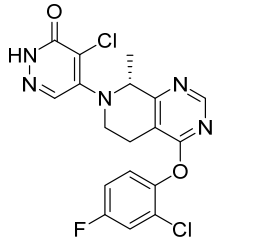
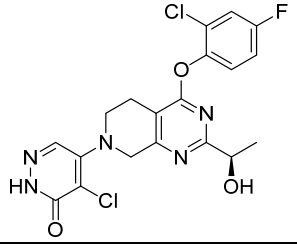
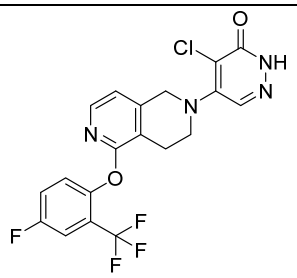
6. The use of claim 3, wherein the TRPC5 inhibitory compound is selected from any one of the following compounds, or a pharmaceutically acceptable salt thereof:

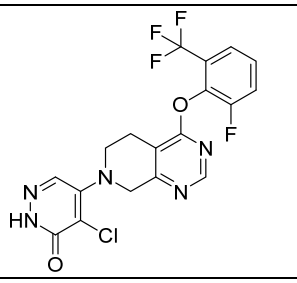
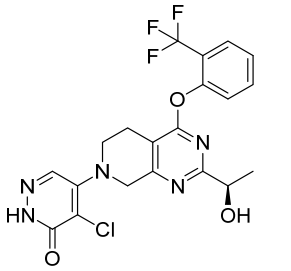
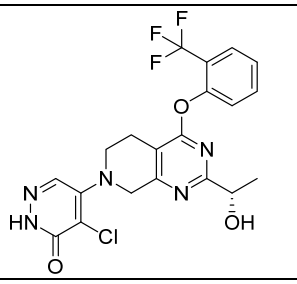
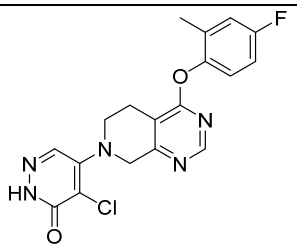
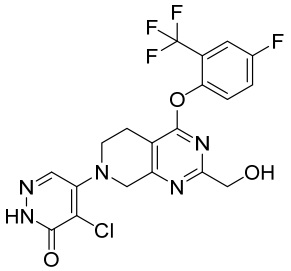
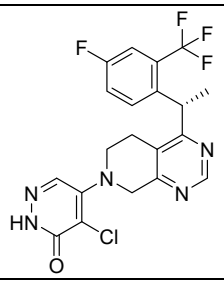
Compound	Structure
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101	

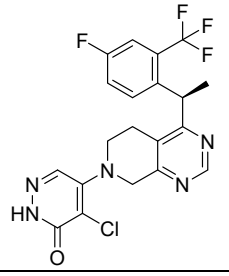
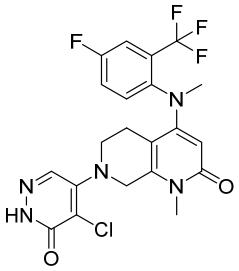
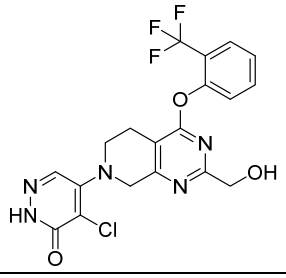
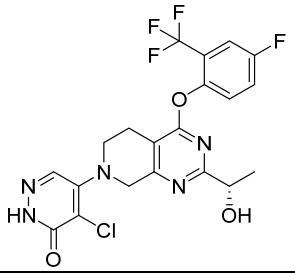
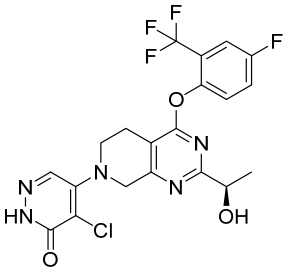
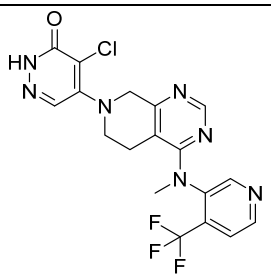
Compound	Structure
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103	

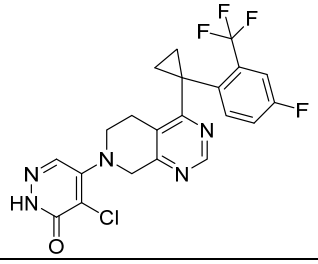
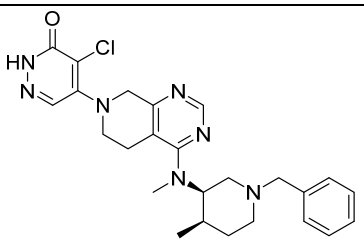
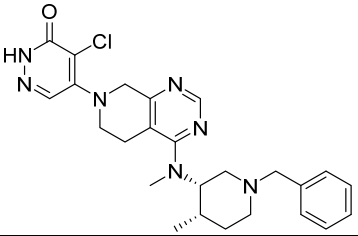
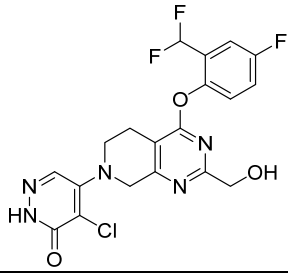
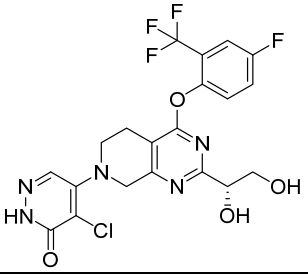
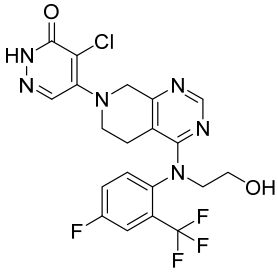
Compound	Structure
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105	
106	
107	
108	
109	

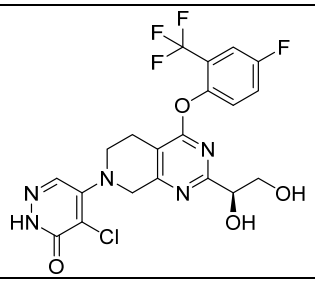
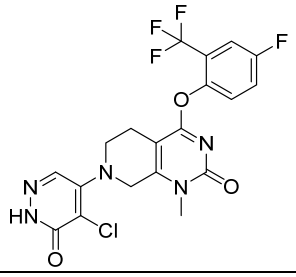
Compound	Structure
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111	
112	
113	
114	
115	

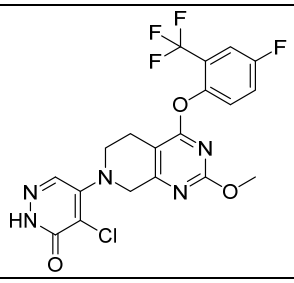
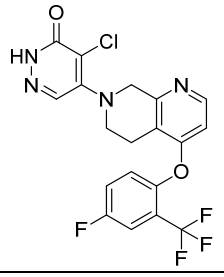
Compound	Structure
116	
117	
117a	
118	
119	
120	

Compound	Structure
121	
122	
123	
124	
125	
126	

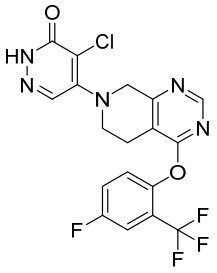
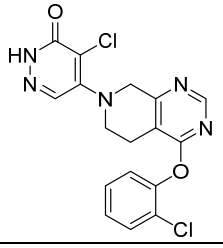
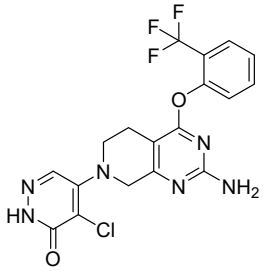
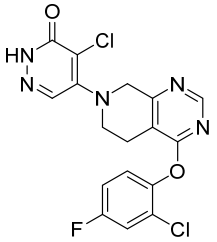
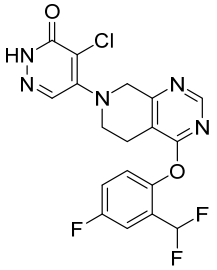
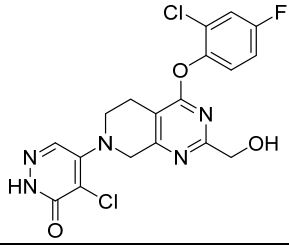
Compound	Structure
126a	
127	
128	
129	
130	
131	

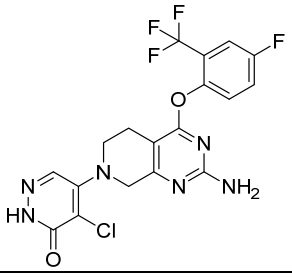
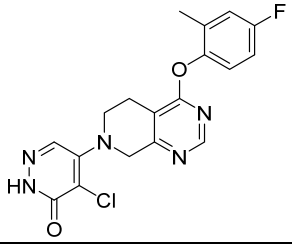
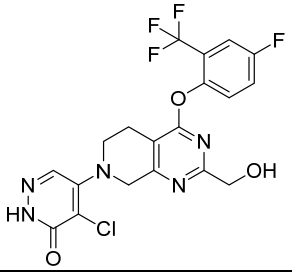
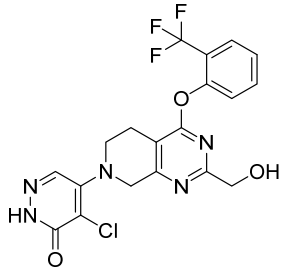
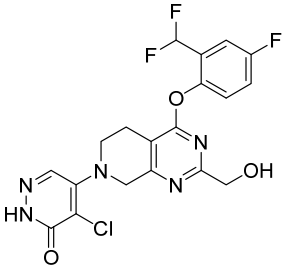
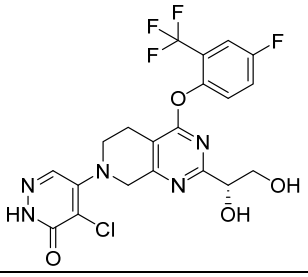
Compound	Structure
132	
133	
133a	
134	
135	
136	

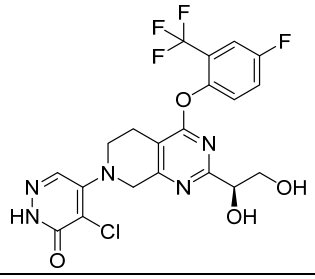
Compound	Structure
137	
138	

Compound	Structure
139	
140	

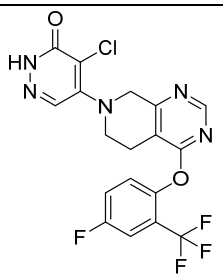
7. The use of claim 6, wherein the TRPC5 inhibitory compound is selected from any one of the following compounds, or a pharmaceutically acceptable salt thereof:

Compound	Structure
100	
101	
102	
104	
105	
114	

Compound	Structure
116	
124	
125	
128	
134	
135	

Compound	Structure
137	

8. The use of claim 7, wherein the TRPC5 inhibitory compound is the following compound, or a pharmaceutically acceptable salt thereof:

Compound	Structure
100	

9. The use of any one of claims 1-8, wherein the immunomodulator is rituximab.

10. The use of any one of claims 1-8, wherein the angiotensin converting enzyme inhibitor is captopril, zofenopril, enalapril, ramipril, quinapril, perindopril, lisinopril, benazepril, imidapril, trandolapril, or cilazapril.

11. The use of any one of claims 1-8, wherein the angiotensin receptor blocker is losartan, candesartan, valsartan, irbesartan, telmisartan, eprosartan, olmesartan, azilsartan, or fimasartan.

12. The use of any one of claims 1-8, wherein the renin angiotensin aldosterone system inhibitor is aliskiren.

13. The use of any one of claims 1-8, wherein the endothelin 1 receptor antagonist is ambrisentan, atrasentan, bosentan, or sparsentan.

14. The use of any one of claims 1-8, wherein the anti-proliferative agent is mycophenolate mofetil.

15. The use of any one of claims 1-8, wherein the SGLT2 inhibitor is canagliflozin, dapagliflozin, empagliflozin, a combination of empagliflozin and linagliptin, a combination of empagliflozin and metformin, or a combination of dapagliflozin and metformin.

16. The use of any one of claims 1-8, wherein the calcineurin inhibitor is cyclosporine A or tacrolimus.

17. The use of any one of claims 1-8, wherein the nuclear Factor-1 (erythroid-derived 2)-like 2 agonist is bardoxolone or CXA-10.

18. The use of any one of claims 1-8, wherein the chemokine receptor 2 inhibitor is PF-04136309 or ccx140.

19. The use of any one of claims 1-8, wherein the second therapeutic agent is tacrolimus, cyclosporine A, rituximab, mycophenolate mofetil, a corticosteroid, sparsentan, enalapril, or losartan.

20. The use of claim 19, wherein the second therapeutic agent is enalapril, losartan, or cyclosporine A.

21. The use of any one of claims 1-20, wherein the disease or disorder is a kidney disease ~~or condition is~~selected from Focal Segmental Glomerulosclerosis (FSGS), Primary Focal Segmental Glomerulosclerosis, genetic Focal Segmental Glomerulosclerosis, secondary Focal Segmental Glomerulosclerosis, Diabetic nephropathy, Alport syndrome, hypertensive kidney disease, nephrotic syndrome, steroid-resistant nephrotic syndrome, minimal change disease, membranous nephropathy, idiopathic membranous nephropathy, membranoproliferative glomerulonephritis (MPGN), immune complex-mediated MPGN, complement-mediated MPGN, Lupus nephritis, postinfectious glomerulonephritis, thin basement membrane disease, mesangial

proliferative glomerulonephritis, amyloidosis (primary), c1q nephropathy, rapidly progressive glomerulonephritis (GN), anti-GBM disease, C3 glomerulonephritis, hypertensive nephrosclerosis, IgA nephropathy, autosomal recessive polycystic kidney disease, or autosomal dominant polycystic kidney disease.

22. The use of claim 21 wherein the kidney disease ~~or condition~~ is Focal Segmental Glomerulosclerosis (FSGS), Primary Focal Segmental Glomerulosclerosis, genetic Focal Segmental Glomerulosclerosis, transplant-related FSGS, or secondary Focal Segmental Glomerulosclerosis.

23. The use of claim 21, wherein the kidney disease is proteinuric kidney disease.

24. The use of claim 21, wherein the kidney disease is microalbuminuria or macroalbuminuria kidney disease.

25. The use of any one of claims 1-20, wherein the disease or disorder is anxiety or depression.

26. The use of any one of claims 1-20, wherein the disease or disorder is pain.

~~25. The use of any one of claims 1-24, wherein the subject is a human.~~

27~~26~~. The use of claim 22 ~~or 25~~, wherein the disease or condition is focal segmental glomerulosclerosis.

28. The use of any one of claims 1-27, wherein the subject is a human.

29~~27~~. The use of any one of claims 1-28~~26~~, wherein the components of the medicament are in the same formulation or in a separate formulation to be co-administered sequentially or concomitantly.