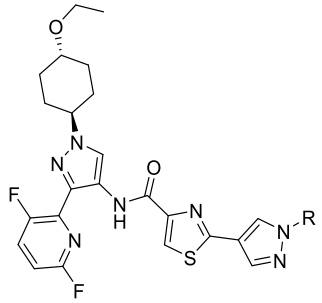
Claims

We claim:

1. A compound, having a formula 1

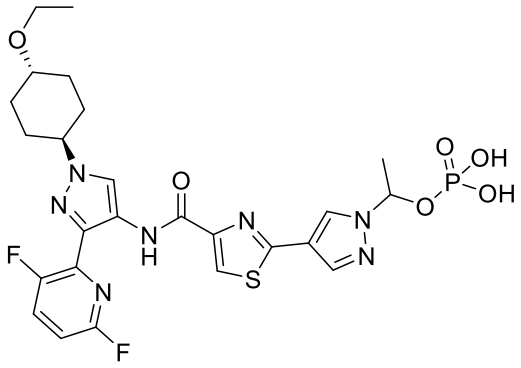


Formula 1

or a pharmaceutically acceptable salt thereof, wherein:

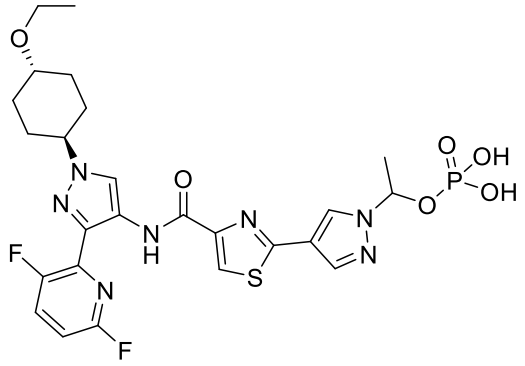
R is C_{1-4} alkyl phosphate.

2. The compound or pharmaceutically acceptable salt of claim 1, wherein the compound is



.

3. The compound of claim 1 having formula:



.

4. The compound of claim 2, wherein the compound is an alkali metal salt, an alkaline earth metal salt, an ammonium salt, an amino acid salt, an amino sugar salt, or a tris salt.

5. The compound of claim 2 or 4, wherein the compound is a mono-salt, or a di-salt.

6. The compound of any one of claims 2 or 4-5, wherein the C_{1-4} alkyl phosphate is a mono-or di- sodium salt, mono-or di-potassium salt, calcium salt, magnesium salt, arginine salt, lysine salt, mono- or di-tris salt, ammonium salt, choline salt, or meglumine salt.

7. The compound of claim 1 or 2, wherein the compound is an organic base salt; optionally wherein the compound is a mono-organic base salt or a di-organic base salt.

8. The compound of claim 1 or 2, wherein the compound is an inorganic base salt; optionally wherein the compound dis a mono-inorganic base salt or a di-inorganic base salt.

9. The compound or pharmaceutically acceptable salt of claim 1is:

I-2: (4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)methyl dihydrogen phosphate;

I-3: di-tert-butyl ((4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)methyl) phosphate;

I-4: (4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)methyl phosphate disodium salt;

I-5: N-(3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)-2-(1-methyl-1H-pyrazol-4-yl)thiazole-4-carboxamide;

I-18: 1-(4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)ethyl dihydrogen phosphate;

I-20: 1-(4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)ethyl phosphate disodium salt;

I-44: tert-butyl (1-(4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)ethyl) hydrogen phosphate sodium acetate salt;

I-46: (4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)methyl di(((isopropoxycarbonyl)oxy)methyl) phosphate;

I-49: 1-(4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)ethyl dihydrogen phosphate tris salt;

I-60: ((((4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)methoxy)(hydroxy)phosphoryl)oxy)methyl isopropyl carbonate;

I-63: (4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)methyl dihydrogen phosphate tris salt;

I-64: N-(3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)-2-(1H-pyrazol-4-yl)thiazole-4-carboxamide hydrochloride;

I-65: N-(3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)-2-(1H-pyrazol-4-yl)thiazole-4-carboxamide benzene sulfonate;

I-66: N-(3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)-2-(1H-pyrazol-4-yl)thiazole-4-carboxamide tartrate;

I-67: N-(3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)-2-(1H-pyrazol-4-yl)thiazole-4-carboxamide sodium salt;

I-68: N-(3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)-2-(1H-pyrazol-4-yl)thiazole-4-carboxamide hemicitrate;

I-69: (4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)methyl dihydrogen phosphate ditris salt;

I-104: N-(3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)-2-(1H-pyrazol-4-yl)thiazole-4-carboxamide phosphate;

I-105: N-(3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)-2-(1H-pyrazol-4-yl)thiazole-4-carboxamide gentisate;

I-106: N-(3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)-2-(1H-pyrazol-4-yl)thiazole-4-carboxamide succinate;

I-107: sodium 1-(4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)ethyl hydrogen phosphate;

I-108: potassium 1-(4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)ethyl hydrogen phosphate;

I-109: potassium 1-(4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)ethyl phosphate;

I-110: 1-(4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)ethyl dihydrogen phosphate arginine salt;

I-111: 1-(4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)ethyl dihydrogen phosphate choline salt;

I-112: ammonium 1-(4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)ethyl hydrogen phosphate;

I-113: 1-(4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)ethyl dihydrogen phosphate lysine salt;

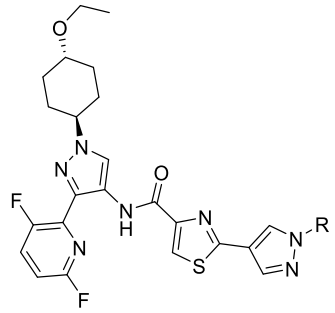
I-114: 1-(4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)ethyl dihydrogen phosphate meglumine salt;

I-115: magnesium 1-(4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)ethyl phosphate; or

I-116: Calcium 1-(4-(4-((3-(3,6-difluoropyridin-2-yl)-1-((1r,4r)-4-ethoxycyclohexyl)-1H-pyrazol-4-yl)carbamoyl)thiazol-2-yl)-1H-pyrazol-1-yl)ethyl phosphate.

10. A composition, comprising a compound according to any one of claims 1-9, and a pharmaceutically acceptable excipient.

11. A spray-dried composition, comprising a polymer carrier and a compound according to Formula I:



Formula I

or pharmaceutically acceptable salt thereof where R is C_{1-4} alkyl phosphate.

12. The spray-dried composition of claim 11, wherein the spray-dried composition comprises from 1% to 50% w/w of the compound with respect to the carrier; optionally

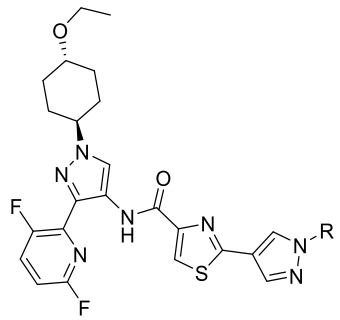
wherein the polymer is a cellulose derivative, vinyl polymer, lactide polymer, sugar, or a combination thereof; optionally

wherein the composition is amorphous; optionally

wherein the composition has a glass transition temperature of from 100 °C to 120 °C, or a combination thereof.

13. A method of making a spray-dried composition, comprising:

forming a mixture comprising a carrier, a solvent and a compound according to Formula I



Formula I

or a pharmaceutically acceptable salt thereof;

where R is C_{1-4} alkyl phosphate; and

spray drying the mixture to form a spray-dried formulation comprising the compound or a pharmaceutically acceptable salt thereof; and the carrier.

14. A compound according to any one of claims 1-9 or a composition according to any one of claims 10-12 for use in therapy.

15. Use of a compound according to any one of claims 1-9 or a composition according to any one of claims 10-12 in the manufacture of a medicament for treating a disease or condition for which an IRAK inhibitor is indicated, wherein the disease or condition is an auto-immune disease, inflammatory disorder, cardiovascular disease, neurodegenerative disorder, allergic disorder, multi-organ failure, kidney disease, platelet aggregation, cancer, transplantation, sperm motility, erythrocyte deficiency, graft rejection, lung injury, respiratory disease, ischemic condition, bacterial infection, viral infection, immune regulatory disorder or a combination thereof.

16. The use of claim 15, wherein the disease or condition is graft-versus-host diseases brought about by transplantation, rheumatoid arthritis, systemic lupus erythematosus, lupus nephritis, Hashimoto's thyroiditis, multiple sclerosis, systemic sclerosis, myasthenia gravis, type I diabetes, uveitis, posterior uveitis, allergic encephalomyelitis, glomerulonephritis, rheumatic fever, post-infectious glomerulonephritis, inflammatory and hyperproliferative skin diseases, psoriasis, atopic dermatitis, contact dermatitis, eczematous dermatitis, seborrhoeic dermatitis, lichen planus, pemphigus, bullous pemphigoid, epidermolysis bullosa, urticaria, angioedemas, vasculitis, erythema, cutaneous eosinophilia, lupus erythematosus, acne, alopecia areata, keratoconjunctivitis, vernal conjunctivitis, uveitis associated with Behcet's disease, keratitis, herpetic keratitis, conical cornea, dystrophia epithelialis corneae, corneal leukoma, ocular pemphigus, Mooren's ulcer, scleritis, Graves' opthalmopathy, Vogt-Koyanagi-Harada syndrome,

sarcoidosis, pollen allergies, driv, bronchial asthma, allergic asthma, intrinsic asthma, extrinsic asthma, dust asthma, chronic or inveterate asthma, late asthma and airway hyper-responsiveness, bronchitis, gastric ulcers, vascular damage caused by ischemic diseases and thrombosis, ischemic bowel diseases, inflammatory bowel diseases, necrotizing enterocolitis, intestinal lesions associated with thermal burns, celiac diseases, proctitis, eosinophilic gastroenteritis, mastocytosis, Crohn's disease, ulcerative colitis, migraine, rhinitis, eczema, interstitial nephritis, Goodpasture's syndrome, hemolytic-uremic syndrome, diabetic nephropathy, multiple myositis, Guillain-Barre syndrome, Meniere's disease, polyneuritis, multiple neuritis, mononeuritis, radiculopathy, hyperthyroidism, Basedow's disease, pure red cell aplasia, aplastic anemia, hypoplastic anemia, idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, agranulocytosis, pernicious anemia, megaloblastic anemia, anerythroplasia, osteoporosis, sarcoidosis, fibroid lung, idiopathic interstitial pneumonia, dermatomyositis, leukoderma vulgaris, ichthyosis vulgaris, photoallergic sensitivity, cutaneous T cell lymphoma, chronic lymphocytic leukemia, arteriosclerosis, atherosclerosis, aortitis syndrome, polyarteritis nodosa, myocardosis, scleroderma, Wegener's granuloma, Sjögren's syndrome, adiposis, eosinophilic fascitis, lesions of gingiva, periodontium, alveolar bone, substantia ossea dentis, glomerulonephritis, male pattern alopecia or alopecia senilis by preventing epilation or providing hair germination and/or promoting hair generation and hair growth, muscular dystrophy, pyoderma and Sezary's syndrome, Addison's disease, ischemia-reperfusion injury of organs which occurs upon preservation, transplantation or ischemic disease, endotoxin-shock, pseudomembranous colitis, colitis caused by drug or radiation, ischemic acute renal insufficiency, chronic renal insufficiency, toxinosis caused by lung-oxygen or drugs, lung cancer, pulmonary emphysema, cataracta, siderosis, retinitis pigmentosa, senile macular degeneration, vitreal scarring, corneal alkali burn, dermatitis erythema multiforme, linear IgA ballous dermatitis and cement dermatitis, gingivitis, periodontitis, sepsis, pancreatitis, cytokine release syndrome (CRS), diseases caused by environmental pollution, aging, carcinogenesis, metastasis of carcinoma and hypobaropathy, disease caused by histamine or leukotriene-C4 release, Behcet's disease, autoimmune hepatitis, primary biliary cirrhosis, sclerosing cholangitis, partial liver resection, acute liver necrosis, necrosis caused by toxin, viral hepatitis, shock, or anoxia, B-virus hepatitis, non-A/non-B hepatitis, cirrhosis, alcoholic liver disease, non-alcoholic steatohepatitis (NASH), hepatic failure, fulminant hepatic failure, late-onset hepatic failure, "acute-on-chronic" liver failure, augmentation of chemotherapeutic effect, cytomegalovirus infection, HCMV infection, AIDS, cancer, senile dementia, Parkinson’s disease, trauma, or chronic bacterial infection.

17. The use according to claim 15, wherein the disease or condition is rheumatoid arthritis, psoriatic arthritis, osteoarthritis, systemic lupus erythematosus, lupus nephritis, ankylosing spondylitis, osteoporosis, systemic sclerosis, multiple sclerosis, psoriasis, in particular pustular psoriasis, type I diabetes, type II diabetes, inflammatory bowel disease (Crohn's disease and ulcerative colitis), hyperimmunoglobulinemia d and periodic fever syndrome, cryopyrin-associated periodic syndromes, Schnitzler's syndrome, systemic juvenile

idiopathic arthritis, adult-onset Still's disease, gout, gout flares, pseudogout, SAPHO syndrome, Castleman's disease, sepsis, stroke, atherosclerosis, celiac disease, DIRA (deficiency of Il-1 receptor antagonist), Alzheimer's disease, Parkinson's disease or a combination thereof.

18. The use of claim 15, wherein the disease or condition is benign or malignant tumors, solid tumor, carcinoma of the brain, kidney, liver, adrenal gland, bladder, breast, stomach, gastric tumors, ovaries, colon, rectum, prostate, pancreas, lung, vagina, cervix, testis, genitourinary tract, esophagus, larynx, skin, bone or thyroid, sarcoma, glioblastomas, neuroblastomas, multiple myeloma, gastrointestinal cancer, colon carcinoma, colorectal adenoma, a tumor of the neck and head, an epidermal hyperproliferation, psoriasis, prostate hyperplasia, a neoplasia, a neoplasia of epithelial character, adenoma, adenocarcinoma, keratoacanthoma, epidermoid carcinoma, large cell carcinoma, non-small-cell lung carcinoma, lymphomas, Hodgkins and Non-Hodgkins, a mammary carcinoma, follicular carcinoma, undifferentiated carcinoma, papillary carcinoma, seminoma, melanoma, IL-1 driven disorders, a MyD88 driven disorder, Hodgkin's lymphoma, primary cutaneous T-cell lymphoma, smoldering or indolent multiple myeloma, hematologic malignancy, leukemia, acute myeloid leukemia (AML), DLBCL, ABC DLBCL, chronic lymphocytic leukemia (CLL), chronic lymphocytic lymphoma, primary effusion lymphoma, Burkitt lymphoma/leukemia, acute lymphocytic leukemia, B-cell prolymphocytic leukemia, lymphoplasmacytic lymphoma, myelodysplastic syndromes (MDS), myelofibrosis, polycythemia vera, Kaposi’s sarcoma, Waldenström's macroglobulinemia (WM), splenic marginal zone lymphoma, multiple myeloma, plasmacytoma, or intravascular large B-cell lymphoma).

19. The use of claim 15, wherein the disease or condition is rheumatoid arthritis.

20. The use of claim 15, wherein the disease or condition is psoriasis.

21. The use of claim 15, wherein the disease or condition is pustular psoriasis.

22. The use of claim 15, wherein the disease or condition is periodic fever syndrome.

23. The use of claim 15, wherein the disease or condition is Schnitzler's syndrome.

24. The use of claim 15, wherein the disease or condition is adult's onset Still's disease.

25. The use of claim 15, wherein the disease or condition is DIRA (deficiency of Il-1 receptor antagonist).

26. The use of claim 15, wherein the disease or condition is myelodysplastic syndromes (MDS).

27. The use of claim 15, wherein the disease or condition is myelofibrosis.

28. The use of claim 15, wherein the disease or condition is atopic dermatitis.

29. The use of claim 15, wherein the disease or condition is cytokine release syndrome (CRS).

30. The use of claim 15 further comprising a second therapeutic agent.

31. The use of claim 30, wherein the second therapeutic agent is an analgesic, an antibiotic, an anticoagulant, an antibody, an anti-inflammatory agent, an immunosuppressant, a guanylate cyclase-C agonist, an intestinal secretagogue, an antiviral, anticancer, antifungal, cell therapy or a combination thereof.

32. The use according to any one of claims 14 to 31, wherein the compound or pharmaceutically acceptable salt is administered in an amount of 0.0001 mg/kg/day up to at least 100 mg/kg/day.

33. The use according to any one of claims 14 to 31, wherein the compound or pharmaceutically acceptable salt is administered in an amount of 0.0025 mg/kg to 1 mg/kg at least once per day.

34. The use according to any one of claims 14 to 31, wherein the compound or pharmaceutically acceptable salt is administered in an amount of 0.1 mg/kg to 20 mg/kg per day.