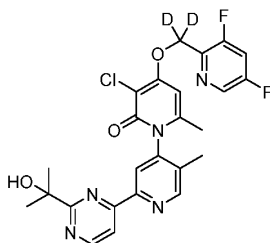


Claims

1. A compound having the structure:



- 3-Chloro-4-((3,5-difluoropyridin-2-yl)methoxy-d₂)-2'-(2-(2-hydroxypropan-2-yl)pyrimidin-4-yl)-5',6-dimethyl-2*H*-[1,4'-bipyridin]-2-one, or a derivative thereof.
2. The compound of Claim 1, wherein 3-Chloro-4-((3,5-difluoropyridin-2-yl)methoxy-d₂)-2'-(2-(2-hydroxypropan-2-yl)pyrimidin-4-yl)-5',6-dimethyl-2*H*-[1,4'-bipyridin]-2-one, or a derivative thereof, is a single atropisomer and wherein the single atropisomer is (*P*)-3-Chloro-4-((3,5-difluoropyridin-2-yl)methoxy-d₂)-2'-(2-(2-hydroxypropan-2-yl)pyrimidin-4-yl)-5',6-dimethyl-2*H*-[1,4'-bipyridin]-2-one, or a derivative thereof.
3. The compound of Claim 1, wherein 3-Chloro-4-((3,5-difluoropyridin-2-yl)methoxy-d₂)-2'-(2-(2-hydroxypropan-2-yl)pyrimidin-4-yl)-5',6-dimethyl-2*H*-[1,4'-bipyridin]-2-one, or a derivative thereof, is a single atropisomer and wherein the single atropisomer is (*M*)-3-Chloro-4-((3,5-difluoropyridin-2-yl)methoxy-d₂)-2'-(2-(2-hydroxypropan-2-yl)pyrimidin-4-yl)-5',6-dimethyl-2*H*-[1,4'-bipyridin]-2-one, or a derivative thereof.
4. The compound of any one of Claims 1-3, wherein the isotopic enrichment at each position labeled in the structure is equal to or greater than 70%.
5. The compound of any one of Claims 1-3, wherein the isotopic enrichment at each position labeled in the structure is equal to or greater than 80%.
6. The compound of any one of Claims 1-3, wherein the isotopic enrichment at each position labeled in the structure is equal to or greater than 90%.

7. The compound of any one of Claims 1-3, wherein the isotopic enrichment at each position labeled in the structure is equal to or greater than 95%.
8. The compound of any one of Claims 1-3, wherein the isotopic enrichment at each position labeled in the structure is equal to or greater than 99%.
9. A pharmaceutical composition comprising a therapeutically effective amount of a compound of any one of Claims 1-3, a derivative thereof, or a combination thereof; and a pharmaceutically acceptable excipient.
10. A method of treating a p38 MAP Kinase mediated disease in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a compound of any one of Claims 1-9, a derivative thereof, or a combination thereof.
11. The method of Claim 10, further comprising administering another therapeutic agent.
12. The method of Claim 10, wherein said p38 MAP Kinase mediated disease is selected from the group consisting of an autoimmune disorders or responses, activation of immune responses, bacterial infection, viral infection, inflammation, a chronic inflammatory conditions, an acute inflammatory disorder or condition, an auto-inflammatory disorder, fibrotic disorders, metabolic disorders, a neoplasm, a cardiovascular, a cerebrovascular disorder, a skin disorder, pruritus, a hair loss disorder, , an autoimmune connective tissue disease, Still's disease, adult-onset Still's disease, Th17-associated inflammation, polychondritis, relapsing polychondritis, myositis, polymyositis, autoimmune myositis, dermatomyositis, juvenile dermatomyositis, myasthenia gravis, Arthritis, rheumatoid arthritis, juvenile rheumatoid arthritis, systemic-onset juvenile rheumatoid arthritis, osteoarthritis, infectious arthritis, inflammatory arthritis, inflammatory bowel disease-associated arthritis, idiopathic arthritis, juvenile idiopathic arthritis, systemic juvenile idiopathic arthritis, psoriatic arthritis, spondylitis/spondyloarthritis/spondyloarthropathy, gout, scleroderma, Reiter's syndrome/reactive arthritis, Lyme disease, systemic lupus erythematosus (SLE), lupus erythematosus, pediatric systemic lupus erythematosus, cutaneous lupus, subacute cutaneous lupus, chronic cutaneous lupus/discoid lupus, chilblain lupus erythematosus, polymyalgia rheumatica, enthesitis, mixed connective tissue disease, enthesopathy, carditis, myocarditis, angiogenesis disorders,

myelodysplastic syndrome, atherosclerosis, restenosis, acute coronary syndrome, myocardial infarction, cardiac-allograft vasculopathy, transplant arteriopathy, vasculitis, large vessel vasculitis, small vessel vasculitis, giant-cell arteritis, polyarteritis nodosa, Takayasu's arteritis, Wegener's granulomatosis, Behcet's Disease, stimulator of interferon genes (STING) associated vasculopathy with onset in infancy (SAVI), a gastrointestinal disorder, enterocolitis, colitis, inflammatory bowel disease, ulcerative colitis, Crohn's disease, irritable bowel syndrome, enteritis syndrome/spastic colon, celiac disease, acute pancreatitis, chronic pancreatitis, primary biliary cirrhosis, primary sclerosing cholangitis, jaundice, cirrhosis, primary biliary cirrhosis, cirrhosis due to fatty liver disease, esophagitis, gastritis, a gastric ulcer, a duodenal ulcer, peritonitis, a nephropathy, immunologically mediated glomerulonephropathy, autoimmune nephropathy, membranous glomerulopathy, chronic progressive nephropathy, diabetic kidney disease/diabetic nephropathy, renal fibrosis, renal ischemic/reperfusion injury, HIV associated nephropathy, ureteral obstructive nephropathy, glomerulosclerosis, proteinuria, nephrotic syndrome, polycystic kidney disease, autosomal dominant polycystic kidney disease, a nephropathy is an immunologically mediated nephropathy, autoimmune nephropathy, chronic progressive nephropathies, diabetic nephropathy, ischemic/reperfusion injury associated, ureteral obstructive nephropathy, glomerulonephritis, chronic kidney disease, hypertension induced nephropathy, glomerulosclerosis, proteinuria, nephrotic syndrome, polycystic kidney disease, autosomal dominant polycystic kidney disease, diabetic kidney disease, lupus nephritis, interstitial cystitis, periodontitis, gingivitis, pulmonary inflammation, sinusitis, pneumonia, bronchitis, asthma, bronchial asthma, allergic asthma, non-allergic asthma, allergic bronchopulmonary mycosis, aspirin-induced asthma, adult-onset asthma, asthma with fixed airflow obstruction, exercise-induced asthma, cough-variant asthma, work-related asthma, nighttime asthma, asthma with obesity, eosinophilic asthma, steroid-resistant asthma/severe asthma, extrinsic asthma, intrinsic/cryptogenic asthma, Churg-Strauss syndrome, bronchiolitis, bronchiolitis obliterans, chronic obstructive pulmonary disease (COPD), interstitial lung disease, pulmonary fibrosis, idiopathic pulmonary fibrosis, acute lung injury, cystic fibrosis, adult respiratory distress syndrome, acute lung injury, drug-induced lung injury, Meniere's disease, an ocular disorder, ocular inflammation, uveitis, dry eye/keratoconjunctivitis sicca, scleritis, episcleritis, keratitis/keratopathy, choroiditis,

retinal vasculitis, optic neuritis, retinopathy, diabetic retinopathy, immune mediated retinopathy, macular degeneration, wet macular degeneration, dry (age related) macular degeneration, mastocytosis, iron deficiency anemia, uremia, hypereosinophilic syndrome (HES), systemic mast cell disease (SMCD), myelodysplastic syndrome, idiopathic thrombocytic purpura, a bone resorption disease, a neurodegenerative disorder, a neurological/ neuromuscular disorder, multiple sclerosis, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis (ALS),, Alzheimer's disease, Lambert-Eaton myasthenic syndrome (LEMS), Guillain-Barret syndrome, meningitis, encephalitis, traumatic brain injury, nervous system damage, delusional parasitosis, dysregulation of neuronal processes and sensory perception, stroke/neuronal ischemia, spinal cord injury, peripheral neuropathy, tactile hallucinations, spinal cord injury, psychiatric disease, pain, acute pain, chronic pain, neuropathic pain, fibromyalgia, paresthetica, nerve irritation, peripheral neuropathy, pruritus/itch, atopic pruritus, xerotic pruritus, pruritus associated with psoriasis/psoriatic itch/psoriasis-associated itch, acute pruritus, chronic pruritus, idiopathic pruritus, chronic idiopathic itch, biliary itch, hepatobiliary-associated itch, renal associated itch/renal itch, uremic itch, cholestasis, intrahepatic cholestasis of pregnancy, lichen simplex chronicus associated pruritus, lymphoma-associated itch, leukemia-associated itch, prurigo nodularis, atopic dermatitis-associated itch, atopic itch/atopic pruritus, bullous itch, brachioradial pruritus, neurogenic itch, neuropathic itch, notalgia paresthetica, pruritic popular eruption of HIV, psychogenic itch, swimmer's itch, pruritus or uremic itch, urticarial itch, a dermatologic disorder, dermatologic drug reactions/drug eruptions, xerosis/dry skin, skin rash, skin sensitization, skin irritation, sunburn, shaving, body louse, head lice/pediculosis, pubic lice, cutaneous larva migrans, scabies, parasitic infection, insect infestation, urticaria/hives, papular urticaria, insect bites, insect stings, dandruff, fungal infection, herpes, varicella/chicken pox, eosinophilic folliculitis, dermatosis of pregnancy/pruritic urticarial papules and plaques of pregnancy (PUPP), inflammatory dermatoses, neutrophilic dermatoses, histiocytoid neutrophilic dermatosis, bowel-bypass syndrome dermatosis, psoriasis/psoriasis vulgaris, lichen planus, lichen sclerosus, acne, acne vulgaris, comedonal acne, inflammatory acne, nodulo-cystic acne, scarring acne, acne keloidalis nuchae, an atopy, allergic contact sensitization, allergic dermatitis, dermatitis, atopic dermatitis/eczema, contact

dermatitis, photodermatitis, seborrheic dermatitis, stasis dermatitis, acute febrile neutrophilic dermatosis (Sweet's syndrome), chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature syndrome (CANDLE Syndrome), hidradenitis suppurativa, hives, pyoderma gangrenosum, alopecia, eyebrow alopecia, intranasal hair alopecia, scarring alopecia, cicatricial alopecia, central centrifugal cicatricial alopecia, lichen planopilaris, frontal fibrosing alopecia, folliculitis decalvans, nonscarring alopecia, alopecia areata (AA), patchy AA, alopecia totalis (AT), alopecia universalis (AU), ophiasis pattern alopecia areata, sisaihp pattern alopecia areata, androgenetic/androgenic alopecia (AGA)/male and female pattern AGA), telogen effluvium, tinea capitis, hypotrichosis (hereditary hypotrichosis simplex), lichen planopilaris (frontal fibrosing alopecia), punctate palmoplantar keratoderma, erythema elevatum diutinum (EED), neutrophilic eccrine hidradenitis, palisading neutrophilic granulomatous dermatitis, neutrophilic urticarial dermatosis, vitiligo, segmental vitiligo, unisegmental vitiligo, bisegmental vitiligo, multisegmental vitiligo, non-segmental vitiligo, acral vitiligo, facial vitiligo, acrofacial vitiligo, centrofacial vitiligo, mucosal vitiligo, confetti vitiligo, trichrome vitiligo, marginal inflammatory vitiligo, quadrichrome vitiligo, blue vitiligo, Koebner phenomenon, vulgaris vitiligo, generalized vitiligo, universal vitiligo, mixed vitiligo/nonsegmental associated with segmental vitiligo, focal vitiligo, solitary mucosal vitiligo, vitiligo with or without leukotrichia, a bullous disease, an immunobullous disease, bullous pemphigoid, cicatricial pemphigoid, pemphigus vulgaris, linear IgA disease, gestational pemphigoid, xeroderma pigmentosum, fibroids, hepatic fibrosis, scleroderma, fibrosis, keloids, post-surgical scars, wound healing, surgical scarring, radiation induced fibrosis, CNS scarring, gastrointestinal fibrosis, biliary fibrosis, liver fibrosis, nonalcoholic steatohepatitis, hepatitis C, hepatocellular carcinoma, cardiac fibrosis, endomyocardial fibrosis, atrial fibrosis, ophthalmic scarring, fibrosclerosis, scar growth, keloid, mediastinal fibrosis, retroperitoneal fibrosis/Ormond's disease, progressive massive fibrosis, nephrogenic systemic fibrosis, Sjogren's syndrome, sarcoidosis, familial Mediterranean fever, Cryopyrin associated periodic syndrome, Muckle-Wells syndrome, familial cold auto-inflammatory syndrome/familial cold urticaria/TNF receptor associated periodic syndrome, neonatal-onset multisystem inflammatory disease, hyperoxia induced inflammation, post-surgical trauma, tissue injury, elevated temperature syndrome;

diabetes, Type I diabetes, Type II diabetes, diabetes mellitus, Hashimoto's thyroiditis, Graves' disease, Addison's disease, Castleman's disease, hyperparathyroidism, menopause, obesity, steroid-resistance, glucose intolerance, metabolic syndrome, thyroid illness, hypophysitis, systemic immune senescence, autoimmune atrophic gastritis, autoimmune atrophic gastritis of pernicious anemia, autoimmune encephalomyelitis, autoimmune orchitis, Goodpasture's disease, autoimmune thrombocytopenia, sympathetic ophthalmia, a secondary hematologic manifestations of autoimmune disease, an autoimmune hemolytic syndrome, autoimmune and inflammatory hepatitis, autoimmune ovarian failure, autoimmune thrombocytopenia, silicone implant associated autoimmune disease, drug-induced autoimmunity, HIV-related autoimmune syndromes, metal-induced autoimmunity, autoimmune deafness, autoimmune thyroid disorders, a Type I hypersensitivity reaction, a Type II hypersensitivity reaction, a Type III hypersensitivity reaction diseases, a Type IV hypersensitivity reactions, acute infection, chronic infection, sepsis, septic shock, endotoxic shock, exotoxin-induced toxic shock, gram negative sepsis, gram positive sepsis, fungal sepsis, toxic shock syndrome, graft vs. host disease, allograft rejections, early transplantation rejection, lymphoma, leukemia, a solid tumor, a teratoma, an internal cancer, bone cancer, mouth/pharynx cancer, esophagus cancer, larynx cancer, stomach cancer, intestinal cancer, colon cancer, rectal cancer, lung cancer, liver cancer, pancreatic cancer, nerve cancer, brain cancer, head and neck cancer, throat cancer, ovarian cancer, uterine cancer, prostate cancer, testicular cancer, bladder cancer, kidney (renal) cancer, breast cancer, gall bladder cancer, cervical cancer, thyroid cancer, eye cancer, skin cancer, a fibrotic cancer, fibroma, fibroadenoma, fibrosarcoma, a myeloproliferative disorder, a hematopoietic neoplasm, a myeloid neoplasm, a lymphoid neoplasm, myelofibrosis, primary myelofibrosis, polycythemia vera, essential thrombocythemia, acute lymphocytic leukemia, acute and chronic myelogenous leukemia, chronic lymphocytic leukemia, acute lymphoblastic leukemia, chronic myelomonocytic leukemia (CMML), promyelocytic leukemia, multiple myeloma, myeloid metaplasia with myelofibrosis (MMM), idiopathic myelofibrosis (IMF), Hodgkin's disease, cutaneous lymphomas, cutaneous T-cell lymphoma, mycosis fungoides, B-cell lymphoma, T-cell lymphoma, mantle cell lymphoma, hairy cell lymphoma, Burkitt's lymphoma, mast cell tumors, non-Hodgkin's disease, Kaposi's sarcoma, rhabdomyosarcoma, seminoma,

teratocarcinoma, osteosarcoma, thyroid follicular cancer, increased accumulation of exogenous opioids or synthetic opioids, notalgia paraesthetica, obsessive-compulsive disorders, nostalgia associated with obsessive-compulsive disorders, and a combination thereof.

13. The method of Claim 11, wherein the other therapeutic agent is selected from a chemotherapeutic agent, an anti-proliferative agent, an anti-inflammatory agent, an immunomodulatory agent, immunosuppressive agent, a neurotrophic factor, an agent for treating cardiovascular disease, an agent for treating diabetes, an agent for treating immunodeficiency disorders, and a combination thereof.