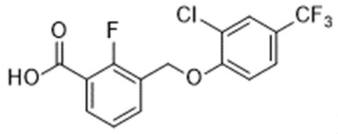
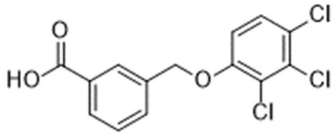
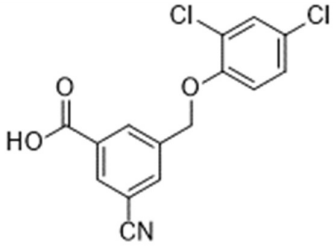
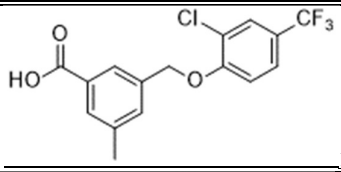
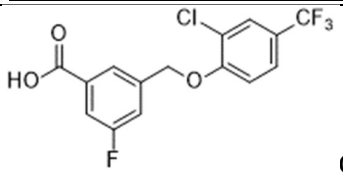
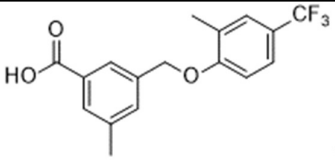
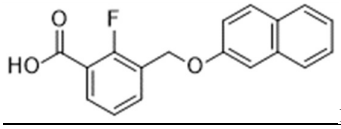
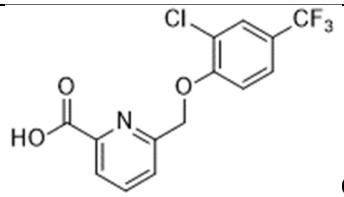
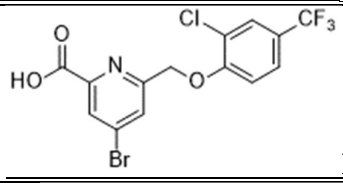
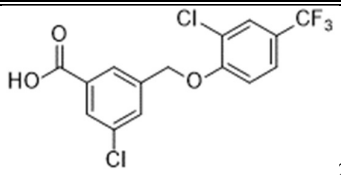
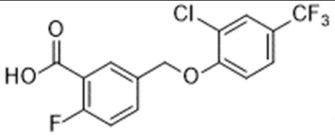
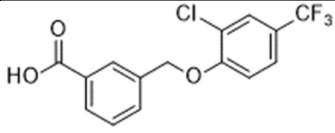
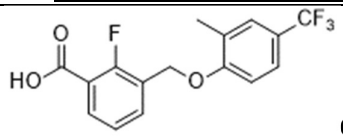
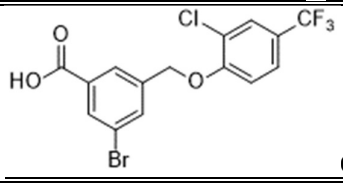
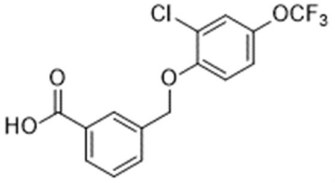
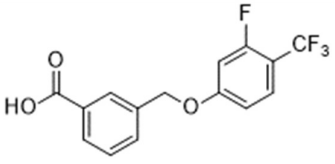
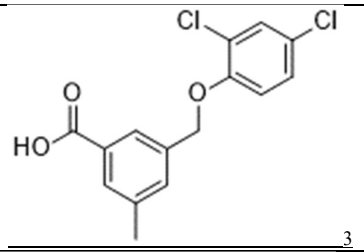
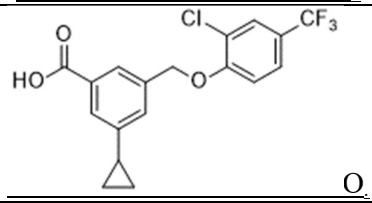
CLAIMS

1. A compound having one of the following structures, or a pharmaceutically acceptable hydrate, solvate, isotope, or salt thereof:

Cpd No.	Structure
1-55	 $H_9ClF_4O_3$
1-78	 $C_{14}H_9Cl_3O_3$
5-1	 $C_{15}H_9Cl_2NO_3$
4-10	 $_{16}H_{12}ClF_3O_3$
1-65	 $C_{15}H_9ClF_4O_3$
4-11	 $C_{17}H_{15}F_3O_3$
1-58	 $_{18}H_{13}FO_3$

1-56	 $C_{14}H_9ClF_3NO_3$
9-1	 $BrClF_3NO_3$
1-82	 $_2F_3O_3$
1-85	 F_4O_3
1-29	 $_3O_3$
1-101	 $C_{16}H_{12}F_4O_3$
2-3	 O_3
1-103	 $_4$
1-112	 $_3$

4-7	
11-1	

2. The compound of claim 1, wherein the compound is Cpd. No. 1-55 or a pharmaceutically acceptable hydrate, solvate, isotope, or salt thereof.

3. The compound of claim 1, wherein the compound is Cpd. No. 1-78 or a pharmaceutically acceptable hydrate, solvate, isotope, or salt thereof.

4. The compound of claim 1, wherein the compound is Cpd. No. 5-1 or a pharmaceutically acceptable hydrate, solvate, isotope, or salt thereof.

5. The compound of claim 1, wherein the compound is Cpd. No. 4-10 or a pharmaceutically acceptable hydrate, solvate, isotope, or salt thereof.

6. The compound of claim 1, wherein the compound is Cpd. No. 1-65 or a pharmaceutically acceptable hydrate, solvate, isotope, or salt thereof.

7. The compound of claim 1, wherein the compound is Cpd. No. 4-11 or a pharmaceutically acceptable hydrate, solvate, isotope, or salt thereof.

8. The compound of claim 1, wherein the compound is Cpd. No. 1-58 or a pharmaceutically acceptable hydrate, solvate, isotope, or salt thereof.

9. The compound of claim 1, wherein the compound is Cpd. No. 1-56 or a pharmaceutically acceptable hydrate, solvate, isotope, or salt thereof.

10. The compound of claim 1, wherein the compound is Cpd. No. 9-1 or a pharmaceutically acceptable hydrate, solvate, isotope, or salt thereof.

11. The compound of claim 1, wherein the compound is Cpd. No. 1-82 or a pharmaceutically acceptable hydrate, solvate, isotope, or salt thereof.

12. The compound of claim 1, wherein the compound is Cpd. No. 1-85 or a pharmaceutically acceptable hydrate, solvate, isotope, or salt thereof.

13. The compound of claim 1, wherein the compound is Cpd. No. 1-29 or a pharmaceutically acceptable hydrate, solvate, isotope, or salt thereof.

14. The compound of claim 1, wherein the compound is Cpd. No. 1-101 or a pharmaceutically acceptable hydrate, solvate, isotope, or salt thereof.

15. The compound of claim 1, wherein the compound is Cpd. No. 2-3 or a pharmaceutically acceptable hydrate, solvate, isotope, or salt thereof.

16. The compound of claim 1, wherein the compound is Cpd. No. 1-103 or a pharmaceutically acceptable hydrate, solvate, isotope, or salt thereof.

17. The compound of claim 1, wherein the compound is Cpd. No. 1-112 or a pharmaceutically acceptable hydrate, solvate, isotope, or salt thereof.

18. The compound of claim 1, wherein the compound is Cpd. No. 4-7 or a pharmaceutically acceptable hydrate, solvate, isotope, or salt thereof.

19. The compound of claim 1, wherein the compound is Cpd. No. 11-1 or a pharmaceutically acceptable hydrate, solvate, isotope, or salt thereof.

20. A pharmaceutical composition comprising a compound of any one of claims 1–19, or a pharmaceutically acceptable hydrate, solvate, isotope, or salt thereof, and a

pharmaceutically acceptable excipient.

21. The pharmaceutical composition of claim 20, further comprising a second therapeutic agent.

22. The pharmaceutical composition of claim 21, wherein the second therapeutic agent is ursodeoxycholic acid (UDCA), *nor*Ursodeoxycholic acid, cholestyramine, stanozolol, naltrexone, rifampicin, Alisol B 23-acetate (AB23A), curcumin, dihydroartemisinin, fenofibrate, bezafibrate, metronidazole, methotrexate, colchicine, metformin, betaine, glucagon, naltrexone, a farnesoid X-receptor (FXR) agonist, a peroxisome proliferator-activated receptor (PPAR) agonist, a thyroid hormone receptor beta (TRβ) agonist, or any combination thereof.

23. The pharmaceutical composition of claim 22 wherein:

(a) the FXR agonist is obeticholic acid, Turofexorate isopropyl (WAY-362450), 3-(2,6-dichlorophenyl)-4-(3'-carboxy-2-chlorostilben-4-yl)oxymethyl-5-isopropyl-isoxazole (GW4064), PX20606 (PX-102), PX-101, INT-767, INT-787, TERN-101, altenusin, tropifexor (LJN452), nidufexor, turofexorate isopropyl, fexaramine, silymarin, silybin, hedragonic acid, cafestol, Cilofexor (GS-9674 or Px-104), EDP-305, BAR704, BAR502, EYP-001, RDX-023, AGN-242266, HPG-1860, MET-409, AGN-242256, EP-024297, IOT-022, M-480, INV-33, RDX023-02, or any combination thereof;

(b) the PPAR agonist is a PPAR-alpha agonist, a PPAR-gamma agonist, a PPAR-delta agonist, a PPAR-alpha/gamma dual agonist, a PPAR alpha/delta dual agonist, a PPAR gamma/delta dual agonist, or PPAR alpha/gamma/delta pan agonist, optionally wherein:

the PPAR alpha agonist is fenofibrate, ciprofibrate, pemafibrate, gemfibrozil, clofibrate, binifibrate, clinofibrate, clofibric acid, nicofibrate, pirifibrate, plafibride, ronifibrate, theofibrate, tocofibrate, or SRI 0171;

the PPAR gamma agonist is rosiglitazone, pioglitazone, deuterium-stabilized R-pioglitazone, efatutazone, ATx08-001, OMS-405, CHS-131, THR-0921, SER-150-DN, KDT-501, GED-0507-34-

Levo, CLC-3001, or ALL-4;

the PPAR delta agonist is GW501516 (endurabol or ({4-[({4-methyl-2-[4-(trifluoromethyl)phenyl]-l,3-thiazol-5-yl}methyl)sulfanyl]-2-methylphenoxy} acetic acid)), MBX8025 (seladelpar or {2-methyl-4-[5- methyl-2-(4-trifluoromethyl- phenyl)-2H-[l,2,3]triazol-4-ylmethylsylfanyl]-phenoxy}-acetic acid), GW0742 ([4-[[[2-[3-fluoro-4-(trifluoromethyl)phenyl]-4-methyl-5-thiazolyl]methyl]-thio]-2-methyl phenoxy] acetic acid), L165041, HPP-593, or NCP-1046;

the PPAR alpha/gamma agonist is saroglitazar, aleglitazar, muraglitazar, tesaglitazar, or DSP-8658;

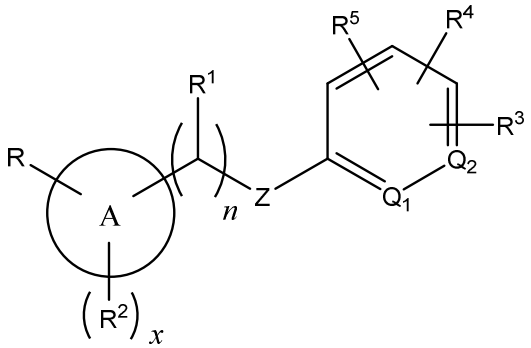
the PPAR alpha/delta agonist is elafibranor or T913659;

the PPAR gamma/delta agonist is a conjugated linoleic acid (CLA) or T3D-959; and

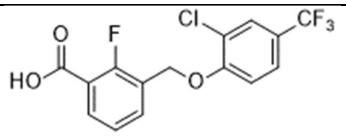
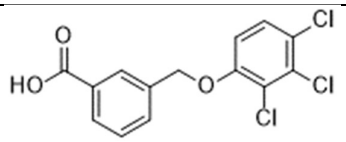
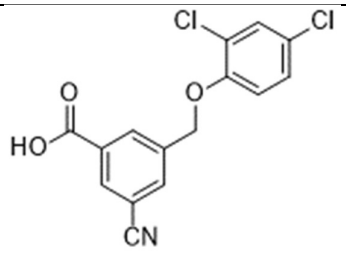
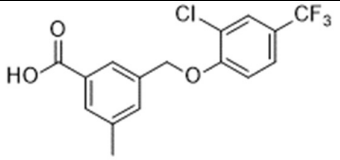
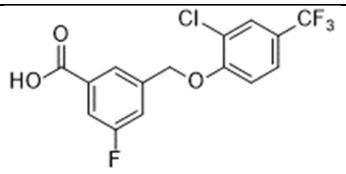
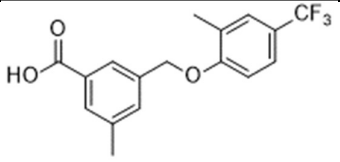
the PPAR alpha/gamma/delta agonist is IVA337 (lanifibranor), TTA (tetradecylthioacetic acid), bavachinin, GW4148, GW9135, bezafibrate, lobeglitazone, 2-(4-(5,6-methylenedioxybenzo[d]-thiazol-2-yl)-2-methylphenoxy)-2-methylpropanoic acid (MHY2013), or CS038; or

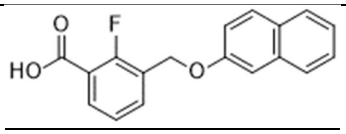
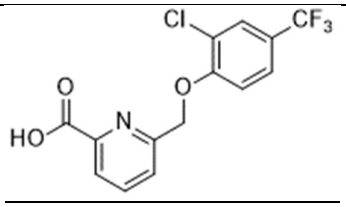
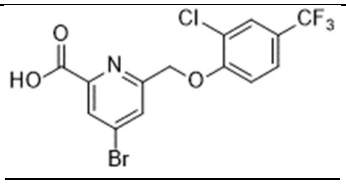
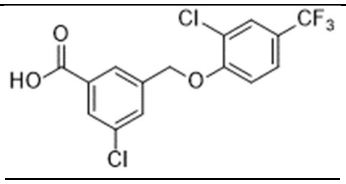
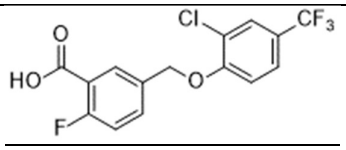
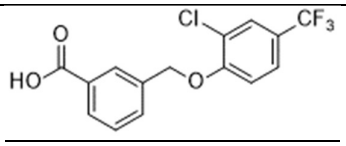
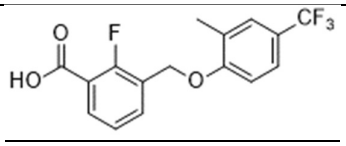
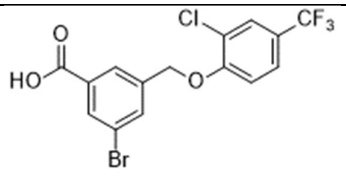
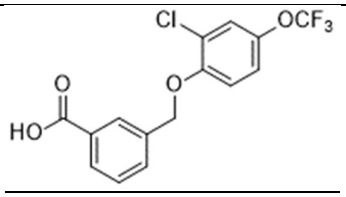
(c) the TRβ agonist is sobetirome, eprotirome, GC-24, MGL-3196, MGL-3745, VK-2809, KB141 [3,5-dichloro-4-(4-hydroxy-3-isopropylphenoxy) phenylacetic acid], MB07811 (2*R*,4*S*)-4-(3-chlorophenyl)-2-[(3,5-dimethyl-4-(4′-hydroxy-3′-isopropylbenzyl)phenoxy)-methyl]-2-oxido-[1,3,2]-dioxaphosphonane), or any combination thereof.

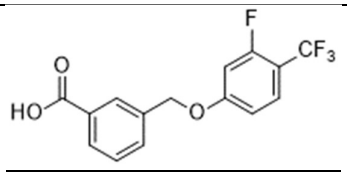
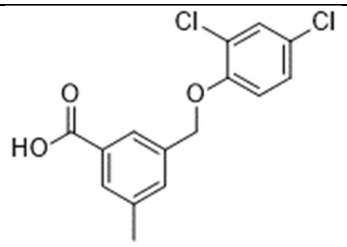
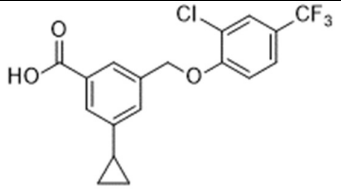
~~1~~24. ~~A method for modulating a Mas-Related G-Protein Receptor (MRGPR) X4 by contacting the MRGPRX4 with an effective amount of~~ Use of a compound having ~~the~~ one of the following structure~~s of Formula (I):~~, or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope, or salt thereof:



(I)

Cpd No.	Structure
1-55	
1-78	
5-1	
4-10	
1-65	
4-11	

1-58	
1-56	
9-1	
1-82	
1-85	
1-29	
1-101	
2-3	
1-103	

1-112	
4-7	
11-1	

in the manufacture of a medicament for modulating a Mas-Related G-Protein Receptor (MRGPR) X4 ~~or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope, or salt thereof, wherein:~~

~~*n* is 0 or 1;~~

~~*x* is 0, 1 or 2;~~

~~A is aryl or heteroaryl;~~

~~Q_1 and Q_2 are both CR^{10}, or one of Q_1 or Q_2 is CR^{10} and the other is N;~~

~~Z is O, S, $N(R^{11})$, CH_2 or C≡C ;~~

~~each R^{10} is H or alkyl;~~

~~R is $(CH_2)_mC(=O)OR^{12}$, $(CH_2)_mNHR^{13}$, $(C=O)NR^{14}R^{15}$, CH_2OH, CN, haloalkyl, carbocycle, heterocycle, or a carboxylic acid isostere;~~

~~*m* is 0 or 1;~~

~~R^{11}, R^{12} and R^{13} are the same or different and individually H or alkyl;~~

~~R^{14} is H and R^{15} is H, $-SO_2CH_3$, carbocycle, heterocyle, or alkyl substituted with 0, 1, 2 or 3 substituents selected from OH, CN, NR'R", C(=O)OH, C(=O)NR'R", SO_2OH, alkoxy, carbocycle, or heterocycyle, wherein R' and R" are individually H or alkyl, or~~

~~R^{14} and R^{15} are taken together with the nitrogen atom to which they are attached to form heterocycle;~~

~~R^1 is H or alkyl;~~

~~R^2 is halo, cyano, amino, alkyl, alkoxy, carbocycle or heterocycle;~~

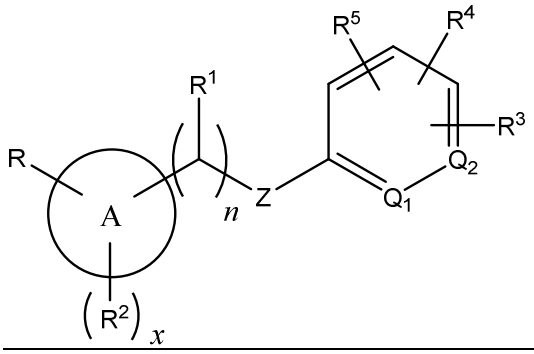
~~R^3, R^4 and R^5 are the same or different and either absent or, when present, cyano, nitro, halogen, alkyl, haloalkyl, cyanoalkyl, alkoxy, haloalkoxy, (C=O)alkyl, (C=O)NHalkyl, carbocycle, heterocycle, O carbocycle or O heterocycle, or~~

~~any two R and R^2 taken together with the atoms to which they are attached form heterocycle;~~

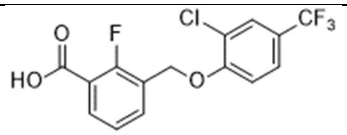
~~any two R^3, R^4, R^5 and R^{10}, taken together with the atoms to which they are attached form carbocycle or heterocycle;~~

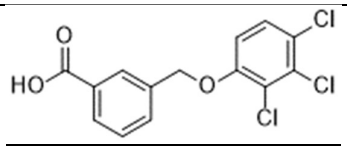
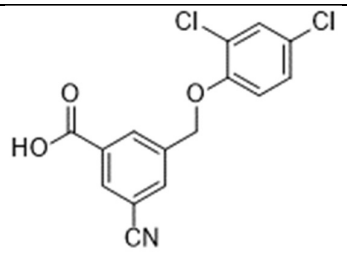
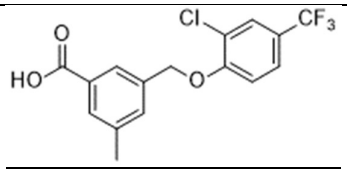
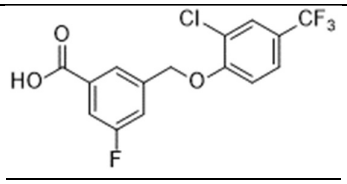
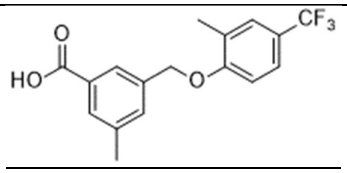
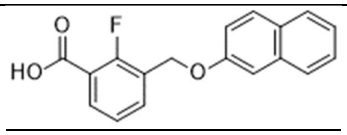
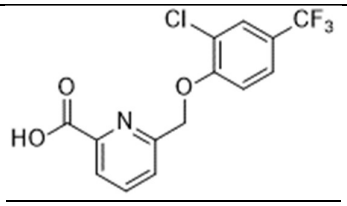
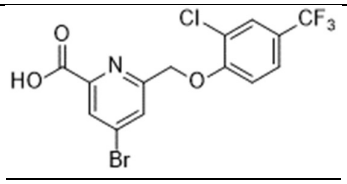
~~and wherein each occurrence of carbocycle or heterocycle is substituted with 0, 1, 2 or 3 substituents individually selected from halogen, hydroxyl, oxo, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, carbocycle, or heterocycle.~~

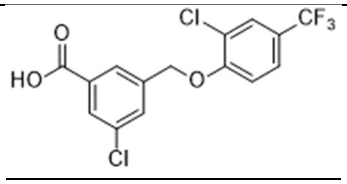
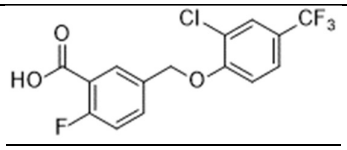
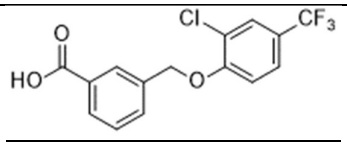
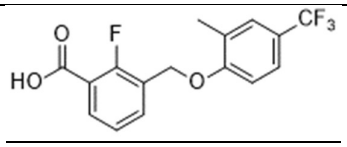
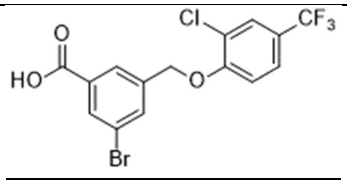
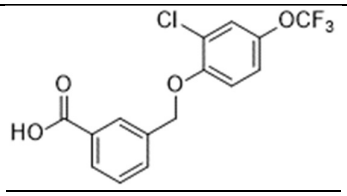
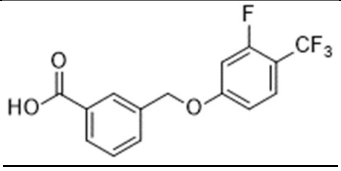
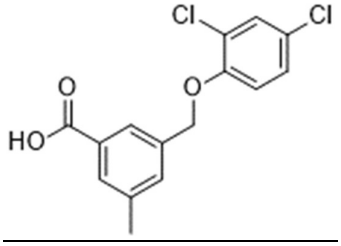
~~2~~25. ~~A method for treating an MRGPR X4 dependent condition by administering to a subject in need thereof an effective amount~~ Use of a compound having one of the following~~the~~ structure~~s of Formula (I):~~, or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope, or salt thereof:

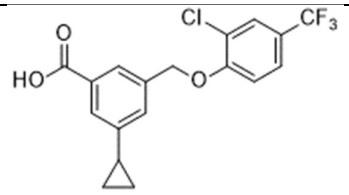


~~(I)~~

Cpd No.	Structure
1-55	

1-78	
5-1	
4-10	
1-65	
4-11	
1-58	
1-56	
9-1	

1-82	
1-85	
1-29	
1-101	
2-3	
1-103	
1-112	
4-7	

11-1	

in the manufacture of a medicament for treating an Mas-Related G-Protein Receptor (MRGPR) X4 dependent condition.

~~or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope, or salt thereof, wherein:~~

~~*n* is 0 or 1;~~

~~*x* is 0, 1 or 2;~~

~~A is aryl or heteroaryl;~~

~~Q_1 and Q_2 are both CR^{10}, or one of Q_1 or Q_2 is CR^{10} and the other is N;~~

~~Z is –O–, –S–, $N(R^{11})$–, $–CH_2–$ or –C≡C–;~~

~~each R^{10} is H or alkyl;~~

~~R is $(CH_2)_m C(=O)OR^{12}$, $(CH_2)_m NHR^{13}$, $(C=O)NR^{14}R^{15}$, CH_2OH, CN, haloalkyl, carbocycle, heterocycle, or a carboxylic acid isostere;~~

~~*m* is 0 or 1;~~

~~R^{11}, R^{12} and R^{13} are the same or different and individually H or alkyl;~~

~~R^{14} is H and R^{15} is H, $-SO_2CH_3$, carbocycle, heterocyle, or alkyl substituted with 0, 1, 2 or 3 substituents selected from –OH, –CN, –NR'R", C(=O)OH, C(=O)NR'R", SO_2OH, alkoxy, carbocycle, or heterocycyle, wherein R' and R" are individually H or alkyl, or~~

~~R^{14} and R^{15} are taken together with the nitrogen atom to which they are attached to form heterocycle;~~

~~R^1 is H or alkyl;~~

~~R^2 is halo, cyano, amino, alkyl, alkoxy, carbocycle or heterocycle;~~

~~R^3, R^4 and R^5 are the same or different and either absent or, when present, cyano, nitro, halogen, alkyl, haloalkyl, cyanoalkyl, alkoxy, haloalkoxy, (C=O)alkyl, (C=O)NHalkyl, carbocycle, heterocycle, –O-carbocycle or –O-heterocycle, or~~

~~any two R and R^2 taken together with the atoms to which they are attached form heterocycle;~~

~~any two R^3, R^4, R^5 and R^{10}, taken together with the atoms to which they are attached form carbocycle or heterocycle;~~

~~and wherein each occurrence of carbocycle or heterocycle is substituted with 0, 1, 2 or 3 substituents individually selected from halogen, hydroxyl, oxo, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, carbocycle, or heterocycle.~~

~~3~~26. The ~~method~~use of claim ~~2~~25, wherein the MRGPR X4 dependent condition is a condition that is caused by the activation of MRGPR X4 by a bile acid or analog thereof.

~~4~~27. The ~~method~~use of claim ~~2~~25 wherein the MRGPR X4 dependent condition is an itch associated condition, a pain associated condition, or an autoimmune disorder.

~~5~~28. The ~~method~~use of claim ~~4~~27 wherein the itch associated condition is chronic itch, cholestatic pruritus, contact dermatitis, allergic blepharitis, anemia, atopic dermatitis, bullous pemphigoid, candidiasis, chicken pox, cholestasis, end-stage renal failure, hemodialysis, contact dermatitis, dermatitis herpetiformis, diabetes, drug allergy, dry skin, dyshidrotic dermatitis, ectopic eczema, eczema, erythrasma, folliculitis, fungal skin infection, hemorrhoids, herpes, HIV infection, Hodgkin's disease, hyperthyroidism, iron deficiency anemia, kidney disease, leukemia, liver disease, lymphoma, malignancy, multiple myeloma, neurodermatitis, onchocerciasis, Paget's disease, pediculosis, polycythemia rubra vera, pruritus ani, pseudorabies, psoriasis, rectal prolapse, scabies, schistosomiasis, scleroderma, severe stress, stasia dermatitis, swimmer's itch, thyroid disease, tinea cruris, uremic pruritus, or urticaria.

~~6~~29. The ~~method~~use of claim ~~5~~28 wherein the itch associated condition is cholestatic pruritus, uremic pruritus, atopic dermatitis, dry skin, psoriasis, contact dermatitis, or eczema.

~~7~~30. The ~~method~~use of claim ~~5~~28, wherein the itch associated condition is a liver disease, wherein the liver disease is primary biliary cholangitis, primary sclerosing

cholangitis, Alagille syndrome, Progressive familial intrahepatic cholestasis, Intrahepatic cholestasis of pregnancy, nonalcoholic steatohepatitis (NASH), nonalcoholic fatty liver disease (NAFLD), biliary atresia, chronic B hepatitis, drug-chronic viral hepatitis, induced liver injury (DILI), liver fibrosis, cholestatic liver disease, or alcoholic liver disease.

~~8~~31. The ~~method~~use of claim ~~2~~25, ~~further comprises administering to the subject~~ wherein a pharmaceutically effective amount of a second therapeutic agent is to be further administered to the subject.

~~9~~32. The ~~method~~use of claim ~~8~~31, wherein the MRGPR X4 dependent condition is a liver disease and the second therapeutic agent is ursodeoxycholic acid (UDCA), *nor*Ursodeoxycholic acid, cholestyramine, stanozolol, naltrexone, rifampicin, Alisol B 23-acetate (AB23A), curcumin, dihydroartemisinin, fenofibrate, bezafibrate, metronidazole, methotrexate, colchicine, metformin, betaine, glucagon, naltrexone, a farnesoid X-receptor (FXR) agonist, a peroxisome proliferator-activated receptor (PPAR) agonist, a thyroid hormone receptor beta (TRβ) agonist, or any combination thereof.

~~10~~33. The ~~method~~use of claim ~~9~~32, wherein the FXR agonist is obeticholic acid, Turofexorate isopropyl (WAY-362450), 3-(2,6-dichlorophenyl)-4-(3'-carboxy-2-chlorostilben-4-yl)oxymethyl-5-isopropylisoxazole (GW4064), PX20606 (PX-102), PX-101, INT-767, INT-787, TERN-101, altenusin, tropifexor (LJN452), nidufexor, turofexorate isopropyl, fexaramine, silymarin, silybin, hedragonic acid, cafestol, Cilofexor (GS-9674 or Px-104), EDP-305, BAR704, BAR502, EYP-001, RDX-023, AGN-242266, HPG-1860, MET-409, AGN-242256, EP-024297, IOT-022, M-480, INV-33, RDX023-02, or any combination thereof.

~~11~~34. The ~~method~~use of claim ~~9~~32, wherein the PPAR agonist is a PPAR-alpha agonist, a PPAR-gamma agonist, a PPAR-delta agonist, a PPAR-alpha/gamma dual agonist, a PPAR alpha/delta dual agonist, a PPAR gamma/delta dual agonist, or PPAR alpha/gamma/delta pan agonist, optionally wherein:

the PPAR alpha agonist is fenofibrate, ciprofibrate, pemafibrate, gemfibrozil, clofibrate, binifibrate, clinofibrate, clofibric acid, nicofibrate, pirifibrate, plafibride, ronifibrate, theofibrate, tocofibrate, or SRI 0171;

the PPAR gamma agonist is rosiglitazone, pioglitazone, deuterium-stabilized R-pioglitazone, efatutazone, ATx08-001, OMS-405, CHS-131, THR-0921, SER-150-DN, KDT-501, GED-0507-34-Levo, CLC-3001, or ALL-4;

the PPAR delta agonist is GW501516 (endurabol or ({4-[({4-methyl-2-[4-(trifluoromethyl)phenyl]-l,3-thiazol-5-yl}methyl)sulfanyl]-2-methylphenoxy} acetic acid)), MBX8025 (seladelpar or {2-methyl-4-[5- methyl-2-(4-trifluoromethyl- phenyl)-2H-[l,2,3]triazol-4-ylmethylsylfanyl]-phenoxy}-acetic acid), GW0742 ([4-[[[2-[3-fluoro-4-(trifluoromethyl)phenyl]-4-methyl-5-thiazolyl]methyl]thio]-2-methyl phenoxy] acetic acid), L165041, HPP-593, or NCP-1046;

the PPAR alpha/gamma agonist is saroglitazar, aleglitazar, muraglitazar, tesaglitazar, or DSP-8658;

the PPAR alpha/delta agonist is elafibranor or T913659;

the PPAR gamma/delta agonist is a conjugated linoleic acid (CLA) or T3D-959; and

the PPAR alpha/gamma/delta agonist is IVA337 (lanifibranor), TTA (tetradecylthioacetic acid), bavachinin, GW4148, GW9135, bezafibrate, lobeglitazone, 2-(4-(5,6-methylenedioxybenzo[d]thiazol-2-yl)-2-methylphenoxy)-2-methylpropanoic acid (MHY2013), or CS038.

~~12~~35. The ~~method~~use of claim ~~9~~32, wherein the TRβ agonist is sobetirome, eprotirome, GC-24, MGL-3196, MGL-3745, VK-2809, KB141 [3,5-dichloro-4-(4-hydroxy-3-isopropylphenoxy) phenylacetic acid], MB07811 (2*R*,4*S*)-4-(3-chlorophenyl)-2-[(3,5-dimethyl-4-(4′-hydroxy-3′-isopropylbenzyl)phenoxy)methyl]-2-oxido-[1,3,2]-dioxaphosphonane), or any combination thereof.

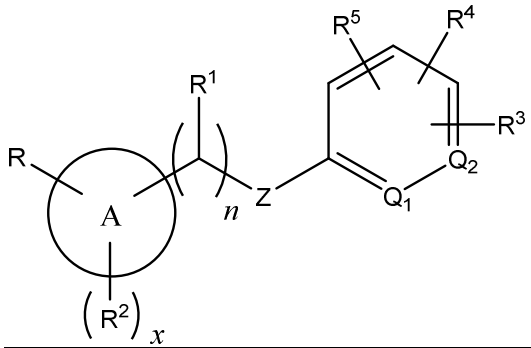
~~13~~36. The ~~method~~use of claim ~~4~~27 wherein the pain associated condition is acute pain, advanced prostate cancer, AIDS-related pain, ankylosing spondylitis, arachnoiditis, arthritis, arthrofibrosis, ataxic cerebral palsy, autoimmune atrophic gastritis, avascular necrosis, back pain, Behcet's disease (syndrome), burning mouth syndrome, bursitis, cancer pain, carpal tunnel, cauda equina syndrome, central pain syndrome, cerebral palsy, cervical stenosis, Charcot-Marie-Tooth (CMT) disease, chronic fatigue syndrome (CFS), chronic

functional abdominal pain (CFAP), chronic pain, chronic pancreatitis, collapsed lung (pneumothorax), complex regional pain syndrome (RSD), corneal neuropathic pain, Crohn's disease, degenerative disc disease, Dercum's disease, dermatomyositis, diabetic peripheral neuropathy (DPN), dystonia, Ehlers-Danlos syndrome (EDS), endometriosis, eosinophilia-myalgia syndrome (EMS), erythromelalgia, fibromyalgia, gout, headaches, herniated disc, hydrocephalus, intercostal neuraligia, interstitial cystitis, irritable bowel syndrome (IBS), juvenile dermatositis, knee injury, leg pain, loin pain-haematuria syndrome, lupus, lyme disease, medullary sponge kidney (MSK), meralgia paresthetica, mesothelioma, migraine, musculoskeletal pain, myofascial pain, myositis, neck pain, neuropathic pain, occipital neuralgia, osteoarthritis, Paget's disease, Parsonage Turner syndrome, pelvic pain, peripheral neuropathy, phantom limb pain, pinched nerve, polycystic kidney disease, polymyalgia rhuematica, polymyositis, porphyria, post herniorraphy pain syndrome, post mastectomy pain syndrome, post stroke pain, post thorocotomy pain syndrome, postherpetic neuralgia (Shingles), post-polio syndrome, primary lateral sclerosis, psoriatic arthritis, pudendal neuralgia, radiculopathy, Raynaud's disease, rheumatoid arthritis (RA), sacroiliac joint dysfunction, sarcoidosi, Scheuemann's kyphosis disease, sciatica, Scoliosis, shingles (Herpes Zoster), Sjogren's syndrome, spasmodic torticollis, sphincter of oddi dysfunction, spinal cerebellum ataxia (SCA ataxia), spinal cord injury, spinal stenosis, syringomyelia, tarlov cysts, transverse myelitis, trigeminal neuralgia, neuropathic pain, ulcerative colitis, vascular pain or vulvodynia.

~~14~~37. The ~~method~~use of claim ~~4~~27 wherein the autoimmune disorder is chronic inflammation, multiple sclerosis, Steven Johnson's syndrome, appendicitis, bursitis, colitis, cystitis, dermatitis, phlebitis, reflex sympathetic dystrophy/complex regional pain syndrome (rsd/crps), rhinitis, tendonitis, tonsillitis, acne vulgaris, reactive airway disorder, asthma, airway infection, autoinflammatory disease, celiac disease, chronic prostatitis, diverticulitis, glomerulonephritis, hidradenitis suppurativa, hypersensitivities, intestinal disorder, epithelial intestinal disorder, inflammatory bowel disease, irritable bowel syndrome, colitis, interstitial cystitis, otitis, pelvic inflammatory disease, endometrial pain, reperfusion injury, rheumatic fever, rheumatoid arthritis, sarcoidosis, transplant rejection, or vasculitis.

15. The method of any one of claims 1-14, wherein the compound has the structure of a compound listed Table A or B, or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope, or salt thereof.

16. A pharmaceutical composition comprising a compound having the structure of Formula (I), or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope, or salt thereof, and a pharmaceutically acceptable excipient:



(I)

or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope, or salt thereof, wherein:

n is 0 or 1;

x is 0, 1 or 2;

A is aryl or heteroaryl;

Q_1 and Q_2 are both CR^{10}, or one of Q_1 or Q_2 is CR^{10} and the other is N;

Z is O, S, $N(R^{11})$, CH_2 or C≡C ;

each R^{10} is H or alkyl;

R is $(CH_2)_mC(=O)OR^{12}$, $(CH_2)_mNHR^{13}$, $(C=O)NR^{14}R^{15}$, CH_2OH, CN, haloalkyl, carbocycle, heterocycle, or a carboxylic acid isostere;

m is 0 or 1;

R^{11}, R^{12} and R^{13} are the same or different and individually H or alkyl;

R^{14} is H and R^{15} is H, SO_2CH_3, carbocycle, heterocyle, or alkyl substituted with 0, 1, 2 or 3 substituents selected from OH, CN, NR'R", C(=O)OH, C(=O)NR'R", SO_2OH, alkoxy, carbocycle, or heterocycyle, wherein R' and R" are individually H or alkyl, or

R^{14} and R^{15} are taken together with the nitrogen atom to which they are attached to form heterocycle;

R^1 is H or alkyl;

R^2 is halo, cyano, amino, alkyl, alkoxy, carbocycle or heterocycle;

R^3, R^4 and R^5 are the same or different and either absent or, when present, cyano, nitro, halogen, alkyl, haloalkyl, cyanoalkyl, alkoxy, haloalkoxy, (C=O)alkyl, (C=O)NHalkyl, carbocycle, heterocycle, O carbocycle or O heterocycle, or

any two R and R^2 taken together with the atoms to which they are attached form heterocycle;

any two R^3, R^4, R^5 and R^{10}, taken together with the atoms to which they are attached form carbocycle or heterocycle;

and wherein each occurrence of carbocycle or heterocycle is substituted with 0, 1, 2 or 3 substituents individually selected from halogen, hydroxyl, oxo, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, carbocycle, or heterocycle.

17. The pharmaceutical composition of claim 16, further comprising a second therapeutic agent.

18. The pharmaceutical composition of claim 17, wherein the second therapeutic agent is ursodeoxycholic acid (UDCA), *nor*Ursodeoxycholic acid, cholestyramine, stanozolol, naltrexone, rifampicin, Alisol B 23-acetate (AB23A), curcumin, dihydroartemisinin, fenofibrate, bezafibrate, metronidazole, methotrexate, colchicine, metformin, betaine, glucagon, naltrexone, a farnesoid X receptor (FXR) agonist, a peroxisome proliferator activated receptor (PPAR) agonist, a thyroid hormone receptor beta (TRβ) agonist, or any combination thereof.

19. The pharmaceutical composition of claim 18, wherein:

(a) the FXR agonist is obeticholic acid, Turofexorate isopropyl (WAY-362450), 3-(2,6-dichlorophenyl)-4-(3'-carboxy-2-chlorostilben-4-yl)oxymethyl-5-isopropylisoxazole (GW4064), PX20606 (PX-102), PX-101, INT-767, INT-787, TERN-101, altenusin, tropifexor (LJN452), nidufexor, turofexorate isopropyl, fexaramine, silymarin, silybin, hedragonic acid, cafestol, Cilofexor (GS-9674 or Px-104), EDP-305, BAR704, BAR502, EYP-001, RDX-023, AGN-242266, HPG-1860, MET-409, AGN-242256, EP-024297, IOT-022, M-480, INV-33, RDX023-02, or any combination thereof;

(b) the PPAR agonist is a PPAR-alpha agonist, a PPAR-gamma agonist, a PPAR-delta agonist, a PPAR-alpha/gamma dual agonist, a PPAR-alpha/delta dual agonist, a PPAR gamma/delta dual agonist, or PPAR-alpha/gamma/delta pan agonist, optionally wherein:

the PPAR alpha agonist is fenofibrate, ciprofibrate, pemafibrate, gemfibrozil, clofibrate, binifibrate, clinofibrate, clofibric acid, nicofibrate, pirifibrate, plafibride, ronifibrate, theofibrate, tocofibrate, or SRI 0171;

the PPAR gamma agonist is rosiglitazone, pioglitazone, deuterium stabilized R pioglitazone, efatutazone, ATx08 001, OMS 405, CHS 131, THR 0921, SER 150 DN, KDT 501, GED 0507 34 Levo, CLC 3001, or ALL 4;

the PPAR delta agonist is GW501516 (endurabol or ({4 [({4 methyl 2 [4 (trifluoromethyl)phenyl] 1,3 thiazol 5 yl}methyl)sulfanyl] 2 methylphenoxy} acetic acid)), MBX8025 (seladelpar or {2 methyl 4 [5 methyl 2 (4 trifluoromethyl phenyl) 2H [1,2,3]triazol 4 ylmethylsylfanyl] phenoxy} acetic acid), GW0742 ([4 [[[2 [3 fluoro 4 (trifluoromethyl)phenyl] 4 methyl 5 thiazolyl]methyl]thio] 2 methyl phenoxy] acetic acid), L165041, HPP 593, or NCP 1046;

the PPAR alpha/gamma agonist is saroglitazar, aleglitazar, muraglitazar, tesaglitazar, or DSP 8658;

the PPAR alpha/delta agonist is elafibranor or T913659;

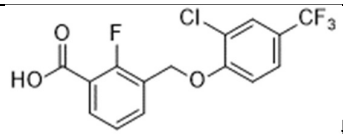
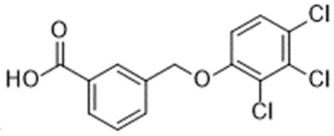
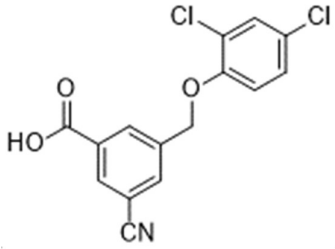
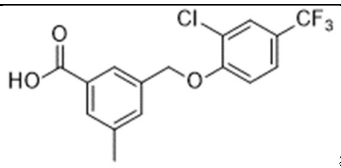
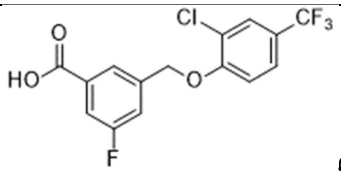
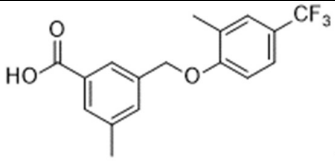
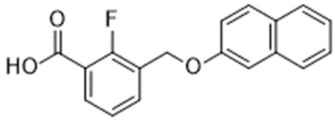
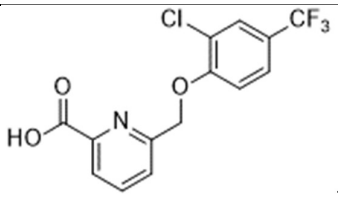
the PPAR gamma/delta agonist is a conjugated linoleic acid (CLA) or T3D 959; and

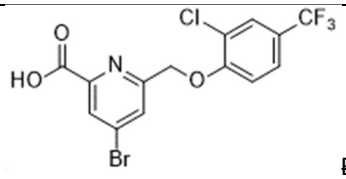
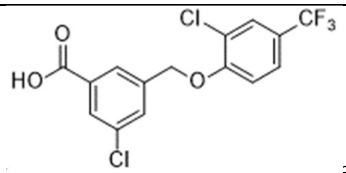
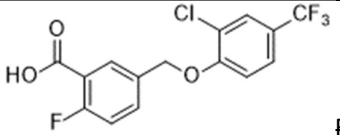
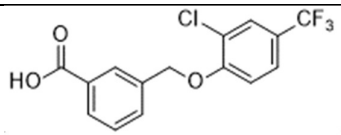
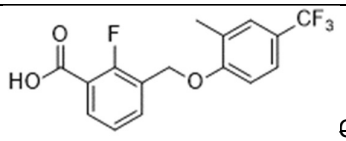
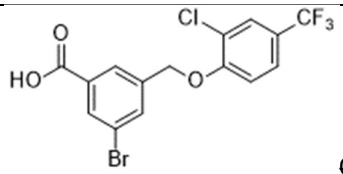
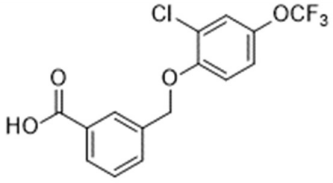
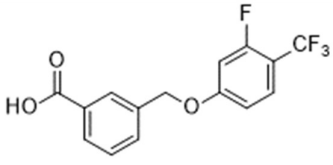
the PPAR alpha/gamma/delta agonist is IVA337 (lanifibranor), TTA (tetradecylthioacetic acid), bavachinin, GW4148, GW9135, bezafibrate, lobeglitazone, 2 (4 (5,6 methylenedioxybenzo[d]thiazol 2 yl) 2 methylphenoxy) 2 methylpropanoic acid (MHY2013), or CS038; or

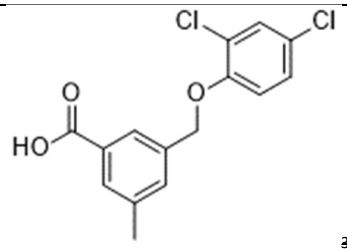
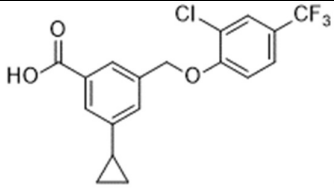
(c) the TRβ agonist is sobetirome, eprotirome, GC 24, MGL 3196, MGL 3745, VK 2809, KB141 [3,5 dichloro 4 (4 hydroxy 3 isopropylphenoxy) phenylacetic acid], MB07811 (2*R*,4*S*) 4 (3 chlorophenyl) 2 [(3,5 dimethyl 4 (4′ hydroxy 3′ isopropylbenzyl)phenoxy)methyl] 2 oxido [1,3,2] dioxaphosphonane), or any combination thereof.

20. A compound having one of the following structures, or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope, or salt thereof:

Cpd No.	Structure

~~1-55~~	 ~~$H_9ClF_4O_3$~~
~~1-78~~	 ~~$C_{14}H_9Cl_3O_3$~~
~~5-1~~	 ~~$C_{15}H_9Cl_2NO_3$~~
~~4-10~~	 ~~$_{16}H_{12}ClF_3O_3$~~
~~1-65~~	 ~~$C_{15}H_9ClF_4O_3$~~
~~4-11~~	 ~~$C_{17}H_{15}F_3O_3$~~
~~1-58~~	 ~~$_{18}H_{13}FO_3$~~
~~1-56~~	 ~~$C_{14}H_9ClF_3NO_3$~~

~~9-1~~	 ~~$BrClF_3NO_3$~~
~~1-82~~	 ~~$_2F_3O_3$~~
~~1-85~~	 ~~F_4O_3~~
~~1-29~~	 ~~$_3O_3$~~
~~1-101~~	 ~~$C_{16}H_{12}F_4O_3$~~
~~2-3~~	 ~~O_3~~
~~1-103~~	 ~~4~~
~~1-112~~	 ~~3~~

~~4-7~~	 ~~3~~
~~11-1~~	 ~~O3~~

~~21. A compound having one of the structures listed in Table A, or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope, or salt thereof.~~

~~22. A compound having one of the structures listed in Table B, or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope, or salt thereof.~~

~~23. The method of claim 4 wherein the itch associated condition is end-stage renal failure.~~

~~24. The method of claim 4 wherein the itch associated condition is kidney disease.~~

~~25. The method of claim 4 wherein the pain associated condition is medullary sponge kidney (MSK).~~

~~26. The method of claim 4 wherein the pain associated condition is polycystic kidney disease.~~

~~27. The method of claim 4 wherein the itch associated condition is associated with a metabolite of heme.~~

~~28. The method of claim 27 wherein the metabolite of heme is bilirubin.~~

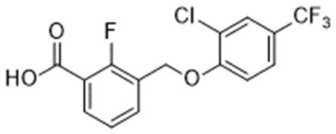
~~29. The method of claim 27 wherein the metabolite of heme is urobilin.~~

~~30. The method of claim 27 wherein the metabolite of heme is biliverdin.~~

~~31. The method of claim 27 wherein the metabolite of heme is urobilinogen.~~

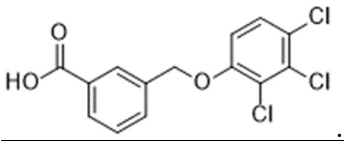
~~32. The method of claim 27 wherein the metabolite of heme is stercobilin.~~

38. The use of claim 29, wherein the compound is Cpd. No. 1-55 having the following structure, or a pharmaceutically acceptable hydrate, solvate, isotope, or salt thereof:



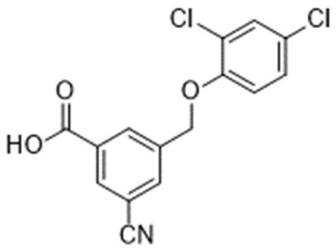
.

39. The use of claim 29, wherein the compound is Cpd. No. 1-78 having the following structure, or a pharmaceutically acceptable hydrate, solvate, isotope, or salt thereof



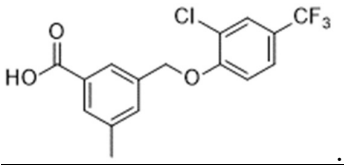
.

40. The use of claim 29, wherein the compound is Cpd. No. 5-1 having the following structure, or a pharmaceutically acceptable hydrate, solvate, isotope, or salt thereof



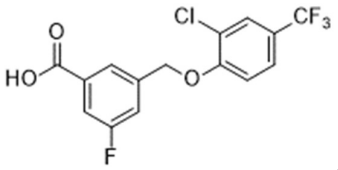
.

41. The use of claim 29, wherein the compound is Cpd. No. 4-10 having the following structure, or a pharmaceutically acceptable hydrate, solvate, isotope, or salt thereof



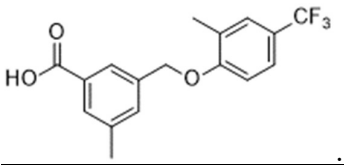
.

42. The use of claim 29, wherein the compound is Cpd. No. 1-65 having the following structure, or a pharmaceutically acceptable hydrate, solvate, isotope, or salt thereof



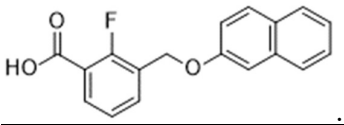
.

43. The use of claim 29, wherein the compound is Cpd. No. 4-11 having the following structure, or a pharmaceutically acceptable hydrate, solvate, isotope, or salt thereof



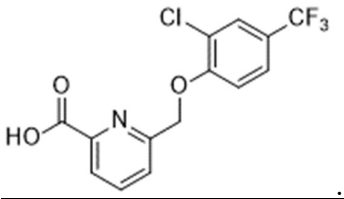
.

44. The use of claim 29, wherein the compound is Cpd. No. 1-58 having the following structure, or a pharmaceutically acceptable hydrate, solvate, isotope, or salt thereof



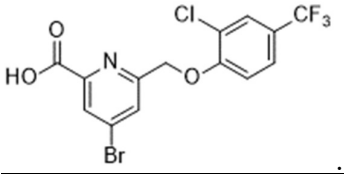
.

45. The use of claim 29, wherein the compound is Cpd. No. 1-56 having the following structure, or a pharmaceutically acceptable hydrate, solvate, isotope, or salt thereof



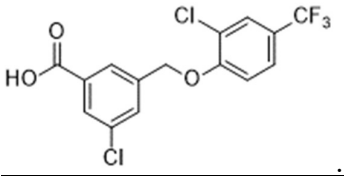
.

46. The use of claim 29, wherein the compound is Cpd. No. 9-1 having the following structure, or a pharmaceutically acceptable hydrate, solvate, isotope, or salt thereof



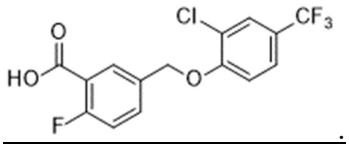
.

47. The use of claim 29, wherein the compound is Cpd. No. 1-82 having the following structure, or a pharmaceutically acceptable hydrate, solvate, isotope, or salt thereof



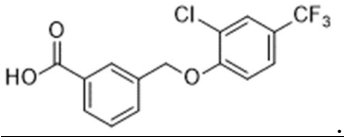
.

48. The use of claim 29, wherein the compound is Cpd. No. 1-85 having the following structure, or a pharmaceutically acceptable hydrate, solvate, isotope, or salt thereof



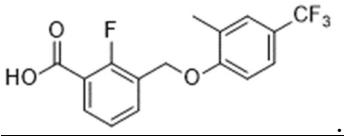
.

49. The use of claim 29, wherein the compound is Cpd. No. 1-29 having the following structure, or a pharmaceutically acceptable hydrate, solvate, isotope, or salt thereof



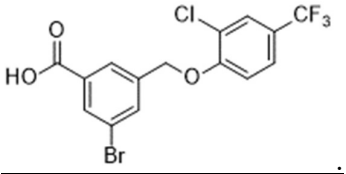
.

50. The use of claim 29, wherein the compound is Cpd. No. 1-101 having the following structure, or a pharmaceutically acceptable hydrate, solvate, isotope, or salt thereof



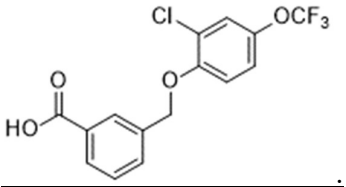
.

51. The use of claim 29, wherein the compound is Cpd. No. 2-3 having the following structure, or a pharmaceutically acceptable hydrate, solvate, isotope, or salt thereof



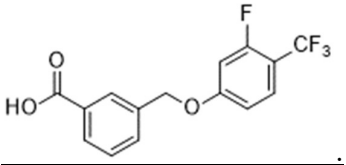
.

52. The use of claim 29, wherein the compound is Cpd. No. 1-103 having the following structure, or a pharmaceutically acceptable hydrate, solvate, isotope, or salt thereof



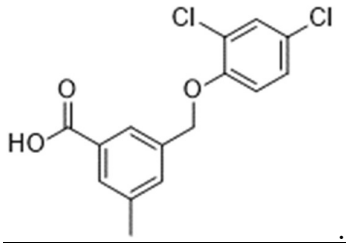
.

53. The use of claim 29, wherein the compound is Cpd. No. 1-112 having the following structure, or a pharmaceutically acceptable hydrate, solvate, isotope, or salt thereof



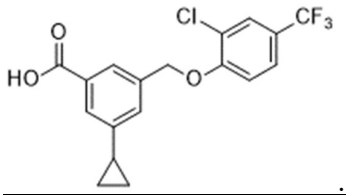
.

54. The use of claim 29, wherein the compound is Cpd. No. 4-7 having the following structure, or a pharmaceutically acceptable hydrate, solvate, isotope, or salt thereof



.

55. The use of claim 29, wherein the compound is Cpd. No. 11-1 having the following structure, or a pharmaceutically acceptable hydrate, solvate, isotope, or salt thereof



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