

PYRROLO[2,3-D]PYRIMIDINE DERIVATIVES

FIELD OF THE INVENTION

5 The present invention relates to pyrrolo[2,3-d]pyrimidine compounds and isolated forms of such compounds. The invention also relates to the preparation of said compounds and intermediates used in said preparation, compositions containing said compounds and uses of said compound for inhibiting Janus Kinase (JAK) and methods for treating and preventing conditions mediated by JAK1.

BACKGROUND OF THE INVENTION

10 Protein kinases are families of enzymes that catalyze the phosphorylation of specific residues in proteins, broadly classified into tyrosine and serine/threonine kinases. Inappropriate kinase activity, arising from mutation, over-expression, or inappropriate regulation, dysregulation or de-regulation, as well as over- or under-production of growth factors or cytokines has been implicated in many diseases, including but not limited to cancer, cardiovascular diseases,
15 allergies, asthma and other respiratory diseases, autoimmune diseases, inflammatory diseases, bone diseases, metabolic disorders, and neurological and neurodegenerative disorders such as Alzheimer's disease. Inappropriate kinase activity triggers a variety of biological cellular responses relating to cell growth, cell differentiation, survival, apoptosis, mitogenesis, cell cycle control, and cell mobility implicated in the aforementioned and related diseases.

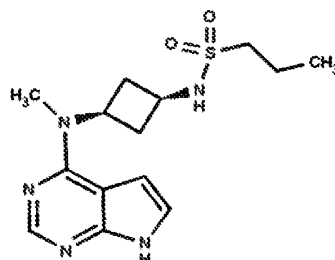
20 Thus, protein kinases have emerged as an important class of enzymes as targets for therapeutic intervention. In particular, the JAK family of cellular protein tyrosine kinases (JAK1, JAK2, JAK3, and Tyk2) play a central role in cytokine signaling (Kisseleva et al., Gene, 2002, 285, 1; Yamaoka et al. Genome Biology 2004, 5, 253)). Upon binding to their receptors, cytokines activate JAK which then phosphorylate the cytokine receptor, thereby creating docking sites for
25 signaling molecules, notably, members of the signal transducer and activator of transcription (STAT) family that ultimately lead to gene expression. Numerous cytokines are known to activate the JAK family. These cytokines include, the IFN family (IFN-alpha, IFN-beta, IFN-omega, Limitin, IFN-gamma, IL-10, IL-19, IL-20, IL-22), the gp130 family (IL-6, IL-11, OSM, LIF, CNTF, NNT-1/BSF-3, G-CSF, CT-1, Leptin, IL-12, IL-23), gamma C family (IL-2, IL-7, TSLP, IL-9, IL-15,
30 IL-21, IL-4, IL-13), IL-3 family (IL-3, IL-5, GM-CSF), single chain family (EPO, GH, PRL, TPO), receptor tyrosine kinases (EGF, PDGF, CSF-1, HGF), and G-protein coupled receptors (AT1).

There remains a need for new compounds that effectively and selectively inhibit specific JAK enzymes, and JAK1 in particular, vs. JAK2. JAK1 is a member of the Janus family of protein kinases composed of JAK1, JAK2, JAK3 and TYK2. JAK1 is expressed to various levels in all
35 tissues. Many cytokine receptors signal through pairs of JAK kinases in the following combinations: JAK1/JAK2, JAK1/JAK3, JAK1/TYK2, JAK2/TYK2 or JAK2/JAK2. JAK1 is the

most broadly paired JAK kinase in this context and is required for signaling by γ -common (IL-2R γ) cytokine receptors, IL-6 receptor family, Type I, II and III receptor families and IL-10 receptor family. Animal studies have shown that JAK1 is required for the development, function and homeostasis of the immune system. Modulation of immune activity through inhibition of JAK1 kinase activity can prove useful in the treatment of various immune disorders (Murray, P.J. *J. Immunol.*, 178, 2623–2629 (2007); Kisseleva, T., *et al.*, *Gene*, 285, 1–24 (2002); O'Shea, J. J., *et al.*, *Cell*, 109, (suppl.) S121–S131 (2002)) while avoiding JAK2 dependent erythropoietin (EPO) and thrombopoietin (TPO) signaling (Neubauer H., *et al.*, *Cell*, 93(3), 397-409 (1998); Parganas E., *et al.*, *Cell*, 93(3), 385-95 (1998)).

There are substantial needs for safe and efficacious agents to control disorders related to JAK, such as atopic dermatitis, both in human and animals. The market for treating atopic dermatitis is currently dominated by corticosteroids, which cause distressing and undesirable side effects. Antihistamines are also used, but are poorly effective. New compounds which are JAK inhibitors with selective efficacy against JAK1 are needed which provide an alternative to steroid usage and promote resolution of chronic pruritus and inflammation that would either persist in atopic dermatitis or slowly regress following removal of allergen or causative agent.

Recently identified N-((1S,3S)-3-(Methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)cyclobutyl)propane-1-sulfonamide, generically known as abrocitinib, is described in commonly assigned US9,035,074, the contents of which are incorporated herein by reference in their entirety, and has the chemical formula C₁₄H₂₁N₅O₂S and the following structural formula:



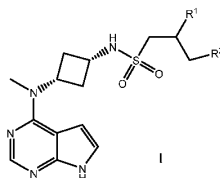
It is known that abrocitinib is a highly promising inhibitor of JAK, and is useful therapeutically for the treatment of a variety of disorders including atopic dermatitis. Novel metabolites of abrocitinib have now been discovered by the present inventors that are highly active as inhibitors of JAK and surprisingly capable of greater therapeutic index, and accordingly, have the potential to be superior pharmaceutical agents for the treatment of JAK-mediated disorders.

SUMMARY OF THE INVENTION

The present invention relates to pyrrolo[2,3-d]pyrimidine compounds and isolated forms of such compounds. The isolated compounds of the invention have been found to possess unexpectedly advantageous activity including higher efficacy and reduced incidence of adverse

effects. The isolated compounds may be employed in pharmaceutical compositions in combination with pharmaceutically acceptable excipients and in methods of treating conditions mediated by JAK1.

The present invention provides compounds of formula I having the structure:



or a pharmaceutically acceptable salt thereof, wherein R¹ and R² are independently hydrogen or hydroxy; wherein if R¹ is hydrogen, then R² is hydroxy; and, wherein if R² is hydrogen, then R¹ is hydroxy.

In other aspects, the present invention also provides compounds of formula I or a pharmaceutically acceptable salt in an isolated form.

In other aspects, the present invention also provides pharmaceutical compositions which comprise a pharmaceutically acceptable excipient and a compound of formula I or a pharmaceutically acceptable salt thereof.

In another aspect the present invention also provides methods for treating conditions or disorders including myositis, vasculitis, pemphigus, Crohn's disease, lupus, nephritis, psoriasis, multiple sclerosis, major depression disorder, allergy, asthma, Sjogren's disease, dry eye syndrome, transplant rejection, cancer, inflammatory bowel disease, septic shock, cardiopulmonary dysfunction, acute respiratory disease, or cachexia by administering to a subject in need thereof a therapeutically effective amount of a compound of formula I or a pharmaceutically acceptable salt.

In another aspect, the present invention also provides methods for treating conditions or disorders including atopic dermatitis, eczema, psoriasis, scleroderma, lupus, pruritus, other pruritic conditions, allergic reactions including allergic dermatitis in mammal, inflammatory airway disease, recurrent airway obstruction, airway hyper-responsiveness, and chronic obstruction pulmonary disease by comprising administering to a subject in need thereof a therapeutically effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof.

In another aspect the present invention also provides methods for the preparation of compounds of the present invention.

The present invention will be further understood from the following description given by way of example only. While the present invention is not so limited, an appreciation of various aspects of the invention will be gained through the following discussion and the examples.

The term "subject" refers to human, livestock or companion animals.

The term "treating" or "treatment" means an alleviation of symptoms associated with a disease, disorder or condition, or halt of further progression or worsening of those symptoms.

Depending on the disease and condition of the subject, the term "treatment" as used herein may include one or more of curative, palliative and prophylactic treatment. Treatment can also include administering a pharmaceutical formulation of the present invention in combination with other therapies.

5 The term "therapeutically effective" indicates the capability of an agent to prevent, or improve the severity of, the disorder, while avoiding adverse side effects typically associated with alternative therapies. The phrase "therapeutically effective" is to be understood to be equivalent to the phrase "effective for the treatment, prevention, or amelioration", and both are intended to qualify the amount of each agent for use in the combination therapy which will achieve the goal
10 of improvement in the severity of cancer, cardiovascular disease, or pain and inflammation and the frequency of incidence over treatment of each agent by itself, while avoiding adverse side effects typically associated with alternative therapies.

"Pharmaceutically acceptable" means suitable for use in a subject.

If substituents are described as being "independently selected" from a group, each
15 substituent is selected independent of the other. Each substituent therefore may be identical to or different from the other substituent(s). In some embodiments, the metabolite compounds, or salts thereof, are substantially isolated.

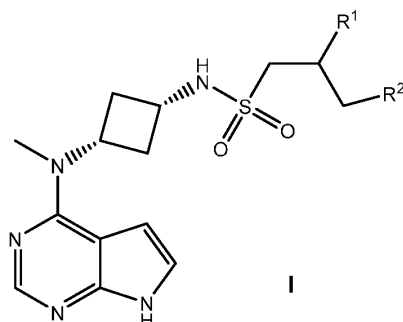
The terms "isolated", "purified", "in purified form", "in isolated form" or "purified substance" means that a compound, or salt thereof, for a compound refers to the physical state of the
20 compound after being isolated from a synthetic process, *e.g.*, from a reaction mixture. Thus the terms "isolated", "purified", "in purified form", "in isolated form" or "purified substance" for a compound refers to the physical state of said compound after being obtained from a purification process or processes described herein or well known to the skilled artisan (*e.g.*, chromatography, recrystallization and the like), in sufficient purity to be characterizable by standard analytical
25 techniques described herein or well known to the skilled artisan. As examples, the purification techniques disclosed herein (*e.g.*, LC-MS and LC-MS/MS techniques) result in isolated forms of the subject compounds. Such isolation and purification techniques would be expected to result in product purities containing at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 97%, or at least about 99% by weight of the compound, or salt thereof.

30

DETAILED DESCRIPTION OF THE INVENTION

The present invention is related to compounds which are selective JAK1 modulators useful for the treatment of diseases and conditions associated with dysregulation of the JAK1. The present invention further provides isolated compounds which are selective JAK1 modulators
35 useful for the treatment of diseases and conditions associated with dysregulation of the JAK1. The present invention also provides prodrugs and pharmaceutical compositions comprising such JAK1 modulators as well as methods of treating and/or preventing such diseases and conditions.

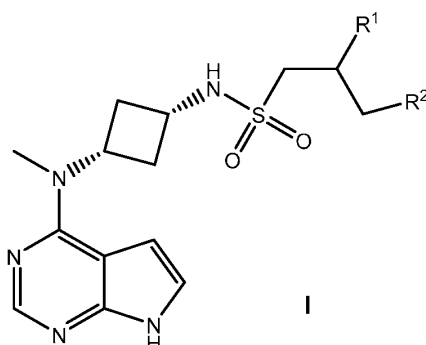
In a first aspect the invention provides a compound of formula I having the structure:



or a pharmaceutically acceptable salt thereof, wherein R^1 and R^2 are independently hydrogen or hydroxy; wherein if R^1 is hydrogen, then R^2 is hydroxy; and, wherein if R^2 is hydrogen, then R^1 is hydroxy.

- 5 Described below are embodiments (E) of this first aspect of the invention where, for convenience, E1 is identical thereto.

E1. A compound of formula I having the structure:

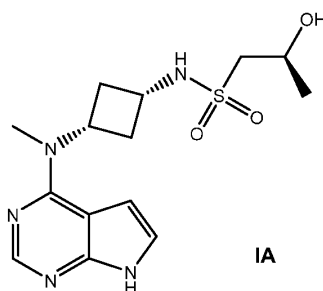


- 10 or a pharmaceutically acceptable salt thereof, wherein R^1 and R^2 are independently hydrogen or hydroxy; wherein if R^1 is hydrogen, then R^2 is hydroxy; and, wherein if R^2 is hydrogen, then R^1 is hydroxy.

E2. The compound according to E1 or a pharmaceutically acceptable salt thereof, wherein R^1 is hydroxy and R^2 is hydrogen.

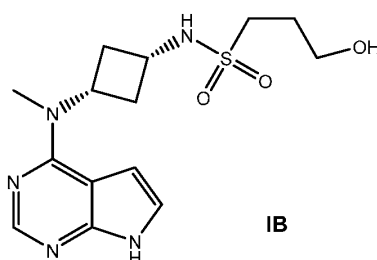
- 15 E3. The compound according to E1 or a pharmaceutically acceptable salt thereof, wherein R^1 is hydrogen and R^2 is hydroxy.

E4. A compound of formula **IA** having the structure:



or a pharmaceutically acceptable salt thereof.

E5. A compound of formula **IB** having the structure:



5 or a pharmaceutically acceptable salt thereof.

E6. A compound selected from the group consisting of:

(S)-2-hydroxy-N-(3-(methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)cyclobutyl)propane-1-sulfonamide; and,

3-hydroxy-N-(3-(methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)cyclobutyl)propane-1-sulfonamide; or, a pharmaceutically acceptable salt thereof.

E7. (S)-2-Hydroxy-N-(3-(methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)cyclobutyl)propane-1-sulfonamide or a pharmaceutically acceptable salt thereof.

E8. 3-Hydroxy-N-(3-(methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)cyclobutyl)propane-1-sulfonamide or a pharmaceutically acceptable salt thereof.

15 E9. (S)-2-Hydroxy-N-(3-(methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)cyclobutyl)propane-1-sulfonamide.

E10. 3-Hydroxy-N-(3-(methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)cyclobutyl)propane-1-sulfonamide.

20 E11. The compound according to any one of embodiments E1 to E10, in an isolated form.

E12. The compound according to any one of embodiments E1 to E11, in crystalline form.

25 E13. A method or preventing of treating a disease or condition for which a JAK1 inhibitor is indicated, in a subject in need of such treatment, comprising administering to the subject a therapeutically effective amount of the compound according to any one of embodiments E1 to E12, or a pharmaceutically acceptable salt.

E14. A method of treating or preventing an inflammatory or autoimmune condition comprising administering to a subject suffering therefrom a therapeutically effective amount of the compound according to any one of embodiments E1 to E12 or a pharmaceutically acceptable salt thereof.

5 E15. A pharmaceutical composition comprising a compound according to any one of embodiments E1 to E12 and a pharmaceutically acceptable excipient.

E16. A method of treating or preventing a disease or condition selected from inflammation, autoimmune disease, neuroinflammation, arthritis, rheumatoid arthritis, spondyloarthropathies, systemic lupus erythematosus, lupus nephritis, osteoarthritis, gouty
 10 arthritis, pain, fever, pulmonary sarcoidosis, silicosis, cardiovascular disease, atherosclerosis, myocardial infarction, thrombosis, congestive heart failure and cardiac reperfusion injury, cardiomyopathy, stroke, ischemia, reperfusion injury, brain edema, brain trauma, neurodegeneration, liver disease, inflammatory bowel disease, Crohn's disease, ulcerative colitis, nephritis, retinitis, retinopathy, macular degeneration, glaucoma, diabetes (type 1 and type 2),
 15 diabetic neuropathy, viral and bacterial infection, myalgia, endotoxic shock, toxic shock syndrome, osteoporosis, multiple sclerosis, endometriosis, menstrual cramps, vaginitis, candidiasis, cancer, fibrosis, obesity, muscular dystrophy, polymyositis, dermatomyositis, autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, vitiligo, Alzheimer's disease, skin flushing, eczema, psoriasis, atopic dermatitis, sunburn, keloid, hypertrophic scar,
 20 rheumatic diseases, urticaria, discoid lupus, cutaneous lupus, central nervous system lupus, psoriatic arthritis, asthma, allergic asthma, type I interferonopathies including Aicardi-Goutières syndrome and other mendelian diseases of overexpression of type I interferon, primary progressive multiple sclerosis, relapsing remitting multiple sclerosis, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, scleroderma, alopecia areata, scarring alopecia, prurigo,
 25 prurigo nodularis, CPUO, lichen diseases, lichen planus, Steven's Johnson's syndrome, spondylopathy, myositis, vasculitis, pemphigus, lupus, major depression disorder, allergy, dry eye syndrome, transplant rejection, cancer, septic shock, cardiopulmonary dysfunction, acute respiratory disease, ankylosing spondylitis, cachexia, chronic graft-versus-host disease, acute graft-versus-host disease, Celiac Sprue, idiopathic thrombocytopenic thrombotic purpura,
 30 thrombotic thrombocytopenic purpura, myasthenia gravis, Sjogren's syndrome, epidermal hyperplasia, cartilage inflammation, bone degradation, juvenile arthritis, juvenile rheumatoid arthritis, pauciarticular juvenile rheumatoid arthritis, polyarticular juvenile rheumatoid arthritis, systemic onset juvenile rheumatoid arthritis, juvenile ankylosing spondylitis, juvenile enteropathic arthritis, juvenile Reter's Syndrome, SEA Syndrome, juvenile dermatomyositis, juvenile psoriatic arthritis, juvenile scleroderma, juvenile systemic lupus erythematosus, juvenile vasculitis, pauciarticular rheumatoid arthritis, polyarticular rheumatoid arthritis, systemic onset rheumatoid arthritis, enteropathic arthritis, reactive arthritis, Reter's Syndrome, myolitis, polymyolitis, dermatomyolitis, polyarteritis nodosa, Wegener's granulomatosis, arteritis, polymyalgia

rheumatica, sarcoidosis, sclerosis, primary biliary sclerosis, sclerosing cholangitis, dermatitis, Still's disease, chronic obstructive pulmonary disease, Guillain-Barre disease, Graves' disease, Addison's disease, Raynaud's phenomenon, psoriatic epidermal hyperplasia, plaque psoriasis, guttate psoriasis, inverse psoriasis, pustular psoriasis, erythrodermic psoriasis, an immune disorder associated with or arising from activity of pathogenic lymphocytes, noninfectious uveitis, Behcet's disease and Vogt-Koyanagi-Harada syndrome, comprising administering to a subject in need thereof a therapeutically effective amount of a compound or a pharmaceutically acceptable salt thereof according to any one of embodiments E1 to E12.

5 E17. A method for treating or preventing psoriasis, comprising the step of administering to a subject in need thereof a therapeutically effective amount of a composition comprising a compound or a pharmaceutically acceptable salt thereof according to any one of embodiments E1 to E12.

10 E18. A method for treating or preventing atopic dermatitis, comprising the step of administering to a subject in need thereof a therapeutically effective amount of a composition comprising a compound or a pharmaceutically acceptable salt thereof according to any one of embodiments E1 to E12.

15 E19. A method for treating or preventing hand eczema, comprising the step of administering to a subject in need thereof a therapeutically effective amount of a compound or a pharmaceutically acceptable salt thereof according to any one of embodiments E1 to E12.

20 E20. A method for treating or preventing pruritis, comprising the step of administering to a subject in need thereof a therapeutically effective amount of a compound or a pharmaceutically acceptable salt thereof according to any one of embodiments E1 to E12.

25 E21. A method for treating or preventing cutaneous lupus, comprising the step of administering to a subject in need thereof a therapeutically effective amount of a compound or a pharmaceutically acceptable salt thereof according to any one of embodiments E1 to E12.

E22. A method of treating a disorder or condition related to dysregulation of JAK, and particularly of JAK1, in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of the compound or a pharmaceutically acceptable salt thereof according to any one of embodiments E1 to E12.

30 E23. The method according to E22, wherein the disorder or condition treated or prevented is selected from the group consisting of inflammation, autoimmune disease, neuroinflammation, arthritis, rheumatoid arthritis, spondyloarthropathies, systemic lupus erythematosus, lupus nephritis, osteoarthritis, gouty arthritis, pain, fever, pulmonary sarcoidosis, silicosis, cardiovascular disease, atherosclerosis, myocardial infarction, thrombosis, congestive heart failure and cardiac reperfusion injury, cardiomyopathy, stroke, ischemia, reperfusion injury, brain edema, brain trauma, neurodegeneration, liver disease, inflammatory bowel disease, Crohn's disease, ulcerative colitis, nephritis, retinitis, retinopathy, macular degeneration, glaucoma, diabetes (type 1 and type 2), diabetic neuropathy, viral and bacterial infection, myalgia, endotoxic

- shock, toxic shock syndrome, osteoporosis, multiple sclerosis, endometriosis, menstrual cramps, vaginitis, candidiasis, cancer, fibrosis, obesity, muscular dystrophy, polymyositis, dermatomyositis, autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, vitiligo, Alzheimer's disease, skin flushing, eczema, psoriasis, atopic dermatitis, sunburn, keloid,
- 5 hypertrophic scar, rheumatic diseases, urticaria, discoid lupus, cutaneous lupus, central nervous system lupus, psoriatic arthritis, asthma, allergic asthma, type I interferonopathies including Aicardi–Goutières syndrome and other mendelian diseases of overexpression of type I interferon, primary progressive multiple sclerosis, relapsing remitting multiple sclerosis, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, scleroderma, alopecia areata, spondylopathy,
- 10 myositis, vasculitis, pemphigus, lupus, major depression disorder, allergy, dry eye syndrome, transplant rejection, cancer, septic shock, cardiopulmonary dysfunction, acute respiratory disease, ankylosing spondylitis, cachexia, chronic graft-versus-host disease, acute graft-versus-host disease, Celiac Sprue, idiopathic thrombocytopenic thrombotic purpura, myasthenia gravis, Sjogren's syndrome, epidermal hyperplasia, cartilage inflammation, bone degradation, juvenile
- 15 arthritis, juvenile rheumatoid arthritis, pauciarticular juvenile rheumatoid arthritis, polyarticular juvenile rheumatoid arthritis, systemic onset juvenile rheumatoid arthritis, juvenile ankylosing spondylitis, juvenile enteropathic arthritis, juvenile Reter's Syndrome, SEA Syndrome, juvenile dermatomyositis, juvenile psoriatic arthritis, juvenile scleroderma, juvenile systemic lupus erythematosus, juvenile vasculitis, pauciarticular rheumatoid arthritis, polyarticular rheumatoid
- 20 arthritis, systemic onset rheumatoid arthritis, enteropathic arthritis, reactive arthritis, Reter's Syndrome, myolitis, polymyolitis, dermatomyolitis, polyarteritis nodosa, Wegener's granulomatosis, arteritis, polymyalgia rheumatica, sarcoidosis, sclerosis, primary biliary sclerosis, sclerosing cholangitis, dermatitis, Still's disease, chronic obstructive pulmonary disease, Guillain-Barre disease, Graves' disease, Addison's disease, Raynaud's phenomenon, psoriatic epidermal
- 25 hyperplasia, plaque psoriasis, guttate psoriasis, inverse psoriasis, pustular psoriasis, erythrodermic psoriasis, an immune disorder associated with or arising from activity of pathogenic lymphocytes, noninfectious uveitis, Behcet's disease and Vogt–Koyanagi–Harada syndrome.

E24. The method according to embodiments E13 to E23, wherein the therapeutically effective amount is from 0.01 mg/kg of body weight/day to 100 mg/kg of body weight/day.

30 E25. The method according to E24, wherein the therapeutically effective is from 0.1 mg/kg of body weight/day to 10 mg/kg of body weight/day.

E26. Use of a compound according to any of embodiments E1 to E12 for the manufacture of a medicament for the treatment of a disorder for which a JAK1 inhibitor is indicated.

E29. A compound according to any of embodiments E1 to E12 for use in the treatment

35 of a disorder for which a JAK1 inhibitor is indicated.

E30. Use of a compound in an isolated form according to any of embodiments E1 to E12 for the manufacture of a medicament for the treatment of a disorder for which a JAK1 inhibitor is indicated.

E31. A compound in an isolated form according to any of embodiments E1 to E12 for use in the treatment of a disorder for which a JAK1 inhibitor is indicated

E32. A pharmaceutical combination comprising a compound of embodiments E1 to E12, or a pharmaceutically acceptable salt thereof, and one or more additional pharmacologically active compounds.

Compounds or compounds in an isolated form that have the same molecular formula but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space are termed "isomers". Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers". It will be appreciated by those skilled in the art that the compound or compound in an isolated form of formula I, IA or IB can exist as *cis*- and *trans*- achiral diastereomers. An example is the compound or compound in an isolated form of formula IC.

Included within the scope of the described compounds and compounds in an isolated form are all isomers (*e.g.*, *cis*-, *trans*-, or diastereomers) of the compounds described herein alone as well as any mixtures. All of these forms, including enantiomers, diastereomers, *cis*, *trans*, *syn*, *anti*, solvates (including hydrates), tautomers, and mixtures thereof, are included in the described compounds or compounds in an isolated form. Stereoisomeric mixtures, *e.g.*, mixtures of diastereomers, can be separated into their corresponding isomers in a known manner by means of suitable separation methods. Diastereomeric mixtures for example may be separated into their individual diastereomers by means of fractionated crystallization, chromatography, solvent distribution, and similar procedures. This separation may take place either at the level of one of the starting compounds or in a compound of formula I, IA or IB itself. Enantiomers may be separated through the formation of diastereomeric salts, for example by salt formation with an enantiomer-pure chiral acid, or by means of chromatography, for example by HPLC, using chromatographic substrates with chiral ligands.

In therapeutic use for treating disorders in a subject, a compound or compound in an isolated form of the present invention or its pharmaceutical compositions can be administered orally, parenterally, topically, rectally, transmucosally, or intestinally. Parenteral administrations include indirect injections to generate a systemic effect or direct injections to the afflicted area. Topical administrations include the treatment of skin or organs readily accessible by local application, for example, eyes or ears. It also includes transdermal delivery to generate a systemic effect. The rectal administration includes the form of suppositories. The preferred routes of administration are oral and parenteral.

Pharmaceutically acceptable salts of the compounds or compounds in an isolated form of formula I, IA or IB include the acid addition and base salts thereof. Suitable acid addition salts are formed from acids which form non-toxic salts. Examples include the acetate, adipate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulphate/sulfate, borate, camsylate, citrate, cyclamate, edisylate, esylate, formate, fumarate, gluceptate, gluconate, glucuronate, hexafluorophosphate, hibenzate, hydrochloride/chloride, hydrobromide/bromide,

hydroiodide/iodide, isethionate, lactate, malate, maleate, malonate, mesylate, methylsulfate, naphthylate, 2-napsylate, nicotinate, nitrate, orotate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, pyroglutamate, saccharate, stearate, succinate, tannate, tartrate, tosylate, trifluoroacetate and xinofoate salts.

5 Suitable base salts are formed from bases which form non-toxic salts. Examples include the aluminium, arginine, benzathine, calcium, choline, diethylamine, diolamine, glycine, lysine, magnesium, meglumine, olamine, potassium, sodium, tromethamine and zinc salts.

 Hemisalts of acids and bases may also be formed, for example, hemisulphate and hemicalcium salts. For a review on suitable salts, see *Handbook of Pharmaceutical Salts: Properties, Selection, and Use* by Stahl and Wermuth (Wiley-VCH, 2002).

10 *Properties, Selection, and Use* by Stahl and Wermuth (Wiley-VCH, 2002).

 Pharmaceutically acceptable salts of compounds and compounds in an isolated form of formula I, IA or IB may be prepared, respectively, by one or more of three methods: (i) by reacting the compound or compound in an isolated form of formula I, IA or IB with the desired acid or base; (ii) by removing an acid- or base-labile protecting group from a suitable precursor of the compound or compound in an isolated form of formula I, IA or IB or by ring-opening a suitable cyclic precursor, for example, a lactone or lactam, using the desired acid or base; or (iii) by converting one salt of the compound or compound in an isolated form of formula I, IA or IB to another by reaction with an appropriate acid or base or by means of a suitable ion exchange column. All three reactions are typically carried out in solution. The resulting salt may precipitate out and be collected by filtration or may be recovered by evaporation of the solvent. The degree of ionization in the resulting salt may vary from completely ionized to almost non-ionized.

15 Pharmaceutically acceptable salts of compounds and compounds in an isolated form of formula I, IA or IB may be prepared, respectively, by one or more of three methods: (i) by reacting the compound or compound in an isolated form of formula I, IA or IB with the desired acid or base; (ii) by removing an acid- or base-labile protecting group from a suitable precursor of the compound or compound in an isolated form of formula I, IA or IB or by ring-opening a suitable cyclic precursor, for example, a lactone or lactam, using the desired acid or base; or (iii) by converting one salt of the compound or compound in an isolated form of formula I, IA or IB to another by reaction with an appropriate acid or base or by means of a suitable ion exchange column. All three reactions are typically carried out in solution. The resulting salt may precipitate out and be collected by filtration or may be recovered by evaporation of the solvent. The degree of ionization in the resulting salt may vary from completely ionized to almost non-ionized.

20 Pharmaceutically acceptable salts of compounds and compounds in an isolated form of formula I, IA or IB may be prepared, respectively, by one or more of three methods: (i) by reacting the compound or compound in an isolated form of formula I, IA or IB with the desired acid or base; (ii) by removing an acid- or base-labile protecting group from a suitable precursor of the compound or compound in an isolated form of formula I, IA or IB or by ring-opening a suitable cyclic precursor, for example, a lactone or lactam, using the desired acid or base; or (iii) by converting one salt of the compound or compound in an isolated form of formula I, IA or IB to another by reaction with an appropriate acid or base or by means of a suitable ion exchange column. All three reactions are typically carried out in solution. The resulting salt may precipitate out and be collected by filtration or may be recovered by evaporation of the solvent. The degree of ionization in the resulting salt may vary from completely ionized to almost non-ionized.

 Pharmaceutical compositions of the present invention may be manufactured by methods well known in the art, e.g., by means of conventional mixing, dissolving, granulation, dragee-making, levigating, emulsifying, encapsulating, entrapping, lyophilizing processes or spray drying.

25 Pharmaceutical compositions for use in accordance with the present invention may be formulated in conventional manner using one or more pharmaceutically acceptable carriers comprising excipients and auxiliaries, which facilitate processing of the active compound or compound in an isolated form into preparations, which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. Pharmaceutically acceptable excipients and carriers are generally known to those skilled in the art and are thus included in the instant invention. Such excipients and carriers are described, for example, in "Remington's Pharmaceutical Sciences" Mack Pub. Co., New Jersey (1991). The formulations of the invention can be designed to be short-acting, fast-releasing, long-acting, and sustained-releasing. Thus, the pharmaceutical formulations can also be formulated for controlled release or for slow release.

30 Pharmaceutical compositions suitable for use in the present invention include compositions wherein the active ingredients are contained in an amount sufficient to achieve the intended purpose, i.e., control or the treatment of disorders or diseases. More specifically, a therapeutically effective amount means an amount of compound or compound in an isolated form

35 Pharmaceutical compositions suitable for use in the present invention include compositions wherein the active ingredients are contained in an amount sufficient to achieve the intended purpose, i.e., control or the treatment of disorders or diseases. More specifically, a therapeutically effective amount means an amount of compound or compound in an isolated form

effective to prevent, alleviate or ameliorate symptoms/signs of disease or prolong the survival of the subject being treated.

The quantity of active component, which is the compound or compound in an isolated form of this invention, in the pharmaceutical composition and unit dosage form thereof, may be varied or adjusted widely depending upon the manner of administration, the potency of the particular compound or compound in an isolated form and the desired concentration. Determination of a therapeutically effective amount is well within the capability of those skilled in the art. Generally, the quantity of active component will range between 0.01% to 99% by weight of the composition.

Generally, a therapeutically effective amount of dosage of the active component will be in the range of about 0.01 to about 100 mg/kg of body weight/day, preferably about 0.1 to about 10 mg/kg of body weight/day, more preferably about 0.3 to 3 mg/kg of body weight/day, even more preferably about 0.3 to 1.5 mg/kg of body weight/day. It is to be understood that the dosages may vary depending upon the requirements of each subject and the severity of the disorders or diseases being treated.

The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example, as two, three, four or more sub-doses per day. The sub-dose itself may be further divided, *e.g.*, into a number of discrete loosely spaced administrations; such as multiple inhalations from an insufflator or by application of a plurality of drops into the eye.

Also, it is to be understood that the initial dosage administered may be increased beyond the above upper level in order to rapidly achieve the desired plasma concentration. On the other hand, the initial dosage may be smaller than the optimum and the daily dosage may be progressively increased during the course of treatment depending on the particular situation. If desired, the daily dose may also be divided into multiple doses for administration, *e.g.*, two to four times per day.

Compounds and compounds in an isolated form of the present invention may be administered in a pharmaceutically acceptable form either alone or in combination with one or more additional agents which modulate a mammalian immune system or with anti-inflammatory agents. These agents may include but are not limited to a 5-lipoxygenase activating protein (FLAP) antagonist; a leukotriene antagonist (LTRA) such as an antagonist of LTB₄, LTC₄, LTD₄, LTE₄, CysLT₁ or CysLT₂, *e.g.*, montelukast or zafirlukast; a histamine receptor antagonist, such as a histamine type 1 receptor antagonist or a histamine type 2 receptor antagonist, *e.g.*, loratidine, fexofenadine, desloratidine, levocetirizine, methapyrilene or cetirizine; an α -adrenoceptor agonist or an α 2-adrenoceptor agonist, *e.g.*, phenylephrine, methoxamine, oxymetazoline or methylnorephrine; a muscarinic M₃ receptor antagonist, *e.g.* tiotropium or ipratropium; a dual muscarinic M₃ receptor antagonist/ β 2 agonist; a PDE inhibitor, such as a PDE3 inhibitor, a PDE4 inhibitor or a PDE5 inhibitor, *e.g.*, theophylline, sildenafil, vardenafil,

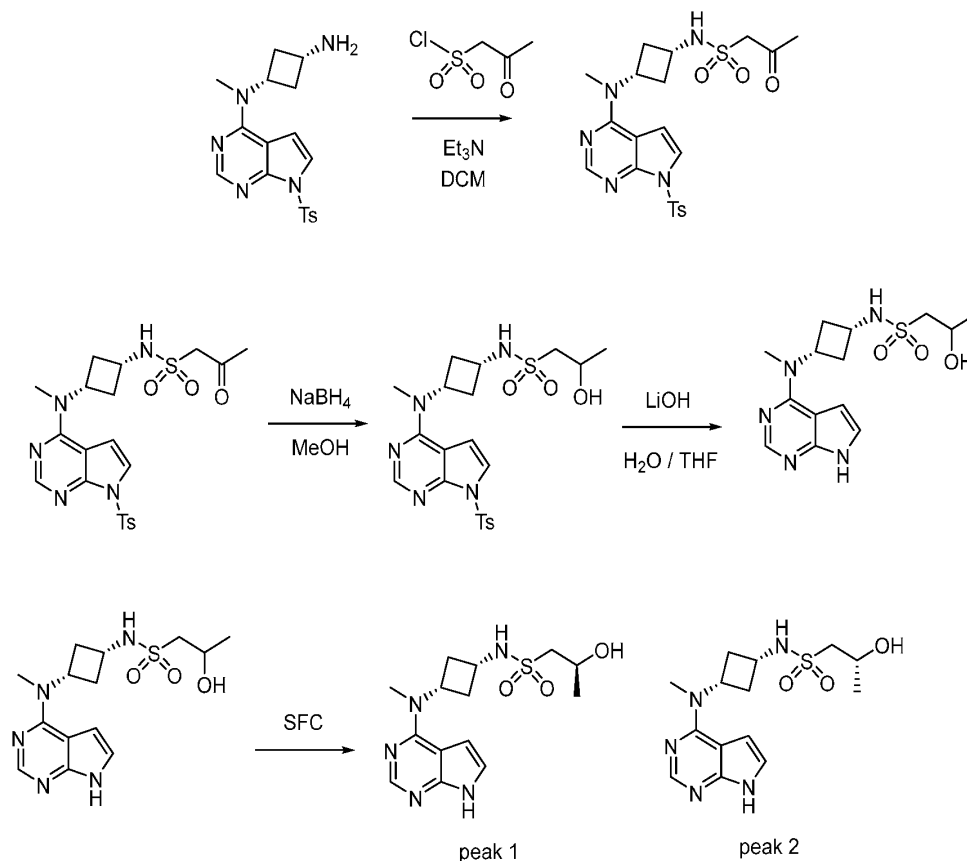
tadalafil, ibudilast, cilomilast or roflumilast; sodium cromoglycate or sodium nedocromil; a cyclooxygenase (COX) inhibitor, such as a non-selective inhibitor (e.g., aspirin or ibuprofen) or a selective inhibitor (e.g. celecoxib or valdecoxib); a glucocorticosteroid, e.g., fluticasone, mometasone, dexamethasone, prednisolone, budesonide, ciclesonide or beclamethasone; an anti-inflammatory monoclonal antibody, e.g., infliximab, adalimumab, tanezumab, ranibizumab, bevacizumab or mepolizumab; a $\beta 2$ agonist, e.g., salmeterol, albuterol, salbutamol, fenoterol or formoterol, particularly a long-acting $\beta 2$ agonist; an integrin antagonist, e.g., natalizumab; an adhesion molecule inhibitor, such as a VLA-4 antagonist; a kinin B1 or B2 receptor antagonist; an immunosuppressive agent, such as an inhibitor of the IgE pathway (e.g., omalizumab) or cyclosporine; a matrix metalloprotease (MMP) inhibitor, such as an inhibitor of MMP-9 or MMP-12; a tachykinin NK1, NK2 or NK3 receptor antagonist; a protease inhibitor, such as an inhibitor of elastase, chymase or cathepsin G; an adenosine A2a receptor agonist; an adenosine A2b receptor antagonist; a urokinase inhibitor; a dopamine receptor agonist (e.g., ropinirole), particularly a dopamine D2 receptor agonist (e.g., bromocriptine); a modulator of the NF κ B pathway, such as an IKK inhibitor; a further modulator of a cytokine signaling pathway such as an inhibitor of JAK kinase, syk kinase, p38 kinase, SPHK-1 kinase, Rho kinase, EGF-R or MK-2; a mucolytic, mucokinetic or anti-tussive agent; an antibiotic; an antiviral agent; a vaccine; a chemokine; an epithelial sodium channel (ENaC) blocker or Epithelial sodium channel (ENaC) inhibitor; a nucleotide receptor agonist, such as a P2Y2 agonist; a thromboxane inhibitor; niacin; a 5-lipoxygenase (5-LO) inhibitor, e.g., Zileuton; an adhesion factor, such as VLAM, ICAM or ELAM; a CRTH2 receptor (DP2) antagonist; a prostaglandin D2 receptor (DP1) antagonist; a haematopoietic prostaglandin D2 synthase (HPGDS) inhibitor; interferon- β ; a soluble human TNF receptor, e.g., Etanercept; a HDAC inhibitor; a phosphoinositide 3-kinase gamma (PI3K γ) inhibitor; a phosphoinositide 3-kinase delta (PI3K δ) inhibitor; a CXCR-1 or a CXCR-2 receptor antagonist; an IRAK-4 inhibitor; and, a TLR-4 or TLR-9 inhibitor, including the pharmaceutically acceptable salts of the specifically named compounds. The agents may be administered with another active agent, wherein the second active agent may be administered either orally or topically.

Suitable specific agents for use in combination therapy with a compound or compound in an isolated form of formula I, IA or IB, or a pharmaceutically acceptable salt thereof, sulfasalazine, mesalazine, prednisone, azathioprine, infliximab, adalimumab, belimumab, becertolizumab, natalizumab, vedolizumab, hydrocortisone, budesonide, cyclosporin, tacrolimus, fexofenadine, 6-mercaptopurine, methotrexate, ursodeoxycholic acid, obeticholic acid, anti-histamines, rifampin, prednisone, methotrexate, azathioprine, cyclophosphamide, hydroxychloroquine, mofetil, sodium mycophenolate, tacrolimus, leflunomide, chloroquine and quinacrine, thalidomide, rituxan, NSAIDs, solumedrol, depomedrol and dexamethasone.

Chemical Synthesis

The following schemes and written descriptions provide general details regarding the preparation of the compounds of the invention.

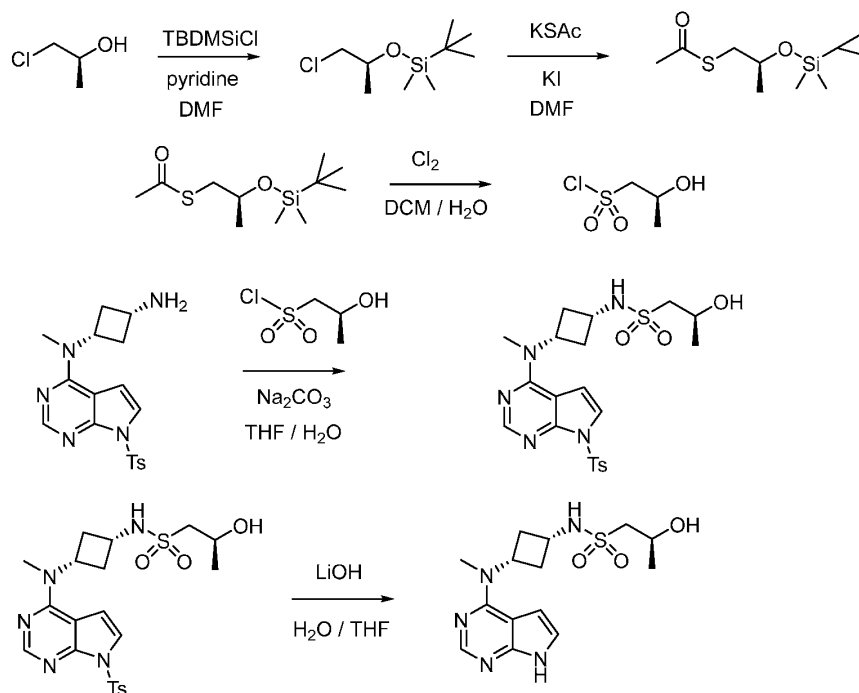
5

Scheme 1.

A synthetic route relating to both Example 1 and Example 2 is depicted in Scheme 1. The primary amine (*J. Med. Chem.* **2018**, 61(3), 1130-1152) is treated with 2-oxo-1-propanesulfonyl chloride (prepared in two steps from chloroacetone) in dichloromethane containing triethylamine. The resulting sulfonamide is then treated with sodium borohydride in methanol to reduce the ketone and afford an isomeric mixture of secondary alcohols. The tosyl protecting is then removed from the pyrrolopyrimidine ring. The secondary alcohols are then separated via SFC to afford the compound formed in Example 1 (peak 1) corresponding to compound **1A** and the compound formed in Example 2 (peak 2), under the conditions described.

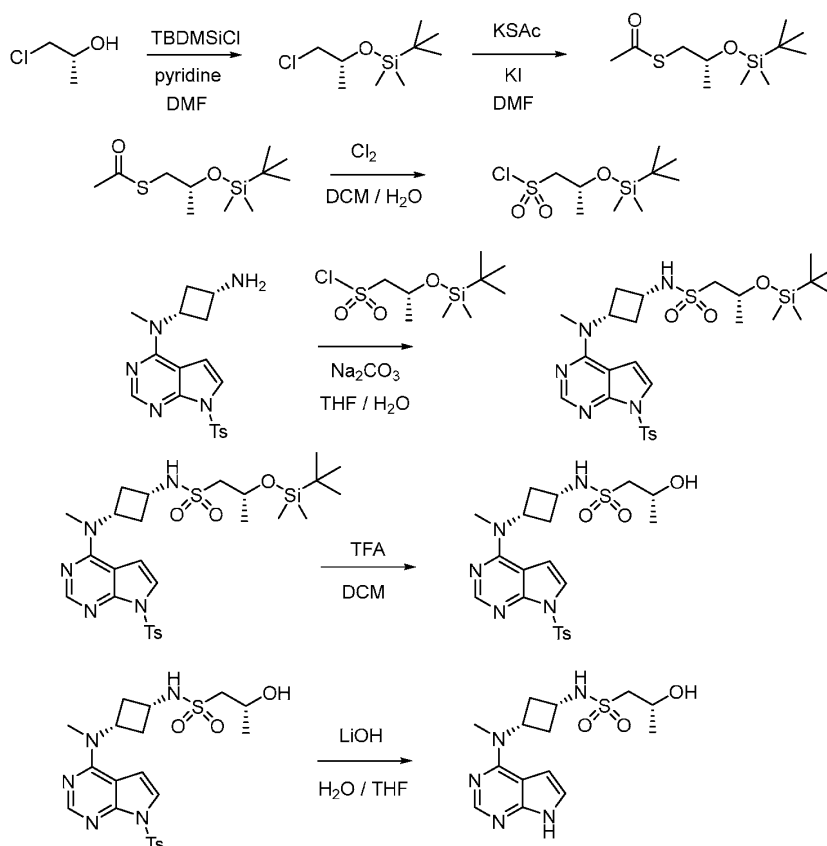
An alternative preparation of Example 1 is depicted in Scheme 2.

Scheme 2.



- (S)-1-Chloro-2-propanol is protected as a silyl ether using *tert*-butyldimethylsilyl chloride in dimethyl formamide as the solvent and pyridine as the base. The primary chloride is displaced with potassium thioacetate to give the thioester. The thioester is oxidized with chlorine gas to give the sulfonyl chloride. Under the reaction conditions, the silyl protecting group can be concomitantly removed. *cis*-N-Methyl-N-[(4-methylphenyl)sulfonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-ylcyclobutane-1,3-diamine is reacted with the sulfonyl chloride to afford the sulfonamide. The tosyl protecting group is then removed from the pyrrolopyrimidine using lithium hydroxide in a mixture of water and tetrahydrofuran to yield compound **1A** (Example 1) after SFC purification.

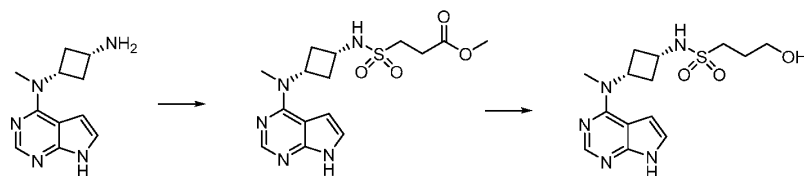
Scheme 3.



(*R*)-1-Chloro-2-propanol is protected as a silyl ether using *tert*-butyldimethylsilyl chloride in dimethyl formamide as the solvent and pyridine as the base. The primary chloride is displaced with potassium thioacetate to give the thioester. The thioester is oxidized with chlorine gas to give the sulfonyl chloride; some loss of the silyl protecting group is observed. *cis*-N-Methyl-N-{7-[(4-methylphenyl)sulfonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}cyclobutane-1,3-diamine is reacted with the sulfonyl chloride to afford the sulfonamide. The silyl protecting group is cleaved with trifluoroacetic acid to give the secondary alcohol. The tosyl protecting group is then removed from the pyrrolopyrimidine using lithium hydroxide in a mixture of water and tetrahydrofuran to yield the compound of Example 2 after SFC purification.

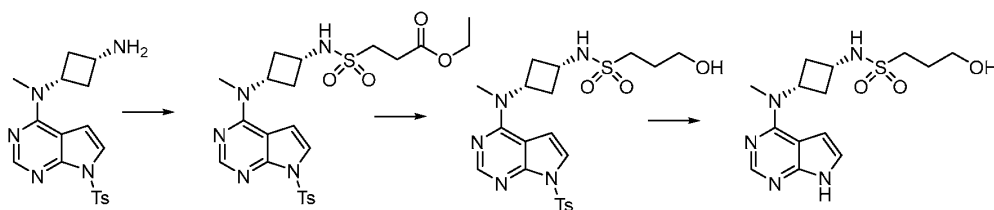
A preparation of the compound IB is depicted in Scheme 4, as set forth in Example 5. *cis*-N-Methyl-N-{7-[(4-methylphenyl)sulfonyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}cyclobutane-1,3-diamine is reacted with methyl 3-(chlorosulfonyl)propanoate to afford the sulfonamide. The sulfonamide was reduced with lithium aluminum hydride to afford 3-hydroxy-N-(*cis*-3-(methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)cyclobutyl)propane-1-sulfonamide (IB).

Scheme 4.



An alternative preparation of the compound IB is depicted in Scheme 5, as set forth in Example 6. *cis*-N-Methyl-N-{7-[(4-methylphenyl)sulfonyl]-7H-pyrrolo[2,3-d]-pyrimidin-4-yl}cyclobutane-1,3-diamine dihydrobromide was treated with a base such as triethylamine and ethyl 3-(chlorosulfonyl)propanoate to afford ethyl 3-(N-(*cis*-3-(methyl(7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)cyclobutyl)sulfamoyl)propanoate. The latter sulfamoylpropanoate was reduced with lithium aluminum hydride, and worked up to afford the crude product 3-hydroxy-N-(*cis*-3-(methyl(7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)cyclobutyl)propane-1-sulfonamide which was used directly without further purification. The latter sulfonamide was treated with base such as LiOH to give 3-hydroxy-N-(*cis*-3-(methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)cyclobutyl)propane-1-sulfonamide (IB).

Scheme 5.



In executing the synthesis of the compounds of the invention, one skilled in the art will recognize the need to sample and assay reaction mixtures prior to work up in order to monitor the progress of reactions and decide whether the reaction should be continued or whether it is ready to be worked up to obtain the desired product. Common methods for assaying reaction mixtures include thin-layer chromatography (TLC), liquid chromatography/mass spectroscopy (LCMS), and nuclear magnetic resonance (NMR).

One skilled in the art will also recognize that the compounds and compounds in an isolated form of the invention may be prepared as mixtures of diastereomers or geometric isomers (e.g., *cis* and *trans* substitution on a cycloalkane ring). These isomers can be separated by standard chromatographic techniques, such as normal phase chromatography on silica gel, reverse phase preparative high pressure liquid chromatography or supercritical fluid chromatography. One

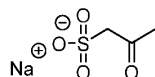
skilled in the art will also recognize that some compounds of the invention are chiral and thus may be prepared as racemic or scalemic mixtures of enantiomers. Several methods are available and are well known to those skilled in the art for the separation of enantiomers. A preferred method for the routine separation enantiomers is supercritical fluid chromatography employing a
5 chiral stationary phase.

EXPERIMENTAL SECTION

Except where otherwise noted, reactions were run under an atmosphere of nitrogen. Chromatography on silica gel was carried out using 250-400 mesh silica gel using pressurized
10 nitrogen (~10-15 psi) to drive solvent through the column ("flash chromatography"). Where indicated, solutions and reaction mixtures were concentrated by rotary evaporation under vacuum.

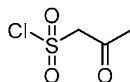
Preparations and Examples.

15 Preparation 1. 2-oxopropane-1-sulfonic acid, sodium salt



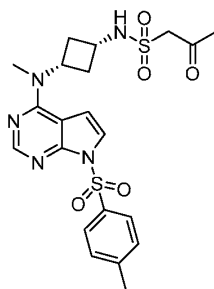
A mixture of chloroacetone (9.25 g, 100 mmol) and sodium sulphite (14.5 g, 115 mmol) in water (100 mL) was stirred for 24 h. The mixture was concentrated to dryness and the resulting solids suspended in methanol (300 mL). The mixture was sonicated for 3 minutes then filtered. The
20 cake was washed with methanol and the filtrates concentrated to give the title compound (15.5 g) which was used directly without further purification.

Preparation 2. 2-oxopropane-1-sulfonyl chloride



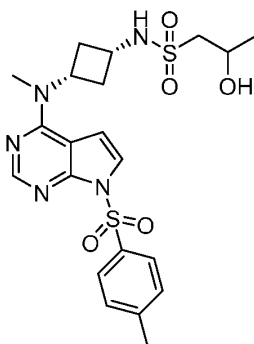
To a stirred suspension of 2-oxopropane-1-sulfonic acid sodium salt (15.5 g, 97 mmol) in dry
25 toluene (40 mL) was added phosphorus oxychloride (40 mL). The mixture was refluxed for 3 h then removed from heat and chilled to 20°C. The mixture was concentrated under reduced pressure and the residue treated with dichloromethane (100 mL). The mixture was filtered and the cake washed with dichloromethane (20 mL). The filtrate was concentrated to give the title compound (11.8 g). ¹H NMR (400 MHz, CDCl₃-d) δ 4.76 - 4.53 (m, 2H), 2.49 (s, 3H).

30 Preparation 3. *cis*-N-(3-(Methyl(7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)cyclobutyl)-2-oxopropane-1-sulfonamide



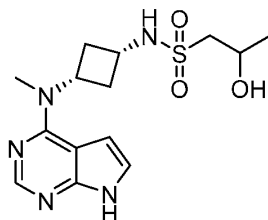
To a solution of *cis*-N¹-methyl-N¹-(7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)cyclobutane-1,3-diamine (2.4 g, 5.3 mmol) in dichloromethane (45 mL) was added triethylamine (2.68 g, 26.5 mmol). A solution of 2-oxopropane-1-sulfonyl chloride (1.24 g, 6.27 mmol) in dichloromethane (5 mL) was added at 0°C and the mixture was allowed to warm to 20°C and stirred for 3 h. The mixture was quenched with saturated ammonium chloride (30 mL). The layers were separated, and the aqueous layer was extracted twice with dichloromethane (2 x 10 mL). The combined organic layers were washed with brine, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified via flash chromatography using (petroleum ether:ethyl acetate, 1:2) to give the title compound (801 mg). LC/MS [M+H] = 491.9.

Preparation 4. 2-Hydroxy-N-(*cis*-3-(methyl(7-(4-methylbenzenesulfonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)cyclobutyl)propane-1-sulfonamide



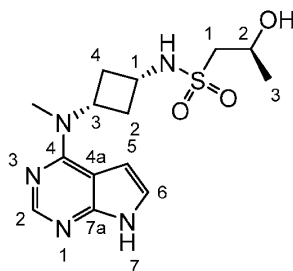
To a solution of N-(3-{methyl[7-(4-methylbenzenesulfonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}cyclobutyl)-2-oxopropane-1-sulfonamide (0.801 g, 1.62 mmol) in methanol (10 mL) was added sodium borohydride (123 mg, 2.26 mmol) in 10% sodium hydroxide (1.6 mL) and methanol (1.6 mL) at 0°C. The mixture was stirred for 30 minutes and then removed from the cooling bath and stirred at 20°C for 30 minutes. The methanol was removed under reduced pressure. The residue was dissolved in ethyl acetate (15 mL), washed with brine (10 mL), dried over sodium sulfate and concentrated under reduced pressure. The residue was purified via flash chromatography using 0-80% ethyl acetate in petroleum ether to give the title compound (0.76 g). LC/MS [M+H] = 494.2.

Preparation 5. 2-Hydroxy-N-(*cis*-3-(methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)cyclobutyl)propane-1-sulfonamide



- 5 To a mixture of 2-hydroxy-N-(*cis*-3-{methyl[7-(4-methylbenzene-1-sulfonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}cyclobutyl)propane-1-sulfonamide (1.13 g, 2.3 mmol) in tetrahydrofuran (10 mL) and water (10 mL) was added lithium hydroxide monohydrate (273 mg, 11.4 mmol) at 20°C for 24 h. The mixture was concentrated and purified via flash chromatography using 0-10% methanol in dichloromethane. The mixture was then dissolved in water/acetonitrile then
- 10 lyophilized. The residue was purified via prep thin layer chromatography (dichloromethane:methanol, 10:1). The residue was dissolved in water/acetonitrile and lyophilized. The residue was then purified via supercritical fluid chromatography (Chiralpak AD-H™ 250x30mm I.D., 5μ Mobile phase: 45% methanol (0.1%) NH₄OH) in CO₂, flow rate 50 mL/min, Temp 35°C, RT 3.53 and 4.07 min.) to give the title compound (552 mg, 71%). ¹H NMR (400 MHz, DMSO-d₆) δ 11.64 (br s, 1H), 8.11 (s, 1H), 7.44 (d, *J* = 9.0 Hz, 1H), 7.16 - 7.15 (m, 1H), 6.65 - 6.64 (m, 1H), 5.02 - 4.81 (m, 2H), 4.15 - 3.94 (m, 1H), 3.67 - 3.54 (m, 1H), 3.26 (s, 3H), 3.14 - 2.95 (m, 2H), 2.71 - 2.56 (m, 2H), 2.31 - 2.19 (m, 2H), 1.22 (d, *J* = 6.0 Hz, 3H), LC/MS [M+H] = 339.9.

- 20 **Example 1. (S)-2-Hydroxy-N-(*cis*-3-(methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)cyclobutyl)propane-1-sulfonamide (IA)**



- 2-hydroxy-N-{3-[methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]cyclobutyl}propane-1-sulfonamide (532 mg, 1.57 mmol) was purified via SFC ((Chiralpak AD-H™ 250x30mm I.D., 5μ Mobile phase: 45% ethanol (0.1%) NH₄OH) in CO₂, flow rate 50 mL/min, Temp 35°C, RT 3.44min.) to give the title compound (223.7 mg, 42%). ¹H NMR (400 MHz, DMSO-d₆) δ = 11.69 - 11.57 (m, 1H), 8.10 (s, 1H), 7.43 (d, *J* = 9.0 Hz, 1H), 7.16 - 7.12 (m, 1H), 6.67 - 6.61 (m, 1H), 4.92 (d, *J* = 5.0 Hz, 1H),

4.90 - 4.84 (m, 1H), 4.11 - 4.01 (m, 1H), 3.63 - 3.53 (m, 1H), 3.27 - 3.23 (m, 3H), 3.11 - 2.96 (m, 2H), 2.63 - 2.53 (m, 2H), 2.29 - 2.20 (m, 2H), 1.21 (d, $J = 6.0$ Hz, 3H), LC/MS $[M+H] = 340.2$. Crystalline material can be prepared from ethyl acetate.

5 Single Crystal X-Ray Structure

Data collection was performed on a Bruker D8 Quest diffractometer at room temperature. Data collection consisted of omega and phi scans. The structure was solved by intrinsic phasing using SHELX software suite in the Triclinic space group P1. The structure was subsequently refined by the full-matrix least squares method. All non-hydrogen atoms were found and refined using anisotropic displacement parameters.

The hydrogen atoms located on nitrogen and oxygen were found from the Fourier difference map and refined with distances restrained. The remaining hydrogen atoms were placed in calculated positions and were allowed to ride on their carrier atoms. The final refinement included isotropic displacement parameters for all hydrogen atoms. Analysis of the absolute structure using likelihood methods (Hooft 2008) was performed using PLATON (Spek 2010). Assuming the sample submitted is enantiopure, the results indicate that the absolute structure has been correctly assigned. The method calculates that the probability that the structure is correctly assigned is 100%. The Hooft parameter is reported as 0.104 with an Esd of (15) and the Parson's parameter is reported as 0.097 with an Esd of (16). Absolute configuration at C13_C27 for two identical molecules per Asymmetric Unit was confirmed as (-S)_(-S). The final R-index was 5.9%. A final difference Fourier revealed no missing or misplaced electron density. Pertinent crystal, data collection and refinement are summarized in Table 1. Atomic coordinates are listed in Table 2.

25

Software and References

SHELXTL, Version 5.1, Bruker AXS, 1997. **PLATON**, A.L. Spek, *J. Appl. Cryst.* 2003, 36, 7-13. **MERCURY**, C.F. Macrae, P.R. Edington, P. McCabe, E. Pidcock, G.P. Shields, R. Taylor, M. Towler and J. van de Streek, *J. Appl. Cryst.* 39, 453-457, 2006. **OLEX2**, Dolomanov, O.V.; Bourhis, L.J.; Gildea, R.J.; Howard, J.A.K.; Puschmann, H., (2009). *J. Appl. Cryst.*, 42, 339-341. R.W.W. Hooft et al. *J. Appl. Cryst.* (2008). 41. 96-103. H.D. Flack, *Acta Cryst.* 1983, A39, 867-881.

Table 1. Crystal data and structure refinement for **IA**

Crystallization Solvent:	Ethyl Acetate - Acetone
Empirical formula	C ₁₄ H ₂₁ N ₅ O ₃ S
Formula weight	339.42
Temperature	296(2) K

	Wavelength	1.54178 Å	
	Crystal system	Triclinic	
	Space group	P1	
5	Unit cell dimensions	a = 5.5384(2) Å α = 88.745(2)° b = 6.9183(2) Å β = 83.850(2)° c = 21.8043(7) Å γ = 79.656(2)°	
	Volume	817.15(5) Å ³	
	Z	2	
	Density (calculated)	1.379 Mg/m ³	
10	Absorption coefficient	1.963 mm ⁻¹	
	F(000)	360	
	Crystal size	0.140 x 0.120 x 0.020 mm ³	
	Theta range for data collection	4.078 to 72.163°	
	Index ranges	-6 ≤ h ≤ 5, -8 ≤ k ≤ 8, -26 ≤ l ≤ 26	
15	Reflections collected	11795	
	Independent reflections	4989 [R(int) = 0.0466]	
	Completeness to theta = 67.679°	98.4 %	
	Absorption correction	Empirical	
	Refinement method	Full-matrix least-squares on F ²	
20	Data / restraints / parameters	4989 / 9 / 437	
	Goodness-of-fit on F ²	1.100	
	Final R indices [I > 2σ(I)]	R1 = 0.0589, wR2 = 0.1557	
	R indices (all data)	R1 = 0.0610, wR2 = 0.1579	
	Absolute structure parameter	0.091(15)	
25	Extinction coefficient	n/a	
	Largest diff. peak and hole	0.339 and -0.483 e.Å ⁻³	

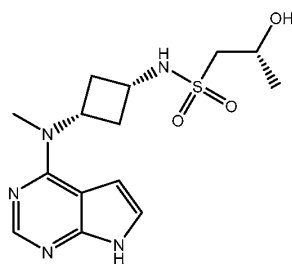
Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **IA**. $U(\text{eq})$ is defined as one third of the trace of the orthogonalized $U^{\#}$ tensor.

		x	y	z	U(eq)
5					
	S(1)	10411(2)	184(1)	1306(1)	44(1)
	S(2)	-172(2)	9984(1)	8832(1)	50(1)
	N(1)	2278(7)	3071(5)	4042(2)	46(1)
	N(2)	-1535(7)	3927(5)	4678(2)	46(1)
10	N(3)	-3541(8)	7256(6)	4570(2)	49(1)
	N(4)	3905(8)	5099(6)	3318(2)	49(1)
	N(5)	9233(9)	2050(6)	1714(2)	54(1)
	N(6)	8576(7)	7489(5)	6091(2)	46(1)
	N(7)	12380(7)	6612(5)	5446(2)	46(1)
15	N(8)	14370(8)	3292(6)	5560(2)	50(1)
	N(9)	6925(8)	5461(6)	6813(2)	49(1)
	N(10)	1745(10)	8319(6)	8458(2)	59(1)
	O(1)	11777(8)	841(6)	779(2)	63(1)
	O(2)	11703(8)	-1282(6)	1692(2)	62(1)
20	O(3)	9634(14)	-4205(6)	1264(3)	109(2)
	O(4)	-1217(8)	11398(6)	8398(2)	59(1)
	O(5)	-1797(10)	9021(7)	9231(2)	80(1)
	O(6)	1326(14)	14200(7)	8702(3)	105(2)
	C(1)	500(9)	2733(7)	4470(2)	48(1)
25	C(2)	-1643(8)	5753(6)	4425(2)	42(1)
	C(3)	91(8)	6360(6)	3992(2)	40(1)
	C(4)	-839(11)	8403(7)	3882(3)	56(1)
	C(5)	-2995(12)	8885(8)	4244(3)	62(1)
	C(6)	2119(8)	4884(6)	3778(2)	40(1)
30	C(7)	3866(13)	6954(10)	2995(3)	80(2)
	C(8)	5543(10)	3357(8)	3056(2)	55(1)
	C(9)	5176(11)	2533(10)	2439(3)	74(2)
	C(10)	7956(10)	1932(8)	2329(2)	54(1)
	C(11)	8219(10)	3427(11)	2796(3)	72(2)
35	C(12)	7928(10)	-831(7)	1061(3)	54(1)
	C(13)	8819(12)	-2883(7)	797(3)	63(1)
	C(14)	6800(19)	-3640(12)	526(4)	95(3)
	C(15)	10333(9)	7808(6)	5665(2)	47(1)

	C(16)	12468(8)	4801(6)	5706(2)	39(1)
	C(17)	10720(9)	4202(6)	6146(2)	41(1)
	C(18)	11687(11)	2153(7)	6259(3)	58(1)
	C(19)	13841(12)	1671(7)	5903(3)	63(1)
5	C(20)	8716(8)	5678(6)	6352(2)	40(1)
	C(21)	6983(15)	3596(9)	7127(3)	80(2)
	C(22)	5366(10)	7195(8)	7091(2)	55(1)
	C(23)	2676(10)	7212(9)	7330(2)	57(1)
	C(24)	2987(10)	8554(8)	7848(2)	54(1)
10	C(25)	5758(11)	7857(11)	7732(3)	77(2)
	C(26)	1395(12)	11250(8)	9315(2)	61(1)
	C(27)	2857(11)	12692(8)	8997(3)	63(1)
	C(28)	4098(16)	13634(13)	9462(4)	91(2)

15

Example 2. (*R*)-2-Hydroxy-N-(*cis*-3-(methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)cyclobutyl)propane-1-sulfonamide (IC)



2-hydroxy-N-{3-[methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]cyclobutyl}propane-1-sulfonamide
 20 (532 mg, 1.57 mmol) was purified via SFC ((Chiralpak AD-H™ 250x30mm I.D., 5μ Mobile phase: 45% ethanol (0.1%) NH₄OH) in CO₂, flow rate 50 mL/min, Temp 35°C, RT 3.88min.) to give the title compound (222.7 mg, 42%). ¹H NMR (400 MHz, DMSO-d₆) δ = 11.69 - 11.56 (m, 1H), 8.10 (s, 1H), 7.43 (d, *J* = 9.0 Hz, 1H), 7.18 - 7.11 (m, 1H), 6.66 - 6.60 (m, 1H), 4.96 - 4.84 (m, 2H), 4.12 - 3.99 (m, 1H), 3.66 - 3.54 (m, 1H), 3.24 (s, 3H), 3.12 - 2.94 (m, 2H), 2.64 - 2.56 (m, 2H),
 25 2.30 - 2.18 (m, 2H), 1.20 (d, *J* = 6.5 Hz, 3H), LC/MS [*M*+*H*] = 340.2. Crystalline material can be prepared from ethyl acetate.

Single Crystal X-Ray Structure

Data collection was performed on a Bruker D8 Quest diffractometer at room temperature. Data
 30 collection consisted of omega and phi scans. This lot gave plate like crystals stacked together, a crystal was separated and mounted for collection. The structure was solved by intrinsic phasing using SHELX software suite in the Triclinic class space group P1. The structure was

subsequently refined by the full-matrix least squares method. All non-hydrogen atoms were found and refined using anisotropic displacement parameters. The hydrogen atoms located on nitrogen and oxygen were found from the Fourier difference map and refined with distances restrained. The remaining hydrogen atoms were placed in calculated positions and were allowed to ride on their carrier atoms. The final refinement included isotropic displacement parameters for all hydrogen atoms. Analysis of the absolute structure using likelihood methods (Hooft 2008) was performed using PLATON (Spek 2010). Assuming the sample submitted is enantiopure, the results indicate that the absolute structure has been correctly assigned. The method calculates that the probability that the structure is correctly assigned is 100.0. The Hooft parameter is reported as 0.044 with an Esd of (18) and the Parson's parameter is reported as 0.050 with an Esd of (19). Absolute configuration at C13 and C27 for two identical molecules per asymmetric Unit was confirmed as (-R)₂(-R). Pseudo-symmetry to P-1. The final R-index was 4.5%. A final difference Fourier revealed no missing or misplaced electron density. Pertinent crystal, data collection and refinement are summarized in Table 3. Atomic coordinates are listed in Table 4.

15

Software and References

SHELXTL, Version 5.1, Bruker AXS, 1997. **PLATON**, A.L. Spek, *J. Appl. Cryst.* 2003, 36, 7-13. **MERCURY**, C.F. Macrae, P.R. Edington, P. McCabe, E. Pidcock, G.P. Shields, R. Taylor, M. Towler and J. van de Streek, *J. Appl. Cryst.* 39, 453-457, 2006. **OLEX2**, Dolomanov, O.V.; Bourhis, L.J.; Gildea, R.J.; Howard, J.A.K.; Puschmann, H., (2009). *J. Appl. Cryst.*, 42, 339-341. R.W.W. Hooft et al. *J. Appl. Cryst.* (2008). 41. 96-103. H.D. Flack, *Acta Cryst.* 1983, A39, 867-881.

Table 3. Crystal data and structure refinement for **IC**.

25	Crystallization Solvent	Ethyl Acetate / Acetone	
	Empirical formula	C ₁₄ H ₂₁ N ₅ O ₃ S	
	Formula weight	339.42	
	Temperature	296(2) K	
	Wavelength	1.54178 Å	
30	Crystal system	Triclinic	
	Space group	P1	
	Unit cell dimensions	a = 5.5384(2) Å	α = 88.745(2)°.
		b = 6.9183(2) Å	β = 83.850(2)°.
		c = 21.8043(7) Å	γ = 79.656(2)°.
35	Volume	817.15(5) Å ³	
	Z	2	
	Density (calculated)	1.379 Mg/m ³	
	Absorption coefficient	1.963 mm ⁻¹	

	F(000)	360
	Crystal size	0.140 x 0.120 x 0.020 mm ³
	Theta range for data collection	4.078 to 80.472°
	Index ranges	-5<=h<=6, -8<=k<=8, -27<=l<=27
5	Reflections collected	11873
	Independent reflections	5335 [R(int) = 0.0440]
	Completeness to theta = 67.679°	96.5 %
	Absorption correction	Empirical
	Refinement method	Full-matrix least-squares on F ²
10	Data / restraints / parameters	5335 / 9 / 437
	Goodness-of-fit on F ²	1.019
	Final R indices [I>2sigma(I)]	R1 = 0.0450, wR2 = 0.1085
	R indices (all data)	R1 = 0.0553, wR2 = 0.1161
	Absolute structure parameter	0.052(18)
15	Extinction coefficient	n/a
	Largest diff. peak and hole	0.331 and -0.263 e.Å ⁻³

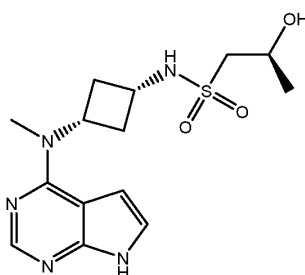
Table 4. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **IB**. $U(\text{eq})$ is defined as one third of the trace of the orthogonalized $U^{\#}$ tensor.

		x	y	z	U(eq)
5					
	S(1)	-424(2)	9823(1)	8694(1)	46(1)
	S(2)	10185(2)	11(1)	1169(1)	51(1)
	N(1)	7725(7)	6925(5)	5959(2)	47(1)
	N(2)	11519(7)	6066(5)	5323(2)	48(1)
10	N(3)	13535(7)	2746(6)	5433(2)	51(1)
	N(4)	6084(8)	4900(6)	6681(2)	52(1)
	N(5)	772(9)	7946(6)	8284(2)	56(1)
	N(6)	1429(7)	2512(5)	3909(2)	49(1)
	N(7)	-2370(7)	3389(5)	4553(2)	48(1)
15	N(8)	-4351(8)	6711(6)	4439(2)	53(1)
	N(9)	3079(8)	4538(6)	3189(2)	50(1)
	N(10)	8275(9)	1678(6)	1538(2)	60(1)
	O(1)	-1804(8)	9164(6)	9221(2)	64(1)
	O(2)	-1703(7)	11274(6)	8311(2)	64(1)
20	O(3)	358(12)	14213(6)	8737(3)	109(2)
	O(4)	11221(7)	-1412(6)	1605(2)	61(1)
	O(5)	11836(9)	976(7)	769(2)	82(1)
	O(6)	8669(12)	-4215(7)	1300(3)	102(2)
	C(1)	9497(9)	7251(7)	5530(2)	51(1)
25	C(2)	11653(8)	4257(6)	5572(2)	42(1)
	C(3)	9901(8)	3648(6)	6010(2)	43(1)
	C(4)	10849(10)	1597(7)	6121(2)	58(1)
	C(5)	13010(11)	1139(7)	5754(3)	63(1)
	C(6)	7881(8)	5125(6)	6218(2)	42(1)
30	C(7)	6126(13)	3052(10)	6998(3)	83(2)
	C(8)	4441(10)	6629(8)	6943(2)	59(1)
	C(9)	4822(11)	7443(10)	7560(3)	78(2)
	C(10)	2036(10)	8076(7)	7672(2)	54(1)
	C(11)	1787(10)	6576(11)	7200(3)	74(2)
35	C(12)	2049(10)	10828(7)	8938(2)	56(1)
	C(13)	1179(11)	12887(7)	9205(2)	64(1)
	C(14)	3201(16)	13652(11)	9476(3)	91(2)
	C(15)	-328(9)	2187(6)	4336(2)	50(1)

	C(16)	-2489(8)	5197(6)	4295(2)	42(1)
	C(17)	-735(8)	5804(6)	3855(2)	44(1)
	C(18)	-1668(10)	7834(7)	3739(3)	60(1)
	C(19)	-3824(11)	8328(7)	4100(3)	64(1)
5	C(20)	1289(8)	4314(6)	3650(2)	41(1)
	C(21)	3017(14)	6400(9)	2870(3)	81(2)
	C(22)	4650(9)	2801(7)	2908(2)	54(1)
	C(23)	7350(9)	2784(8)	2665(2)	58(1)
	C(24)	7023(9)	1446(7)	2151(2)	55(1)
10	C(25)	4269(11)	2146(11)	2263(3)	76(2)
	C(26)	8625(11)	-1251(8)	688(2)	63(1)
	C(27)	7162(10)	-2701(8)	1003(3)	64(1)
	C(28)	5897(14)	-3640(12)	540(4)	93(2)

15

Example 3 - Alternate Preparation for (S)-2-Hydroxy-N-(*cis*-3-(methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)cyclobutyl)propane-1-sulfonamide (IA)



Step 1. (S)-tert-Butyl((1-chloropropan-2-yl)oxy)dimethylsilane

- 20 To a solution of (S)-(+)-1-chloropropan-2-ol (1.0 g, 10.6 mmol) in N,N-dimethylformamide (20 mL) at 20 °C was added pyridine (1.0 g, 12.7 mmol) and *tert*-butyldimethylsilyl chloride (1.91 g, 12.7 mmol). After stirring for 20 °C, the reaction was diluted with water (40 mL). The resulting mixture was extracted with methyl *tert*-butyl ether (2 x 40 mL). The organic extracts were combined, washed with brine (50 mL), and dried (Na₂SO₄). The solvent was removed to give the title compound (2.2 g), which was used without further purification. ¹H NMR (400 MHz, CDCl₃) δ 3.96 (m, 1H), 3.42 (dd, *J* = 10.8, 5.9 Hz, 1H), 3.34 (dd, *J* = 10.7, 5.9 Hz, 1H), 1.23 (d, *J* = 6.1 Hz, 3H), 0.89 (s, 9H), 0.08 (d, *J* = 4.1 Hz, 6H).

Step 2. (S)-S-(2-((*tert*-Butyldimethylsilyl)oxy)propyl) ethanethioate

- 30 To a solution of (S)-tert-butyl((1-chloropropan-2-yl)oxy)dimethylsilane (2.2 g, 10.5 mmol) in N,N-dimethylformamide (20 mL) at 20 °C was added potassium thioacetate (2.41 g, 21.1 mmol) and potassium iodide (17.5 mg, 0.10 mmol). The reaction was warmed to 80 °C and stirred for 20

hours. The reaction was cooled to room temperature, diluted with water (50 mL) and the mixture extracted with methyl *tert*-butyl ether (40 mL x 2). The organic extracts were collected, washed with brine (60 mL), dried (Na₂SO₄) and the solvent removed to give the title compound (2.40g), which was used without purification. ¹H NMR (400 MHz, CDCl₃) δ 3.91 (m, 1H), 3.00 – 2.91 (m, 2H), 2.33 (s, 3H), 1.18 (d, *J* = 6.1 Hz, 3H), 0.89 (s, 9H), 0.07 (d, *J* = 6.8 Hz, 6H).

Step 3. (S)-2-Hydroxypropane-1-sulfonyl chloride

Cl_{2(g)} was passed through a solution of (S)-S-(2-((*tert*-butyldimethylsilyl)oxy)propyl) ethanethioate (0.5 g, 2.01 mmol) in dichloromethane (20 mL) and water (10 mL) at 0 °C for 5 min and the solution became yellow. The flow of Cl_{2(g)} was stopped and the reaction stirred at 0 °C for 0.5 hr. N_{2(g)} was then bubbled through the reaction to give a colorless solution. TLC indicated consumption of starting material and formation of a new spot. Water (20 mL) was added to the reaction mixture, which was then extracted with dichloromethane (40 mL). The organic extract was washed with 10% NaHCO₃ (50 mL), brine (50 mL) and dried (Na₂SO₄). The solvent was removed to afford the crude title compound (0.6 g) as a colorless oil, which was used in next step without purification.

Step 4. (S)-2-Hydroxy-N-(*cis*-3-(methyl(7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)cyclobutyl)propane-1-sulfonamide

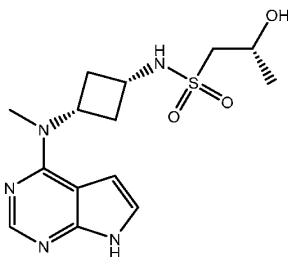
To a 40 mL vial was added *cis*-N¹-methyl-N¹-(7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)cyclobutane-1,3-diamine (200 mg, 0.375 mmol), Na₂CO₃ (199 mg 1.88 mmol), tetrahydrofuran (7 mL) and water (2.5 mL). After 2 min, a solution of Example 1, Step 3 (292 mg) in tetrahydrofuran (2 mL) was added. The resulting suspension was heated to 50 °C and stirred for 18 hrs. The reaction was cooled to room temperature and water (20 mL) was added. The resulting mixture was extracted with ethyl acetate (20 mL x 2). The organic extracts were collected, dried (Na₂SO₄) and the solvent removed to give crude material, which was purified by chromatography (silica, EtOAc/PetEther, 20-100%) to give the title compound (30 mg). LC/MS *m/z* (M+H)⁺ = 494.3.

Step 5. (S)-2-Hydroxy-N-(*cis*-3-(methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)cyclobutyl)propane-1-sulfonamide

To a solution of (S)-2-hydroxy-N-(*cis*-3-(methyl(7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)cyclobutyl)propane-1-sulfonamide (45 mg, 0.091 mmol) in tetrahydrofuran:water (5 mL:1 mL) at 15 °C was added lithium hydroxide monohydrate (23.0 mg, 0.547 mmol). The reaction was then warmed to 60 °C and stirred for 16 hrs. Water (10 mL) was added to the reaction and the resulting mixture extracted with ethyl acetate (15 mL x 4). The organic extracts were combined, dried (Na₂SO₄) and the solvent removed to give the crude material (30 mg), which was then purified by RP-HPLC (Phenomenex Gemini C-18™, 250 x 50 mm, 10μ,

H₂O/CH₃CN+0.05% NH₄OH, 15-35% over 10 min) to give title compound (16 mg). ¹H NMR (400 MHz, DMSO) δ 11.63 (s, 1H), 8.09 (s, 1H), 7.41 (s, 1H), 7.14 (d, *J* = 3.6 Hz, 1H), 6.62 (d, *J* = 3.6 Hz, 1H), 4.89 (ddd, *J* = 17.2, 7.9, 5.9 Hz, 2H), 4.04 (m, 1H), 3.58 (m, 1H), 3.24 (s, 3H), 3.14 – 2.86 (m, 2H), 2.62 – 2.51 (m, 2H), 2.23 (m, 2H), 1.20 (d, *J* = 6.2 Hz, 3H); LC/MS *m/z* (M+H)⁺ = 340.1.; Chiral SFC™ (Chiralpak AD-3™, 150 x 4.6mm, 3μ, 40% MeOH (0.05% DEA) in CO₂ isocratic 10 min, 2.5 mL/min, T = 35 °C) R_t = 5.54 min, 99% ee.

Example 4 - Alternate Preparation for (R)-2-Hydroxy-N-(*cis*-3-(methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)cyclobutyl)propane-1-sulfonamide (IC)



10

Step 1. (R)-tert-Butyl((1-chloropropan-2-yl)oxy)dimethylsilane

To a solution of (R)-(-)-1-chloropropan-2-ol (2.0 g, 21.2 mmol, CAS: 19141-39-0) in N,N-dimethylformamide (40 mL) at 20 °C was added pyridine (2.0 g, 25.4 mmol) and tert-butyldimethylsilyl chloride (3.83 g, 25.4 mmol). After stirring for 20 hrs, the reaction was diluted with water (60 mL) and the resulting mixture was extracted with methyl *tert*-butyl ether (2 x 80 mL). The organic extracts were collected, washed with brine (100 mL) and dried (Na₂SO₄). The solvent was removed to give the title compound (4.60 g), which was used without further purification. ¹H NMR (400 MHz, CDCl₃) δ 3.96 (m, 1H), 3.42 (dd, *J* = 10.8, 5.9 Hz, 1H), 3.34 (dd, *J* = 10.7, 5.9 Hz, 1H), 1.23 (d, *J* = 6.1 Hz, 3H), 0.89 (s, 9H), 0.08 (d, *J* = 4.1 Hz, 6H).

20

Step 2. (R)-S-(2-((tert-Butyldimethylsilyl)oxy)propyl) ethanethioate

To a solution (R)-tert-butyl((1-chloropropan-2-yl)oxy)dimethylsilane (4.60 g, 22.03 mmol) in N,N-dimethylformamide (40 mL) was added potassium thioacetate (5.03 g, 44.1 mmol) and potassium iodide (36.6 mg, 0.22 mmol). After 20 hrs at 80 °C, the reaction was cooled to room temperature, diluted with water (100 mL) and the resulting mixture extracted with methyl *tert*-butyl ether (100 mL x 2). The organic extracts were combined, dried (Na₂SO₄) and the solvent removed to give the title compound (5.0 g). ¹H NMR (400 MHz, CDCl₃) δ 3.90 (m, 1H), 3.00 – 2.91 (m, 2H), 2.33 (s, 3H), 1.18 (d, *J* = 6.1 Hz, 3H), 0.88 (s, 9H), 0.06 (d, *J* = 6.7 Hz, 6H).

30

Step 3. (R)-2-((tert-Butyldimethylsilyl)oxy)propane-1-sulfonyl chloride

Cl_{2(g)} was passed through a solution of (R)-S-(2-((tert-butyldimethylsilyl)oxy)propyl) ethanethioate (0.5 g, 2.01 mmol) in dichloromethane (20 mL) and water (10.0 mL) at 0 °C for 5 min and the

- solution became yellow. The flow of $\text{Cl}_{2(g)}$ was stopped and the reaction stirred at 0 °C for 0.5 hr. N_2 was then bubbled through the reaction to give a colorless solution. TLC indicated consumption of starting material and formation of a new spot. Water (20 mL) was added to the reaction mixture, which was then extracted with dichloromethane (40 mL). The organic extract was washed with
- 5 10% NaHCO_3 (50 mL), brine (50 mL) and dried (Na_2SO_4). The solvent was removed to afford the title compound (0.4 g) as a colorless oil, which was used in next step without purification.

- Step 4. (*R*)-2-((tert-Butyldimethylsilyl)oxy)-N-((1*s*,3*S*)-3-(methyl(7-tosyl-7H-pyrrolo[2,3-
d]pyrimidin-4-yl)amino)cyclobutyl)propane-1-sulfonamide
- 10 To a 40 mL vial was added *cis*-N¹-methyl-N¹-(7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)cyclobutane-1,3-diamine (150 mg, 0.281 mmol), Na_2CO_3 (149 mg 1.41 mmol), tetrahydrofuran (5 mL) and water (2.0 mL). After 2 min, a solution of Example 2, step 3 (292 mg, 0.75 mmol) in THF (2 mL) was added. The resulting suspension was heated to 50 °C and stirred for 20 hrs. The reaction was cooled to rt and water (20 mL) was added. The resulting mixture was extracted
- 15 with EtOAc (20 mL x 2). The organic extracts were collected, dried (Na_2SO_4) and the solvent removed to give crude material, which was purified by chromatography (silica, EtOAc/PetEther, 20-100%) to give the title compound (60 mg) and material lacking TBS group (20 mg). LC/MS m/z ($\text{M}+\text{H}$)⁺ = 608.3 (pk 1); LC/MS m/z ($\text{M}+\text{H}$)⁺ = 494.3 (pk 2).

- 20 Step 5. (*R*)-2-Hydroxy-N-(*cis*-3-(methyl(7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)cyclobutyl)propane-1-sulfonamide
- To a solution of (*R*)-2-((tert-butyldimethylsilyl)oxy)-N-(*cis*-3-(methyl(7-tosyl-7H-pyrrolo[2,3-
d]pyrimidin-4-yl)amino)cyclobutyl)propane-1-sulfonamide (60 mg, 0.099 mmol) in dichloromethane (5 mL) at 0 °C was added trifluoroacetic acid (1.5 mL). After 16 hrs at 15 °C,
- 25 the solvent was removed, and the residue dissolved in ethyl acetate (15 mL). The mixture was washed with saturated $\text{NaHCO}_3(\text{aq})$, dried (Na_2SO_4) and the solvent removed to give the title compound (50 mg), which was used in next step without purification. LC/MS m/z ($\text{M}+\text{H}$)⁺ = 494.3.

- Step 6. (*R*)-2-Hydroxy-N-(*cis*-3-(methyl(7H-pyrrolo[2,3-d]pyrimidin-4-
yl)amino)cyclobutyl)propane-1-sulfonamide
- 30 To a solution of (*R*)-2-hydroxy-N-(*cis*-3-(methyl(7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)cyclobutyl)propane-1-sulfonamide (50 mg, 0.10 mmol) in tetrahydrofuran:water (5 mL:1 mL) at 15 °C was added lithium hydroxide monohydrate (42.5 mg, 1.01 mmol). After 16 hrs at 65 °C, water (10 mL) was added and the mixture extracted with ethyl acetate (4 x 10 mL). The
- 35 organic extracts were combined, dried (Na_2SO_4) and the solvent removed to give crude material, which was purified by prep-HPLC (Phenomenex Gemini C-18™, 250 x 50 mm, 10μ, $\text{H}_2\text{O}/\text{CH}_3\text{CN}+0.05\% \text{NH}_4\text{OH}$, 15-35% over 10 min) to give title compound (18 mg). ¹H NMR (400 MHz, DMSO) δ 11.63 (s, 1H), 8.10 (s, 1H), 7.43 (d, *J* = 9.1 Hz, 1H), 7.15 (dd, *J* = 3.6, 2.4 Hz,

1H), 6.64 (dd, $J = 3.6, 1.9$ Hz, 1H), 4.97 – 4.83 (m, 2H), 4.12 – 3.98 (m, 1H), 3.59 (m, 1H), 3.25 (s, 3H), 3.13 – 2.92 (m, 2H), 2.58 (m, 2H), 2.24 (m, 2H), 1.21 (d, $J = 6.2$ Hz, 3H).; LC/MS m/z (M+H)⁺ = 340.0.; Chiral SFC (Chiralpak AD-3™, 150 x 4.6mm, 3μ, 40% MeOH (0.05% DEA) in CO₂ isocratic 10 min, 2.5 mL/min, T = 35 °C) R_t = 6.75 min, 99% ee.

5

Example 5 -- 3-Hydroxy-N-(cis-3-(methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)cyclobutyl)propane-1-sulfonamide (IB)

To a stirred mixture of cis-N-Methyl-N-7H-pyrrolo[2,3-d]pyrimidin-4-ylcyclobutane-1,3- diamine (190 mg) and potassium carbonate (240 mg) in solvent mixture of 1:1 tetrahydrofuran:water (5 mL each) at 10 °C was added methyl 3-(chlorosulfonyl)propanoate (250 mg). The mixture was warmed to room temperature and stirred for 10 min. The mixture was concentrated in vacuo. The residue was purified by column chromatography (MeOH/DCM 1:20) to afford methyl 3-(N-(cis-3-(methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)cyclobutyl)sulfamoyl)propanoate (140 mg) as a white solid. ¹H NMR (400 MHz, Methanol-*d*₄): 8.13 (s, 1H), 7.13 (d, 1H), 6.70 (d, 1H), 4.89 (m, 1H), 3.73 (s, 3H), 3.69 (m, 1H), 3.4 (m, 5H), 2.82 (m, 4H), 2.34 (m, 2H). MS m/z for C₁₅H₂₁N₅O₄S: 390.2 (M+Na)⁺. HPLC: Ultimate XB-C18 3pm 3.0*50mm column, retention time: 2.13 min, mobile phase: 0% acetonitrile (0.1% TFA) in water to 60% acetonitrile (0.1% TFA) in water, wavelength: 220 nm.

To a stirred solution of methyl 3-(N-(cis-3-(methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)cyclobutyl)sulfamoyl)propanoate (120 mg) in dry tetrahydrofuran (5 mL) was added lithium aluminum hydride (50 mg) at 0 °C under nitrogen. The reaction mixture was warmed to room temperature and was stirred for 0.5 hours. The mixture was quenched by the careful addition of methanol and purified directly by column chromatography (MeOH/DCM 1:10) to afford 3-hydroxy-N-(cis-3-(methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)cyclobutyl)propane-1-sulfonamide (50 mg) as a white solid. ¹H NMR (400 MHz, Methanol-*d*₄): 8.12 (s, 1H), 7.13 (d, 1H), 6.70 (d, 1H), 4.89 (m, 1H), 3.73 (m, 3H), 3.36 (s, 3H), 3.15 (m, 2H), 2.81 (m, 2H), 2.35 (m, 2H), 2.03 (m, 2H); MS m/z for C₁₄H₂₁N₅O₃S: 340.2 (M+H)⁺; HPLC: Ultimate XB-C18 3pm 3.0*50mm column, retention time: 1.85 min, mobile phase: 0% acetonitrile (0.1% TFA) in water to 60% acetonitrile (0.1% TFA) in water, wavelength: 220 nm.

30

Example 6 -- Alternative Preparation of 3-Hydroxy-N-(cis-3-(methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)cyclobutyl)propane-1-sulfonamide

To a mixture of cis-N-methyl-N-{7-[(4-methylphenyl)sulfonyl]-7H-pyrrolo[2,3-d]-pyrimidin-4-yl}cyclobutane-1,3-diamine dihydrobromide (988 mg) in 50 mL dichloromethane was added triethylamine (562 mg) and ethyl 3-(chlorosulfonyl)propanoate (743 mg) at 0°C. The reaction mixture was warmed to 25°C and stirred for 2h. The reaction mixture was evaporated in vacuo and purified by silica gel chromatography (Biotage, 20 g silicon column, petroleum ether:ethyl acetate 1:0 to 0:1, ethyl acetate:methanol 20:1) to afford ethyl 3-(N-(cis-3-(methyl(7-tosyl-7H-

pyrrolo[2,3-d]pyrimidin-4-yl)amino)cyclobutyl)sulfamoyl)propanoate. LCMS m/z for $C_{23}H_{29}N_5O_6S_2$: 535.9 (M+H)+.

- To a solution of ethyl 3-(N-(cis-3-(methyl(7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)cyclobutyl)sulfamoyl)propanoate (700 mg) in 50 mL tetrahydrofuran was added lithium aluminum hydride (74.4 mg) at 0 °C. The reaction mixture was allowed to warm to 25 °C for 15h. The reaction mixture was carefully quenched with 1 mL water, then filtered. The filtrate was evaporated in vacuo to afford the crude product 3-hydroxy-N-(cis-3-(methyl(7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)cyclobutyl)propane-1-sulfonamide which was used directly without further purification. LCMS m/z for $C_{21}H_{27}N_5O_5S_2$: 494.0 (M+H)+.
- To a solution of 3-hydroxy-N-(cis-3-(methyl(7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)cyclobutyl)propane-1-sulfonamide (400 mg) in 20 mL ethanol and 10 mL water was added LiOH (97 mg) at 25 °C. The reaction mixture was heated 90 °C and stirred for 2 h. The reaction mixture was cooled and evaporated in vacuo to afford the crude product which was purified by prep-HPLC to give 181 mg of 3-hydroxy-N-(cis-3-(methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)cyclobutyl)propane-1-sulfonamide as a white solid. HPLC conditions: column: DuraShell™ 150*25mm*5um, water (0.05% ammonia hydroxide v/v)-acetonitrile, 1-41%B, gradient 10 min, hold time 1 min 100%B, flow rate 25mL/min; 1H NMR (400 MHz, DMSO- d_6): 11.6 (s, 1H), 8.11 (s, 1H), 7.53 (s, 1H), 7.15 (d, 1H), 6.65 (d, 1H), 4.89 (m, 1H), 4.68 (s, 1H), 3.58 (m, 1H), 3.49 (m, 2H), 3.26 (s, 3H), 3.0 (m, 2H), 2.58 (m, 2H), 2.24 (m, 2H), 1.81 (m, 2H).

Biological Evaluation

JAK Caliper Enzyme Assay at 1mM ATP

- Test article was solubilized in dimethyl sulfoxide (DMSO) to a stock concentration of 30 mM. An 11-point half log dilution series was created in DMSO with a top concentration of 600 μ M. The test compound plate also contained positive control wells containing a known inhibitor to define 100% inhibition and negative control wells containing DMSO to define no inhibition. The compound plates were diluted 1 to 60 resulting in a top final assay compound concentration of 10 μ M and a 2% DMSO concentration. Test article and assay controls were added to a 384-well plate. Reaction mixtures contained 20 mM HEPES, pH 7.4, 10 mM magnesium chloride, 0.01% bovine serum albumin (BSA), 0.0005% Tween 20, 1 mM ATP and 1 μ M peptide substrate. The JAK1 and TYK2 assays contained 1 μ M of the IRStide peptide (5FAM-KKSRGDYMTMQID) and the JAK2 and JAK3 assays contained 1 μ M of the JAKtide peptide (FITC-KGGEEEEYFELVKK). The assays were initiated by the addition of 20 nM JAK1, 1 nM JAK2, 1 nM JAK3 or 1 nM TYK2 enzyme and were incubated at room temperature for three hours for JAK1, 60 minutes for JAK2, 75 minutes for JAK3 or 135 minutes for TYK2. Enzyme concentrations and incubation times were optimized for each new enzyme preps and were modified slightly over time to ensure 20%-30% phosphorylation. The assays were stopped with a final concentration of 10 mM EDTA, 0.1% Coating Reagent and 100 mM HEPES, pH=7.4. The assay plates were placed on a Caliper Life

Science Lab Chip 3000 (LC3000) instrument, and each well was sampled using appropriate separation conditions to measure the unphosphorylated and phosphorylated peptide. Data are shown in Table 5.

5

Table 5. JAK Caliper Enzyme Assay at 1mM ATP.

Kinase	IC ₅₀ nM			
	Abrocitinib	IA (M2)	IB (M1)	IC (M3)
	1 mM ATP	1 mM ATP	1 mM ATP	1 mM ATP
JAK1	29.2	17.9	43.4	56.7
JAK2	803	886	1140	2280
JAK3	>10,000	>10,000	>10,000	>10000
TYK2	1250	1210	3190	3420 ¹⁵

Cellular Potency Assays: Cytokine-induced Phosphorylation of STATs in Human Whole Blood, Human Keratinocytes and IFN γ -primed THP-1 cells

- 20 Human whole blood was collected from healthy donors via vein puncture into Vacutainer collection tubes containing sodium heparin in accordance with Pfizer protocols (Protocol No. GOHW RDP-01) approved by the Shulman Institutional Review Board. Blood was warmed to 37°C prior to use. Human whole blood was aliquoted (90 μ L/well) in 96-well, deep-well, V-bottom plates and treated with compounds (5 μ L/well) at different concentrations up to 60 μ M (0.2% DMSO final) at 37°C for 60 minutes. This was followed by a challenge with IFN α (5000 U/mL), IFN γ (100 ng/mL), IL-6 (50 ng/mL), IL-10 (30 ng/mL), IL-12 (30 ng/mL), IL-15 (30 ng/mL), IL-21 (50 ng/mL), IL-23 (25 ng/mL), IL-27 (1000 ng/mL), EPO (2U/mL), TSLP (50 ng/mL) or PBS and incubated for 15 minutes. Anti-cell surface antibodies were added 15 minutes prior to cytokine stimulation; anti-CD3-BV421 (0.5 μ L/well) to IL-6-treated and TSLP-treated samples and anti-CD14-BV421 (0.5 μ L/well) to IFN γ -treated samples. Samples were treated with warm 1x Lyse/Fix buffer (700 μ L/well) to terminate activation and further incubated at 37°C for 20 minutes to lyse red blood cells. Plates were centrifuged at 300x g for 5 minutes, supernatant was aspirated, and cells were washed with 800 μ L/well of staining buffer (D-PBS containing 0.1% FBS and 0.01% sodium azide). Washed cell pellets were resuspended in 350 μ L/well of prechilled 90% methanol and incubated at 4°C for 30 minutes. After the removal of 90% methanol, cells were washed once with staining buffer. All samples were finally suspended in 150 μ L/well of the desired anti-phospho-STAT antibodies at 1:150 dilution in staining buffer; anti-pSTAT1-AF647 in IFN γ treated samples; anti-pSTAT1-AF488 and anti-pSTAT3-AF647 in IL-6-treated samples, anti-pSTAT3-

AF647 in IFN α , IL-10, IL-21, IL-23 and IL-27 treated samples, anti-pSTAT4-AF647 in IL-12 treated samples, anti-pSTAT5-AF-647 in EPO, IL-15 and TSLP-treated samples.

Human primary keratinocytes were cultured in DermaLife™ medium with supplement kit to expand cell population. Cell passages 2 to 5 were used in the assays. Cells were harvested at
5 ~80% confluence, suspended in warm DermaLife™ medium, aliquoted (90 μ L/well) in 96-well, deep-well, V-bottom plates, and incubated at 37°C for 30 minutes. Cells were then treated with compounds (0.0003 to 20 μ M) for 60 minutes and followed by stimulation with IL-4 (2 ng/mL) or IL-13 (20 ng/mL) at 37°C for 15 minutes. For the IL-22 induced pSTAT3 assay, keratinocytes were seeded in 24-well plates and cultured for 18 hours. Cells were switched to DermaLife™
10 basal medium, treated with compounds (0.0003 to 20 μ M) for 60 minutes, and then stimulated with IL-22 (100 ng/mL) for 30 minutes. Cells were detached by the treatment of 0.25% trypsin/EDTA. Stimulated keratinocytes were fixed by 2% paraformaldehyde and permeabilized by 90% methanol. Fixed and permeabilized cells were stained with AlexaFluor647™ labeled anti-pSTAT6 antibody (1 to 150 dilution) for IL-4 and IL-13-treated samples and AlexaFluor647 labeled
15 anti-pSTAT3 (1 to 150 dilution) for IL-22 treated samples.

THP-1 cells were maintained in RPMI 1640 medium containing 10% FBS, 50 μ M 2 mercaptoethanol, 50 U/mL penicillin, 50 μ g/mL streptomycin and 2 mM L-glutamine. THP 1 cells were treated with IFN γ (20 ng/mL) for 18 hours. IFN γ primed THP-1 cells were resuspended in fresh RPMI 1640 medium, treated with compounds (0.0003 to 20 μ M) for 60 minutes, followed by
20 stimulation with IL-31(1 μ g/mL) for additional 10 minutes. Cells were then fixed by 2% paraformaldehyde and permeabilized by 90% methanol. Fixed and permeabilized cells were stained with AlexaFluor647™ labeled anti-pSTAT3 antibody (1 to 150 dilution).

After overnight incubation at 4°C, anti-pSTAT stained samples were transferred into 96-well polypropylene U-bottom plates and flow cytometric analysis was performed on a LSR Fortessa™
25 equipped with a HTS plate loader. For human whole blood samples, lymphocyte population was gated for pSTAT histogram analysis for IFN α , IL-10, IL-12, IL-15, IL-21, IL-23, and IL-27-treated samples; CD14⁺ cells for IFN γ -treated samples; CD3⁺ cells for IL-6 and TSLP-treated samples; all events (entire populations) for EPO-treated samples. Entire populations of keratinocytes and THP-1 cells were gated for the IL-4, IL-13, IL-22 and IL-31 assays. Background fluorescence
30 was defined using unstimulated cells and a gate was placed at the foot of the peak to include ~0.5% gated population. Histogram statistical analysis was performed using FACSDiva version 8.0. Relative fluorescence unit, which measures the level of pSTAT, was calculated by multiplying the percent positive population and its mean fluorescence. Inhibition curves and half maximal inhibitory concentration (IC₅₀) values were determined using Prism™ software (Version
35 8) or the Activity Base data analysis software (ID Business Solutions).

Cellular Potency Against Cytokine-induced Phosphorylation of STATs

Compounds of formula **IA** and **IB**, prepared in accord with Examples 1 and 3 and Examples 5 and 6, respectively, are formed *in vivo* in human metabolism upon ingestion of abrocitinib, and demonstrate activity similar to abrocitinib, a potent JAK1 inhibitor, against IL-4, IL-13, IL-22, IL 31 and TSLP induced phosphorylation of STATs in human keratinocytes, interferon- γ primed THP-1 cells or human whole blood. Gooderham M.J., *et al.*, *JAMA Dermatology*, 155(12), 1371-1379 (October 2019). Notably, like abrocitinib, these compounds are all more potent against cytokines which transduce their signals via JAK1-dependent pathways versus those which transduce their signals via JAK1-independent pathways, and therefore likely contribute to the pharmacological activity mainly via effects on JAK1. A comparison of the cellular potency for abrocitinib and the compounds of formula **IA** and **IB** across similar signaling pathways is shown in Table 6.

Table 6. Cellular potency (IC₅₀, nM) of Compounds **IA**, **IB** and **IC**: STAT phosphorylation in IL-4, IL-13, IL-22, IL-31 and TSLP treated keratinocytes, IFN γ primed THP-1 cells or whole blood.

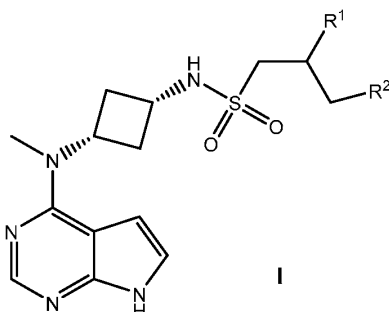
		Abrocitinib	IA (M2)	IB (M1)	IC (M3)
IFN γ induced pSTAT1	JAK1/JAK2	1690	2160	1950	4250
IL-4 induced pSTAT6	JAK1/JAK2	77.0	134	433	
IL-6 induced pSTAT1	JAK1/JAK2	343	136	171	333
IL-13 induced pSTAT6	JAK1/JAK2	81.9	84.1	236	
IL-27 induced pSTAT3	JAK1/JAK2	228	234	382	572
IL-31 induced pSTAT3	JAK1/JAK2	40.0	56.0	79.6	
TSLP induced pSTAT5	JAK1/JAK2	1020	271	785	
IL-15 induced pSTAT5	JAK1/JAK3	537	353	558	800
IL-21 induced pSTAT3	JAK1/JAK3	516	487	844	1050

IL-22 induced pSTAT3	JAK1/TYK2	420	198	703	
IL-10 induced pSTAT3	JAK1/TYK2	3700	233	675	488
IFN α induced pSTAT3	JAK1/TYK2	174	90.5	296	225
EPO induced pSTAT5	JAK2/JAK2	7180	9470	9750	18100
IL-23 induced pSTAT3	JAK2/TYK2	>16500	6210	26200	13800

CLAIMS

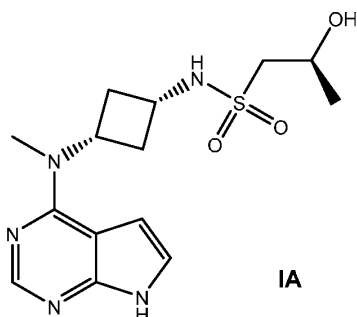
What is claimed is:

1. A compound of formula **I** having the structure:



- 5 or a pharmaceutically acceptable salt, wherein R¹ and R² are each independently hydrogen or hydroxy; wherein if R¹ is hydrogen, then R² is hydroxy; and, wherein if R² is hydrogen, then R¹ is hydroxy.

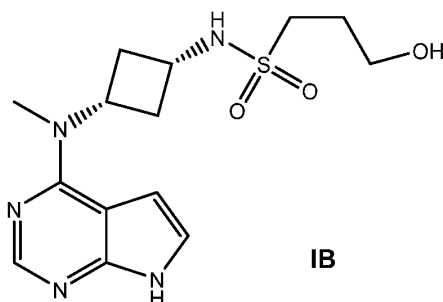
2. A compound of formula **IA** having the structure:



10

or a pharmaceutically acceptable salt thereof.

3. A compound of formula **IB** having the structure:



15

or a pharmaceutically acceptable salt thereof.

4. (S)-2-Hydroxy-N-(3-(methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)cyclobutyl)propane-1-sulfonamide or a pharmaceutically acceptable salt thereof.
5. 3-Hydroxy-N-(3-(methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)cyclobutyl)propane-1-sulfonamide or a pharmaceutically acceptable salt thereof.
6. The compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 5 in an isolated form.
7. A pharmaceutical composition comprising a compound of claims 1 to 6, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.
8. A method of treating or preventing a disease or condition selected from inflammation, autoimmune disease, neuroinflammation, arthritis, rheumatoid arthritis, spondyloarthropathies, systemic lupus erythematosus, lupus nephritis, osteoarthritis, gouty arthritis, pain, fever, pulmonary sarcoidosis, silicosis, cardiovascular disease, atherosclerosis, myocardial infarction, thrombosis, congestive heart failure and cardiac reperfusion injury, cardiomyopathy, stroke, ischemia, reperfusion injury, brain edema, brain trauma, neurodegeneration, liver disease, inflammatory bowel disease, Crohn's disease, ulcerative colitis, nephritis, retinitis, retinopathy, macular degeneration, glaucoma, diabetes (type 1 and type 2), diabetic neuropathy, viral and bacterial infection, myalgia, endotoxic shock, toxic shock syndrome, osteoporosis, multiple sclerosis, endometriosis, menstrual cramps, vaginitis, candidiasis, cancer, fibrosis, obesity, muscular dystrophy, polymyositis, dermatomyositis, autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, vitiligo, Alzheimer's disease, skin flushing, eczema, psoriasis, atopic dermatitis, sunburn, keloid, hypertrophic scar, rheumatic diseases, urticaria, discoid lupus, cutaneous lupus, central nervous system lupus, psoriatic arthritis, asthma, allergic asthma, type I interferonopathies including Aicardi-Goutières syndrome and other mendelian diseases of overexpression of type I interferon, primary progressive multiple sclerosis, relapsing remitting multiple sclerosis, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, scleroderma, alopecia areata, scarring alopecia, prurigo, prurigo nodularis, CPUO, lichen diseases, lichen planus, Steven's Johnson's syndrome, spondylopathy, myositis, vasculitis, pemphigus, lupus, major depression disorder, allergy, dry eye syndrome, transplant rejection, cancer, septic shock, cardiopulmonary dysfunction, acute respiratory disease, ankylosing spondylitis, cachexia, chronic graft-versus-host disease, acute graft-versus-host disease, Celiac Sprue, idiopathic thrombocytopenic thrombotic purpura, thrombotic thrombocytopenic purpura, myasthenia gravis, Sjogren's syndrome, epidermal hyperplasia, cartilage inflammation, bone degradation, juvenile arthritis, juvenile rheumatoid arthritis, pauciarticular juvenile rheumatoid arthritis, polyarticular juvenile rheumatoid arthritis,

systemic onset juvenile rheumatoid arthritis, juvenile ankylosing spondylitis, juvenile enteropathic arthritis, juvenile Reter's Syndrome, SEA Syndrome, juvenile dermatomyositis, juvenile psoriatic arthritis, juvenile scleroderma, juvenile systemic lupus erythematosus, juvenile vasculitis, pauciarticular rheumatoid arthritis, polyarticular rheumatoid arthritis, systemic onset rheumatoid
5 arthritis, enteropathic arthritis, reactive arthritis, Reter's Syndrome, myolitis, polymyolitis, dermatomyolitis, polyarteritis nodosa, Wegener's granulomatosis, arteritis, polymyalgia rheumatica, sarcoidosis, sclerosis, primary biliary sclerosis, sclerosing cholangitis, dermatitis, Still's disease, chronic obstructive pulmonary disease, Guillain-Barre disease, Graves' disease, Addison's disease, Raynaud's phenomenon, psoriatic epidermal hyperplasia, plaque psoriasis,
10 guttate psoriasis, inverse psoriasis, pustular psoriasis, erythrodermic psoriasis, an immune disorder associated with or arising from activity of pathogenic lymphocytes, noninfectious uveitis, Behcet's disease and Vogt-Koyanagi-Harada syndrome, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of claim 1 to 7, or a pharmaceutically acceptable salt thereof.

15

9. The method of claim 8 wherein the compound is (S)-2-hydroxy-N-(3-(methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)cyclobutyl)propane-1-sulfonamide; or, a pharmaceutically acceptable salt thereof, in an isolated form.

20

10. The method of claim 8 wherein the compound is 3-hydroxy-N-(3-(methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)cyclobutyl)propane-1-sulfonamide; or, a pharmaceutically acceptable salt, in an isolated form.

25

11. The method of any of claims 8 to 10, wherein the disease or condition is atopic dermatitis.

12. The method of any of claims 8 to 10, wherein the disease or condition is hand eczema.

30

13. The method of any of claims 8 to 10, wherein the disease or condition is cutaneous lupus.

35

14. Use of a compound in an isolated form according to any of claims 1 to 13 for the manufacture of a medicament for the treatment of a disorder for which a JAK1 inhibitor is indicated.