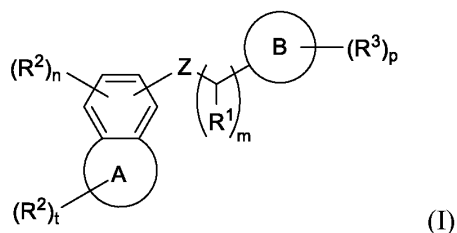


CLAIMS

1. A method for modulating a Mas-Related G-Protein Receptor (MRGPR) X4 by contacting the MRGPR X4 with an effective amount of a compound having the structure of Formula (I):



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

A is a 5- or 6-membered carbocycle or a 5- or 6-membered heterocycle;

B is a carbocycle or a heterocycle;

Z is $-O-$, $-CH_2O-$, $-S-$, $-N(R')$, $-N(R')S(O)_2-$, $-S(O)_2N(R')$, $-N(R')C(O)-$, or $-C(O)N(R)-$;

each R^1 is, independently, H or alkyl;

each R^2 is, independently, halo, alkyl, haloalkyl, or aralkyl, or two R^2 , together, form $=O$ or $=S$;

each R^3 is, independently, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, carbocycle or heterocycle, $-CN$, $-(CH_2)_qC(O)OR^4$, $-(CH_2)_qNHR^5$, $-(CH_2)_qOR^6$, $-C(O)NR^7R^8$, or a carboxylic acid isostere;

each R^4 , R^5 , R^6 , and R^7 is, independently, H or alkyl;

each R^8 is, independently, H, $-SO_2CH_3$, carbocycle, heterocycle, or alkyl, wherein each R^8 is independently substituted with 0, 1, 2, or 3 R^9 ;

each R^9 is $-OH$, $-CN$, $-NR'R''$, $-C(O)OH$, $-C(O)NR'R''$, $-SO_2OH$, alkoxy, carbocycle, or heterocycle;

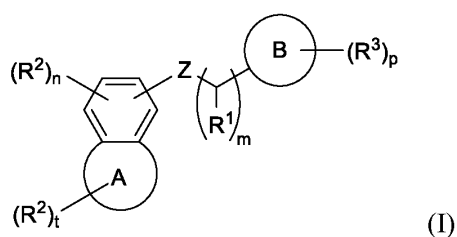
each R' is, independently, H or alkyl;

each R'' is, independently, H or alkyl;

m is 0–2;

n is 0–3;
 p is 0–3;
 q is 0–6; and
 t is 0–6.

2. A method for treating an MRGPR X4 dependent condition by administering to a subject in need thereof an effective amount of a compound having the structure of Formula (I):



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

A is a 5- or 6-membered carbocycle or a 5- or 6-membered heterocycle;

B is a carbocycle or a heterocycle;

Z is $-O-$, $-CH_2-O-$, $-S-$, $-N(R')-$, $-N(R')S(O)_2-$, $-S(O)_2N(R')-$, $-N(R')C(O)-$, or $-C(O)N(R')-$;

each R^1 is, independently, H or alkyl;

each R^2 is, independently, halo, alkyl, haloalkyl, or aralkyl, or two R^2 , together, form $=O$ or $=S$;

each R^3 is, independently, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, carbocycle or heterocycle, $-CN$, $-(CH_2)_qC(O)OR^4$, $-(CH_2)_qNHR^5$, $-(CH_2)_qOR^6$, $-C(O)NR^7R^8$, or a carboxylic acid isostere;

each R^4 , R^5 , R^6 , and R^7 is, independently, H or alkyl;

each R^8 is, independently, H, $-SO_2CH_3$, carbocycle, heterocycle, or alkyl, wherein each R^8 is independently substituted with 0, 1, 2, or 3 R^9 ;

each R^9 is $-OH$, $-CN$, $-NR'R''$, $-C(O)OH$, $-C(O)NR'R''$, $-SO_2OH$, alkoxy, carbocycle, or heterocycle;

each R' is, independently, H or alkyl;
each R'' is, independently, H or alkyl;
m is 0–2;
n is 0–3;
p is 0–3; and
q is 0–6; and
t is 0–6.

3. The method of claim 2 wherein the MRGPR X4 dependent condition is an itch associated condition, a pain associated condition, or an autoimmune disorder.

4. The method of claim 3 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.

5. The method of claim 4 wherein the itch associated condition is cholestatic pruritus, uremic pruritus, atopic dermatitis, dry skin, psoriasis, contact dermatitis, or eczema.

6. The method of claim 4, 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.

7. The method of claim 2, further comprises administering to the subject a pharmaceutically effective amount of a second therapeutic agent.

8. The method of claim 7, 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 (TR β) agonist, or any combination thereof.

9. The method of claim 8, 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.

10. The method of claim 8, 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, pemaifibrate, gemfibrozil, clofibrate, binifibrate, clinofibrate, clofibric acid, nicofibrate, pirifibrate, plafibrade, 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-ylmethylsulfanyl]-phenoxy}-acetic acid), GW0742 ([4-[[[2-[3-fluoro-4-(trifluoromethyl)phenyl]-4-methyl-5-thiazolyl]methyl]thio]-2-methylphenoxy] 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.

11. The method of claim 8, wherein the TR β agonist is sobetirome, eprotrirome, 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.

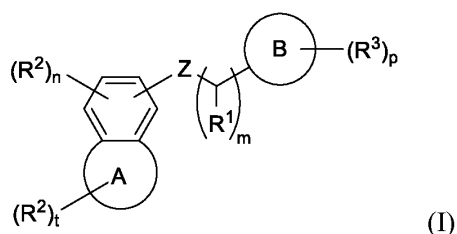
12. The method of claim 3 wherein the pain associated condition is acute pain, advanced prostate cancer, AIDS-related pain, ankylosing spondylitis, arachnoiditis, arthritis, arthrofibrosis, ataxic cerebral palsy, autoimmune atrophic gastritis, avascular necrosis, back pain, Behcet's disease (syndrome), 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 neuralgia, 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 rheumatica, polymyositis, porphyria, post herniorrhaphy 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, sarcoidosis, Scheuermann'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.

13. The method of claim 3 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.

14. The method of any one of claims 1-13, wherein the compound has the structure of a compound listed Table A, or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope, or salt thereof.

15. 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:



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

A is a 5- or 6-membered carbocycle or a 5- or 6-membered heterocycle;

B is a carbocycle or a heterocycle;

Z is $-O-$, $-CH_2-O-$, $-S-$, $-N(R')-$, $-N(R')S(O)_2-$, $-S(O)_2N(R')-$, $-N(R')C(O)-$, or $-C(O)N(R')-$;

each R^1 is, independently, H or alkyl;

each R^2 is, independently, halo, alkyl, haloalkyl, or aralkyl, or two R^2 , together, form $=O$ or $=S$;

each R^3 is, independently, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, carbocycle or heterocycle, $-\text{CN}$, $-(\text{CH}_2)_q\text{C}(\text{O})\text{OR}^4$, $-(\text{CH}_2)_q\text{NHR}^5$, $-(\text{CH}_2)_q\text{OR}^6$, $-\text{C}(\text{O})\text{NR}^7\text{R}^8$, or a carboxylic acid isostere;

each R^4 , R^5 , R^6 , and R^7 is, independently, H or alkyl;

each R^8 is, independently, H, $-\text{SO}_2\text{CH}_3$, carbocycle, heterocycle, or alkyl, wherein each R^8 is independently substituted with 0, 1, 2, or 3 R^9 ;

each R^9 is $-\text{OH}$, $-\text{CN}$, $-\text{NR}'\text{R}''$, $-\text{C}(\text{O})\text{OH}$, $-\text{C}(\text{O})\text{NR}'\text{R}''$, $-\text{SO}_2\text{OH}$, alkoxy, carbocycle, or heterocycle;

each R' is, independently, H or alkyl;

each R'' is, independently, H or alkyl;

m is 0–2;

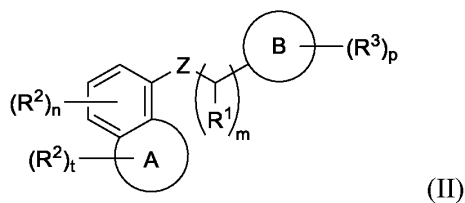
n is 0–3;

p is 0–3;

q is 0–6; and

t is 0–6.

16. The pharmaceutical composition of claim 15, wherein the compound has the structure of Formula (II):



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

A is a 5- or 6-membered carbocycle or a 5- or 6-membered heterocycle;

B is a carbocycle or a heterocycle;

Z is $-\text{O}-$, $-\text{CH}_2-\text{O}-$, $-\text{S}-$, $-\text{N}(\text{R}')-$, $-\text{N}(\text{R}')\text{S}(\text{O})_2-$, $-\text{S}(\text{O})_2\text{N}(\text{R}')-$, $-\text{N}(\text{R}')\text{C}(\text{O})-$, or $-\text{C}(\text{O})\text{N}(\text{R}')-$;

each R^1 is, independently, H or alkyl;

each R^2 is, independently, halo, alkyl, haloalkyl, or aralkyl, or two R^2 , together, form =O or =S;

each R^3 is, independently, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, carbocycle or heterocycle, $-\text{CN}$, $-(\text{CH}_2)_q\text{C}(\text{O})\text{OR}^4$, $-(\text{CH}_2)_q\text{NHR}^5$, $-(\text{CH}_2)_q\text{OR}^6$, $-\text{C}(\text{O})\text{NR}^7\text{R}^8$, or a carboxylic acid isostere;

each R^4 , R^5 , R^6 , and R^7 is, independently, H or alkyl;

each R^8 is, independently, H, $-\text{SO}_2\text{CH}_3$, carbocycle, heterocycle, or alkyl, wherein each R^8 is independently substituted with 0, 1, 2, or 3 R^9 ;

each R^9 is $-\text{OH}$, $-\text{CN}$, $-\text{NR}'\text{R}''$, $-\text{C}(\text{O})\text{OH}$, $-\text{C}(\text{O})\text{NR}'\text{R}''$, $-\text{SO}_2\text{OH}$, alkoxy, carbocycle, or heterocycle;

each R' is, independently, H or alkyl;

each R'' is, independently, H or alkyl;

m is 0–2;

n is 0–3;

p is 0–3;

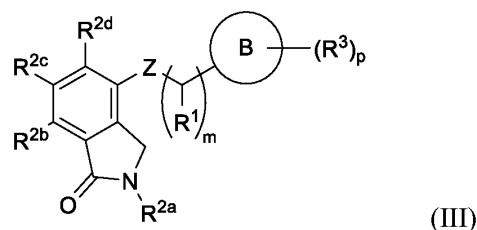
q is 0–6; and

t is 0–6.

17. The pharmaceutical composition of claim 15 or 16 comprising a compound or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope, or salt thereof, wherein A is a 5- or 6-membered carbocycle.

18. The pharmaceutical composition of claim 15 or 16 comprising a compound or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope, or salt thereof, wherein A is a 5- or 6-membered heterocycle.

19. The pharmaceutical composition of any one of claims 15, 16, or 18, wherein the compound has the structure of Formula (III):



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

B is a carbocycle or a heterocycle;

Z is $-\text{O}-$, $-\text{CH}_2-\text{O}-$, $-\text{S}-$, $-\text{N}(\text{R}')-$, $-\text{N}(\text{R}')\text{S}(\text{O})_2-$, $-\text{S}(\text{O})_2\text{N}(\text{R}')-$, $-\text{N}(\text{R}')\text{C}(\text{O})-$, or $-\text{C}(\text{O})\text{N}(\text{R}')-$;

each R^1 is, independently, H or alkyl;

R^{2a} , R^{2b} , R^{2c} , and R^{2d} are each, independently, H, halo, alkyl, haloalkyl, or aralkyl;

each R^3 is, independently, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, carbocycle or heterocycle, $-\text{CN}$, $-(\text{CH}_2)_q\text{C}(\text{O})\text{OR}^4$, $-(\text{CH}_2)_q\text{NHR}^5$, $-(\text{CH}_2)_q\text{OR}^6$, $-\text{C}(\text{O})\text{NR}^7\text{R}^8$, or a carboxylic acid isostere;

each R^4 , R^5 , R^6 , and R^7 is, independently, H or alkyl;

each R^8 is, independently, H, $-\text{SO}_2\text{CH}_3$, carbocycle, heterocycle, or alkyl, wherein each R^8 is independently substituted with 0, 1, 2, or 3 R^9 ;

each R^9 is $-\text{OH}$, $-\text{CN}$, $-\text{NR}'\text{R}''$, $-\text{C}(\text{O})\text{OH}$, $-\text{C}(\text{O})\text{NR}'\text{R}''$, $-\text{SO}_2\text{OH}$, alkoxy, carbocycle, or heterocycle;

each R' is, independently, H or alkyl;

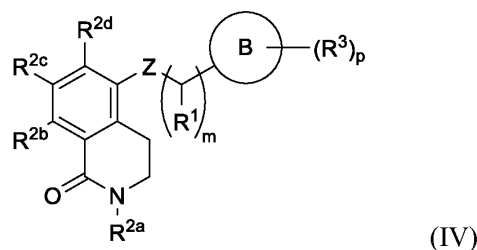
each R'' is, independently, H or alkyl;

m is 0–2;

p is 0–3; and

q is 0–6.

20. The pharmaceutical composition of any one of claims 15, 16, or 18, wherein the compound has the structure of Formula (IV):



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

B is a carbocycle or a heterocycle;

Z is $-\text{O}-$, $-\text{CH}_2-\text{O}-$, $-\text{S}-$, $-\text{N}(\text{R}')-$, $-\text{N}(\text{R}')\text{S}(\text{O})_2-$, $-\text{S}(\text{O})_2\text{N}(\text{R}')-$, $-\text{N}(\text{R}')\text{C}(\text{O})-$, or $-\text{C}(\text{O})\text{N}(\text{R}')-$;

each R^1 is, independently, H or alkyl;

R^{2a} , R^{2b} , R^{2c} , and R^{2d} are each, independently, H, halo, alkyl, haloalkyl, or aralkyl;

each R^3 is, independently, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, carbocycle or heterocycle, $-\text{CN}$, $-(\text{CH}_2)_q\text{C}(\text{O})\text{OR}^4$, $-(\text{CH}_2)_q\text{NHR}^5$, $-(\text{CH}_2)_q\text{OR}^6$, $-\text{C}(\text{O})\text{NR}^7\text{R}^8$, or a carboxylic acid isostere;

each R^4 , R^5 , R^6 , and R^7 is, independently, H or alkyl;

each R^8 is, independently, H, $-\text{SO}_2\text{CH}_3$, carbocycle, heterocycle, or alkyl, wherein each R^8 is independently substituted with 0, 1, 2, or 3 R^9 ;

each R^9 is $-\text{OH}$, $-\text{CN}$, $-\text{NR}'\text{R}''$, $-\text{C}(\text{O})\text{OH}$, $-\text{C}(\text{O})\text{NR}'\text{R}''$, $-\text{SO}_2\text{OH}$, alkoxy, carbocycle, or heterocycle;

each R' is, independently, H or alkyl;

each R'' is, independently, H or alkyl;

m is 0–2;

p is 0–3; and

q is 0–6.

21. The pharmaceutical composition of any one of claim 15–20 comprising a compound, or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope, or salt thereof, wherein B is a heterocycle.

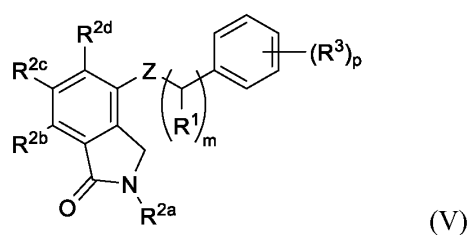
22. The pharmaceutical composition of any one of claim 15–21 comprising a compound, or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope, or salt thereof, wherein B is pyridine, pyrimidine, pyrazole, furan, oxazole, isoxazole, oxadiazole, thiophene, thiazole, thiadiazole, tetrahydro-2*H*-pyran, benzooxadiazole, benzothiazole, benzotriazole, or 2,3-dihydrobenzo[b][1,4]dioxine.

23. The pharmaceutical composition of any one of claim 15–20 comprising a compound, or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope, or salt thereof, wherein B is a carbocycle.

24. The pharmaceutical composition of any one of claim 15–20 or 23 comprising a compound, or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope, or salt thereof, wherein B is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, naphthalene, or tetrahydronaphthalene.

25. The pharmaceutical composition of any one of claim 15–20 or 23–24 comprising a compound, or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope, or salt thereof, wherein B is phenyl.

26. The pharmaceutical composition of any one of claims 15, 16, 18, 19, or 23–25, wherein the compound has the structure of Formula (V):



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

Z is $-\text{O}-$, $-\text{CH}_2-\text{O}-$, $-\text{S}-$, $-\text{N}(\text{R}')-$, $-\text{N}(\text{R}')\text{S}(\text{O})_2-$, $-\text{S}(\text{O})_2\text{N}(\text{R}')-$, $-\text{N}(\text{R}')\text{C}(\text{O})-$, or $-\text{C}(\text{O})\text{N}(\text{R}')-$;

each R^1 is, independently, H or alkyl;

R^{2a} , R^{2b} , R^{2c} , and R^{2d} are each, independently, H, halo, alkyl, haloalkyl, or aralkyl;

each R^3 is, independently, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, carbocycle or heterocycle, $-\text{CN}$, $-(\text{CH}_2)_q\text{C}(\text{O})\text{OR}^4$, $-(\text{CH}_2)_q\text{NHR}^5$, $-(\text{CH}_2)_q\text{OR}^6$, $-\text{C}(\text{O})\text{NR}^7\text{R}^8$, or a carboxylic acid isostere;

each R^4 , R^5 , R^6 , and R^7 is, independently, H or alkyl;

each R^8 is, independently, H, $-\text{SO}_2\text{CH}_3$, carbocycle, heterocycle, or alkyl, wherein each R^8 is independently substituted with 0, 1, 2, or 3 R^9 ;

each R^9 is $-\text{OH}$, $-\text{CN}$, $-\text{NR}'\text{R}''$, $-\text{C}(\text{O})\text{OH}$, $-\text{C}(\text{O})\text{NR}'\text{R}''$, $-\text{SO}_2\text{OH}$, alkoxy, carbocycle, or heterocycle;

each R' is, independently, H or alkyl;

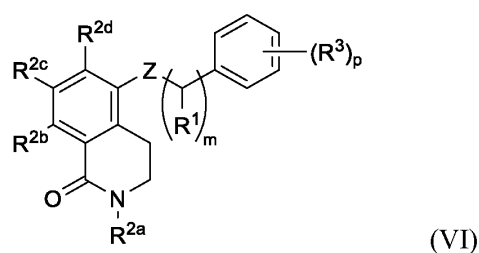
each R'' is, independently, H or alkyl;

m is 0–2;

p is 0–3; and

q is 0–6.

27. The pharmaceutical composition of any one of claims 15, 16, 18, 20, or 23–25, wherein the compound has the structure of Formula (VI):



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

Z is $-\text{O}-$, $-\text{CH}_2-\text{O}-$, $-\text{S}-$, $-\text{N}(\text{R}')-$, $-\text{N}(\text{R}')\text{S}(\text{O})_2-$, $-\text{S}(\text{O})_2\text{N}(\text{R}')-$, $-\text{N}(\text{R}')\text{C}(\text{O})-$, or $-\text{C}(\text{O})\text{N}(\text{R}')-$;

each R^1 is, independently, H or alkyl;

R^{2a} , R^{2b} , R^{2c} , and R^{2d} are each, independently, H, halo, alkyl, haloalkyl, or aralkyl;

each R^3 is, independently, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, carbocycle or heterocycle, $-\text{CN}$, $-(\text{CH}_2)_q\text{C}(\text{O})\text{OR}^4$, $-(\text{CH}_2)_q\text{NHR}^5$, $-(\text{CH}_2)_q\text{OR}^6$, $-\text{C}(\text{O})\text{NR}^7\text{R}^8$, or a carboxylic acid isostere;

each R^4 , R^5 , R^6 , and R^7 is, independently, H or alkyl;

each R^8 is, independently, H, $-\text{SO}_2\text{CH}_3$, carbocycle, heterocycle, or alkyl, wherein each R^8 is independently substituted with 0, 1, 2, or 3 R^9 ;

each R^9 is $-\text{OH}$, $-\text{CN}$, $-\text{NR}'\text{R}''$, $-\text{C}(\text{O})\text{OH}$, $-\text{C}(\text{O})\text{NR}'\text{R}''$, $-\text{SO}_2\text{OH}$, alkoxy, carbocycle, or heterocycle;

each R' is, independently, H or alkyl;

each R'' is, independently, H or alkyl;

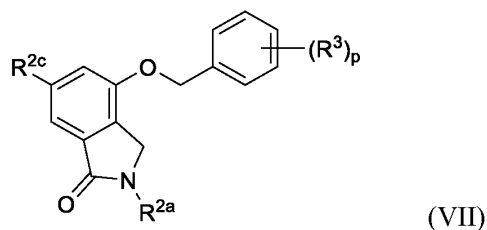
m is 0–2;

p is 0–3; and

q is 0–6.

28. The pharmaceutical composition of any one of claim 15–27 comprising a compound, or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope, or salt thereof, wherein Z is $-\text{O}-$.

29. The pharmaceutical composition of any one of claims 15, 16, 18, 19, 23–26, or 28, wherein the compound has the structure of Formula (VII):



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

R^{2a} and R^{2c} are each, independently, H, halo, alkyl, haloalkyl, or aralkyl;

each R^3 is, independently, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, carbocycle or heterocycle, $-\text{CN}$, $-(\text{CH}_2)_q\text{C}(\text{O})\text{OR}^4$, $-(\text{CH}_2)_q\text{NHR}^5$, $-(\text{CH}_2)_q\text{OR}^6$, $-\text{C}(\text{O})\text{NR}^7\text{R}^8$, or a carboxylic acid isostere;

each R^4 , R^5 , R^6 , and R^7 is, independently, H or alkyl;

each R^8 is, independently, H, $-\text{SO}_2\text{CH}_3$, carbocycle, heterocycle, or alkyl, wherein each R^8 is independently substituted with 0, 1, 2, or 3 R^9 ;

each R^9 is $-\text{OH}$, $-\text{CN}$, $-\text{NR}'\text{R}''$, $-\text{C}(\text{O})\text{OH}$, $-\text{C}(\text{O})\text{NR}'\text{R}''$, $-\text{SO}_2\text{OH}$, alkoxy, carbocycle, or heterocycle;

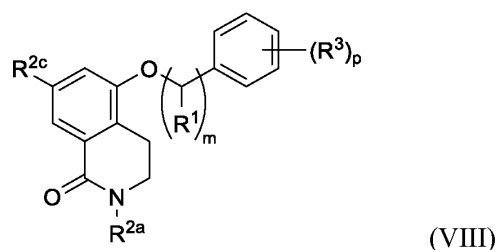
each R' is, independently, H or alkyl;

each R'' is, independently, H or alkyl;

p is 0–3; and

q is 0–6.

30. The pharmaceutical composition of any one of claims 15, 16, 18, 20, 23–25, 27, or 28, wherein the compound has the structure of Formula (VIII):



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

R^{2a} and R^{2c} are each, independently, H, halo, alkyl, haloalkyl, or aralkyl;

each R^3 is, independently, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, carbocycle or heterocycle, $-\text{CN}$, $-(\text{CH}_2)_q\text{C}(\text{O})\text{OR}^4$, $-(\text{CH}_2)_q\text{NHR}^5$, $-(\text{CH}_2)_q\text{OR}^6$, $-\text{C}(\text{O})\text{NR}^7\text{R}^8$, or a carboxylic acid isostere;

each R^4 , R^5 , R^6 , and R^7 is, independently, H or alkyl;

each R^8 is, independently, H, $-\text{SO}_2\text{CH}_3$, carbocycle, heterocycle, or alkyl, wherein each R^8 is independently substituted with 0, 1, 2, or 3 R^9 ;

each R^9 is $-\text{OH}$, $-\text{CN}$, $-\text{NR}'\text{R}''$, $-\text{C}(\text{O})\text{OH}$, $-\text{C}(\text{O})\text{NR}'\text{R}''$, $-\text{SO}_2\text{OH}$, alkoxy, carbocycle, or heterocycle;

each R' is, independently, H or alkyl;

each R'' is, independently, H or alkyl;

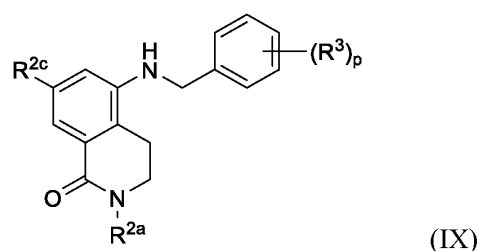
m is 1–2;

p is 0–3; and

q is 0–6.

31. The pharmaceutical composition of any one of claim 15–27 comprising a compound, or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope, or salt thereof, wherein Z is $-\text{N}(\text{R}')-$.

32. The pharmaceutical composition of any one of claims 15, 16, 18, 20, 23–25, 27, or 31, wherein the compound has the structure of Formula (IX):



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

R^{2a} and R^{2c} are each, independently, H, halo, alkyl, haloalkyl, or aralkyl;

each R^3 is, independently, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, carbocycle or heterocycle, $-\text{CN}$, $-(\text{CH}_2)_q\text{C}(\text{O})\text{OR}^4$, $-(\text{CH}_2)_q\text{NHR}^5$, $-(\text{CH}_2)_q\text{OR}^6$, $-\text{C}(\text{O})\text{NR}^7\text{R}^8$, or a carboxylic acid isostere;

each R^4 , R^5 , R^6 , and R^7 is, independently, H or alkyl;

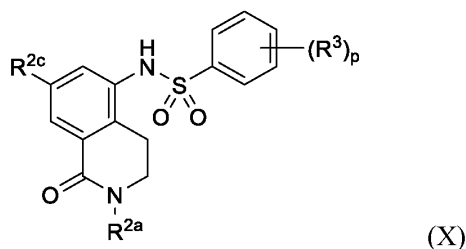
each R^8 is, independently, H, $-\text{SO}_2\text{CH}_3$, carbocycle, heterocycle, or alkyl, wherein each R^8 is independently substituted with 0, 1, 2, or 3 R^9 ;

each R^9 is $-\text{OH}$, $-\text{CN}$, $-\text{NR}'\text{R}''$, $-\text{C}(\text{O})\text{OH}$, $-\text{C}(\text{O})\text{NR}'\text{R}''$, $-\text{SO}_2\text{OH}$, alkoxy, carbocycle, or heterocycle;

each R' is, independently, H or alkyl;
 each R'' is, independently, H or alkyl;
 p is 0–3; and
 q is 0–6.

33. The pharmaceutical composition of any one of claim 15–27 comprising a compound, or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope, or salt thereof, wherein Z is $-\text{N}(\text{R}')\text{SO}_2-$.

34. The pharmaceutical composition of any one of claims 15, 16, 18, 20, 23–25, 27, or 33, wherein the compound has the structure of Formula (X):



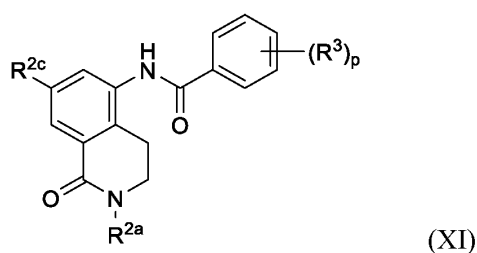
or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope, or salt thereof, wherein:

R^{2a} and R^{2c} are each, independently, H, halo, alkyl, haloalkyl, or aralkyl;
 each R^3 is, independently, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, carbocycle or heterocycle, $-\text{CN}$, $-(\text{CH}_2)_q\text{C}(\text{O})\text{OR}^4$, $-(\text{CH}_2)_q\text{NHR}^5$, $-(\text{CH}_2)_q\text{OR}^6$, $-\text{C}(\text{O})\text{NR}^7\text{R}^8$, or a carboxylic acid isostere;
 each R^4 , R^5 , R^6 , and R^7 is, independently, H or alkyl;
 each R^8 is, independently, H, $-\text{SO}_2\text{CH}_3$, carbocycle, heterocycle, or alkyl, wherein each R^8 is independently substituted with 0, 1, 2, or 3 R^9 ;
 each R^9 is $-\text{OH}$, $-\text{CN}$, $-\text{NR}'\text{R}''$, $-\text{C}(\text{O})\text{OH}$, $-\text{C}(\text{O})\text{NR}'\text{R}''$, $-\text{SO}_2\text{OH}$, alkoxy, carbocycle, or heterocycle;
 each R' is, independently, H or alkyl;
 each R'' is, independently, H or alkyl;
 p is 0–3; and

q is 0–6.

35. The pharmaceutical composition of any one of claim 15–27 comprising a compound, or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope, or salt thereof, wherein Z is $-\text{N}(\text{R}')\text{C}(\text{O})-$.

36. The pharmaceutical composition of any one of claims 15, 16, 18, 20, 23–25, 27, or 35, wherein the compound has the structure of Formula (XI):



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

R^{2a} and R^{2c} are each, independently, H, halo, alkyl, haloalkyl, or aralkyl;
 each R^3 is, independently, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, carbocycle or heterocycle, $-\text{CN}$, $-(\text{CH}_2)_q\text{C}(\text{O})\text{OR}^4$, $-(\text{CH}_2)_q\text{NHR}^5$, $-(\text{CH}_2)_q\text{OR}^6$, $-\text{C}(\text{O})\text{NR}^7\text{R}^8$, or a carboxylic acid isostere;

each R^4 , R^5 , R^6 , and R^7 is, independently, H or alkyl;

each R^8 is, independently, H, $-\text{SO}_2\text{CH}_3$, carbocycle, heterocycle, or alkyl, wherein each R^8 is independently substituted with 0, 1, 2, or 3 R^9 ;

each R^9 is $-\text{OH}$, $-\text{CN}$, $-\text{NR}'\text{R}''$, $-\text{C}(\text{O})\text{OH}$, $-\text{C}(\text{O})\text{NR}'\text{R}''$, $-\text{SO}_2\text{OH}$, alkoxy, carbocycle, or heterocycle;

each R' is, independently, H or alkyl;

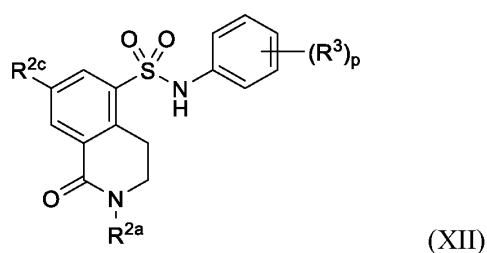
each R'' is, independently, H or alkyl;

p is 0–3; and

q is 0–6.

37. The pharmaceutical composition of any one of claim 15–27 comprising a compound, or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope, or salt thereof, wherein Z is $-\text{SO}_2\text{N}(\text{R}')-$.

38. The pharmaceutical composition of any one of claims 15, 16, 18, 20, 23–25, 27, or 37, wherein the compound has the structure of Formula (XII):



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

R^{2a} and R^{2c} are each, independently, H, halo, alkyl, haloalkyl, or aralkyl;
each R^3 is, independently, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, carbocycle or heterocycle, $-\text{CN}$, $-(\text{CH}_2)_q\text{C}(\text{O})\text{OR}^4$, $-(\text{CH}_2)_q\text{NHR}^5$, $-(\text{CH}_2)_q\text{OR}^6$, $-\text{C}(\text{O})\text{NR}^7\text{R}^8$, or a carboxylic acid isostere;

each R^4 , R^5 , R^6 , and R^7 is, independently, H or alkyl;

each R^8 is, independently, H, $-\text{SO}_2\text{CH}_3$, carbocycle, heterocycle, or alkyl, wherein each R^8 is independently substituted with 0, 1, 2, or 3 R^9 ;

each R^9 is $-\text{OH}$, $-\text{CN}$, $-\text{NR}'\text{R}''$, $-\text{C}(\text{O})\text{OH}$, $-\text{C}(\text{O})\text{NR}'\text{R}''$, $-\text{SO}_2\text{OH}$, alkoxy, carbocycle, or heterocycle;

each R' is, independently, H or alkyl;

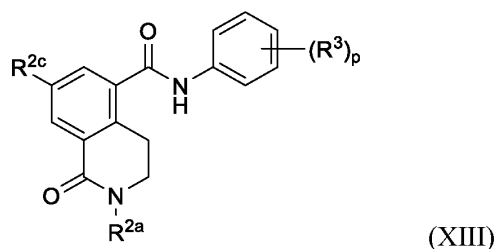
each R'' is, independently, H or alkyl;

p is 0–3; and

q is 0–6.

39. The pharmaceutical composition of any one of claim 15–27 comprising a compound, or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope, or salt thereof, wherein Z is $-\text{C}(\text{O})\text{N}(\text{R}')-$.

40. The pharmaceutical composition of any one of claims 15, 16, 18, 20, 23–25, 27, or 39, wherein the compound has the structure of Formula (XIII):



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

- R^{2a} and R^{2c} are each, independently, H, halo, alkyl, haloalkyl, or aralkyl;
- each R^3 is, independently, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, carbocycle or heterocycle, $-\text{CN}$, $-(\text{CH}_2)_q\text{C}(\text{O})\text{OR}^4$, $-(\text{CH}_2)_q\text{NHR}^5$, $-(\text{CH}_2)_q\text{OR}^6$, $-\text{C}(\text{O})\text{NR}^7\text{R}^8$, or a carboxylic acid isostere;
- each R^4 , R^5 , R^6 , and R^7 is, independently, H or alkyl;
- each R^8 is, independently, H, $-\text{SO}_2\text{CH}_3$, carbocycle, heterocycle, or alkyl, wherein each R^8 is independently substituted with 0, 1, 2, or 3 R^9 ;
- each R^9 is $-\text{OH}$, $-\text{CN}$, $-\text{NR}'\text{R}''$, $-\text{C}(\text{O})\text{OH}$, $-\text{C}(\text{O})\text{NR}'\text{R}''$, $-\text{SO}_2\text{OH}$, alkoxy, carbocycle, or heterocycle;
- each R' is, independently, H or alkyl;
- each R'' is, independently, H or alkyl;
- p is 0–3; and
- q is 0–6.

41. A pharmaceutical composition comprising a compound having the structure of a compound listed Table A, or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope, or salt thereof, and a pharmaceutically acceptable excipient.

42. The pharmaceutical composition of any one of claims 15–41, further comprising a second therapeutic agent.

43. The pharmaceutical composition of claim 42, 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 (TR β) agonist, or any combination thereof.

44. The pharmaceutical composition of claim 43, 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, plafibrade, 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-ylmethylsulfanyl]-phenoxy}-acetic acid), GW0742 ([4-[[[2-[3-fluoro-4-(trifluoromethyl)phenyl]-4-methyl-5-thiazolyl]methyl]thio]-2-methylphenoxy] acetic acid), L165041, HPP-593, or NCP-1046;

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

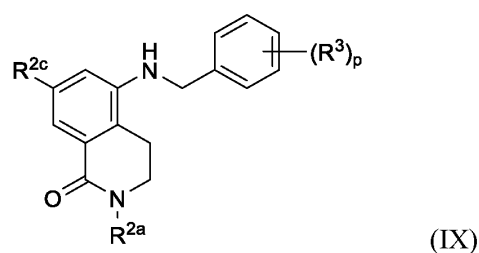
the PPAR alpha/delta agonist is elafibranor or T913659;

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 TR β agonist is sobetirome, eprotrirome, 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.

45. A compound having the structure of Formula (IX):



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

R^{2a} is alkyl;

R^{2c} is H, halo, alkyl, haloalkyl, or aralkyl;

each R^3 is, independently, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, carbocycle or heterocycle, $-\text{CN}$, $-(\text{CH}_2)_q\text{C}(\text{O})\text{OR}^4$, $-(\text{CH}_2)_q\text{NHR}^5$, $-(\text{CH}_2)_q\text{OR}^6$, $-\text{C}(\text{O})\text{NR}^7\text{R}^8$, or a carboxylic acid isostere;

each R^4 , R^5 , R^6 , and R^7 is, independently, H or alkyl;

each R^8 is, independently, H, $-\text{SO}_2\text{CH}_3$, carbocycle, heterocycle, or alkyl, wherein each R^8 is independently substituted with 0, 1, 2, or 3 R^9 ;

each R^9 is $-\text{OH}$, $-\text{CN}$, $-\text{NR}'\text{R}''$, $-\text{C}(\text{O})\text{OH}$, $-\text{C}(\text{O})\text{NR}'\text{R}''$, $-\text{SO}_2\text{OH}$, alkoxy, carbocycle, or heterocycle;

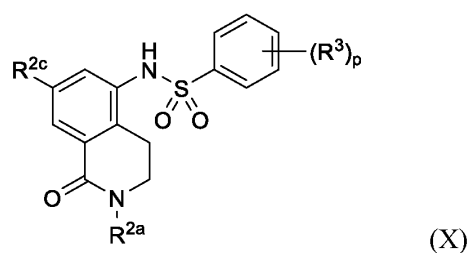
each R' is, independently, H or alkyl;

each R'' is, independently, H or alkyl;

p is 0–3; and

q is 0–6.

46. A compound having the structure of Formula (X):



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

R^{2a} is alkyl;

R^{2c} is H, halo, alkyl, haloalkyl, or aralkyl;

each R^3 is, independently, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, carbocycle or heterocycle, $-\text{CN}$, $-(\text{CH}_2)_q\text{C}(\text{O})\text{OR}^4$, $-(\text{CH}_2)_q\text{NHR}^5$, $-(\text{CH}_2)_q\text{OR}^6$, $-\text{C}(\text{O})\text{NR}^7\text{R}^8$, or a carboxylic acid isostere;

each R^4 , R^5 , R^6 , and R^7 is, independently, H or alkyl;

each R^8 is, independently, H, $-\text{SO}_2\text{CH}_3$, carbocycle, heterocycle, or alkyl, wherein each R^8 is independently substituted with 0, 1, 2, or 3 R^9 ;

each R^9 is $-\text{OH}$, $-\text{CN}$, $-\text{NR}'\text{R}''$, $-\text{C}(\text{O})\text{OH}$, $-\text{C}(\text{O})\text{NR}'\text{R}''$, $-\text{SO}_2\text{OH}$, alkoxy, carbocycle, or heterocycle;

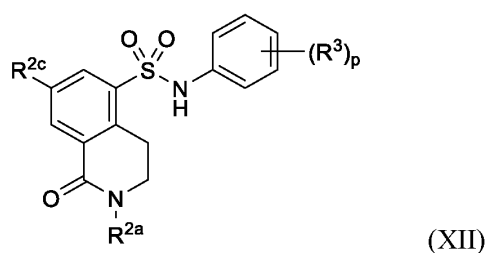
each R' is, independently, H or alkyl;

each R'' is, independently, H or alkyl;

p is 0–3; and

q is 0–6.

47. A compound having the structure of Formula (XII):



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

R^{2a} and R^{2c} are each, independently, H, halo, alkyl, haloalkyl, or aralkyl;

each R^3 is, independently, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, carbocycle or heterocycle, $-\text{CN}$, $-(\text{CH}_2)_q\text{C}(\text{O})\text{OR}^4$, $-(\text{CH}_2)_q\text{NHR}^5$, $-(\text{CH}_2)_q\text{OR}^6$, $-\text{C}(\text{O})\text{NR}^7\text{R}^8$, or a carboxylic acid isostere;

each R^4 , R^5 , R^6 , and R^7 is, independently, H or alkyl;

each R^8 is, independently, H, $-\text{SO}_2\text{CH}_3$, carbocycle, heterocycle, or alkyl, wherein each R^8 is independently substituted with 0, 1, 2, or 3 R^9 ;

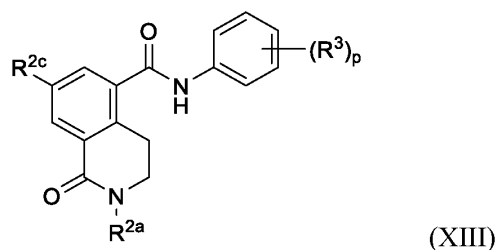
each R^9 is $-\text{OH}$, $-\text{CN}$, $-\text{NR}'\text{R}''$, $-\text{C}(\text{O})\text{OH}$, $-\text{C}(\text{O})\text{NR}'\text{R}''$, $-\text{SO}_2\text{OH}$, alkoxy, carbocycle, or heterocycle;

each R' is, independently, H or alkyl;

each R'' is, independently, H or alkyl; p is 0–3; and

q is 0–6.

48. A compound having the structure of Formula (XIII):



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

R^{2a} H, halo, alkyl, or haloalkyl;

R^{2c} is H, halo, alkyl, haloalkyl, or aralkyl;

each R^3 is, independently, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, carbocycle or heterocycle, $-\text{CN}$, $-(\text{CH}_2)_q\text{C}(\text{O})\text{OR}^4$, $-(\text{CH}_2)_q\text{NHR}^5$, $-(\text{CH}_2)_q\text{OR}^6$, $-\text{C}(\text{O})\text{NR}^7\text{R}^8$, or a carboxylic acid isostere;

each R^4 , R^5 , R^6 , and R^7 is, independently, H or alkyl;

each R^8 is, independently, H, $-\text{SO}_2\text{CH}_3$, carbocycle, heterocycle, or alkyl, wherein each R^8 is independently substituted with 0, 1, 2, or 3 R^9 ;

each R^9 is $-\text{OH}$, $-\text{CN}$, $-\text{NR}'\text{R}''$, $-\text{C}(\text{O})\text{OH}$, $-\text{C}(\text{O})\text{NR}'\text{R}''$, $-\text{SO}_2\text{OH}$, alkoxy, carbocycle, or heterocycle;

each R' is, independently, H or alkyl;

each R'' is, independently, H or alkyl;

p is 0–3; and

q is 0–6.

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