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(54) Titre : PYRROLO [2,3-D] PYRIMIDINYL, PYRROLO[2,3-B] PYRAZINYL, PYRROLO [2,3-B] PYRIDINYL ACRYLAMIDES ET LEUR EPOXYDES

(54) Title: PYRROLO[2,3-D]PYRIMIDINYL, PYRROLO[2,3-B]PYRAZINYL, PYRROLO[2,3-B]PYRIDINYL ACRYLAMIDES AND EPOXIDES THEREOF

(57) Abrégé/Abstract:
The present invention provides pharmaceutically active pyrrolo[2,3-d]pyrimidinyl, pyrrolo[2,3- b]pyrazinyl,and pyrrolo[2,3-b]pyridinyl acrylamides, epoxides,and analogues thereof. Such compounds are useful for inhibiting Janus Kinase (JAK). This invention also is directed to compositions comprising methods for making such compounds, and methods for treating and preventing conditions mediated by JAK.

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(54) Title: PYRROLO[2,3-D]PYRIMIDINYL, PYRROLO[2,3-B]PYRAZINYL, PYRROLO[2,3-B]PYRIDINYL ACRYLAMIDES AND EPOXIDES THEREOF

(57) Abstract: The present invention provides pharmaceutically active pyrrolo[2,3-d]pyrimidinyl, pyrrolo[2,3- b]pyrazinyl,and pyrrolo[2,3-b]pyridinyl acrylamides, epoxides,and analogues thereof. Such compounds are useful for inhibiting Janus Kinase (JAK). This invention also is directed to compositions comprising methods for making such compounds, and methods for treating and preventing conditions mediated by JAK.

Pyrrolo[2,3-d]pyrimidinyl, Pyrrolo[2,3-b]pyrazinyl, Pyrrolo[2,3-b]pyridinyl acrylamides and Epoxides Thereof

FIELD OF THE INVENTION

The present invention provides pharmaceutically active pyrrolo[2,3-d]pyrimidinyl, pyrrolo[2,3-b]pyrazinyl, and pyrrolo[2,3-b]pyridinyl acrylamides, epoxides and analogues thereof. Such compounds are useful for inhibiting one or more Janus Kinase (JAK). This invention also is directed to compositions comprising methods for making such compounds, and methods for treating and preventing conditions mediated by JAK.

BACKGROUND OF THE INVENTION

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, dys-regulation 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, 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.

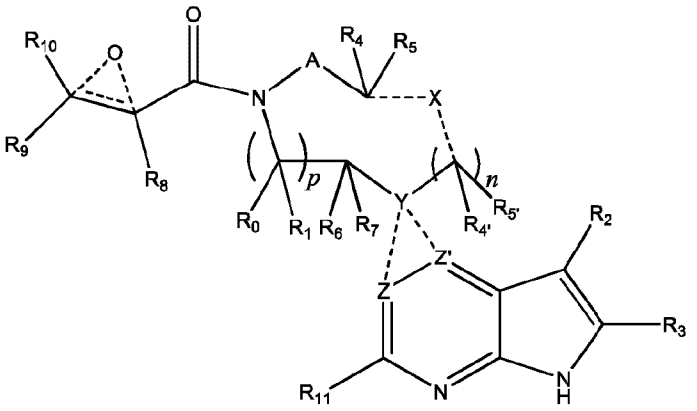
Thus, protein kinases have emerged as an important class of enzymes as targets for therapeutic intervention. In particular, the JAK family of cellular protein tyrosine kinases (JAK1, JAK2, JAK3, and Tyk2) play a central role in cytokine signaling (Kisseleva et al., *Gene,* 2002, 285, 1; Yamaoka et al. *Genome Biology,* 2004, 5, 253)). Upon binding to their receptors, cytokines activate JAK enzymes which then phosphorylate the cytokine receptor, thereby creating docking sites for 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, IL-27 and IL-35), gamma-common chain family (IL-2, IL-4,IL-7, IL-9, IL-15, IL-21,), and IL-13, TLSP, 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 JAK3 in particular. JAK3 is a member of the Janus family of protein kinases composed of JAK1, JAK2, JAK3 and TYK2, and is expressed to various levels in all 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. Animal studies have shown that JAK3 is implicated in the development, function and homeostasis of the immune system. Modulation of immune activity through inhibition of JAK3 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)).

SUMMARY OF THE INVENTION

The present invention provides a compound having the structure:



or a pharmaceutically acceptable salt or solvate thereof, or an enantiomer or diastereomer thereof, and wherein R_2 is selected from the group consisting of hydrogen, deuterium, C_1-C_6 linear or branched chain alkyl, C_3-C_6 cycloalkyl, C_6-C_{10} aryl, monocyclic or bicyclic heteroaryl, comprising 5- and/or 6-membered rings, (aryl)C_1-C_6 linear or branched chain alkyl, (heteroaryl)C_1-C_6 linear or branched chain alkyl, (heterocyclic)C_1-C_6 linear or branched chain alkyl, (C_1-C_6 linear or branched chain alkyl)aryl, (C_1-C_6 linear or branched chain alkyl)heteroaryl, (C_1-C_6 linear or branched chain alkyl)heterocyclic, C_1-C_6 linear or branched chain perfluoroalkyl, C_1-C_6 linear or branched chain alkoxy, C_1-C_6 linear or branched chain perfluoroalkoxy, halogen, cyano, hydroxyl, amino, carboxy, aminocarbonyl, (C_1-C_6 linear or branched chain alkyl)aminocarbonylamino, (C_1-C_6 linear or branched chain alkyl)aminocarbonyl, $-SOR_{12}$, $-SO_2R_{12}$, $-NR_{13}SO_2R_{12}$, $-SO_2NR_{13}R_{14}$, and $-NR_{13}SO_2NR_{14}R_{15}$; where said alkyl, aryl and heteroaryl is independently optionally substituted with one or more substituents selected from the group consisting of halo, hydroxy, methoxy, amino, cyano, alkylamino, dialkylamino, CF_3, aminocarbonyl, (C_1-C_6 linear or branched chain alkyl)aminocarbonyl, and C_3-C_6 cycloalkyl;

the dotted lines to the O atom may be present or absent, and if present, the resulting ring forms an epoxide, or if absent, an ethylene results;

R_3 is selected from the group consisting of hydrogen, deuterium, C_1-C_6 linear or branched chain alkyl, C_1-C_6 linear or branched chain perfluoroalkyl, halogen, and cyano;

A is $-(CR_aR_b)_q-(CR_cR_d)_r-$, wherein R_a, R_b, R_c and R_d are independently selected from hydrogen, C_1-C_6 linear or branched chain alkyl, C_1-C_6 linear or branched chain perfluoroalkyl, C_6-C_{10} aryl, monocyclic or bicyclic heteroaryl, comprising 5- and/or 6-membered rings, alkylaryl, (aryl)C_1-C_6 linear or branched chain alkyl, (heteroaryl)C_1-C_6 linear or branched chain alkyl, halogen, cyano, hydroxyl, C_1-C_6 linear or branched chain alkoxy, amino, carboxy, aminocarbonyl, (heterocyclic)C_1-C_6

linear or branched chain alkyl, (C_1-C_6 linear or branched chain alkyl)aryl, (C_1-C_6 linear or branched chain alkyl)heteroaryl, and (C_1-C_6 linear or branched chain alkyl)heterocyclic, where said alkyl is further optionally substituted with one or more substituents selected from the group consisting of halo, hydroxy, methoxy, amino, alkylamino, dialkylamino, CF_3, and C_3-C_6 cycloalkyl;

R_0, R_1, R_4, R_5, $R_{4'}$, $R_{5'}$, R_6, R_7, R_8, R_9 and R_{10} are independently selected from hydrogen, C_1-C_6 linear or branched chain alkyl, C_1-C_6 linear or branched chain perfluoroalkyl, C_6-C_{10} aryl, monocyclic or bicyclic heteroaryl, comprising 5- and/or 6-membered rings, (aryl)C_1-C_6 linear or branched chain alkyl, (heteroaryl)C_1-C_6 linear or branched chain alkyl, heteroaryl, halogen, cyano, hydroxyl, C_1-C_6 linear or branched chain alkoxy, amino, carboxy, aminocarbonyl, (heterocyclic)C_1-C_6 linear or branched chain alkyl, (C_1-C_6 linear or branched chain alkyl)aryl, (C_1-C_6 linear or branched chain alkyl)heteroaryl, and (C_1-C_6 linear or branched chain alkyl)heterocyclic, where said alkyl is further optionally substituted with one or more substituents selected from the group consisting of halo, hydroxy, methoxy, amino, alkylamino, dialkylamino, CF_3, and C_3-C_6 cycloalkyl; where, alternatively, R_0 or R_1, and/or R_6 or R_7, respectively together with either of R_4, R_5, $R_{4'}$, $R_{5'}$, R_a, R_b, R_c or R_d, may independently form a bond or a C_1-C_6 linear alkyl chain; and/or, alternatively, R_4 or R_5, respectively together with either of R_a, R_b, R_c or R_d, may independently form a bond or a C_1-C_6 linear alkyl chain; and/or, alternatively, R_8 and R_9 may together form a 3-6-membered ring optionally containing one or two O or N atoms; R_{11} is hydrogen or deuterium; R_{12}, R_{13}, R_{14} and R_{15} are independently selected from hydrogen, C_1-C_6 linear or branched chain alkyl, C_1-C_6 linear or branched chain perfluoroalkyl, C_6-C_{10} aryl, alkylaryl, and (aryl)C_1-C_6 linear or branched chain alkyl; Y is O or N, where when Y is O, *n* is 0;

one and only one of the dotted bonds to Z and Z' constitutes a single bond, the other being absent, and either Z is C when the dotted bond to Z is a single bond, and Z' is N or CR_{16}; or, Z is CR_{16} or N when the dotted bond to Z' is a single bond, and Z' is C; where R_{16} is H, C_1-C_4 alkyl, C_6-C_{10} aryl, monocyclic or bicyclic heteroaryl, comprising 5- and/or 6-membered rings, (aryl)C_1-C_6 linear or branched chain alkyl, (heteroaryl)C_1-C_6 linear or branched chain alkyl, (heterocyclic)C_1-C_6 linear or branched chain alkyl, (C_1-C_6 linear or branched chain alkyl)aryl, (C_1-C_6 linear or branched chain alkyl)heteroaryl, or (C_1-C_6 linear or branched chain alkyl)heterocyclic, where said alkyl is further optionally substituted with one or more substituents selected from the group consisting of halo, hydroxy, methoxy, amino, CF_3, and C_3-C_6 cycloalkyl;

X and the dotted bonds thereto may be present or absent, whereby, (a) if X is present, Y N, and X is $-(CR_eR_f)_s-$, where R_e and R_f are independently hydrogen, deuterium, halo, hydroxy, C_1-C_4 alkoxy, amino, CF_3, C_1-C_6 linear or branched chain alkyl, C_3-C_6 cycloalkyl, C_5-C_{10} aryl, monocyclic or bicyclic heteroaryl, comprising 5- and/or 6-membered rings, (aryl)C_1-C_6 linear or branched chain alkyl, (C_1-C_6 linear or branched chain alkyl)heteroaryl, (heteroaryl)C_1-C_6 linear or branched chain alkyl, or (heterocyclic)C_1-C_6 linear or branched chain alkyl, and said dotted bonds are present and are single bonds, where when *n* is 0, X and Y are bonded directly; and (b) if X is absent, said dotted bonds are absent and *n* is 0, and when Y is N, either (i) said N atom is substituted by H, or (ii) Z is C or N, Z' is C, the dotted bond to Z' is a single bond, the dotted bond to Z being absent, and said Y being an N

atom together with R_2 and the atoms intervening therebetween form a 6-membered ring optionally substituted by C_1-C_6 linear or branched chain alkyl or C_3-C_6 cycloalkyl; and, *n, p, q, r* and *s* are independently 0, 1 or 2.

In other aspects, the present invention also provides:

pharmaceutical compositions which comprise a pharmaceutically acceptable carrier and a compound of the invention;

methods for treating or preventing a disorder or condition selected from rheumatoid arthritis, myositis, vasculitis, pemphigus, bullous pemphigoid, inflammatory bowel disease including Crohn's disease and ulcerative colitis, celiac diseases, proctitis, eosinophilic gastroenteritis, or mastocytosis, Alzheimer's disease, lupus, nephritis, systemic lupus erythematosus, psoriasis, eczema dermatitis, pruritus or other pruritic conditions, vitiligo, alopecia, autoimmune thyroid disorders, multiple sclerosis, major depression disorder, allergy, asthma, Sjogren's disease, Reiter's syndrome, polymyositis-dermatomyositis, systemic sclerosis, polyarteritis nodosa, dry eye syndrome, Hashimoto's thyroiditis, autoimmune hemolytic anemia, autoimmune atrophic gastritis of pernicious anemia, autoimmune encephalomyelitis, autoimmune orchitis, Goodpasture's disease, autoimmune thrombocytopenia, sympathetic ophthalmia, myasthenia gravis, Graves' disease, primary biliary cirrhosis, chronic aggressive hepatitis, membranous glomerulopathy ,organ transplant rejection, graft-versus-host disease, organ and cell transplant rejection such as bone marrow, cartilage, cornea, heart, intervertebral disc, islet, kidney, limb, liver, lung, muscle, myoblast, nerve, pancreas, skin, small intestine, or trachea, or xeno transplantation, including Cogan's syndrome, ankylosing spondylitis, Wegener's granulomatosis, autoimmune alopecia, Type I or juvenile onset diabetes, and complications from diabetes, or thyroiditis, chronic pulmonary obstructive disorder, acute respiratory disease, cachexia, cancer, including alimentary/gastrointestinal tract cancer, colon cancer, liver cancer, skin cancer including mast cell tumor and squamous cell carcinoma, breast and mammary cancer, ovarian cancer, prostate cancer, leukemia, adult T cell leukemia activated B-cell like, diffuse large B cell lymphoma, kidney cancer, lung cancer, muscle cancer, bone cancer, bladder cancer, brain cancer, melanoma including oral and metastatic melanoma, Kaposi's sarcoma septic shock, cardiopulmonary dysfunction, acute myeloid leukemia, T cell acute lymphoblastic leukemia, multiple myeloma, myeloproliferative disorders, proliferative diabetic retinopathy, or angiogenic-associated disorders including solid tumors, pancreatic cancer, brain tumors, gliomas including astrocytoma, oligodendroglioma, and glioblastoma, acute CNS trauma including traumatic brain injury, encephalitis, stroke, and spinal cord injury, epilepsy, seizures, chronic neuroinflammation associated with neurodegeneration including Alzheimer's disease, Parkinson's disease, Amyotropic Lateral Sclerosis, Huntington's disease, cerebral ischemia, fronto-temporal lobe dementia, and with neuropsychiatric disorders including schizophrenia, bipolar disorder, treatment resistant depression, Post Traumatic Stress Disorder, anxiety, and auto-antibodies mediated encephalopathies, Eye diseases, disorders or conditions including autoimmune diseases of the eye, keratoconjunctivitis, vernal conjunctivitis, uveitis including uveitis associated with Behcet's disease and lens-induced uveitis, keratitis, herpetic keratitis, conical keratitis, corneal epithelial dystrophy, ker-

atoleukoma, ocular premphigus, Mooren's ulcer, scleritis, Grave's ophthalmopathy, Vogt-Koyanagi-Harada syndrome, keratoconjunctivitis sicca (dry eye), phlyctenule, iridocyclitis, sarcoidosis, endocrine ophthalmopathy, sympathetic ophthalmitis, allergic conjunctivitis, and ocular neovascularization, comprising the step of administering to a subject an effective amount of a composition comprising a compound or a pharmaceutically acceptable salt thereof set forth herein;

methods for treating conditions or disorders including atopic dermatitis, eczema, psoriasis, scleroderma, lupus, pruritus, other pruritic conditions, allergic reactions including allergic dermatitis in mammal, horse allergic diseases including bite hypersensitivity, summer eczema, sweet itch in horses, heaves, inflammatory airway disease, recurrent airway obstruction, airway hyper-responsiveness, and chronic obstruction pulmonary disease by administering to a mammal in need a therapeutically effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof; and,

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. The present invention is directed to a class of pyrrolo[2,3-d]pyrimidinyl, pyrrolo[2,3-b]pyrazinyl, and pyrrolo[2,3-b]pyridinyl acrylamides and analogues thereof. In particular, the present invention is directed to pyrrolo[2,3-b]pyrimidinyl , pyrrolo[2,3-b]pyrazinyl, and pyrrolo[2,3-b]pyridinyl acrylamides and epoxides which are useful as inhibitors of JAK, and particularly JAK3. 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 "alkyl", alone or in combination, means an acyclic, saturated hydrocarbon group of the formula C_nH_{2n+1} which may be linear or branched. Examples of such groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl and hexyl. Unless otherwise specified, an alkyl group comprises from 1 to 6 carbon atoms. The carbon atom content of alkyl and various other hydrocarbon-containing moieties is indicated by a prefix designating a lower and upper number of carbon atoms in the moiety, that is, the prefix C_i-C_j indicates a moiety of the integer "i" to the integer "j" carbon atoms, inclusive. Thus, for example, C_1-C_6 alkyl refers to alkyl of one to six carbon atoms, inclusive.

The term "hydroxy," as used herein, means an OH radical. The term "heterocyclic" refers to a saturated or partially saturated (i.e. non aromatic) heterocycle which may be attached via a ring nitrogen atom (when the heterocycle is attached to a carbon atom) or a ring carbon atom (in all cases). Equally, when substituted, the substituent may be located on a ring nitrogen atom (if the substituent is joined through a carbon atom) or a ring carbon atom (in all cases). Specific examples include oxiranyl, aziridinyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrrolidinyl, tetrahydropyranyl, piperidinyl, 1,4-dioxanyl, morpholinyl, piperazinyl, azepanyl, oxepanyl, oxazepanyl and diazepinyl.

The term "aryl" refers to an aromatic monocyclic or bicyclic hydrocarbon which may be attached via a ring carbon atom. Equally, when substituted, the substituent may be located on a ring carbon atom. Specific examples include phenyl, toluyl, xylyl, trimethylphenyl, and naphthyl. Exam-

ples of aryl substituents include alkyl, hydroxyl, halo, nitrile, alkoxy, trifluoromethyl, carboxamido, SO_2Me, benzyl, and substituted benzyl.

The term "heteroaryl" refers to an aromatic heterocycle which may be attached via a ring carbon atom (in all cases) or a ring nitrogen atom with an appropriate valency (when the heterocycle is attached to a carbon atom). Equally, when substituted, the substituent may be located on a ring carbon atom (in all cases) or a ring nitrogen atom with an appropriate valency (if the substituent is joined through a carbon atom). Specific examples include thienyl, furanyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl and pyrazinyl. The term "cycloalkyl" means a monocyclic, saturated hydrocarbon group of the formula C_nH_{2n-1}. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl. Unless otherwise specified, a cycloalkyl group comprises from 3 to 8 carbon atoms.

The terms "halo" and "halogen" refer to fluoride (F), chloride (Cl), bromide (Br) or iodide (I).

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

The term "companion animal" or "companion animals" refers to animals kept as pets or household animal. Examples of companion animals include dogs, cats, and rodents including hamsters, guinea pigs, gerbils and the like, rabbits, ferrets and birds.

The term "livestock" refers to animals reared or raised in an agricultural setting to make products such as food or fiber, or for its labor. In some embodiments, livestock are suitable for consumption by mammals, for example humans. Examples of livestock animals include cattle, goats, horses, pigs, sheep, including lambs, and rabbits, as well as birds, such as chickens, ducks and turkeys.

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 patient, 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.

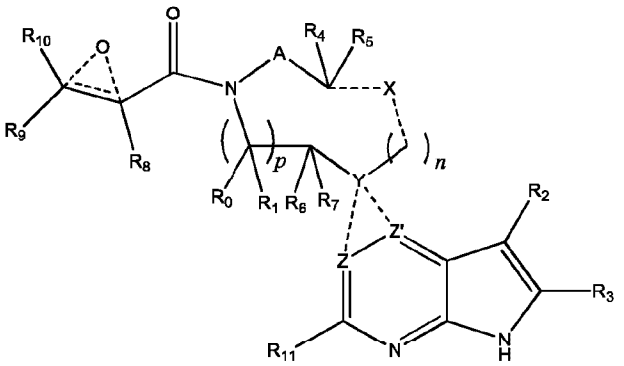
The term "therapeutically-effective" indicates the capability of an agent to prevent, or improve the severity of, the disorder, while avoiding adverse side effects typically associated with alternative therapies. The phrase "therapeutically-effective" is to be understood to be equivalent to the phrase "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 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 mammals, companion animals or livestock animals.

If substituents are described as being "independently selected" from a group, each substituent is selected independent of the other. Each substituent therefore may be identical to or different from the other substituent(s).

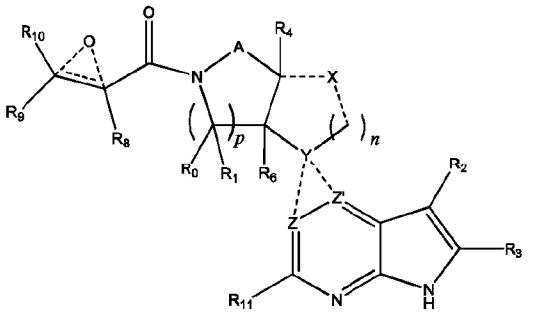
DETAILED DESCRIPTION OF THE INVENTION

The present invention is related to novel compounds which are selective JAK3 modulators useful for the treatment of diseases and conditions associated with dysregulation of the JAK3. The present invention further provides pharmaceutical compositions comprising such JAK3 modulators as well as methods of treating and/or preventing such diseases and conditions. Accordingly, the present invention provides a compound having the structure:



or a pharmaceutically acceptable salt or solvate thereof, or an enantiomer or diastereomer thereof, and wherein variables are defined above.

In one embodiment, the invention provides a compound having the structure:



or a pharmaceutically acceptable salt or solvate thereof, or an enantiomer or diastereomer thereof, and wherein

R_2 is selected from the group consisting of hydrogen, deuterium, C_1-C_6 linear or branched chain alkyl, C_3-C_6 cycloalkyl, C_6-C_{10} aryl, monocyclic or bicyclic heteroaryl, comprising 5- and/or 6-membered rings, (aryl)C_1-C_6 linear or branched chain alkyl, (heteroaryl)C_1-C_6 linear or branched chain alkyl, (heterocyclic)C_1-C_6 linear or branched chain alkyl, (C_1-C_6 linear or branched chain alkyl)aryl, (C_1-C_6 linear or branched chain alkyl)heteroaryl, (C_1-C_6 linear or branched chain alkyl)heterocyclic, C_1-C_6 linear or branched chain perfluoroalkyl, C_1-C_6 linear or branched chain alkoxy, C_1-C_5 linear or branched chain perfluoroalkoxy, halogen, cyano, hydroxyl, amino, carboxy, aminocarbonyl, (C_1-C_6 linear or branched chain alkyl)aminocarbonylamino, (C_1-C_6 linear or branched chain al-

kyl)aminocarbonyl, -SOR_{12}, -SO_2R_{12}, -$NR_{13}SO_2R_{12}$, -$SO_2NR_{13}R_{14}$, and -$NR_{13}SO_2NR_{14}R_{15}$; where said alkyl, aryl and heteroaryl is independently optionally substituted with one or more substituents selected from the group consisting of halo, hydroxy, methoxy, amino, cyano, alkylamino, dialkylamino, CF_3, aminocarbonyl, (C_1-C_6 linear or branched chain alkyl)aminocarbonyl, and C_3-C_6 cycloalkyl;

R_3 is selected from the group consisting of hydrogen, deuterium, C_1-C_6 linear or branched chain alkyl, C_1-C_6 linear or branched chain perfluoroalkyl, halogen, and cyano;

A is —-(CR_aR_b)$_q$-(CR_cR_d)$_r$--, wherein R_a, R_b, R_c and R_d are independently selected from hydrogen, C_1-C_6 linear or branched chain alkyl, C_1-C_6 linear or branched chain perfluoroalkyl, C_6-C_{10} aryl, monocyclic or bicyclic heteroaryl, comprising 5- and/or 6-membered rings, alkylaryl, (aryl)C_1-C_6 linear or branched chain alkyl, (heteroaryl)C_1-C_6 linear or branched chain alkyl, halogen, cyano, hydroxyl, C_1-C_6 linear or branched chain alkoxy, amino, carboxy, aminocarbonyl, (heterocyclic)C_1-C_6 linear or branched chain alkyl, (C_1-C_6 linear or branched chain alkyl)aryl, (C_1-C_6 linear or branched chain alkyl)heteroaryl, and (C_1-C_6 linear or branched chain alkyl)heterocyclic, where said alkyl is further optionally substituted with one or more substituents selected from the group consisting of halo, hydroxy, methoxy, amino, alkylamino, dialkylamino, CF_3, and C_3-C_6 cycloalkyl;

R_0, R_1, R_4, R_6, R_8, R_9 and R_{10} are independently selected from hydrogen, C_1-C_6 linear or branched chain alkyl, C_1-C_6 linear or branched chain perfluoroalkyl, C_6-C_{10} aryl, monocyclic or bicyclic heteroaryl, comprising 5- and/or 6-membered rings, (aryl)C_1-C_6 linear or branched chain alkyl, (heteroaryl)C_1-C_6 linear or branched chain alkyl, heteroaryl, halogen, cyano, hydroxyl, C_1-C_6 linear or branched chain alkoxy, amino, carboxy, aminocarbonyl, (heterocyclic)C_1-C_6 linear or branched chain alkyl, (C_1-C_6 linear or branched chain alkyl)aryl, (C_1-C_6 linear or branched chain alkyl)heteroaryl, and (C_1-C_6 linear or branched chain alkyl)heterocyclic, where said alkyl is further optionally substituted with one or more substituents selected from the group consisting of halo, hydroxy, methoxy, amino, alkylamino, dialkylamino, CF_3, and C_3-C_6 cycloalkyl; where, alternatively, R_0 or R_1, and/or R_6, respectively together with either of R_4, R_a, R_b, R_c or R_d, may independently form a bond or a C_1-C_6 linear alkyl chain; and/or, alternatively, R_4, respectively together with either of R_a, R_b, R_c or R_d, may independently form a bond or a C_1-C_6 linear alkyl chain; and/or, alternatively, R_8 and R_9 may together form a 3-6-membered ring optionally containing one or two O or N atoms; R_{11} is hydrogen or deuterium;

R_{12}, R_{13}, R_{14} and R_{15} are independently selected from hydrogen, C_1-C_6 linear or branched chain alkyl, C_1-C_6 linear or branched chain perfluoroalkyl, C_5-C_{10} aryl, alkylaryl, and (aryl)C_1-C_6 linear or branched chain alkyl;

Y is O or N, where when Y is O, *n* is 0;

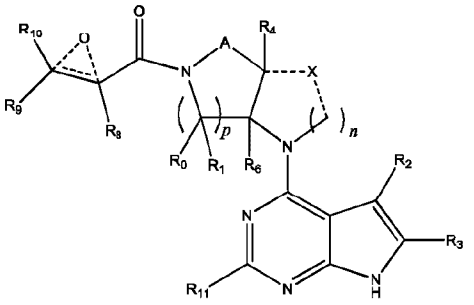
the dotted lines to the O atom may be present or absent, and if present, the resulting ring forms an epoxide, or if absent, an ethylene results;

one and only one of the dotted bonds to Z and Z' constitutes a single bond, the other being absent, and either Z is C when the dotted bond to Z is a single bond, and Z' is N or CR_{16}; or, Z is CR_{16} or N when the dotted bond to Z' is a single bond, and Z' is C; where R_{16} is H, C_1-C_4 alkyl, C_6-C_{10}

aryl, monocyclic or bicyclic heteroaryl, comprising 5- and/or 6-membered rings, (aryl)C_1-C_6 linear or branched chain alkyl, (heteroaryl)C_1-C_6 linear or branched chain alkyl, (heterocyclic)C_1-C_6 linear or branched chain alkyl, (C_1-C_6 linear or branched chain alkyl)aryl, (C_1-C_6 linear or branched chain alkyl)heteroaryl, or (C_1-C_6 linear or branched chain alkyl)heterocyclic, where said alkyl is further optionally substituted with one or more substituents selected from the group consisting of halo, hydroxy, methoxy, amino, CF_3, and C_3-C_6 cycloalkyl;

X and the dotted bonds thereto may be present or absent, whereby, (a) if X is present, Y is N, and X is –-(CR_eR_f)$_s$–-, where R_e and R_f are independently hydrogen, deuterium, halo, hydroxy, C_1-C_4 alkoxy, amino, CF_3, C_1-C_6 linear or branched chain alkyl, C_3-C_6 cycloalkyl, C_5-C_{10} aryl, monocyclic or bicyclic heteroaryl, comprising 5- and/or 6-membered rings, (aryl)C_1-C_6 linear or branched chain alkyl, (C_1-C_6 linear or branched chain alkyl)heteroaryl, (heteroaryl)C_1-C_6 linear or branched chain alkyl, or (heterocyclic)C_1-C_6 linear or branched chain alkyl, and said dotted bonds are present and are single bonds, where when *n* is 0, X and Y are bonded directly; and (b) if X is absent, said dotted bonds are absent and *n* is 0, and when Y is N, either (i) said N atom is substituted by H, or (ii) Z is C or N, Z' is C, the dotted bond to Z' is a single bond, the dotted bond to Z being absent, and said Y being an N atom together with R_2 and the atoms intervening therebetween form a 6-membered ring optionally substituted by C_1-C_6 linear or branched chain alkyl or C_3-C_6 cycloalkyl; and, *n, p, q, r* and *s* are independently 0, 1 or 2.

In another embodiment, the invention provides a compound having the structure:



or a pharmaceutically acceptable salt or solvate thereof, or an enantiomer or diastereomer thereof, and wherein

R_2 is selected from the group consisting of hydrogen, deuterium, C_1-C_6 linear or branched chain alkyl, C_3-C_6 cycloalkyl, C_6-C_{10} aryl, monocyclic or bicyclic heteroaryl, comprising 5- and/or 6-membered rings, (aryl)C_1-C_6 linear or branched chain alkyl, (heteroaryl)C_1-C_6 linear or branched chain alkyl, (heterocyclic)C_1-C_6 linear or branched chain alkyl, (C_1-C_6 linear or branched chain alkyl)aryl, (C_1-C_6 linear or branched chain alkyl)heteroaryl, (C_1-C_6 linear or branched chain alkyl)heterocyclic, C_1-C_6 linear or branched chain perfluoroalkyl, C_1-C_6 linear or branched chain alkoxy, C_1-C_6 linear or branched chain perfluoroalkoxy, halogen, cyano, hydroxyl, amino, carboxy, aminocarbonyl, (C_1-C_6 linear or branched chain alkyl)aminocarbonylamino, (C_1-C_6 linear or branched chain alkyl)aminocarbonyl, -SOR_{12}, -SO_2R_{12}, -$NR_{13}SO_2R_{12}$, -$SO_2NR_{13}R_{14}$, and -$NR_{13}SO_2NR_{14}R_{15}$; where said

alkyl, aryl and heteroaryl is independently optionally substituted with one or more substituents selected from the group consisting of halo, hydroxy, methoxy, amino, cyano, alkylamino, dialkylamino, CF_3, aminocarbonyl, (C_1-C_6 linear or branched chain alkyl)aminocarbonyl, and C_3-C_6 cycloalkyl;

R_3 is selected from the group consisting of hydrogen, deuterium, C_1-C_6 linear or branched chain alkyl, C_1-C_6 linear or branched chain perfluoroalkyl, halogen, and cyano;

A is —$(CR_aR_b)_q$-$(CR_cR_d)_r$—, wherein R_a, R_b, R_c and R_d are independently selected from hydrogen, C_1-C_6 linear or branched chain alkyl, C_1-C_6 linear or branched chain perfluoroalkyl, C_6-C_{10} aryl, monocyclic or bicyclic heteroaryl, comprising 5- and/or 6-membered rings, alkylaryl, (aryl)C_1-C_6 linear or branched chain alkyl, (heteroaryl)C_1-C_6 linear or branched chain alkyl, halogen, cyano, hydroxyl, C_1-C_6 linear or branched chain alkoxy, amino, carboxy, aminocarbonyl, (heterocyclic)C_1-C_6 linear or branched chain alkyl, (C_1-C_6 linear or branched chain alkyl)aryl, (C_1-C_6 linear or branched chain alkyl)heteroaryl, and (C_1-C_6 linear or branched chain alkyl)heterocyclic, where said alkyl is further optionally substituted with one or more substituents selected from the group consisting of halo, hydroxy, methoxy, amino, alkylamino, dialkylamino, CF_3, and C_3-C_6 cycloalkyl;

R_0, R_1, R_4, R_6, R_8, R_9 and R_{10} are independently selected from hydrogen, C_1-C_6 linear or branched chain alkyl, C_1-C_6 linear or branched chain perfluoroalkyl, C_6-C_{10} aryl, monocyclic or bicyclic heteroaryl, comprising 5- and/or 6-membered rings, (aryl)C_1-C_6 linear or branched chain alkyl, (heteroaryl)C_1-C_6 linear or branched chain alkyl, heteroaryl, halogen, cyano, hydroxyl, C_1-C_6 linear or branched chain alkoxy, amino, carboxy, aminocarbonyl, (heterocyclic)C_1-C_6 linear or branched chain alkyl, (C_1-C_6 linear or branched chain alkyl)aryl, (C_1-C_6 linear or branched chain alkyl)heteroaryl, and (C_1-C_6 linear or branched chain alkyl)heterocyclic, where said alkyl is further optionally substituted with one or more substituents selected from the group consisting of halo, hydroxy, methoxy, amino, alkylamino, dialkylamino, CF_3, and C_3-C_6 cycloalkyl; where, alternatively, R_0 or R_1, and/or R_6, respectively together with either of R_4, R_a, R_b, R_c or R_d, may independently form a bond or a C_1-C_6 linear alkyl chain; and/or, alternatively, R_4, respectively together with either of R_a, R_b, R_c or R_d, may independently form a bond or a C_1-C_6 linear alkyl chain; and/or, alternatively, R_8 and R_9 may together form a 3-6-membered ring optionally containing one or two O or N atoms;

Y is O or N, where when Y is O, *n* is 0;

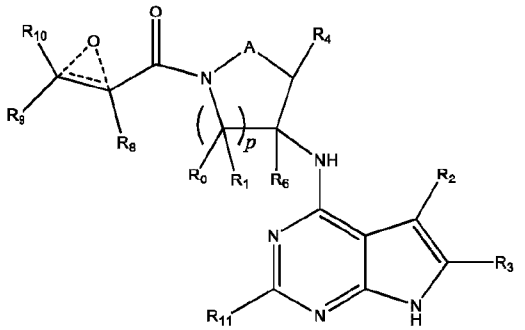
R_{11} is hydrogen or deuterium;

R_{12}, R_{13}, R_{14} and R_{15} are independently selected from hydrogen, C_1-C_6 linear or branched chain alkyl, C_1-C_6 linear or branched chain perfluoroalkyl, C_5-C_{10} aryl, alkylaryl, and (aryl)C_1-C_6 linear or branched chain alkyl;

X and the dotted bonds thereto may be present or absent, whereby, (a) if X is present, Y is N, and X is —(CReRf)s—, where Re and Rf are independently hydrogen, deuterium, halo, hydroxy, C1-C4 alkoxy, amino, CF3, C1-C6 linear or branched chain alkyl, C3-C6 cycloalkyl, C6-C10 aryl, monocyclic or bi-cyclic heteroaryl, comprising 5- and/or 6-membered rings, (aryl)C1-C6 linear or branched chain alkyl, (C1-C6 linear or branched chain alkyl)heteroaryl, (heteroaryl)C1-C6 linear or branched chain alkyl, or (hetero-cyclic)C1-C6 linear or branched chain alkyl, and said dotted bonds

are present and are single bonds, where when n is 0, X and Y are bonded directly; and (b) if X is absent, said dotted bonds are absent and n is 0, and when Y is N, either (i) said N atom is substituted by H, or (ii) Z is C or N, Z' is C, the dotted bond to Z' is a single bond, the dotted bond to Z being absent, and said Y being an N atom together with R2 and the atoms intervening therebetween form a 6-membered ring optionally substituted by C1-C6 linear or branched chain alkyl or C3-C6 cycloalkyl; and, *n, p, q, r* and *s* are independently 0, 1 or 2.

In another embodiment, the invention provides the compound having the structure:



or a pharmaceutically acceptable salt or solvate thereof, or an enantiomer or diastereomer thereof, and wherein R_2 is selected from the group consisting of hydrogen, deuterium, C_1-C_6 linear or branched chain alkyl, C_3-C_6 cycloalkyl, C_6-C_{10} aryl, monocyclic or bicyclic heteroaryl, comprising 5- and/or 6-membered rings, (aryl)C_1-C_6 linear or branched chain alkyl, (heteroaryl)C_1-C_6 linear or branched chain alkyl, (heterocyclic)C_1-C_6 linear or branched chain alkyl, (C_1-C_6 linear or branched chain alkyl)aryl, (C_1-C_6 linear or branched chain alkyl)heteroaryl, (C_1-C_6 linear or branched chain alkyl)heterocyclic, C_1-C_6 linear or branched chain perfluoroalkyl, C_1-C_6 linear or branched chain alkoxy, C_1-C_6 linear or branched chain perfluoroalkoxy, halogen, cyano, hydroxyl, amino, carboxy, aminocarbonyl, (C_1-C_6 linear or branched chain alkyl)aminocarbonylamino, (C_1-C_6 linear or branched chain alkyl)aminocarbonyl, $-SOR_{12}$, $-SO_2R_{12}$, $-NR_{13}SO_2R_{12}$, $-SO_2NR_{13}R_{14}$, and $-NR_{13}SO_2NR_{14}R_{15}$; where said alkyl, aryl and heteroaryl is independently optionally substituted with one or more substituents selected from the group consisting of halo, hydroxy, methoxy, amino, cyano, alkylamino, dialkylamino, CF_3, aminocarbonyl, (C_1-C_6 linear or branched chain alkyl)aminocarbonyl, and C_3-C_6 cycloalkyl;

R_3 is selected from the group consisting of hydrogen, deuterium, C_1-C_6 linear or branched chain alkyl, C_1-C_6 linear or branched chain perfluoroalkyl, halogen, and cyano;

A is $-(CR_aR_b)_q-(CR_cR_d)_r-$, wherein R_a, R_b, R_c and R_d are independently selected from hydrogen, C_1-C_6 linear or branched chain alkyl, C_1-C_6 linear or branched chain perfluoroalkyl, C_6-C_{10} aryl, monocyclic or bicyclic heteroaryl, comprising 5- and/or 6-membered rings, alkylaryl, (aryl)C_1-C_6 linear or branched chain alkyl, (heteroaryl)C_1-C_6 linear or branched chain alkyl, halogen, cyano, hydroxyl, C_1-C_6 linear or branched chain alkoxy, amino, carboxy, aminocarbonyl, (heterocyclic)C_1-C_6 linear or branched chain alkyl, (C_1-C_6 linear or branched chain alkyl)aryl, (C_1-C_6 linear or branched chain alkyl)heteroaryl, and (C_1-C_6 linear or branched chain alkyl)heterocyclic, where said alkyl is further op-

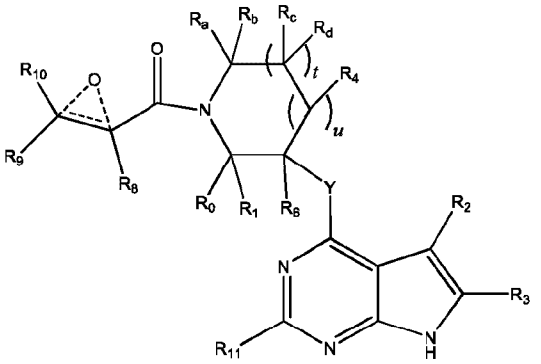
tionally substituted with one or more substituents selected from the group consisting of halo, hydroxy, methoxy, amino, alkylamino, dialkylamino, CF_3, and C_3-C_6 cycloalkyl;

the dotted lines to the O atom may be present or absent, and if present, the resulting ring forms an epoxide, or if absent, an ethylene results;

R_0, R_1, R_4, R_6, R_8, R_9 and R_{10} are independently selected from hydrogen, deuterium, C_1-C_6 linear or branched chain alkyl, C_1-C_6 linear or branched chain perfluoroalkyl, C_5-C_{10} aryl, monocyclic or bicyclic heteroaryl, comprising 5- and/or 6-membered rings, (aryl)C_1-C_6 linear or branched chain alkyl, (heteroaryl)C_1-C_6 linear or branched chain alkyl, heteroaryl, halogen, cyano, hydroxyl, C_1-C_6 linear or branched chain alkoxy, amino, carboxy, aminocarbonyl, (heterocyclic)C_1-C_6 linear or branched chain alkyl, (C_1-C_6 linear or branched chain alkyl)aryl, (C_1-C_6 linear or branched chain alkyl)heteroaryl, and (C_1-C_6 linear or branched chain alkyl)heterocyclic, where said alkyl is further optionally substituted with one or more substituents selected from the group consisting of halo, hydroxy, methoxy, amino, alkylamino, dialkylamino, CF_3, and C_3-C_6 cycloalkyl; where, alternatively, R_0 or R_1, and/or R_6, respectively together with either of R_4, R_a, R_b, R_c or R_d, may independently form a bond or a C_1-C_6 linear alkyl chain; and/or, alternatively, R_4, respectively together with either of R_a, R_b, R_c or R_d, may independently form a bond or a C_1-C_6 linear alkyl chain; and/or, alternatively, R_8 and R_9 may together form a 3-6-membered ring optionally containing one or two O or N atoms; R_{11} is hydrogen or deuterium;

R_{12}, R_{13}, R_{14} and R_{15} are independently selected from hydrogen, deuterium, C_1-C_6 linear or branched chain alkyl, C_1-C_6 linear or branched chain perfluoroalkyl, C_6-C_{10} aryl, alkylaryl, and (aryl)C_1-C_6 linear or branched chain alkyl; and, *p*, *q*, and *r* are independently 0, 1 or 2.

In another embodiment, the invention provides the compound having the structure:



or a pharmaceutically acceptable salt or solvate thereof, or an enantiomer or diastereomer thereof, and wherein R_2 is selected from the group consisting of hydrogen, deuterium, C_1-C_6 linear or branched chain alkyl, C_3-C_6 cycloalkyl, C_6-C_{10} aryl, monocyclic or bicyclic heteroaryl, comprising 5- and/or 6-membered rings, (aryl)C_1-C_6 linear or branched chain alkyl, (heteroaryl)C_1-C_6 linear or

branched chain alkyl, (heterocyclic)C_1-C_6 linear or branched chain alkyl, (C_1-C_6 linear or branched chain alkyl)aryl, (C_1-C_6 linear or branched chain alkyl)heteroaryl, (C_1-C_6 linear or branched chain alkyl)heterocyclic, C_1-C_6 linear or branched chain perfluoroalkyl, C_1-C_6 linear or branched chain alkoxy, C_1-C_6 linear or branched chain perfluoroalkoxy, halogen, cyano, hydroxyl, amino, carboxy, aminocarbonyl, (C_1-C_6 linear or branched chain alkyl)aminocarbonylamino, (C_1-C_6 linear or branched chain alkyl)aminocarbonyl, $-SOR_{12}$, $-SO_2R_{12}$, $-NR_{13}SO_2R_{12}$, $-SO_2NR_{13}R_{14}$, and $-NR_{13}SO_2NR_{14}R_{15}$; where said alkyl, aryl and heteroaryl is independently optionally substituted with one or more substituents selected from the group consisting of halo, hydroxy, methoxy, amino, cyano, alkylamino, dialkylamino, CF_3, aminocarbonyl, (C_1-C_6 linear or branched chain alkyl)aminocarbonyl, and C_3-C_6 cycloalkyl;

R_3 is selected from the group consisting of hydrogen, deuterium, C_1-C_6 linear or branched chain alkyl, C_1-C_6 linear or branched chain perfluoroalkyl, halogen, and cyano;

R_a, R_b, R_c and R_d are independently selected from hydrogen, C_1-C_6 linear or branched chain alkyl, C_1-C_6 linear or branched chain perfluoroalkyl, aryl, alkylaryl, (aryl)C_1-C_6 linear or branched chain alkyl, (heteroaryl)C_1-C_6 linear or branched chain alkyl, heteroaryl, halogen, cyano, hydroxyl, C_1-C_6 linear or branched chain alkoxy, amino, carboxy, aminocarbonyl, (heterocyclic)C_1-C_6 linear or branched chain alkyl, (C_1-C_6 linear or branched chain alkyl)aryl, (C_1-C_6 linear or branched chain alkyl)heteroaryl, and (C_1-C_6 linear or branched chain alkyl)heterocyclic, where said alkyl is further optionally substituted with one or more substituents selected from the group consisting of halo, hydroxy, methoxy, amino, alkylamino, dialkylamino, CF_3, and C_3-C_6 cycloalkyl;

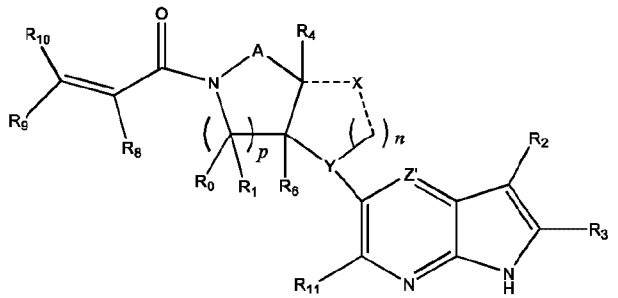
the dotted lines to the O atom may be present or absent, and if present, the resulting ring forms an epoxide, or if absent, an ethylene results;

Y is O or N where N may be substituted by H or alkyl;

R_0, R_1, R_4, R_6, R_8, R_9 and R_{10} are independently selected from hydrogen, deuterium C_1-C_6 linear or branched chain alkyl, C_1-C_6 linear or branched chain perfluoroalkyl, C_3-C_{10} aryl, monocyclic or bicyclic heteroaryl, comprising 5- and/or 6-membered rings, (aryl)C_1-C_6 linear or branched chain alkyl, (heteroaryl)C_1-C_6 linear or branched chain alkyl, heteroaryl, halogen, cyano, hydroxyl, C_1-C_6 linear or branched chain alkoxy, amino, carboxy, aminocarbonyl, (heterocyclic)C_1-C_6 linear or branched chain alkyl, (C_1-C_6 linear or branched chain alkyl)aryl, (C_1-C_6 linear or branched chain alkyl)heteroaryl, and (C_1-C_6 linear or branched chain alkyl)heterocyclic, where said alkyl is further optionally substituted with one or more substituents selected from the group consisting of halo, hydroxy, methoxy, amino, alkylamino, dialkylamino, CF_3, and C_3-C_6 cycloalkyl; where, alternatively, R_0 or R_1, and/or R_6, respectively together with either of R_4, R_a, R_b, R_c or R_d, may independently form a bond or a C_1-C_6 linear alkyl chain; and/or, alternatively, R_4, respectively together with either of R_a, R_b, R_c or R_d, may independently form a bond or a C_1-C_6 linear alkyl chain; and/or, alternatively, R_8 and R_9 may together form a 3-6-membered ring optionally containing one or two O or N atoms; R_{11} is hydrogen or deuterium;

R_{12}, R_{13}, R_{14} and R_{15} are independently selected from hydrogen, deuterium C_1-C_6 linear or branched chain alkyl, C_1-C_6 linear or branched chain perfluoroalkyl, C_6-C_{10} aryl, alkylaryl, and (aryl)C_1-C_6 linear or branched chain alkyl; and, *t* and *u* are independently 0, 1 or 2.

In another embodiment, the invention provides the compound having the structure:



or a pharmaceutically acceptable salt or solvate thereof, or an enantiomer or diastereomer thereof, and wherein R_2 is selected from the group consisting of hydrogen, deuterium, C_1-C_6 linear or branched chain alkyl, C_3-C_6 cycloalkyl, C_6-C_{10} aryl, monocyclic or bicyclic heteroaryl, comprising 5- and/or 6-membered rings, (aryl)C_1-C_6 linear or branched chain alkyl, (heteroaryl)C_1-C_6 linear or branched chain alkyl, (heterocyclic)C_1-C_6 linear or branched chain alkyl, (C_1-C_6 linear or branched chain alkyl)aryl, (C_1-C_6 linear or branched chain alkyl)heteroaryl, (C_1-C_6 linear or branched chain alkyl)heterocyclic, C_1-C_6 linear or branched chain perfluoroalkyl, C_1-C_6 linear or branched chain alkoxy, C_1-C_6 linear or branched chain perfluoroalkoxy, halogen, cyano, hydroxyl, amino, carboxy, aminocarbonyl, (C_1-C_6 linear or branched chain alkyl)aminocarbonylamino, (C_1-C_6 linear or branched chain alkyl)aminocarbonyl, $-SOR_{12}$, $-SO_2R_{12}$, $-NR_{13}SO_2R_{12}$, $-SO_2NR_{13}R_{14}$, and $-NR_{13}SO_2NR_{14}R_{15}$; where said alkyl, aryl and heteroaryl is independently optionally substituted with one or more substituents selected from the group consisting of halo, hydroxy, methoxy, amino, cyano, alkylamino, dialkylamino, CF_3, aminocarbonyl, (C_1-C_6 linear or branched chain alkyl)aminocarbonyl, and C_3-C_6 cycloalkyl;

R_3 is selected from the group consisting of hydrogen, deuterium, C_1-C_6 linear or branched chain alkyl, C_1-C_6 linear or branched chain perfluoroalkyl, halogen, and cyano;

A is $-(CR_aR_b)_q-(CR_cR_d)_r-$, wherein R_a, R_b, R_c and R_d are independently selected from hydrogen, C_1-C_6 linear or branched chain alkyl, C_1-C_6 linear or branched chain perfluoroalkyl, C_6-C_{10} aryl, monocyclic or bicyclic heteroaryl, comprising 5- and/or 6-membered rings, alkylaryl, (aryl)C_1-C_6 linear or branched chain alkyl, (heteroaryl)C_1-C_6 linear or branched chain alkyl, halogen, cyano, hydroxyl, C_1-C_6 linear or branched chain alkoxy, amino, carboxy, aminocarbonyl, (heterocyclic)C_1-C_6 linear or branched chain alkyl, (C_1-C_6 linear or branched chain alkyl)aryl, (C_1-C_6 linear or branched chain alkyl)heteroaryl, and (C_1-C_6 linear or branched chain alkyl)heterocyclic, where said alkyl is further optionally substituted with one or more substituents selected from the group consisting of halo, hydroxy, methoxy, amino, alkylamino, dialkylamino, CF_3, and C_3-C_6 cycloalkyl;

Y is O or N, where when Y is O, *n* is 0;

Z' is CR_{15} or N; where R_{15} is H, C_1-C_4 alkyl, C_5-C_{10} aryl, monocyclic or bicyclic heteroaryl, comprising 5- and/or 6-membered rings, (aryl)C_1-C_6 linear or branched chain alkyl, (heteroaryl)C_1-C_6 linear or branched chain alkyl, (heterocyclic)C_1-C_6 linear or branched chain alkyl, (C_1-C_6 linear or branched chain alkyl)aryl, (C_1-C_6 linear or branched chain alkyl)heteroaryl, or (C_1-C_6 linear or branched chain akyl)heterocyclic, where said alkyl is further optionally substituted with one or more substituents selected from the group consisting of halo, hydroxy, methoxy, amino, CF_3, and C_3-C_6 cycloalkyl;

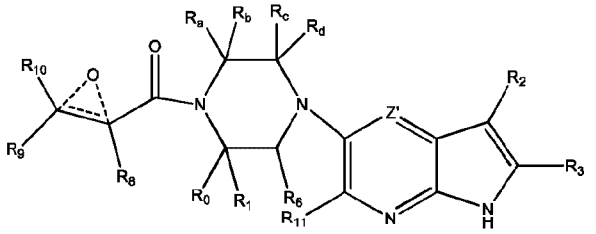
R_a, R_b, R_c and R_d are independently selected from hydrogen, deuterium C_1-C_6 linear or branched chain alkyl, C_1-C_6 linear or branched chain perfluoroalkyl, aryl, alkylaryl, (aryl)C_1-C_5 linear or branched chain alkyl, (heteroaryl)C_1-C_5 linear or branched chain alkyl, heteroaryl, halogen, cyano, hydroxyl, C_1-C_6 linear or branched chain alkoxy, amino, carboxy, aminocarbonyl, (heterocyclic)C_1-C_6 linear or branched chain alkyl, (C_1-C_6 linear or branched chain alkyl)aryl, (C_1-C_6 linear or branched chain alkyl)heteroaryl, and (C_1-C_6 linear or branched chain alkyl)heterocyclic, wherein said alkyl is further optionally substituted with one or more substituents selected from the group consisting of halo, hydroxy, methoxy, amino, alkylamino, dialkylamino, CF_3, and C_3-C_6 cycloalkyl, where said alkyl is further optionally substituted with one or more substituents selected from the group consisting of halo, hydroxy, methoxy, amino, alkylamino, dialkylamino, CF_3, and C_3-C_6 cycloalkyl;

R_0, R_1, R_4, R_6, R_8, R_9 and R_{10} are independently selected from hydrogen, deuterium C_1-C_6 linear or branched chain alkyl, C_1-C_6 linear or branched chain perfluoroalkyl, C_5-C_{10} aryl, monocyclic or bicyclic heteroaryl, comprising 5- and/or 6-membered rings, (aryl)C_1-C_6 linear or branched chain alkyl, (heteroaryl)C_1-C_6 linear or branched chain alkyl, heteroaryl, halogen, cyano, hydroxyl, C_1-C_6 linear or branched chain alkoxy, amino, carboxy, aminocarbonyl, (heterocyclic)C_1-C_6 linear or branched chain alkyl, (C_1-C_6 linear or branched chain alkyl)aryl, (C_1-C_6 linear or branched chain alkyl)heteroaryl, and (C_1-C_6 linear or branched chain alkyl)heterocyclic, where said alkyl is further optionally substituted with one or more substituents selected from the group consisting of halo, hydroxy, methoxy, amino, alkylamino, dialkylamino, CF_3, and C_3-C_6 cycloalkyl; where, alternatively, R_0 or R_1, and/or R_6, respectively together with either of R_4, R_a, R_b, R_c or R_d, may independently form a bond or a C_1-C_6 linear alkyl chain; and/or, alternatively, R_4, respectively together with either of R_a, R_b, R_c or R_d, may independently form a bond or a C_1-C_6 linear alkyl chain; and/or, alternatively, R_8 and R_9 may together form a 3-6-membered ring optionally containing one or two O or N atoms; R_{11} is hydrogen or deuterium; $CR'R_{12}$, R_{13}, R_{14} and R_{15} are independently selected from hydrogen, C_1-C_6 linear or branched chain alkyl, C_1-C_6 linear or branched chain perfluoroalkyl, C_5-C_{10} aryl, alkylaryl, and (aryl)C_1-C_6 linear or branched chain alkyl;

X and the dotted bonds thereto may be present or absent, whereby, (a) if X is present, Y is N, and X is $-(CR_eR_f)_s-$, where R_e and R_f are independently hydrogen, deuterium, halo, hydroxy, C_1-C_4 alkoxy, amino, CF_3, C_1-C_6 linear or branched chain alkyl, C_3-C_6 cycloalkyl, C_5-C_{10} aryl, monocyclic or bicyclic heteroaryl, comprising 5- and/or 6-membered rings, (aryl)C_1-C_6 linear or branched chain alkyl, (C_1-C_6 linear or branched chain alkyl)heteroaryl, (heteroaryl)C_1-C_6 linear or branched chain alkyl, or

(heterocyclic)C_1-C_6 linear or branched chain alkyl, and said dotted bonds are present and are single bonds, where when *n* is 0, X and Y are bonded directly; and (b) if X is absent, said dotted bonds are absent and *n* is 0, and when Y is N, said N atom is substituted by H; and, *n, p, q, r* and *s* are independently 0, 1 or 2.

In another embodiment, the invention provides the compound having the structure:



or a pharmaceutically acceptable salt thereof, and wherein R_2 is selected from the group consisting of hydrogen, deuterium, C_1-C_6 linear or branched chain alkyl, C_3-C_6 cycloalkyl, C_6-C_{10} aryl, monocyclic or bicyclic heteroaryl, comprising 5- and/or 6-membered rings, (aryl)C_1-C_6 linear or branched chain alkyl, (heteroaryl)C_1-C_6 linear or branched chain alkyl, (heterocyclic)C_1-C_6 linear or branched chain alkyl, (C_1-C_6 linear or branched chain alkyl)aryl, (C_1-C_6 linear or branched chain alkyl)heteroaryl, (C_1-C_6 linear or branched chain alkyl)heterocyclic, C_1-C_6 linear or branched chain perfluoroalkyl, C_1-C_6 linear or branched chain alkoxy, C_1-C_6 linear or branched chain perfluoroalkoxy, halogen, cyano, hydroxyl, amino, carboxy, aminocarbonyl, (C_1-C_6 linear or branched chain alkyl)aminocarbonylamino, (C_1-C_6 linear or branched chain alkyl)aminocarbonyl, $-SOR_{12}$, $-SO_2R_{12}$, $-NR_{13}SO_2R_{12}$, $-SO_2NR_{13}R_{14}$, and $-NR_{13}SO_2NR_{14}R_{15}$; where said alkyl, aryl and heteroaryl is independently optionally substituted with one or more substituents selected from the group consisting of halo, hydroxy, methoxy, amino, cyano, alkylamino, dialkylamino, CF_3, aminocarbonyl, (C_1-C_6 linear or branched chain alkyl)aminocarbonyl, and C_3-C_6 cycloalkyl;

R_3 is selected from the group consisting of hydrogen, deuterium, C_1-C_6 linear or branched chain alkyl, C_1-C_6 linear or branched chain perfluoroalkyl, halogen, and cyano;

Z' is CR_{15} or N; where R_{15} is H, C_1-C_4 alkyl, C_6-C_{10} aryl, monocyclic or bicyclic heteroaryl, comprising 5- and/or 6-membered rings, (aryl)C_1-C_6 linear or branched chain alkyl, (heteroaryl)C_1-C_6 linear or branched chain alkyl, (heterocyclic)C_1-C_6 linear or branched chain alkyl, (C_1-C_6 linear or branched chain alkyl)aryl, (C_1-C_6 linear or branched chain alkyl)heteroaryl, or (C_1-C_6 linear or branched chain akyl)heterocyclic, where said alkyl is further optionally substituted with one or more substituents selected from the group consisting of halo, hydroxy, methoxy, amino, CF_3, and C_3-C_6 cycloalkyl;

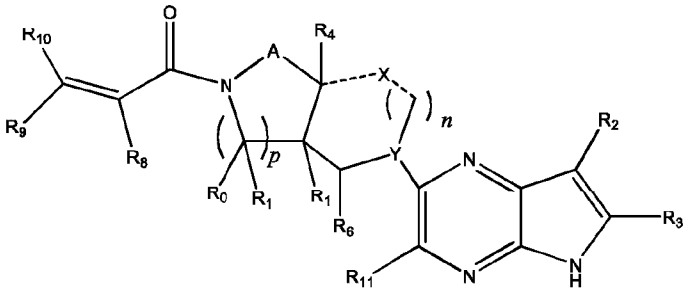
the dotted lines to the O atom may be present or absent, and if present, the resulting ring forms an epoxide, or if absent, an ethylene results;

R_0, R_1, R_6, R_8, R_9 and R_{10} are independently selected from hydrogen, deuterium C_1-C_6 linear or branched chain alkyl, C_1-C_6 linear or branched chain perfluoroalkyl, C_6-C_{10} aryl, monocyclic or bicy-

clic heteroaryl, comprising 5- and/or 6-membered rings, (aryl)C_1-C_6 linear or branched chain alkyl, (heteroaryl)C_1-C_6 linear or branched chain alkyl, heteroaryl, halogen, cyano, hydroxyl, C_1-C_6 linear or branched chain alkoxy, amino, carboxy, aminocarbonyl, (heterocyclic)C_1-C_6 linear or branched chain alkyl, (C_1-C_6 linear or branched chain alkyl)aryl, (C_1-C_6 linear or branched chain alkyl)heteroaryl, and (C_1-C_6 linear or branched chain alkyl)heterocyclic, where said alkyl is further optionally substituted with one or more substituents selected from the group consisting of halo, hydroxy, methoxy, amino, alkylamino, dialkylamino, CF_3, and C_3-C_6 cycloalkyl; where, alternatively, R_0 or R_1, and/or R_6, respectively together with either of R_a, R_b, R_c or R_d, may independently form a bond or a C_1-C_6 linear alkyl chain; and/or, alternatively, R_4, respectively together with either of R_a, R_b, R_c or R_d, may independently form a bond or a C_1-C_6 linear alkyl chain; and/or, alternatively, R_8 and R_9 may together form a 3-6-membered ring optionally containing one or two O or N atoms; R_{11} is hydrogen or deuterium; and,

R_{12}, R_{13}, R_{14} and R_{15} are independently selected from hydrogen, deuterium C_1-C_6 linear or branched chain alkyl, C_1-C_6 linear or branched chain perfluoroalkyl, C_6-C_{10} aryl, alkylaryl, and (aryl)C_1-C_6 linear or branched chain alkyl.

In another embodiment, the invention provides the compound having the structure:



or a pharmaceutically acceptable salt or solvate thereof, or an enantiomer or diastereomer thereof, and wherein R_2 is selected from the group consisting of hydrogen, deuterium, C_1-C_6 linear or branched chain alkyl, C_3-C_6 cycloalkyl, C_6-C_{10} aryl, monocyclic or bicyclic heteroaryl, comprising 5- and/or 6-membered rings, (aryl)C_1-C_6 linear or branched chain alkyl, (heteroaryl)C_1-C_6 linear or branched chain alkyl, (heterocyclic)C_1-C_6 linear or branched chain alkyl, (C_1-C_6 linear or branched chain alkyl)aryl, (C_1-C_6 linear or branched chain alkyl)heteroaryl, (C_1-C_6 linear or branched chain alkyl)heterocyclic, C_1-C_6 linear or branched chain perfluoroalkyl, C_1-C_6 linear or branched chain alkoxy, C_1-C_6 linear or branched chain perfluoroalkoxy, halogen, cyano, hydroxyl, amino, carboxy, aminocarbonyl, (C_1-C_6 linear or branched chain alkyl)aminocarbonylamino, (C_1-C_6 linear or branched chain alkyl)aminocarbonyl, $-SOR_{12}$, $-SO_2R_{12}$, $-NR_{13}SO_2R_{12}$, $-SO_2NR_{13}R_{14}$, and $-NR_{13}SO_2NR_{14}R_{15}$; where said alkyl, aryl and heteroaryl is independently optionally substituted with one or more substituents selected from the group consisting of halo, hydroxy, methoxy, amino, cyano, alkylamino, dialkylamino, CF_3, aminocarbonyl, (C_1-C_6 linear or branched chain alkyl)aminocarbonyl, and C_3-C_6 cycloalkyl;

R_3 is selected from the group consisting of hydrogen, deuterium, C_1-C_6 linear or branched chain alkyl, C_1-C_6 linear or branched chain perfluoroalkyl, halogen, and cyano;

A is —$(CR_aR_b)_q$-$(CR_cR_d)_r$--, wherein R_a, R_b, R_c and R_d are independently selected from hydrogen, C_1-C_6 linear or branched chain alkyl, C_1-C_6 linear or branched chain perfluoroalkyl, C_6-C_{10} aryl, monocyclic or bicyclic heteroaryl, comprising 5- and/or 6-membered rings, alkylaryl, (aryl)C_1-C_6 linear or branched chain alkyl, (heteroaryl)C_1-C_6 linear or branched chain alkyl, halogen, cyano, hydroxyl, C_1-C_6 linear or branched chain alkoxy, amino, carboxy, aminocarbonyl, (heterocyclic)C_1-C_6 linear or branched chain alkyl, (C_1-C_6 linear or branched chain alkyl)aryl, (C_1-C_6 linear or branched chain alkyl)heteroaryl, and (C_1-C_6 linear or branched chain alkyl)heterocyclic, where said alkyl is further optionally substituted with one or more substituents selected from the group consisting of halo, hydroxy, methoxy, amino, alkylamino, dialkylamino, CF_3, and C_3-C_6 cycloalkyl;

R_a, R_b, R_c and R_d are independently selected from hydrogen, C_1-C_6 linear or branched chain alkyl, C_1-C_6 linear or branched chain perfluoroalkyl, aryl, alkylaryl, (aryl)C_1-C_6 linear or branched chain alkyl, (heteroaryl)C_1-C_6 linear or branched chain alkyl, heteroaryl, halogen, cyano, hydroxyl, C_1-C_6 linear or branched chain alkoxy, amino, carboxy, aminocarbonyl, (heterocyclic)C_1-C_6 linear or branched chain alkyl, (C_1-C_6 linear or branched chain alkyl)aryl, (C_1-C_6 linear or branched chain alkyl)heteroaryl, and (C_1-C_6 linear or branched chain alkyl)heterocyclic, wherein said alkyl is further optionally substituted with one or more substituents selected from the group consisting of halo, hydroxy, methoxy, amino, alkylamino, dialkylamino, CF_3, and C_3-C_6 cycloalkyl, where said alkyl is further optionally substituted with one or more substituents selected from the group consisting of halo, hydroxy, methoxy, amino, alkylamino, dialkylamino, CF_3, and C_3-C_6 cycloalkyl;

R_0, R_1, R_4, R_6, R_8, R_9 and R_{10} are independently selected from hydrogen, C_1-C_6 linear or branched chain alkyl, C_1-C_6 linear or branched chain perfluoroalkyl, C_6-C_{10} aryl, monocyclic or bicyclic heteroaryl, comprising 5- and/or 6-membered rings, (aryl)C_1-C_6 linear or branched chain alkyl, (heteroaryl)C_1-C_6 linear or branched chain alkyl, heteroaryl, halogen, cyano, hydroxyl, C_1-C_6 linear or branched chain alkoxy, amino, carboxy, aminocarbonyl, (heterocyclic)C_1-C_6 linear or branched chain alkyl, (C_1-C_6 linear or branched chain alkyl)aryl, (C_1-C_6 linear or branched chain alkyl)heteroaryl, and (C_1-C_6 linear or branched chain alkyl)heterocyclic, where said alkyl is further optionally substituted with one or more substituents selected from the group consisting of halo, hydroxy, methoxy, amino, alkylamino, dialkylamino, CF_3, and C_3-C_6 cycloalkyl; where, alternatively, R_0 or R_1, and/or R_6, respectively together with either of R_4, R_a, R_b, R_c or R_d, may independently form a bond or a C_1-C_6 linear alkyl chain; and/or, alternatively, R_4, respectively together with either of R_a, R_b, R_c or R_d, may independently form a bond or a C_1-C_6 linear alkyl chain; and/or, alternatively, R_8 and R_9 may together form a 3-6-membered ring optionally containing one or two O or N atoms; and, R_{11} is hydrogen or deuterium;

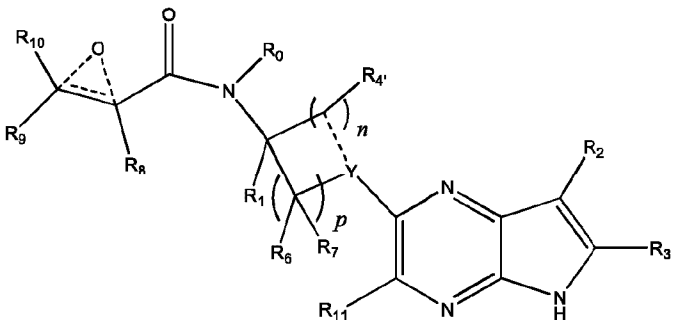
Y is O or N, where when Y is O, *n* is 0;

R_{12}, R_{13}, R_{14} and R_{15} are independently selected from hydrogen, C_1-C_6 linear or branched chain alkyl, C_1-C_6 linear or branched chain perfluoroalkyl, C_6-C_{10} aryl, alkylaryl, and (aryl)C_1-C_6 linear or branched chain alkyl;

X and the dotted bonds thereto may be present or absent, whereby, (a) if X is present, Y is N, and X is —$(CR_eR_f)_s$—, where R_e and R_f are independently hydrogen, deuterium, halo, hydroxy, C_1-C_4 alkoxy, amino, CF_3, C_1-C_6 linear or branched chain alkyl, C_3-C_6 cycloalkyl, C_6-C_{10} aryl, monocyclic or bicyclic heteroaryl, comprising 5- and/or 6-membered rings, (aryl)C_1-C_6 linear or branched chain alkyl, (C_1-C_6 linear or branched chain alkyl)heteroaryl, (heteroaryl)C_1-C_6 linear or branched chain alkyl, or (heterocyclic)C_1-C_6 linear or branched chain alkyl, and said dotted bonds are present and are single bonds, where when *n* is 0, X and Y are bonded directly; and (b) if X is absent, said dotted bonds are absent and *n* is 0, and when Y is N, said N atom is substituted by H; and, *n, p, q, r* and *s* are independently 0, 1 or 2.

The present invention also provides

compound having the structure:



or a pharmaceutically acceptable salt or solvate thereof, or an enantiomer or diastereomer thereof, and wherein R_2 is selected from the group consisting of hydrogen, deuterium, C_1-C_6 linear or branched chain alkyl, C_3-C_6 cycloalkyl, C_6-C_{10} aryl, monocyclic or bicyclic heteroaryl, comprising 5- and/or 6-membered rings, (aryl)C_1-C_6 linear or branched chain alkyl, (heteroaryl)C_1-C_6 linear or branched chain alkyl, (heterocyclic)C_1-C_6 linear or branched chain alkyl, (C_1-C_6 linear or branched chain alkyl)aryl, (C_1-C_6 linear or branched chain alkyl)heteroaryl, (C_1-C_6 linear or branched chain alkyl)heterocyclic, C_1-C_6 linear or branched chain perfluoroalkyl, C_1-C_6 linear or branched chain alkoxy, C_1-C_6 linear or branched chain perfluoroalkoxy, halogen, cyano, hydroxyl, amino, carboxy, aminocarbonyl, (C_1-C_6 linear or branched chain alkyl)aminocarbonylamino, (C_1-C_6 linear or branched chain alkyl)aminocarbonyl, -SOR_{12}, -SO_2R_{12}, -$NR_{13}SO_2R_{12}$, -$SO_2NR_{13}R_{14}$, and -$NR_{13}SO_2NR_{14}R_{15}$; where said alkyl, aryl and heteroaryl is independently optionally substituted with one or more substituents selected from the group consisting of halo, hydroxy, methoxy, amino, cyano, alkylamino, dialkylamino, CF_3, aminocarbonyl, (C_1-C_6 linear or branched chain alkyl)aminocarbonyl, and C_3-C_6 cycloalkyl;

the dotted lines to the O atom may be present or absent, and if present, the resulting ring forms an epoxide, or if absent, an ethylene results;

R_3 is selected from the group consisting of hydrogen, deuterium, C_1-C_6 linear or branched chain alkyl, C_1-C_6 linear or branched chain perfluoroalkyl, halogen, and cyano;

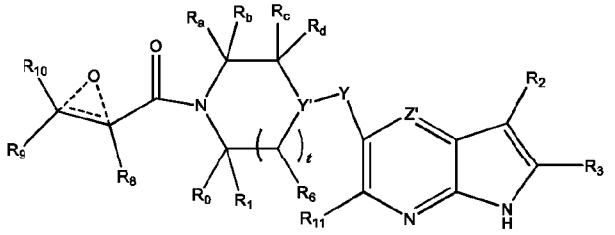
R_0 is selected from hydrogen, C_1-C_6 linear or branched chain alkyl, and C_1-C_6 linear or branched chain perfluoroalkyl;

R_1, R_4, R_5, $R_{4'}$, R_6, R_7, R_8, R_9 and R_{10} are independently selected from hydrogen, C_1-C_6 linear or branched chain alkyl, C_1-C_6 linear or branched chain perfluoroalkyl, C_6-C_{10} aryl, monocyclic or bicyclic heteroaryl, comprising 5- and/or 6-membered rings, (aryl)C_1-C_6 linear or branched chain alkyl, (heteroaryl)C_1-C_6 linear or branched chain alkyl, heteroaryl, halogen, cyano, hydroxyl, C_1-C_6 linear or branched chain alkoxy, amino, carboxy, aminocarbonyl, (heterocyclic)C_1-C_6 linear or branched chain alkyl, (C_1-C_6 linear or branched chain alkyl)aryl, (C_1-C_6 linear or branched chain alkyl)heteroaryl, and (C_1-C_6 linear or branched chain alkyl)heterocyclic, where said alkyl is further optionally substituted with one or more substituents selected from the group consisting of halo, hydroxy, methoxy, amino, alkylamino, dialkylamino, CF_3, and C_3-C_6 cycloalkyl; where R_8 and R_9 may together form a 3-6-membered ring optionally containing one or two O or N atoms; R_{11} is hydrogen or deuterium; R_{12}, R_{13}, R_{14} and R_{15} are independently selected from hydrogen, C_1-C_6 linear or branched chain alkyl, C_1-C_6 linear or branched chain perfluoroalkyl, C_6-C_{10} aryl, alkylaryl, and (aryl)C_1-C_6 linear or branched chain alkyl;

Y is O or N, where when Y is N, the dash bond is a single bond or N is substituted by H or alkyl, and the dash bond thereto is absent, and when Y is O, the dash bond thereto is absent;

and, *n* and *p* are independently 0, 1 or 2.

In another embodiment, the invention provides the compound having the structure:



or a pharmaceutically acceptable salt thereof, and wherein R_2 is selected from the group consisting of hydrogen, deuterium, C_1-C_6 linear or branched chain alkyl, C_3-C_6 cycloalkyl, C_6-C_{10} aryl, monocyclic or bicyclic heteroaryl, comprising 5- and/or 6-membered rings, (aryl)C_1-C_6 linear or branched chain alkyl, (heteroaryl)C_1-C_6 linear or branched chain alkyl, (heterocyclic)C_1-C_6 linear or branched chain alkyl, (C_1-C_6 linear or branched chain alkyl)aryl, (C_1-C_6 linear or branched chain alkyl)heteroaryl, (C_1-C_6 linear or branched chain alkyl)heterocyclic, C_1-C_6 linear or branched chain perfluoroalkyl, C_1-C_6 linear or branched chain alkoxy, C_1-C_6 linear or branched chain perfluoroalkoxy, halogen, cyano, hydroxyl, amino, carboxy, aminocarbonyl, (C_1-C_6 linear or branched chain alkyl)aminocarbonylamino, (C_1-C_6 linear or branched chain alkyl)aminocarbonyl, -SOR_{12}, -SO_2R_{12}, -$NR_{13}SO_2R_{12}$, -$SO_2NR_{13}R_{14}$, and -$NR_{13}SO_2NR_{14}R_{15}$; where said alkyl, aryl and heteroaryl is independently optionally substituted with one or more substituents selected from the group consisting of halo, hydroxy, methoxy, amino, cyano,

alkylamino, dialkylamino, CF_3, aminocarbonyl, (C_1-C_6 linear or branched chain alkyl)aminocarbonyl, and C_3-C_6 cycloalkyl;

R_3 is selected from the group consisting of hydrogen, deuterium, C_1-C_6 linear or branched chain alkyl, C_1-C_6 linear or branched chain perfluoroalkyl, halogen, and cyano;

Z' is CR_{16} or N; where R_{16} is H, C_1-C_4 alkyl, C_5-C_{10} aryl, monocyclic or bicyclic heteroaryl, comprising 5- and/or 6-membered rings, (aryl)C_1-C_6 linear or branched chain alkyl, (heteroaryl)C_1-C_6 linear or branched chain alkyl, (heterocyclic)C_1-C_6 linear or branched chain alkyl, (C_1-C_6 linear or branched chain alkyl)aryl, (C_1-C_6 linear or branched chain alkyl)heteroaryl, or (C_1-C_6 linear or branched chain akyl)heterocyclic, where said alkyl is further optionally substituted with one or more substituents selected from the group consisting of halo, hydroxy, methoxy, amino, CF_3, and C_3-C_6 cycloalkyl;

the dotted lines to the O atom may be present or absent, and if present, the resulting ring forms an epoxide, or if absent, an ethylene results;

R_0, R_1, R_6, R_8, R_9 and R_{10} are independently selected from hydrogen, deuterium C_1-C_6 linear or branched chain alkyl, C_1-C_6 linear or branched chain perfluoroalkyl, C_6-C_{10} aryl, monocyclic or bicyclic heteroaryl, comprising 5- and/or 6-membered rings, (aryl)C_1-C_6 linear or branched chain alkyl, (heteroaryl)C_1-C_6 linear or branched chain alkyl, heteroaryl, halogen, cyano, hydroxyl, C_1-C_6 linear or branched chain alkoxy, amino, carboxy, aminocarbonyl, (heterocyclic)C_1-C_6 linear or branched chain alkyl, (C_1-C_6 linear or branched chain alkyl)aryl, (C_1-C_6 linear or branched chain alkyl)heteroaryl, and (C_1-C_6 linear or branched chain alkyl)heterocyclic, where said alkyl is further optionally substituted with one or more substituents selected from the group consisting of halo, hydroxy, methoxy, amino, alkylamino, dialkylamino, CF_3, and C_3-C_6 cycloalkyl; where, alternatively, R_0 or R_1, and/or R_6, respectively together with either of R_a, R_b, R_c or R_d, may independently form a bond or a C_1-C_6 linear alkyl chain; and/or, alternatively, R_4, respectively together with either of R_a, R_b, R_c or R_d, may independently form a bond or a C_1-C_6 linear alkyl chain; and/or, alternatively, R_8 and R_9 may together form a 3-6-membered ring optionally containing one or two O or N atoms; R_{11} is hydrogen or deuterium;

Y is either a bond, O or N, where N may be substituted by hydrogen or linear or branched chain C_1-C_6 alkyl;

Y' is CR_{17} or N, where Y' is CR_{17} when Y is N or O; where R_{17} is hydrogen, linear or branched chain C_1-C_4 alkyl, or C_6-C_{10} aryl; R_{12}, R_{13}, R_{14} and R_{15} are independently selected from hydrogen, deuterium C_1-C_6 linear or branched chain alkyl, C_1-C_6 linear or branched chain perfluoroalkyl, C_6-C_{10} aryl, alkylaryl, and (aryl)C_1-C_6 linear or branched chain alkyl;

and, *t* is 0, 1 or 2.

The present invention also provides a pharmaceutical or a veterinary composition comprising a compound described above, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

Specifically, the invention provides compounds selected from the group consisting of:

2-{[(2S)-1-acryloylpyrrolidin-2-yl]methoxy}-N-[(2S)-1-methoxypropan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide;

2-[(1-acryloylpiperidin-4-yl)amino]-N-(3-fluorobenzyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide;

2-[(1-acryloylpiperidin-4-yl)amino]-N-(2-cyclopropylethyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide;

2-[(1-acryloylpiperidin-4-yl)amino]-N-benzyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide;

2-[(1-acryloylpiperidin-4-yl)oxy]-N-[(2R)-1-methoxypropan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide;

2-[(1-acryloylpiperidin-4-yl)oxy]-N-[(2S)-1-methoxypropan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide;

2-(4-acryloylpiperazin-1-yl)-N-[(2S)-1-methoxypropan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide;

2-(4-acryloylpiperazin-1-yl)-N-[(2R)-1-cyanobutan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide;

2-{[(3S,4R)-1-acryloyl-3-methoxypiperidin-4-yl]amino}-N-[(2R)-1-methoxypropan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide; and,

2-(4-acryloylpiperazin-1-yl)-N-[(2R)-4,4,4-trifluoro-2-methylbutyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide.

The present invention also provides a pharmaceutical or a veterinary composition comprising a compound described above, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

The present invention also provides a method for treating or preventing a disorder or condition selected from rheumatoid arthritis, myositis, vasculitis, pemphigus, bullous pemphigoid, inflammatory bowel disease including Crohn's disease and ulcerative colitis, celiac diseases, proctitis, eosinophilic gastroenteritis, or mastocytosis, Alzheimer's disease, lupus, nephritis, systemic lupus erythematosus, psoriasis, eczema dermatitis, pruritus or other pruritic conditions, vitiligo, alopecia, autoimmune thyroid disorders, multiple sclerosis, major depression disorder, allergy, asthma, Sjogren's disease, Reiter's syndrome, polymyositis-dermatomyositis, systemic sclerosis, polyarteritis nodosa, dry eye syndrome, Hashimoto's thyroiditis, autoimmune hemolytic anemia, autoimmune atrophic gastritis of pernicious anemia, autoimmune encephalomyelitis, autoimmune orchitis, Goodpasture's disease, autoimmune thrombocytopenia, sympathetic ophthalmia, myasthenia gravis, Graves' disease, primary biliary cirrhosis, chronic aggressive hepatitis, membranous glomerulopathy ,organ transplant rejection, graft-versus-host disease, organ and cell transplant rejection such as bone marrow, cartilage, cornea, heart, intervertebral disc, islet, kidney, limb, liver, lung, muscle, myoblast, nerve, pancreas, skin, small intestine, or trachea, or xeno transplantation, including Cogan's syndrome, ankylosing spondylitis, Wegener's granulomatosis, autoimmune alopecia, Type I or juvenile onset diabetes, and complica-

tions from diabetes, or thyroiditis, chronic pulmonary obstructive disorder, acute respiratory disease, cachexia, cancer, including alimentary/gastrointestinal tract cancer, colon cancer, liver cancer, skin cancer including mast cell tumor and squamous cell carcinoma, breast and mammary cancer, ovarian cancer, prostate cancer, leukemia, adult T cell leukemia activated B-cell like, diffuse large B cell lymphoma, kidney cancer, lung cancer, muscle cancer, bone cancer, bladder cancer, brain cancer, melanoma including oral and metastatic melanoma, Kaposi's sarcoma septic shock, cardiopulmonary dysfunction, acute myeloid leukemia, T cell acute lymphoblastic leukemia, multiple myeloma, myeloproliferative disorders, proliferative diabetic retinopathy, or angiogenic-associated disorders including solid tumors, pancreatic cancer, brain tumors, gliomas including astrocytoma, oligodendroglioma, and glioblastoma, acute CNS trauma including traumatic brain injury, encephalitis, stroke, and spinal cord injury, epilepsy, seizures, chronic neuroinflammation associated with neurodegeneration including Alzheimer's disease, Parkinson's disease, Amyotropic Lateral Sclerosis, Huntington's disease, cerebral ischemia, fronto-temporal lobe dementia, and with neuropsychiatric disorders including schizophrenia, bipolar disorder, treatment resistant depression, Post Traumatic Stress Disorder, anxiety, and auto-antibodies mediated encephalopathies, Eye diseases, disorders or conditions including autoimmune diseases of the eye, keratoconjunctivitis, vernal conjunctivitis, uveitis including uveitis associated with Behcet's disease and lens-induced uveitis, keratitis, herpetic keratitis, conical keratitis, corneal epithelial dystrophy, keratoleukoma, ocular premphigus, Mooren's ulcer, scleritis, Grave's ophthalmopathy, Vogt-Koyanagi-Harada syndrome, keratoconjunctivitis sicca (dry eye), phlyctenule, iridocyclitis, sarcoidosis, endocrine ophthalmopathy, sympathetic ophthalmitis, allergic conjunctivitis, and ocular neovascularization, comprising the step of administering to a subject an effective amount of a composition comprising a compound set forth hereinabove.

The present invention also provides a method for treating or preventing inflammatory bowel disease by administering to a mammal in need a therapeutically effective amount of a compound described above, or a pharmaceutically acceptable salt thereof.

More generally, the present invention provides a method of treating a disorder or condition related to dysregulation of JAK, and particularly of JAK3, in a subject, comprising administering to the subject a therapeutically effective amount of the compound described above, or a pharmaceutically acceptable salt thereof.

In certain embodiments, the therapeutically effective amount used in accord with the method is from 0.01 mg/kg of body weight/day to 100 mg/kg of body weight/day. In certain other embodiments, the therapeutically effective amount used in accord with the method is the therapeutically effective amount is from 0.1 mg/kg of body weight/day to 10 mg/kg of body weight/day. In the practice of the method, the compound is preferably selected from those specified above.

In certain embodiments, the therapeutically effective amount used in accord with the method is from 0.01 mg/kg of body weight/day to 100 mg/kg of body weight/day. In certain other embodiments, the therapeutically effective amount used in accord with the method is wherein the therapeutically effective amount is from 0.1 mg/kg of body weight/day to 10 mg/kg of body weight/day. In ac-

cord with the method, the mammal treated with the compound of the invention is selected from companion animals, dogs, and livestock. In certain embodiments, the compound of the invention, or a pharmaceutically acceptable salt thereof, may be administered in accord with the method orally, parenterally, or topically.

Compounds 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 of the invention can exist as *cis*- and *trans*- achiral diastereomers.

Included within the scope of the described compounds 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. 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 the invention 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 mammal, a compound 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 of the invention 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, 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.

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).

Pharmaceutically acceptable salts of compounds of the invention, may be prepared, respectively, by one or more of three methods: (i) by reacting the compound with the desired acid or base; (ii) by removing an acid- or base-labile protecting group from a suitable precursor of the compound of the invention, 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 of the invention, 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.

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 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.

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 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 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 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 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 of the present invention are directed to pyrrolo[2,3-d]pyrimidinyl, pyrrolo[2,3,D]pyrazinyl, and pyrrolo[2,3-d]pyridinyl acrylamides and epoxides useful as Janus Kinase inhibitors (JAK-i). They are useful as therapeutic agents in connection with the treating or preventing a disorder or condition selected from rheumatoid arthritis, myositis, vasculitis, pemphigus, bullous pemphigoid, inflammatory bowel disease including Crohn's disease and ulcerative colitis, celiac diseases, proctitis, eosinophilic gastroenteritis, or mastocytosis, Alzheimer's disease, lupus, nephritis, systemic lupus erythematosus, psoriasis, eczema dermatitis, pruritus or other pruritic conditions, vitiligo, alopecia, autoimmune thyroid disorders, multiple sclerosis, major depression disorder, allergy, asthma, Sjogren's disease, Reiter's syndrome, polymyositis-dermatomyositis, systemic sclerosis, polyarteritis nodosa, dry eye syndrome, Hashimoto's thyroiditis, autoimmune hemolytic anemia, autoimmune atrophic gastritis of pernicious anemia, autoimmune encephalomyelitis, autoimmune orchitis, Goodpasture's disease, autoimmune thrombocytopenia, sympathetic ophthalmia, myasthenia gravis, Graves' disease, primary biliary cirrhosis, chronic aggressive hepatitis, membranous glomerulopathy ,organ transplant rejection, graft-versus-host disease, organ and cell transplant rejection such as bone marrow, cartilage, cornea, heart, intervertebral disc, islet, kidney, limb, liver, lung, muscle, myoblast, nerve, pancreas, skin, small intestine, or trachea, or xeno transplantation, including Cogan's syndrome, ankylosing spondylitis, Wegener's granulomatosis, autoimmune alopecia, Type I or juvenile onset diabetes, and complications from diabetes, or thyroiditis, chronic pulmonary obstructive disorder, acute respiratory disease, cachexia, cancer, including alimentary/gastrointestinal tract cancer, colon cancer, liver cancer, skin cancer including mast cell tumor and squamous cell carcinoma, breast and mammary cancer, ovarian cancer, prostate cancer, leukemia, adult T cell leukemia activated B-cell like, diffuse large B cell lymphoma, kidney cancer, lung cancer, muscle cancer, bone cancer,

bladder cancer, brain cancer, melanoma including oral and metastatic melanoma, Kaposi's sarcoma septic shock, cardiopulmonary dysfunction, acute myeloid leukemia, T cell acute lymphoblastic leukemia, multiple myeloma, myeloproliferative disorders, proliferative diabetic retinopathy, or angiogenic-associated disorders including solid tumors, pancreatic cancer, brain tumors, gliomas including astrocytoma, oligodendroglioma, and glioblastoma, acute CNS trauma including traumatic brain injury, encephalitis, stroke, and spinal cord injury, epilepsy, seizures, chronic neuroinflammation associated with neurodegeneration including Alzheimer's disease, Parkinson's disease, Amyotropic Lateral Sclerosis, Huntington's disease, cerebral ischemia, fronto-temporal lobe dementia, and with neuropsychiatric disorders including schizophrenia, bipolar disorder, treatment resistant depression, Post Traumatic Stress Disorder, anxiety, and auto-antibodies mediated encephalopathies, Eye diseases, disorders or conditions including autoimmune diseases of the eye, keratoconjunctivitis, vernal conjunctivitis, uveitis including uveitis associated with Behcet's disease and lens-induced uveitis, keratitis, herpetic keratitis, conical keratitis, corneal epithelial dystrophy, keratoleukoma, ocular premphigus, Mooren's ulcer, scleritis, Grave's ophthalmopathy, Vogt-Koyanagi-Harada syndrome, keratoconjunctivitis sicca (dry eye), phlyctenule, iridocyclitis, sarcoidosis, endocrine ophthalmopathy, sympathetic ophthalmitis, allergic conjunctivitis, and ocular neovascularization, ,and other indications where immunosuppression/immunomodulation would be desirable, comprising the step of administering to a subject an effective amount of a compound of the invention.

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 in animals is currently dominated by corticosteroids, which cause distressing and undesirable side effects in animals, specifically in companion animals such as dogs. APOQUEL™ is a pan-JAK inhibitor recently approved for atopic dermatitis in canines. Antihistamines are also used, but are poorly effective. A canine formulation of cyclosporine (ATOPICA™) is currently being marketed for atopic dermatitis, but is expensive and has a slow onset of efficacy. In addition, there are GI toleration issues with ATOPICA™. Compounds of the present invention are JAK inhibitors with selective efficacy against JAK3. These compounds are expected to provide an alternative to steroid usage and provide resolution of chronic pruritus and inflammation that would either persist in atopic dermatitis or slowly regress following removal of allergen or causative agent, such as fleas in flea-allergic dermatitis.

Compounds 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 cyclosporin A (e.g., Sandimmune™ or Neoral™, rapamycin, FK-506 (tacrolimus), leflunomide, deoxyspergualin, mycophenolate (e.g., Cellcept™, azathioprine (e.g., Imuran™), daclizumab (e.g., Zenapax™), OKT3 (e.g., Orthocolone™), AtGam™, aspirin, acetaminophen, ibuprofen, naproxen, piroxicam, and anti-inflammatory steroids (e.g., prednisolone or dexamethasone), IFN-beta, teriflunomide, Laquinimod, glatiramer acetate, dimethyl fumerate, rituximab, fingolimod, natalizumab, alemtuzumab,

mitoxantrone. Sulfasalazine (Azulfidine), Mesalamine (Apriso, Asacol, Lialda, others), balsalazide (Colazal) and olsalazine (Dipentum), and mercaptopurine (Purinethol), antibiotics (antimycobacterial drugs, eg. Metronidazole, ciprofloxacin), Ustekinumab and vedolizumab These agents may be administered as part of the same or separate dosage forms, via the same or different routes of administration, and on the same or different administration schedules according to standard pharmaceutical practice known to one skilled in the art.

Accordingly, the invention provides methods of treating or preventing a disease, condition or disorder associated with JAK in a subject, such as a human or non-human mammal, comprising administering an effective amount of one or more compounds described herein to the subject. Suitable subjects that can be treated include domestic or wild animals, companion animals, such as dogs, cats, horses and the like; livestock including, cows and other ruminants, pigs, poultry, rabbits and the like; primates, for example monkeys, such as rhesus monkeys and cynomolgus (also known as crab-eating or long-tailed) monkeys, marmosets, tamarins, chimpanzees, macaques and the like; and rodents, such as rats, mice, gerbils, guinea pigs and the like. In one embodiment, the compound is administered in a pharmaceutically acceptable form, optionally in a pharmaceutically acceptable carrier.

Another embodiment provides a method of selectively inhibiting a JAK3 enzyme, which includes contacting the JAK enzyme with either a non-therapeutic amount or a therapeutically effective amount of one or more of the presently taught compounds. Such methods can occur *in vivo* or *in vitro*. *In vitro* contact can involve a screening assay to determine the efficacy of the one or more compounds against a selected enzyme at various amounts or concentrations. *In vivo* contact with a therapeutically effective amount of the one or more compounds can involve treatment of a described disease, disorder or condition or prophylaxis of organ transplant rejection in the animal in which the contact occurs. The effect of the one or more compounds on the JAK enzyme and/or host animal can also be determined or measured. Methods for determining JAK activity include those described in the Examples as well as those disclosed in WO99/65908, WO 99/65909, WO01/42246, WO02/00661, WO02/096909, WO2004/046112 and WO2007/012953.

Chemical Synthesis

The following schemes and written descriptions provide general details regarding the preparation of the compounds of the invention. It will be apparent to those skilled in the art that sensitive functional groups may need to be protected (PG) and deprotected during the synthesis of a compound of the invention. Protection and deprotection may be achieved by conventional methods, as described, for example, in *Protective Groups in Organic Synthesis* by T. W. Greene and P. G. M. Wuts, John Wiley & Sons Inc. (1999), and references therein.

Several methods exist for the preparation of such compounds, which are well known to those skilled in the art and have been described in texts such as *Advanced Organic Chemistry* by J. March, John Wiley & Sons (1985). It is noted that certain compounds of the invention can be obtained by functional group transformations at a late stage of the synthesis. Such functional group transfor-

mations may include one step or multiple steps, for example, reduction of an ester to an alcohol, reoxidation to an aldehyde, addition of an organomagesium reagent to form a secondary alcohol, reoxidation to a ketone and, finally, addition of an organomagesium reagent to yield a tertiary alcohol. The intermediates andcompounds were named using ChemDraw11 (CambridgeSoft) structure to name converter or ACD Labs Name Software v12. The inclusion of rac- (or racemic) modifier indicates material is racemic. When rac- (or racemic) is included with R,S indications this is intended to convey relative stereochemistry, however in the absence of the rac- (or racemic) notation the compounds absolute stereochemistry is known. In some instances the rac- (or racemic) notation conveys the stereochemistry of a fragment of the compound, while the R,S designation conveys absolute stereochemistry of another portion. For cases where racemates are separated into their constituent enantiomers the absolute stereochemistry is arbitrarily assigned, unless otherwise noted. Accordingly, the actual absolute enantiomeric form of the biologically active compound may differ from the arbitrarily assigned stereochemcial designation.

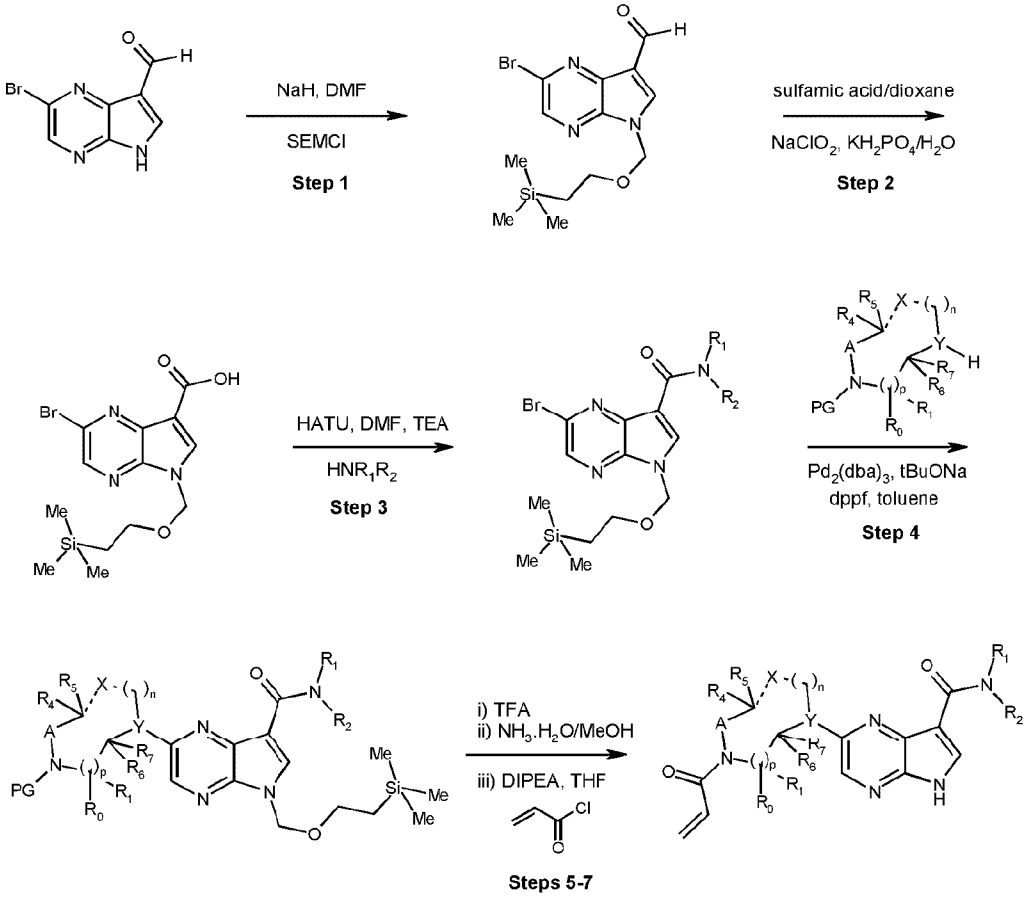
In executing the synthesis of the compounds of the invention, one skilled in the art will recognize the need to sample and assay reaction mixtures prior to work up in order to monitor the progress of reactions and decide whether the reaction should be continued or whether it is ready to be worked up 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 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 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 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.

Examples 1-81 were prepared as described in the Scheme below:



Example 1 Step 0

2-Bromo-5H-pyrrolo[2,3-b]pyrazine-7-carbaldehyde. To a suspension of (2-bromo-5H-pyrrolo[2,3-b]pyrazin-7-yl)methanol (127 g, 556 mmol, described in U.S. Serial No. 14/559,294) in acetone (2.5 L) was added dropwise Jones reagent (253 mL, 675 mmol, 2.67 M) below 10 °C. After the addition, the resulting mixture was stirred at room temperature for 50 min, during which time the suspension became clear and a brown solid precipitated. The three batches were combined for workup together. The reaction mixture was quenched with i-PrOH (60 mL) and filtered, the filter cake was washed with acetone (1 L x 2), the combined filtrate was evaporated to give 2-bromo-5H-pyrrolo[2,3-b]pyrazine-7-carbaldehyde (320 g, 84.4%) as a yellow solid. (A stock of Jones reagent (2.67 M) was prepared by carefully adding concentrated H_2SO_4 (184 mL) to CrO_3 (213.6 g) then diluting to 800 mL with H_2O.)

Step 1 2-Bromo-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazine-7-carbaldehyde

To a suspension of NaH (60% dispersion in oil, 5.1 g, 127 mmol) in DMF (200 mL) was added 2-bromo-5H-pyrrolo[2,3-b]pyrazine-7-carbaldehyde (**Step 0**, 19 g, 84.1 mmol) and the reaction was stirred at 0°C for 10 minutes. SEM-Cl (17 g, 102 mmol) was added dropwise at 0°C and the reaction

stirred at room temperature for 3 hours. The reaction was quenched by the addition of ice-water (600 mL) and extracted into EtOAc (2 x 500 mL). The combined organic layers were washed with water (600 mL), brine (3 x 600 mL), dried over sodium sulphate and concentrated *in vacuo*. The residue was purified using silica gel column chromatography eluting with 0.25-25% EtOAc in petroleum ether to afford the title compound as a yellow solid (15 g, 25%). MS m/z 358 $[M^{81}Br+H]^+$

Example 1 Step 2

2-Bromo-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid

To a solution of 2-bromo-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazine-7-carbaldehyde (**Example 1 Step 1**, 19 g, 53.4 mmol) and sulfamic acid (26 g, 268 mmol) in dioxane and water (200 mL, 1:1) was added a solution of $NaClO_2$ (7.23 g, 80 mmol) and KH_2PO_4 (36.4 g, 268 mmol) in water (50 mL) at 0°C over 20 minutes. The reaction was stirred at room temperature for 16 hours and then partitioned between EtOAc (500 mL) and water (200 mL). The aqueous layer was further extracted with EtOAc (200 mL), the organic layers combined, washed with water (300 mL), brine (300 mL), dried over sodium sulphate and concentrated *in vacuo*. The residue was triturated with TBME to afford the title compound as a white solid (14.5 g, 73%). ^1H NMR (400MHz, DMSO-d_6): δ ppm 12.66 (br s, 1H), 8.80-8.72 (m, 1H), 8.58 (s, 1H), 5.72-5.64 (m, 2H), 3.56 (t, J=7.8 Hz, 2H), 0.83 (t, J=8.0 Hz, 2H), -0.01 (s, 9H).

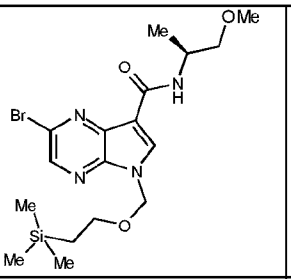
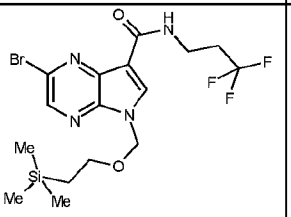
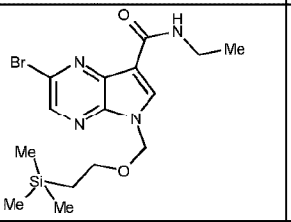
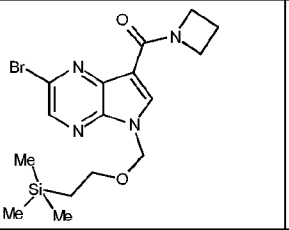
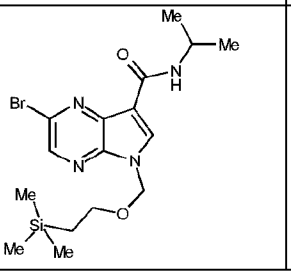
Example 1 Step 3

(R)-2-bromo-N-(1-methoxypropan-2-yl)-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

To a solution of 2-bromo-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid (**Example 1 Step 2**, 6 g, 16.12 mmol) and HATU (7.35 g, 19.3 mmol) in DMF (160 mL) was added TEA (4.89 g, 48.3 mmol) followed by (R)-1-methoxypropan-2-amine (2.15 g, 24.2 mmol) and the reaction was stirred at room temperature for 18 hours. The reaction was concentrated *in vacuo* and partitioned between EtOAc and water. The aqueous layer was further extracted with EtOAc (2 x 10 mL) and the organic layers were combined, washed with brine, dried over sodium sulphate and concentrated *in vacuo*. The residue was purified using silica gel column chromatography eluting with 10-50% EtOAc in petroleum ether to afford the title compound as a white solid (6.2 g, 87%).
MS m/z 445 $[M^{81}Br+H]^+$

The following Preparations were prepared according to the method described for **Example 1 Step 3** using 2-bromo-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid (**Example 1 Step 2**) and the appropriate amine.

Prep No.	Name	Structure	Data/SM

Ex 4 Step 3	(S)-2-bromo-N-(1-methoxypropan-2-yl)-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 445 $[M^{81}Br+H]^+$ (S)-1-methoxypropan-2-amine.
Ex 22 Step 3	2-bromo-N-(3,3,3-trifluoropropyl)-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		Taken on directly to the next step. 3,3,3-trifluoropropylamine.
Ex 25 Step 3	2-bromo-5-[(3,3-dimethylbutoxy)methyl]-N-ethyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		Taken on directly to the next step. Ethylamine.
Ex 62 Step 3	azetidin-1-yl(2-bromo-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-7-yl)methanone		MS m/z 413 $[M^{81}Br+H]^+$ Using TBTU with DIPEA and azetidine.
Ex 64 Step 3	2-bromo-N-isopropyl-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		^1H NMR (400MHz, $CDCl_3$): δ ppm 8.40 (s, 1H), 8.31 (s, 1H), 7.71-7.69 (m, 1H), 5.64 (s, 2H), 4.39-4.27 (m, 1H), 3.56-3.50 (m, 1H), 1.33 (s, 3H), 1.32 (s, 3H), 0.92-0.88 (m, 2H), -0.04 (s, 9H). Isopropylamine.

Example 54 Step 4

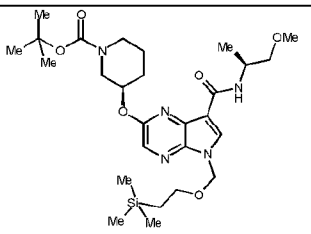
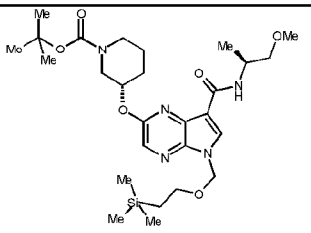
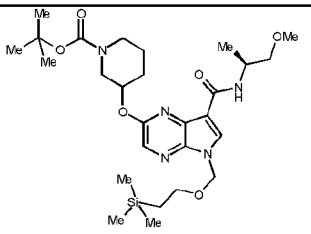
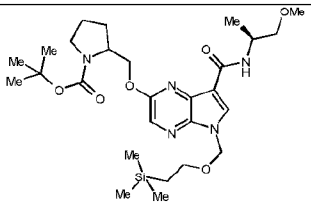
tert-Butyl (S)-3-[(7-[((R)-1-methoxypropan-2-yl)carbamoyl]-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl)oxy]pyrrolidine-1-carboxylate

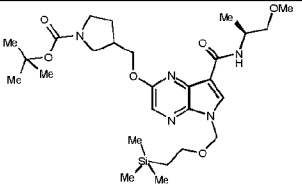
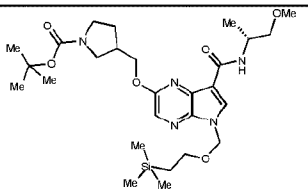
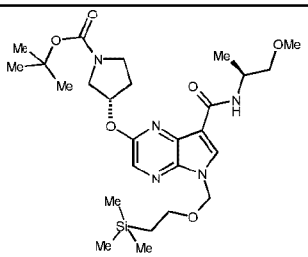
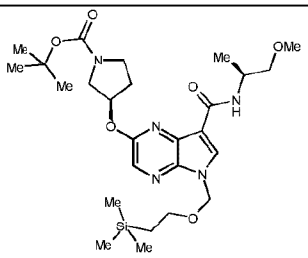
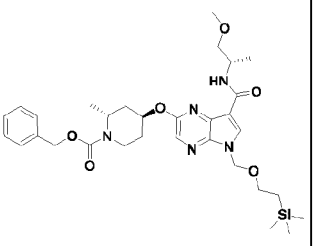
Method A wherein Y=O

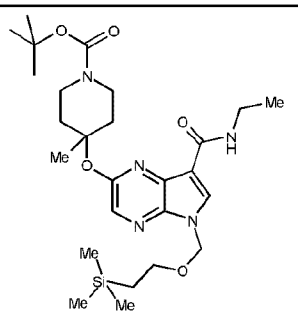
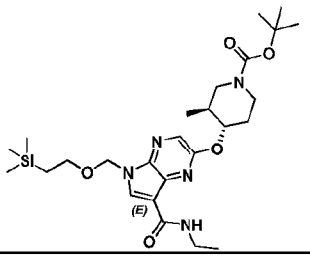
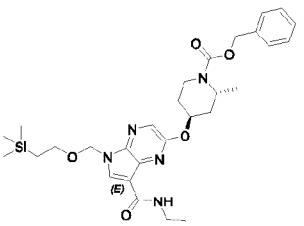
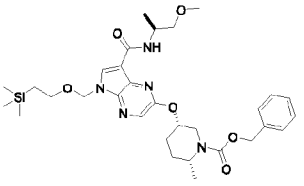
To a solution of (R)-2-bromo-N-(1-methoxypropan-2-yl)-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide (**Example 1 Step 3,** 700 mg, 1.58 mmol), tert-butyl (S)-3-

hydroxypyrrolidine-1-carboxylate (443 mg, 2.37 mmol) and sodium tert-butoxide (455 mg, 4.74 mmol) in toluene (20 mL) was added Pd_2dba_3 (145 mg, 0.158 mmol) followed by dppf (114 mg, 0.21 mmol) and the reaction was heated to 110°C for 18 hours. The reaction was concentrated *in vacuo* and purified using silica gel column chromatography eluting with 20-66% EtOAc in petroleum ether to afford the title compound as a yellow oil (550 mg, 63%).
MS m/z 572 $[M+Na]^+$

The following Preparations were prepared according to **Method A wherein Y=O** as described for **Example 54 Step 4** using the appropriate heteroaryl bromide and alcohol:

Prep No.	Name	Structure	Data/SM
Ex 49 Step 4	tert-butyl (R)-3-[(7-[((S)-1-methoxypropan-2-yl)carbamoyl]-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl)oxy]piperidine-1-carboxylate		MS m/z 586 $[M+Na]^+$ (S)-2-bromo-N-(1-methoxypropan-2-yl)-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide (**Example 4 Step 3**) and tert-butyl (S)-3-hydroxypiperidine-1-carboxylate.
Ex 50 Step 4	tert-butyl (S)-3-[(7-[((S)-1-methoxypropan-2-yl)carbamoyl]-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl)oxy]piperidine-1-carboxylate		MS m/z 586 $[M+Na]^+$ (S)-2-bromo-N-(1-methoxypropan-2-yl)-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide (**Example 4 Step 3**) and tert-butyl (R)-3-hydroxypiperidine-1-carboxylate.
Ex 51 Step 4	Racemic-tert-butyl-3-[(7-[((S)-1-methoxypropan-2-yl)carbamoyl]-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl)oxy]piperidine-1-carboxylate		(S)-2-bromo-N-(1-methoxypropan-2-yl)-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide (**Example 4 Step 3**) and racemic-tert-butyl-3-hydroxypiperidine-1-carboxylate. Taken on directly to the next step.
Ex 7 Step 4	Racemic-tert-butyl 2-{[(7-[((S)-1-methoxypropan-2-yl)carbamoyl]-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl)oxy]methyl}pyrrolidine		MS m/z 586 $[M+Na]^+$ (S)-2-bromo-N-(1-methoxypropan-2-yl)-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide (**Example 4 Step 3**) and racemic-tert-butyl 2-

	-1-carboxylate		(hydroxymethyl)pyrrolidine-1-carboxylate at 100°C and using cesium carbonate as base.
Ex 10 Step 4	Racemic-tert-butyl 3-{[(7-[((S)-1-methoxypropan-2-yl)carbamoyl]-5-{[2-(trimethylsi-lyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl)oxy]methyl}pyrrolidine-1-carboxylate		MS m/z 586 $[M+Na]^+$ (S)-2-bromo-N-(1-methoxypropan-2-yl)-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide (**Example 4 Step 3**) and racemic tert-butyl 3-(hydroxymethyl)pyrrolidine-1-carboxylate at 100°C.
Ex 13 Step 4	Racemic-tert-butyl 3-{[(7-[((R)-1-methoxypropan-2-yl)carbamoyl]-5-{[2-(trimethylsi-lyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl)oxy]methyl}pyrrolidine-1-carboxylate		MS m/z 586 $[M+Na]^+$ (R)-2-bromo-N-(1-methoxypropan-2-yl)-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide (**Example 1 Step 3**) and racemic tert-butyl 3-(hydroxymethyl)pyrrolidine-1-carboxylate at 100°C.
Ex 52 Step 4	tert-butyl (S)-3-[(7-[((S)-1-methoxypropan-2-yl)carbamoyl]-5-{[2-(trimethylsi-lyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl)oxy]pyrrolidine-1-carboxylate		MS m/z 572 $[M+Na]^+$ (S)-2-bromo-N-(1-methoxypropan-2-yl)-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide (**Example 4 Step 3**) and tert-butyl (S)-3-hydroxypyrrolidine-1-carboxylate.
Ex 53 Step 4	tert-butyl (R)-3-[(7-[((S)-1-methoxypropan-2-yl)carbamoyl]-5-{[2-(trimethylsi-lyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl)oxy]pyrrolidine-1-carboxylate		MS m/z 572 $[M+Na]^+$ (S)-2-bromo-N-(1-methoxypropan-2-yl)-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide (**Example 4 Step 3**) and tert-butyl (R)-3-hydroxypyrrolidine-1-carboxylate.
Ex 71 Step 4	Trans-racemic-benzyl-4-[(7-[((S)-1-methoxypropan-2-yl)carbamoyl]-5-{[2-(trimethylsi-lyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl)oxy]-2-methylpiperidine-1-carboxylate		MS m/z 612 $[M+H]^+$ Trans-racemic-benzyl (2R,4S)-4-hydroxy-2-methylpiperidine-1-carboxylate (**Bioorg. Chem. (1999), 27 (2), 81-90**) and (S)-2-bromo-N-(1-methoxypropan-2-yl)-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide (**Example 4 Step 3**).

Ex 61 Step 4	tert-butyl 4-{[7-(ethylcarbamoyl)-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl]oxy}-4-methylpiperidine-1-carboxylate		6 h's missing 43 reqd, 37 obsvd ^{1}H NMR (400 MHz, DMSO-d_6) □ ppm 8.43 (s, 1 H) 8.08 (s, 1 H) 7.69 (t, *J*=5.02 Hz, 1 H) 5.63 (s, 2 H) 3.71 (d, *J*=13.05 Hz, 2 H) 3.49 - 3.60 (m, 3 H) 3.38 - 3.46 (m, 2 H) 3.03 - 3.23 (m, 3 H) 2.19 - 2.37 (m, 2 H) 1.59 - 1.79 (m, 2 H) 1.32 - 1.47 (m, 9 H) 1.21 (m, 3 H) 0.82 (m, 2 H) 0.09 (s, 9 H))2-bromo-5-[(3,3-dimethylbutoxy)methyl]-N-ethyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide and tert-butyl 4-hydroxy-4-methylpiperidine-1-carboxylate (**Example 25 Step 3**).
Ex 46 Step 4	Trans-racemic-tert-butyl 4-{[7-(ethylcarbamoyl)-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl]oxy}-3-methylpiperidine-1-carboxylate		2-bromo-5-[(3,3-dimethylbutoxy)methyl]-N-ethyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide and trans-racemic-tert-butyl 4-hydroxy-3-methylpiperidine-1-carboxylate (**Example 25 Step 3**). Taken on directly to the next step.
Ex 77 Step 4	Trans-racemic-benzyl 4-{[7-(ethylcarbamoyl)-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl]oxy}-2-methylpiperidine-1-carboxylate		2-bromo-5-[(3,3-dimethylbutoxy)methyl]-N-ethyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide (**Bioorg. Med. Chem. (1999), 27 (2), 81-90**) and trans-racemic-benzyl 4-hydroxy-2-methylpiperidine-1-carboxylate (**Example 25 Step 3**). Taken on directly to the next step.
Ex 80 Step 4	Cis-racemic-benzyl 5-[(7-[(1-methoxypropan-2-yl)carbamoyl]-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl)oxy]-2-methylpiperidine-1-carboxylate		MS m/z 612 [M+H]+ (S)-2-bromo-N-(1-methoxypropan-2-yl)-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide (**Example 4 Step 3**) and cis-racemic-benzyl 5-hydroxy-2-methylpiperidine-1-carboxylate.

Example 1 Step 4

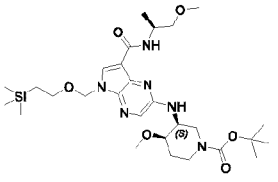
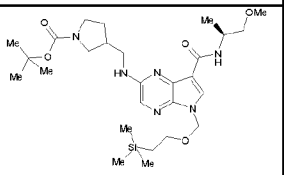
tert-Butyl-(cis-racemic)-4-methoxy-3-[(7-[((S)-1-methoxypropan-2-yl)carbamoyl]-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl)amino]piperidine-1-carboxylate

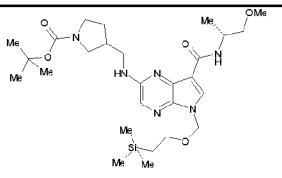
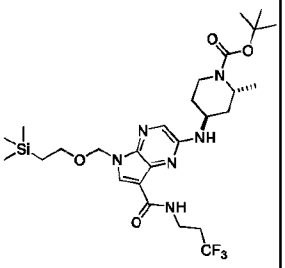
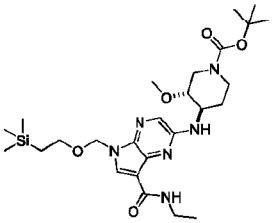
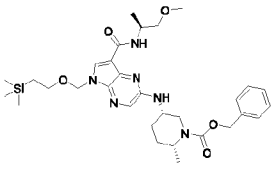
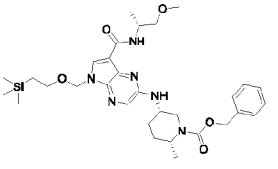
Method B wherein Y=N

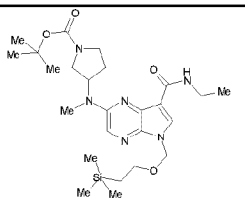
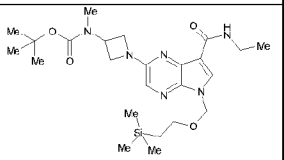
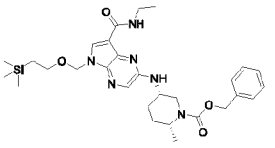
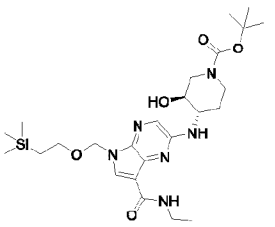
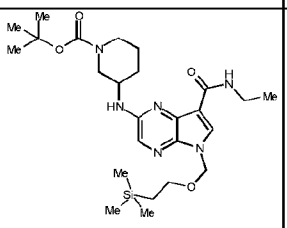
To a mixture of (S)-2-bromo-N-(1-methoxypropan-2-yl)-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide (**Example 4 Step 3**, 1 g, 2.26 mmol), tert-butyl (cis-racemic)-3-

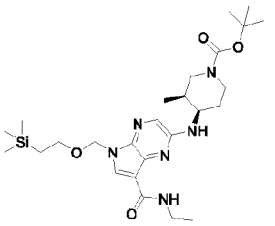
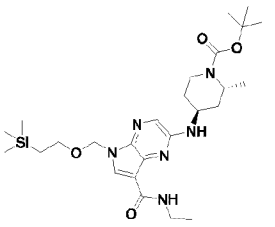
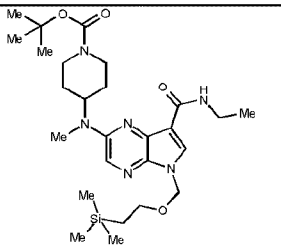
amino-4-methoxypiperidine-1-carboxylate (675 mg, 2.93 mmol) and sodium tert-butoxide (650 mg, 6.77 mmol) in toluene (40 mL) was added $Pd_2(dba)_3$ (207 mg, 0.23 mmol) and the reaction was heated to 110°C under nitrogen for 18 hours. The reaction was concentrated *in vacuo* and purified using silica gel column chromatography eluting with 20-66% EtOAc in petroleum ether to afford the title compound as a yellow solid (1.2 g, 78%).
MS m/z 615 $[M+Na]^+$

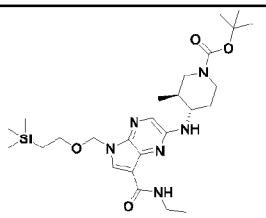
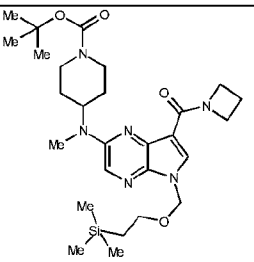
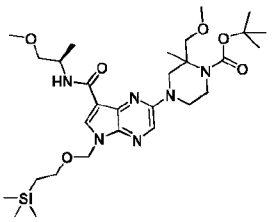
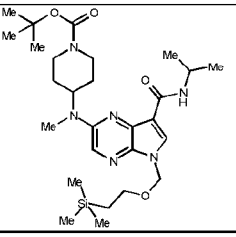
The following Preparations were prepared according to **Method B wherein Y=N** as described for **Example 1 Step 4** using the appropriate heteroaryl bromide and amine with either sodium tert-butoxide or cesium carbonate as base.

Prep No.	Name	Structure	Data/SM
Ex 4 Step 4	tert-butyl (cis-racemic)-4-methoxy-3-[(7-[((R)-1-methoxypropan-2-yl)carbamoyl]-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl)amino]piperidine-1-carboxylate		MS m/z 593 $[M+H]^+$ tert-butyl (cis-racemic)-3-amino-4-methoxypiperidine-1-carboxylate and (S)-2-bromo-N-(1-methoxypropan-2-yl)-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide (**Example 4 Step 3**).
Ex 16 Step 4	Racemic-tert-butyl 3-{[(7-[((S)-1-methoxypropan-2-yl)carbamoyl]-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl)amino]methyl}pyrrolidine-1-carboxylate		MS m/z 593 $[M+Na]^+$ (S)-2-bromo-N-(1-methoxypropan-2-yl)-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide (**Example 4 Step 3**) and racemic tert-butyl 3-(aminomethyl)pyrrolidine-1-carboxylate.

Ex 19 Step 4	Racemic-tert-butyl 3-{[(7-[((R)-1-methoxypropan-2-yl)carbamoyl]-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl)amino]methyl}pyrrolidine-1-carboxylate		MS m/z 593 $[M+Na]^+$ (R)-2-bromo-N-(1-methoxypropan-2-yl)-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide (**Example 1 Step 3**) and racemic tert-butyl 3-(aminomethyl)pyrrolidine-1-carboxylate.
Ex 22 Step 4	Cis-racemic-tert-butyl 2-methyl-4-[(7-[(3,3,3-trifluoropropyl)carbamoyl]-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl)amino]piperidine-1-carboxylate		2-bromo-N-(3,3,3-trifluoropropyl)-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide (**Example 22 Step 3**) and cis-racemic tert-butyl 4-amino-2-methylpiperidine-1-carboxylate. Taken on directly to the next step
Ex 25 Step 4	Trans-racemic-tert-butyl 4-{[7-(ethylcarbamoyl)-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl]amino}-3-methoxypiperidine-1-carboxylate		MS m/z 571 $[M+Na]^+$ 2-bromo-5-[(3,3-dimethylbutoxy)methyl]-N-ethyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide and trans-racemic-tert-butyl 4-amino-3-methoxypiperidine-1-carboxylate (**Example 25 Step 3**).
Ex 65 Step 4	Cis-racemic-benzyl -5-[(7-[((S)-1-methoxypropan-2-yl)carbamoyl]-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl)amino]-2-methylpiperidine-1-carboxylate		MS m/z 611 $[M+H]^+$ Cis-racemic-benzyl 5-amino-2-methylpiperidine-1-carboxylate (**WO2010016005**) and (S)-2-bromo-N-(1-methoxypropan-2-yl)-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide (**Example 4 Step 3**).
Ex 68 Step 4	Cis-racemic-benzyl -5-[(7-[((R)-1-methoxypropan-2-yl)carbamoyl]-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl)amino]-2-methylpiperidine-1-carboxylate		MS m/z 611 $[M+H]^+$ Cis-racemic-benzyl 5-amino-2-methylpiperidine-1-carboxylate (**WO2010016005**) and (R)-2-bromo-N-(1-methoxypropan-2-yl)-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide (**Example 1 Step 3**).

Ex 28 Step 4	Racemic tert-butyl 3-{[7-(ethylcarbamoyl)-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl](methyl)amino}pyrrolidine-1-carboxylate		Taken on directly to the next step. 2-bromo-5-[(3,3-dimethylbutoxy)methyl]-N-ethyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide (**Example 25 Step 3**) and racemic tert-butyl 3-(methylamino)pyrrolidine-1-carboxylate.
Ex 59 Step 4	tert-butyl {1-[7-(ethylcarbamoyl)-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl]azetidin-3-yl}methylcarbamate		MS m/z 527 $[M+Na]^+$ 2-bromo-5-[(3,3-dimethylbutoxy)methyl]-N-ethyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide (**Example 25 Step 3**) and tert-butyl azetidin-3-yl(methyl)carbamate.
Ex 74 Step 4	Cis-racemic-benzyl 5-{[7-(ethylcarbamoyl)-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl]amino}-2-methylpiperidine-1-carboxylate		MS m/z 567 $[M+H]^+$ 2-bromo-5-[(3,3-dimethylbutoxy)methyl]-N-ethyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide (**Example 25 Step 3**) and cis-racemic-benzyl 5-amino-2-methylpiperidine-1-carboxylate.
Ex 31 Step 4	Trans-racemic-tert-butyl 4-{[7-(ethylcarbamoyl)-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl]amino}-3-hydroxypiperidine-1-carboxylate		MS m/z 535 $[M+H]^+$ ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.17 - 8.25 (m, 1 H) 8.07 - 8.14 (m, 1 H) 7.86 (s, 1 H) 7.32-7.34 (m, 1 H) 5.46 - 5.59 (m, 2 H) 5.27-5.29 (m,1 H) 3.98 (br. s., 1 H) 3.83 (d, 1 H) 3.72 (br. s, 1 H) 3.45 - 3.55 (m, 3 H) 2.61-3.33 (m, 2 H) 2.15 (d, 1 H) 1.42 (s, 9 H) 1.12 - 1.31 (m, 5 H) 0.81 (t, 3 H) 0.09 (s, 9 H) 2-bromo-5-[(3,3-dimethylbutoxy)methyl]-N-ethyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide (**Example 25 Step 3**) and trans-racemic-tert-butyl 4-amino-3-hydroxypiperidine-1-carboxylate.
Ex 34 Step 4	Racemic-tert-butyl 3-{[7-(ethylcarbamoyl)-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl]amino}piperidine-1-carboxylate		2-bromo-5-[(3,3-dimethylbutoxy)methyl]-N-ethyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide (**Example 25 Step 3**) and racemic-tert-butyl 3-aminopiperidine-1-carboxylate. Taken on directly to the next step.

Ex 37 Step 4	Cis-racemic-tert-butyl 4-{[7-(ethylcarbamoyl)-5-{[2-(trimethylsi-lyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl]amino}-3-methylpiperidine-1-carboxylate		^{1}H NMR (400MHz, $CDCl_3$): δ ppm 8.24-8.07 (m, 1H), 8.03 (s, 1H), 7.69-7.59 (m, 1H), 5.55 (s, 2H), 4.41 (br s, 1H), 4.26-3.98 (m, 2H), 3.77-3.60 (m, 1H), 3.57-3.35 (m, 4H), 2.88 (t, 1H), 2.58 (br s, 1H), 2.21-2.20 (m, 1H), 1.50-1.45 (m, 9H), 1.36-1.25 (m, 4H), 1.03 (d, 4H), 0.93-0.84 (m, 2H), -0.33- -0.11 (m, 9H). 2-bromo-5-[(3,3-dimethylbutoxy)methyl]-N-ethyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide (**Example 25 Step 3**) and cis-racemic-tert-butyl 4-amino-3-methylpiperidine-1-carboxylate (**US 20050085518**).
Ex 40 Step 4	Trans-racemic-tert-butyl 4-{[7-(ethylcarbamoyl)-5-{[2-(trimethylsi-lyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl]amino}-2-methylpiperidine-1-carboxylate		^{1}H NMR (400MHz, DMSO-d_6): δ ppm 8.18-8.07 (m, 2H), 7.73 (s, 1H), 7.04 (d, J=7.3 Hz, 1H), 5.57-5.47 (m, 2H), 4.40 (br s, 1H), 4.24-4.06 (m, 1H), 3.93 (d, J=13.1 Hz, 1H), 3.55-3.34 (m, 4H), 3.08-2.86 (m, 1H), 2.07-1.98 (m, 1H), 1.91 (d, J=12.5 Hz, 1H), 1.52-1.33 (m, 10H), 1.29-1.11 (m, 7H), 0.80 (t, J=7.9 Hz, 2H), 0.06- -0.19 (m, 9H). 2-bromo-5-[(3,3-dimethylbutoxy)methyl]-N-ethyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide (**Example 25 Step 3**) and trans-racemic-tert-butyl 4-amino-2-methylpiperidine-1-carboxylate.
Ex 60 Step 4	tert-butyl 4-{[7-(ethylcarbamoyl)-5-{[2-(trimethylsi-lyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl](methyl)amino}piperidine-1-carboxylate		MS m/z 533 $[M+H]^+$ 2-bromo-5-[(3,3-dimethylbutoxy)methyl]-N-ethyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide (**Example 25 Step 3**) and tert-butyl 4-(methylamino)piperidine-1-carboxylate.

Ex 43 Step 4	Trans-racemic-tert-butyl 4-{[7-(ethylcarbamoyl)-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl]amino}-3-methylpiperidine-1-carboxylate		^{1}H NMR (400MHz, DMSO-d_6): δ ppm 8.14-8.07 (m, 2H), 7.86 (s, 1H), 7.23-7.22 (m, 1H), 5.52 (s, 2H), 4.15-4.05 (m, 1H), 3.80-3.50 (m, 4H), 3.40-3.30 (m, 1H), 3.25-3.05 (m, 2H), 2.25-2.15 (m, 1H), 1.75-1.60 (m, 2H), 1.40 (s, 9H), 1.25-1.10 (m, 5H), 0.90-0.75 (m, 5H), -0.08 (s, 9H). 2-bromo-5-[(3,3-dimethylbutoxy)methyl]-N-ethyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide (**Example 25 Step 3**) and trans-racemic-tert-butyl 4-amino-3-methylpiperidine-1-carboxylate (**US 20050085518**).
Ex 62 Step 4	tert-butyl 4-{[7-(azetidin-1-ylcarbonyl)-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl](methyl)amino}piperidine-1-carboxylate		MS m/z 567 $[M+Na]^+$ Azetidin-1-yl(2-bromo-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-7-yl)methanone (**Example 62 Step 3**) and tert-butyl 4-(methylamino)piperidine-1-carboxylate.
Ex 63 Step 4	tert-butyl 2-(methoxymethyl)-4-(7-(((R)-1-methoxypropan-2-yl)carbamoyl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl)-2-methylpiperazine-1-carboxylate		(S)-2-bromo-N-(1-methoxypropan-2-yl)-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide (**Example 4 Step 3**) and racemic-benzyl-5-amino-2-methoxymethyl-2-methylpiperidine-1-carboxylate. Taken on directly to the next step.
Ex 64 Step 4	tert-butyl 4-((7-(isopropylcarbamoyl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl)(methyl)amino)piperidine-1-carboxylate		2-bromo-N-isopropyl-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide (**Example 64 Step 3**) and tert-butyl 4-(methylamino)piperidine-1-carboxylate. MS m/z 569 $[M+H]^+$

Examples 55 and 56 Step 4

Cis-racemic-tert-butyl-4-[(7-[((S)-1-methoxypropan-2-yl)carbamoyl]-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl)amino]-2-methylpiperidine-1-carboxylate

The title compound was prepared according to the method described for **Example 1 Step 4** using (S)-2-bromo-N-(1-methoxypropan-2-yl)-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide (**Example 4 Step 3**) and cis-racemic-tert-butyl 4-amino-2-methylpiperidine-1-carboxylate.

^{1}H NMR (400MHz, DMSO-d_6): δ ppm 8.39-8.37 (m, 0.5H), 8.30-8.28 (m, 0.5H), 8.09-8.07 (m, 1H), 7.82 (s, 1H), 7.17-7.13 (m, 1H), 5.53-5.50 (m, 2H), 4.25-4.15 (m, 1H), 4.10-3.90 (m, 3H), 3.75-3.70 (m, 1H), 3.51-3.47 (m, 2H), 3.40-3.27 (m, 4H), 2.05-1.95 (m, 1H), 1.95-1.60 (m, 3H), 1.40 (s, 9H), 1.17-1.10 (m, 7H), 0.80 (t, 2H), -0.07 (s, 9H).

The residue was separated into the two cis-isomers using preparative chiral column chromatography according to the conditions described below:

Column: OD (250x30mm, 10 micron); Mobile phase: 40% IPA in NH_3/H_2O

Flow rate: 70 mL/min.

The two cis-isomers were arbitrarily assigned absolute stereochemistry:

Example 55 Step 4

Pk1:tert-butyl-(2S,4S)-4-[(7-[((S)-1-methoxypropan-2-yl)carbamoyl]-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl)amino]-2-methylpiperidine-1-carboxylate

Example 56 Step 4

Pk2: tert-butyl-(2R,4R)-4-[(7-[((S)-1-methoxypropan-2-yl)carbamoyl]-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl)amino]-2-methylpiperidine-1-carboxylate

Examples 57 and 58 Step 4

Cis-racemic-tert-butyl-4-[(7-[((R)-1-methoxypropan-2-yl)carbamoyl]-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl)amino]-2-methylpiperidine-1-carboxylate

The title compound was prepared according to the method described for **Example 1 Step 4** using (R)-2-bromo-N-(1-methoxypropan-2-yl)-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide (**Example 1 Step 3**) and cis-racemic-tert-butyl 4-amino-2-methylpiperidine-1-carboxylate. ^{1}H NMR (400MHz, DMSO-d_6): δ ppm 8.39-8.37 (m, 0.5H), 8.30-8.28 (m, 0.5H), 8.09-8.07 (m, 1H), 7.82 (s, 1H), 7.17-7.13 (m, 1H), 5.53-5.50 (m, 2H), 4.25-4.15 (m, 1H), 4.10-3.90 (m, 3H), 3.75-3.70 (m, 1H), 3.51-3.47 (m, 2H), 3.40-3.27 (m, 4H), 2.05-1.95 (m, 1H), 1.95-1.60 (m, 3H), 1.40 (s, 9H), 1.17-1.10 (m, 7H), 0.80 (t, 2H), -0.07 (s, 9H).

The residue was separated into its cis-isomers using preparative chiral column chromatography according to the conditions described below:

Column: OD (250x30mm, 10 micron); Mobile phase: 45% IPA in NH_3/H_2O

Flow rate: 80 mL/min.

The two cis-isomers were arbitrarily assigned absolute stereochemistry:

Example 57 Step 4

tert-butyl-(2S,4S)-4-[(7-[((R)-1-methoxypropan-2-yl)carbamoyl]-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl)amino]-2-methylpiperidine-1-carboxylate

Example 58 Step 4

tert-butyl-(2R,4R)-4-[(7-[((R)-1-methoxypropan-2-yl)carbamoyl]-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl)amino]-2-methylpiperidine-1-carboxylate

Example 1 Steps 5-7

2-{[(cis-racemic)-1-acryloyl-4-methoxypiperidin-3-yl]amino}-N-[(2S)-1-methoxypropan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

To a solution of tert-butyl (cis-racemic)-4-methoxy-3-[(7-[((S)-1-methoxypropan-2-yl)carbamoyl]-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl)amino]piperidine-1-carboxylate (**Example 1 Step 4**, 1.2 g, 2.02 mmol) in DCM (40 mL) was added TFA (12 mL) and the reaction was stirred at room temperature for 3 hours. The reaction was concentrated *in vacuo*. The residue was dissolved in MeOH (30 mL) and treated with 28% aqueous ammonia (10 mL). The reaction was stirred at room temperature for 18 hours. The reaction was concentrated *in vacuo* and the residue dissolved in THF (30 mL) and water (30 mL). To the solution was added DIPEA (792 mg, 6.13 mmol) followed by acryloyl chloride (370 mg, 4.08 mmol) dropwise at 0°C. The reaction was stirred at 0°C for 2 hours before concentrating *in vacuo*. The residue was purified using silica gel column chromatography eluting with 10% MeOH in DCM followed by Preparative HPLC to afford the title compound as a grey solid (350 mg, 41%).

Preparative HPLC Method:

Column: Phenomenex Gemini C18 250x21.2 mm, 8 micron.

Mobile phase: From 22-42% MeCN in water, both mobile phases modified with ammonia (pH=10).

QC Analytical LCMS Method:

Column: Ultimate XB-C18, 3x50 mm, 3 micron

Mobile phase: From 1-100% MeCN in water, both mobile phases modified with 0.1% TFA

^{1}H NMR (400MHz, DMSO-d_6): δ ppm 12.11 (br s, 1H), 8.29-8.26 (m, 1H), 7.89-7.85 (m, 2H), 6.94-6.84 (m, 2H), 6.14-6.10 (m, 1H), 5.71-5.67 (m, 1H), 4.69-4.66 (m, 0.5H), 4.33-4.11 (m, 3.5H), 3.70-3.60 (m, 2H), 3.45-3.34 (m, 5H), 3.00-2.80 (m, 4H), 1.78-1.63 (m, 2H), 1.22 (d, 3H).

Rt = 3.31 minutes MS m/z 439 $[M+Na]^+$

The cis-racemic material was separated into its enantiomers using preparative chiral column chromatography according to the conditions described below:

Preparative Chiral Method:

Column: OD (250x30 mm, 10 micron); Mobile phase: 35% MeOH in NH_3/H_2O

Flow rate: 80 mL/min

QC Analytical LCMS Method:

Column: Chiralcel™ OD-3 150x4.6 mm, 3 micron; Mobile phase: MeOH (0.05% DEA) in CO_2 from 5-40%; Flow rate: 2.5 mL/min

The two enantiomers were arbitrarily assigned absolute stereochemistry:

First eluting isomer: Example 2

2-{[(3S,4R)-1-acryloyl-4-methoxypiperidin-3-yl]amino}-N-[(2S)-1-methoxypropan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide; Rt = 7.55 minutes MS m/z 439 $[M+Na]^+$

Second eluting isomer: Example 3

2-{[(3R,4S)-1-acryloyl-4-methoxypiperidin-3-yl]amino}-N-[(2S)-1-methoxypropan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide; Rt = 8.62 minutes MS m/z 439 $[M+Na]^+$

Example 4

2-{[(cis-racemic)-1-acryloyl-4-methoxypiperidin-3-yl]amino}-N-[(2R)-1-methoxypropan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

The title compound was prepared and purified according to the method described for **Example 1 Steps 5-7** using tert-butyl (cis-racemic)-4-methoxy-3-[(7-[((R)-1-methoxypropan-2-yl)carbamoyl]-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl)amino]piperidine-1-carboxylate (**Example 4 Step 4**) and an HPLC gradient of from 19-39% MeCN in water, both mobile phases modified with ammonia (pH=10).

^{1}H NMR (400MHz, DMSO-d_6): δ ppm 12.11 (br s, 1H), 8.29-8.26 (m, 1H), 7.89-7.85 (m, 2H), 6.94-6.84 (m, 2H), 6.14-6.10 (m, 1H), 5.71-5.67 (m, 1H), 4.69-4.66 (m, 0.5H), 4.33-4.11 (m, 3.5H), 3.70-3.60 (m, 2H), 3.45-3.34 (m, 5H), 3.00-2.80 (m, 4H), 1.78-1.63 (m, 2H), 1.22 (d, 3H).

Rt = 3.31 minutes MS m/z 439 $[M+Na]^+$

The cis-racemic material was separated into its enantiomers using preparative chiral column chromatography according to the conditions described below;

Column: OD (250x30 mm, 10 micron); Mobile phase: 25% MeOH in NH_3/H_2O

Flow rate: 70 mL/min

QC Analytical LCMS Method:

Column: Chiralpak™ AD-H 250x4.6 mm, 5 micron; Mobile phase: IPA (0.05% DEA) in CO_2 from 5-40%; Flow rate: 2.5 mL/min

The two enantiomers were arbitrarily assigned absolute stereochemistry:

First eluting isomer: Example 5

2-{[(3S,4R)-1-acryloyl-4-methoxypiperidin-3-yl]amino}-N-[(2R)-1-methoxypropan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide; Rt = 8.57 minutes MS m/z 439 $[M+Na]^+$

Second eluting isomer: Example 6

2-{[(3R,4S)-1-acryloyl-4-methoxypiperidin-3-yl]amino}-N-[(2R)-1-methoxypropan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide; Rt = 8.99 minutes MS m/z 439 $[M+Na]^+$

Example 7

Racemic-2-[(1-acryloylpyrrolidin-2-yl)methoxy]-N-[(2S)-1-methoxypropan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

The title compound was prepared and purified according to the method described for **Example 1 Steps 5-7** using racemic-tert-butyl 2-{[(7-[((S)-1-methoxypropan-2-yl)carbamoyl]-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl)oxy]methyl}pyrrolidine-1-carboxylate (**Example 7 Step 4**) and an HPLC gradient of from 29-49% MeCN in water, both mobile phases modified

with ammonia (pH=10). ^{1}H NMR (400MHz, DMSO-d_6): δ ppm 12.48 (br s, 1H), 8.20-8.18 (m, 1H), 8.11-7.99 (m, 2H), 6.75-6.60 (m, 0.5H), 6.58-6.56 (m, 0.5H), 6.16-6.12 (m, 1H), 5.69-5.66 (m, 1H), 4.59-4.18 (m, 4H), 3.70-3.27 (m, 7H), 2.09-1.91 (m, 4H), 1.23 (d, 3H).

The racemic material was separated into its enantiomers using preparative chiral column chromatography according to the conditions described below;

Column: WEEK-1 (300x25mm, 5 micron); Mobile phase: 20% MeOH in NH_3/H_2O

Flow rate: 60 mL/min

QC Analytical LCMS Method:

Column: Whelk-O1 (250x4.6mm, 5 micron); Mobile phase: 50% EtOH with 5% DEA in CO_2.

Flow rate: 2 mL/min

The two enantiomers were arbitrarily assigned absolute stereochemistry:

First eluting isomer: Example 8

2-{[(2S)-1-acryloylpyrrolidin-2-yl]methoxy}-N-[(2S)-1-methoxypropan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide; Rt = 5.53 minutes MS m/z 410 $[M+Na]^+$

Second eluting isomer: Example 9

2-{[(2R)-1-acryloylpyrrolidin-2-yl]methoxy}-N-[(2S)-1-methoxypropan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide; Rt = 6.51 minutes MS m/z 410 $[M+Na]^+$

Example 10

Racemic-2-[(1-acryloylpyrrolidin-3-yl)methoxy]-N-[(2S)-1-methoxypropan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

The title compound was prepared and purified according to the method described for **Example 1** using racemic-tert-butyl 3-{[(7-[((S)-1-methoxypropan-2-yl)carbamoyl]-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl)oxy]methyl}pyrrolidine-1-carboxylate (**Example 10 Step 4**). The residue was purified by silica gel column chromatography eluting with 5% MeOH in DCM followed by preparative HPLC using a gradient of from 20-40% MeCN in water, both mobile phases modified with ammonia (pH=10). ^{1}H NMR (400MHz, DMSO-d_6): δ ppm 12.58 (br s, 1H), 8.19 (s, 1H), 8.11-8.09 (m, 1H), 8.04 (s, 1H), 6.62-6.56 (m, 1H), 6.16-6.11 (m, 1H), 5.68-5.63 (m, 1H), 4.42-4.39 (m, 2H), 4.25-4.15 (m, 1H), 3.85-3.32 (m, 10H), 2.16-2.06 (m, 1H), 1.88-1.74 (m, 1H), 1.21 (d, 3H). Rt = 3.34 minutes MS m/z 410 $[M+Na]^+$

The racemic material was separated into its enantiomers using preparative chiral column chromatography according to the conditions described below;

Column: AD (250x30mm), 5 micron

Mobile phase: 30% EtOH in NH_3/H_2O; Flow rate: 60 mL/min

QC Analytical LCMS Method:

Column: Chiralcel OD-H (250x4.6mm, 5 micron); Mobile phase: A/B=75/25 A:Hexane with 0.1%DEA ,B: Ethanol; Flow rate: 0.5 mL/min

The two enantiomers were arbitrarily assigned absolute stereochemistry:

First eluting isomer: Example 11

2-{[(3S)-1-acryloylpyrrolidin-3-yl]methoxy}-N-[(2S)-1-methoxypropan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

This isomer was purified for a second time using chiral preparative HPLC using column OD (250x30mm, 5 micron) and eluting with 35% EtOH in NH_3/H_2O with a flow rate of 50 mL/min to obtain the chirally pure title compound.

Rt = 21.64 minutes, 95% de; MS m/z 410 $[M+Na]^+$

Second eluting isomer: Example 12

2-{[(3R)-1-acryloylpyrrolidin-3-yl]methoxy}-N-[(2S)-1-methoxypropan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

Rt = 23.87 minutes, 99% de; MS m/z 410 $[M+Na]^+$

Example 13– intermediate

Racemic-2-[(1-acryloylpyrrolidin-3-yl)methoxy]-N-[(2R)-1-methoxypropan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

The title compound was prepared and purified according to the method described for **Example 1 Steps 5-7** using racemic-tert-butyl 3-{[(7-[((R)-1-methoxypropan-2-yl)carbamoyl]-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl)oxy]methyl}pyrrolidine-1-carboxylate (**Preparation 13 Step 4**). The residue was purified by silica gel column chromatography eluting with 5% MeOH in DCM followed by preparative HPLC using a gradient of from 20-40% MeCN in water, both mobile phases modified with ammonia (pH=10).

MS m/z 410 $[M+Na]^+$

The racemic material was separated into its enantiomers using preparative chiral column chromatography according to the conditions described below; Column: AD (250x30mm), 5 micron; Mobile phase: 30% EtOH in NH_3/H_2O; Flow rate: 60 mL/min

QC Analytical LCMS Method:

Column: Chiralpak AD-3 (150x4.6mm, 3 micron); Mobile phase: 5-40% EtOH with 0.05% DEA in CO_2; Flow rate: 2.5 mL/min

The two enantiomers were arbitrarily assigned absolute stereochemistry:

First eluting isomer: Example 14

2-{[(3R)-1-acryloylpyrrolidin-3-yl]methoxy}-N-[(2R)-1-methoxypropan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide. ^1H NMR (400MHz, DMSO-d_6): δ ppm 12.57 (br s, 1H), 8.19 (s, 1H), 8.12-8.09 (m, 1H), 8.04 (s, 1H), 6.62-6.58 (m, 1H), 6.16-6.11 (m, 1H), 5.68-5.65 (m, 1H), 4.43-4.39 (m, 2H), 4.25-4.15 (m, 1H), 3.90-3.55 (m, 5H), 3.44-3.28 (m, 4H), 2.90-2.70 (m, 1H), 2.20-2.05 (m, 1H), 1.90-1.75 (m, 1H), 1.22 (d, 3H).

Rt = 5.04 minutes, 99% de; MS m/z 410 $[M+Na]^+$

Second eluting isomer: Example 15

2-{[(3S)-1-acryloylpyrrolidin-3-yl]methoxy}-N-[(2R)-1-methoxypropan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide ^1H NMR (400MHz, DMSO-d_6): δ ppm 12.57 (br s, 1H),8.19 (s, 1H), 8.12-8.09 (m, 1H), 8.04 (s, 1H), 6.62-6.55 (m, 1H), 6.15-6.10 (m, 1H), 5.68-5.65 (m, 1H), 4.48-4.45 (m, 1H), 4.35-4.32

(m, 1H), 4.19-4.17 (m, 1H), 3.90-3.55 (m, 3H), 3.50-3.30 (m, 6H), 2.84-2.74 (m, 1H), 2.14-2.00 (m, 1H), 1.87-1.75 (m, 1H), 1.20 (d, 3H). Rt = 5.44 minutes, 91% de; MS m/z 410 $[M+Na]^+$

Example 16

Racemic-2-{[(1-acryloylpyrrolidin-3-yl)methyl]amino}-N-(2S)-(1-methoxypropan-2-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

The title compound was prepared and purified according to the method described for **Example 1** using racemic-tert-butyl 3-{[(7-[((S)-1-methoxypropan-2-yl)carbamoyl]-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl)amino]methyl}pyrrolidine-1-carboxylate (**Example 16 Step 4**). The residue was purified by silica gel column chromatography eluting with 5% MeOH in DCM followed by preparative HPLC using a gradient of from 19-39% MeCN in water, both mobile phases modified with ammonia (pH=10).

MS m/z 409 $[M+Na]^+$

The racemic material was separated into its enantiomers using preparative chiral column chromatography according to the conditions described below;

Column: OJ (250x30mm), 5 micron; Mobile phase: 20% EtOH in NH_3/H_2O

Flow rate: 60 mL/min

QC Analytical LCMS Method:

Column: Chiralcel OJ-3 (150x4.6mm, 3 micron); Mobile phase: 5-40% EtOH with 0.05% DEA in CO_2; Flow rate: 2.5 mL/min

The two enantiomers were arbitrarily assigned absolute stereochemistry:

First eluting isomer: Example 17

2-({[(3S)-1-acryloylpyrrolidin-3-yl]methyl}amino)-N-[(2S)-1-methoxypropan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide. ^{1}H NMR (400MHz, DMSO-d_6): δ ppm 12.08 (br s, 1H), 8.41-8.36 (m, 1H), 7.87 (s, 1H), 7.72 (m, 1H), 7.30-7.20 (m, 1H), 6.60-6.50 (m, 1H), 6.20-6.10 (m, 1H), 5.66-5.62 (m, 1H), 4.25-4.15 (m, 1H), 3.75-3.50 (m, 7H), 3.40-3.10 (m, 4H), 2.66-2.40 (m, 1H), 2.08-1.95 (m, 1H), 1.78-1.60 (m, 1H), 1.18 (d, 3H). Rt = 4.22 minutes; 99% de; MS m/z 409 $[M+Na]^+$

Second eluting isomer: Example 18

2-({[(3R)-1-acryloylpyrrolidin-3-yl]methyl}amino)-N-[(2S)-1-methoxypropan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide. ^{1}H NMR (400MHz, DMSO-d_6): δ ppm 12.06 (br s, 1H), 8.42-8.38 (m, 1H), 7.86 (s, 1H), 7.72 (m, 1H), 7.25-7.23 (m, 1H), 6.57-6.52 (m, 1H), 6.14-6.09 (m, 1H), 5.66-5.62 (m, 1H), 4.21-4.18 (m, 1H), 3.67-3.17 (m, 10.5H), 2.67-2.50 (m, 1.5H), 2.08-1.98 (m, 1H), 1.78-1.60 (m, 1H), 1.18 (d, 3H). Rt = 4.63 minutes, 98% de; MS m/z 409 $[M+Na]^+$

Example 19

Racemic-2-{[(1-acryloylpyrrolidin-3-yl)methyl]amino}-N-(2R)-(1-methoxypropan-2-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

The title compound was prepared and purified according to the method described for **Example 1 Steps 5-7** using racemic-tert-butyl 3-{[(7-[((R)-1-methoxypropan-2-yl)carbamoyl]-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl)amino]methyl}pyrrolidine-1-carboxylate

(**Example 19 Step 4**). The residue was purified by silica gel column chromatography eluting with 5% MeOH in DCM followed by preparative HPLC using a gradient of from 15-35% MeCN in water, both mobile phases modified with ammonia (pH=10).

MS m/z 409 $[M+Na]^+$

The racemic material was separated into its enantiomers using preparative chiral column chromatography according to the conditions described below;

Column: AD (250x30mm), 5 micron; Mobile phase: 30% IPA in NH_3/H_2O

Flow rate: 60 mL/min

QC Analytical LCMS Method:

Column: Chiralcel OD-H (250x4.6mm, 5 micron)

Mobile phase: A/B=75/25 A:Hexane with 0.1%DEA ,B: Ethanol; Flow rate: 0.5 mL/min

The two enantiomers were arbitrarily assigned absolute stereochemistry:

First eluting isomer: Example 20

2-({[(3S)-1-acryloylpyrrolidin-3-yl]methyl}amino)-N-[(2R)-1-methoxypropan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide. ^{1}H NMR (400MHz, DMSO-d_6): δ ppm 12.08 (br s, 1H), 8.41-8.36 (m, 1H), 7.86 (s, 1H), 7.72 (s, 1H), 7.22-7.21 (m, 1H), 6.57-6.49 (m, 1H), 6.13-6.08 (m, 1H), 5.66-5.62 (m, 1H), 4.25-4.15 (m, 1H), 3.80-3.20 (m, 11H), 2.70-2.40 (m, 1H), 2.08-1.98 (m, 1H), 1.98-1.75 (m, 1H), 1.18 (d, 3H). Rt = 26.79 minutes, 98% de; MS m/z 409 $[M+Na]^+$

Second eluting isomer: Example 21

2-({[(3R)-1-acryloylpyrrolidin-3-yl]methyl}amino)-N-[(2R)-1-methoxypropan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide. ^{1}H NMR (400MHz, DMSO-d_6): δ ppm 12.08 (br s, 1H), 8.42-8.38 (m, 1H), 7.87 (s, 1H), 7.72 (s, 1H), 7.25-7.24 (m, 1H), 6.60-6.50 (m, 1H), 6.13-6.09 (m, 1H), 5.66-5.63 (m, 1H), 4.25-4.15 (m, 1H), 3.75-3.15 (m, 11H), 2.67-2.50 (m, 1H), 2.08-1.98 (m, 1H), 1.98-1.75 (m, 1H), 1.18 (d, 3H). Rt = 30.55 minutes, 89% de; MS m/z 409 $[M+Na]^+$

Example 22

Cis-racemic 2-{[1-acryloyl-2-methylpiperidin-4-yl]amino}-N-(3,3,3-trifluoropropyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

The title compound was prepared and purified according to the method described for **Example 1 Steps 5-7** using cis-racemic-tert-butyl 2-methyl-4-[(7-[(3,3,3-trifluoropropyl)carbamoyl]-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl)amino]piperidine-1-carboxylate (**Example 22 Step 4**). The residue was purified by silica gel column chromatography eluting with 0-10% MeOH in DCM followed by preparative HPLC using a gradient of from 27-47% MeCN in water, both mobile phases modified with ammonia (pH=10).

^{1}H NMR (400MHz, DMSO-d_6): δ ppm 12.17 (br s, 1H), 8.40-8.37 (m, 1H), 7.92 (s, 1H), 7.97 (s, 1H), 7.09-7.07 (m, 1H), 6.82-6.75 (m, 1H), 6.14-6.09 (m, 1H), 5.68-5.65 (m, 1H), 4.40-4.38 (m, 1H), 4.10-4.00 (m, 2H), 3.64-3.58 (m, 2H), 3.35-3.33 (m, 1H), 2.60-2.56 (m, 2H), 1.99-1.90 (m, 3H), 1.77-1.76 (m, 1H), 1.22 (d, 3H).

The cis-racemic material was separated into its enantiomers using preparative chiral column chromatography according to the conditions described below;
Column: IC (250x50mm), 10 micron; Mobile phase: 45% EtOH in NH_3/H_2O
Flow rate: 80 mL/min
QC Analytical SFC Method:
Column: IC-3 (150x4.6mm, 3 micron); Mobile phase: 40% EtOH with 0.05% DEA in CO_2
Flow rate: 2.35 mL/min
QC Analytical LC/MS Method:
Column: Ultimate XB-C18, 3um, 3x50mm; Rt =3.59 min. Mobile phase: 1% AcCN/H2O (0.1% TFA) to 100% AcCN/H2O (0.1% TFA);λ = 220 nM

The two enantiomers were arbitrarily assigned absolute stereochemistry

Example 23

2-{[(2R,4R)-1-acryloyl-2-methylpiperidin-4-yl]amino}-N-(3,3,3-trifluoropropyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide. ^{1}H NMR (400MHz, DMSO-d_6): δ ppm 12.17 (br s, 1H), 8.40-8.37 (m, 1H), 7.92 (s, 1H), 7.97 (s, 1H), 7.09-7.07 (m, 1H), 6.82-6.75 (m, 1H), 6.14-6.09 (m, 1H), 5.68-5.65 (m, 1H), 4.40-4.38 (m, 1H), 4.10-4.00 (m, 2H), 3.64-3.58 (m, 2H), 3.35-3.33 (m, 1H), 2.60-2.56 (m, 2H), 1.99-1.90 (m, 3H), 1.77-1.76 (m, 1H), 1.22 (d, 3H).
Chiral SFC analysis: Rt = 3.63, >98% ee, SFC; MS m/z 447 $(M+Na)^+$

Example 24

2-{[(2R,4R)-1-acryloyl-2-methylpiperidin-4-yl]amino}-N-(3,3,3-trifluoropropyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide. ^{1}H NMR (400MHz, DMSO-d_6): δ ppm 12.17 (br s, 1H), 8.40-8.37 (m, 1H), 7.92 (s, 1H), 7.97 (s, 1H), 7.09-7.07 (m, 1H), 6.82-6.75 (m, 1H), 6.14-6.09 (m, 1H), 5.68-5.65 (m, 1H), 4.40-4.38 (m, 1H), 4.10-4.00 (m, 2H), 3.64-3.58 (m, 2H), 3.35-3.33 (m, 1H), 2.60-2.56 (m, 2H), 1.99-1.90 (m, 3H), 1.77-1.76 (m, 1H), 1.22 (d, 3H).
Chiral SFC analysis: Rt = 6.02, >98% ee, SFC; MS m/z 447 $(M+Na)^+$

Example 25

Trans-racemic-2-{[1-acryloyl-3-methoxypiperidin-4-yl]amino}-N-ethyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

The title compound was prepared and purified according to the method described for **Example 1 Steps 5-7** using trans-racemic-tert-butyl 4-{[7-(ethylcarbamoyl)-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl]amino}-3-methoxypiperidine-1-carboxylate (**Example 25 Step 4**). The residue was purified by silica gel column chromatography eluting with 2-10% MeOH in DCM followed by preparative HPLC using a gradient of from 14-34% MeCN in water, both mobile phases modified with ammonia (pH=10).

^{1}H NMR (400MHz, MeOH-d_4): δ ppm 8.63 (br s, 1H), 7.93 (s, 1H), 7.80 (s, 1H), 6.88-6.80 (m, 1H), 6.27-6.22 (m, 1H), 5.80-5.77 (m, 1H), 4.20-4.05 (m, 1.5H), 3.90-3.45 (m, 9.5H), 2.28-2.17 (m, 1H), 1.66-1.64 (m, 1H), 1.38-1.30 (m, 3H).

MS m/z 373 $[M+H]^+$

The trans-racemic material was separated into its enantiomers using preparative chiral column chromatography according to the conditions described below;

Column: OD (250x30mm), 10 micron; Mobile phase: 50% EtOH in NH_3/H_2O

Flow rate: 80 mL/min

QC Analytical LCMS Method:

Column: Chiralcel OD-H (150x4.6mm, 5 micron); Mobile phase: 40% MeOH with 0.05% DEA in CO_2;

Flow rate: 2.35 mL/min

The two isomers were arbitrarily assigned absolute stereochemistry

First eluting isomer: Example 26

2-{[(3R,4R)-1-acryloyl-3-methoxypiperidin-4-yl]amino}-N-ethyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide. Rt = 2.57 minutes, 100% de; MS m/z 373 $[M+H]^+$

Second eluting isomer: Example 27

2-{[(3S,4S)-1-acryloyl-3-methoxypiperidin-4-yl]amino}-N-ethyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide. Rt = 5.28 minutes, 99% de, MS m/z 395 $[M+Na]^+$

Example 28

Racemic-2-[(1-acryloylpyrrolidin-3-yl)(methyl)amino]-N-ethyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

The title compound was prepared and purified according to the method described for **Example 1 Steps 5-7** using racemic-tert-butyl 3-{[7-(ethylcarbamoyl)-5-{[2-(tri-methylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl](methyl)amino}pyrrolidine-1-carboxylate (**Example 28 Step 4**). The residue was purified by silica gel column chromatography eluting with 5% MeOH in DCM followed by preparative HPLC using a gradient of from 19-39% MeCN in water, both mobile phases modified with ammonia (pH=10).

^{1}H NMR (400MHz, DMSO-d_6): δ ppm 12.20 (br s, 1H), 8.11-8.02 (m, 3H), 6.67-6.59 (m, 1H), 6.18-6.12 (m, 1H), 5.71-5.65 (m, 1H), 5.13-5.02 (m, 1H), 3.91-3.40 (m, 4H), 3.40-3.30 (m, 2H), 3.02 (s, 3H), 2.20-2.10 (m, 2H), 1.14 (t, 3H). MS m/z 343 $[M+H]^+$

The racemic material was separated into its enantiomers using preparative chiral column chromatography according to the conditions described below;

Column: AS (250x30mm), 5 micron; Mobile phase: 35% EtOH in NH_3/H_2O

Flow rate: 50 mL/min

QC Analytical LCMS Method:

Column: Chiralpak AS-H (250x4.6mm, 5 micron); Mobile phase: 5-40% EtOH with 0.05% DEA in CO_2;

Flow rate: 2.35 mL/min

The two isomers were arbitrarily assigned absolute stereochemistry

First eluting isomer: Example 29

2-{[(3R)-1-acryloylpyrrolidin-3-yl](methyl)amino}-N-ethyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide. Rt = 8.02 minutes MS m/z 343 $[M+H]^+$

Second eluting isomer: Example 30

2-{[(3S)-1-acryloylpyrrolidin-3-yl](methyl)amino}-N-ethyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide. Rt = 8.32 minutes MS m/z 343 $[M+H]^+$

Example 31

Trans-racemic-2-{[(3S,4S)-1-acryloyl-3-hydroxypiperidin-4-yl]amino}-N-ethyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

The title compound was prepared and purified according to the method described for **Example 1 Steps 5-7** using trans-racemic-tert-butyl 4-{[7-(ethylcarbamoyl)-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl]amino}-3-hydroxypiperidine-1-carboxylate (**Example 31 Step 4**). The residue was purified using silica gel column chromatography eluting with 0-10% MeOH in DCM followed by preparative HPLC using a gradient of from 6-26% MeCN in water, both mobile phases modified with ammonia (pH=10) using Kromasil Eternity XT18 (250x21.2 mm), 10 micron).

^{1}H NMR (400MHz, DMSO-d_6): δ ppm 12.06 (br s, 1H), 8.20-8.17 (m, 1H), 7.87 (s, 1H), 7.76-7.75 (m, 1H), 7.01-6.96 (m, 1H), 6.84-6.80 (m, 1H), 6.13-6.08 (m, 1H), 5.69-5.66 (m, 1H), 5.17-5.15 4.37-4.35 (m, 0.5H), 4.00-3.75 (m, 3H), 3.60-3.20 (m, 5H), 2.80-2.75 (m, 0.5H), 2.30-2.10 (m, 1H), 1.40-1.30 (m, 1H), 1.19 (t, 3H). MS m/z 359 $[M+H]^+$

The racemic material was separated into its enantiomers using preparative chiral column chromatography according to the conditions described below;

Column: OJ (200x30mm), 5 micron. Mobile phase: 20% EtOH in NH_3/H_2O

Flow rate: 60 mL/min

QC Analytical LCMS Method:

Column: Chiralcel OJ-H (250x4.6mm, 5 micron); Mobile phase: 5-40% MeOH with 0.05% DEA in CO_2; Flow rate: 2.5 mL/min

The two isomers were arbitrarily assigned absolute stereochemistry

First eluting isomer: Example 32

2-{[(3S,4S)-1-acryloyl-3-hydroxypiperidin-4-yl]amino}-N-ethyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide. Rt = 6.93 minutes MS m/z 359 $[M+H]^+$

Second eluting isomer: Example 33

2-{[(3R,4R)-1-acryloyl-3-hydroxypiperidin-4-yl]amino}-N-ethyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide. Rt = 7.43 minutes MS m/z 359 $[M+H]^+$

Example 34

Racemic-2-[(1-acryloylpiperidin-3-yl)amino]-N-ethyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

The title compound was prepared and purified according to the method described for **Example 1 Steps 5-7** using racemic-tert-butyl 3-{[7-(ethylcarbamoyl)-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl]amino}piperidine-1-carboxylate (**Example 34 Step 4**). The residue was pu-

rified using silica gel column chromatography eluting with 0-11% MeOH in DCM. ^{1}H NMR (400MHz, DMSO-d_6): δ ppm 12.09 (br s, 1H), 8.19-8.05 (m, 1H), 7.91 (s, 1H), 7.77-7.74 (m, 1H), 7.10-7.00 (m, 1H), 6.91-6.85 (m, 1H), 6.59-6.54 (m, 0.5H), 6.17-6.07 (m, 1H), 5.72-5.52 (m, 1.5H), 4.77-4.75 (m, 1H), 3.98-3.80 (m, 3H), 3.19-3.16 (m, 1H), 2.09-2.06 (m, 1H), 1.84-1.83 (m, 1H), 1.63-1.51 (m, 2H), 1.15-1.12 (m, 3H).

The racemic material was separated into its enantiomers using preparative chiral column chromatography.

SFC separation condition:

Column: OJ (250 x 30 mm, 5 um); Mobil Phase 25% EtOH/NH3/H2O; Flow rate = 60 mL/min.

Prep HPLC:

Column: Kromasil Eternity XT C18 25*21.2*10µm

Mobile Phase: 10% MeCN to 30% MeCN/H2O (0.225%FA)

LC/MS analysis:

Column: UltimateXB-C18, 3µm,3*50mm, Rt = 3.38 min

Mobile Phase 1% MeCN/H2O to 100% MeCN/H_2O (0.1 % TFA); λ = 220 nm

Chiral SFC Analysis:

Column: Chiralpak AS-H 250*4.mm, ID 5µM; Rt = 6.92

Mobile Phase :EtOH (0.05% DEA) in CO2 from 5% to 40%; Flow rate: 2.35 mL/min; λ = 220 nm

The two isomers were arbitrarily assigned absolute stereochemistry.

Example 35

2-{[(3R)-1-acryloylpiperidin-3-yl]amino}-N-ethyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

1H NMR as above. Rt (chiral SFC) = 6.92; Rt (LC) = 3.38 ; MS m/z 365 $(M+Na)^+$

Example 36

2-{[(3S)-1-acryloylpiperidin-3-yl]amino}-N-ethyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

1H NMR as above. Rt (chiral SFC) = 7.81 Rt (LC) = 3.38 ; MS m/z 365 $(M+Na)^+$

Example 37

Cis-racemic-2-{[(3S,4R)-1-acryloyl-3-methylpiperidin-4-yl]amino}-N-ethyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

The title compound was prepared and purified according to the method described for **Example 1 Steps 5-7** using cis-racemic-tert-butyl 4-{[7-(ethylcarbamoyl)-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl]amino}-3-methylpiperidine-1-carboxylate (**Example 37 Step 4**). The residue was purified using silica gel column chromatography eluting with 2-10% MeOH in DCM followed by preparative HPLC eluting with 19-39% MeCN in water modified with 0.05% ammonia. ^{1}H NMR (400MHz, DMSO-d_6): δ ppm 12.07 (br s, 1H), 8.20-8.17 (m, 1H), 7.87 (s, 1H), 7.72 (s, 1H), 6.99-6.82 (m, 2H), 6.14-6.10 (m, 1H), 5.70-5.67 (m, 1H), 4.39-4.37 (m, 1H), 4.12-4.09 (m, 1H), 3.71-3.68 (m, 1H), 3.41-3.16 (m, 3H), 2.97-2.83 (m, 1H), 2.14-2.10 (m, 1H), 1.64-1.62 (m, 1H), 1.31-1.18 (m, 4H), 0.98 (d, 3H).

MS m/z 357 $[M+H]^+$

The cis-racemic material was separated into its enantiomers using preparative chiral column chromatography according to the conditions described below;

Column: OD (250x30mm), 5 micron; Mobile phase: 40% EtOH in NH_3/H_2O in supercritical CO_2

Flow rate: 50 mL/min

QC Analytical LCMS Method:

Column: Chiralpak AS-H (250x4.6mm, 5 micron); Mobile phase: 5-40% MeOH with 0.05% DEA in CO_2; Flow rate: 2.35 mL/min

The two isomers were arbitrarily assigned absolute stereochemistry

First eluting isomer: Example 38

2-{[(3S,4R)-1-acryloyl-3-methylpiperidin-4-yl]amino}-N-ethyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide. Rt = 5.99 minutes MS m/z 357 $[M+H]^+$

Second eluting isomer: Example 39

2-{[(3R,4S)-1-acryloyl-3-methylpiperidin-4-yl]amino}-N-ethyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide. Rt = 6.47 minutes. MS m/z 357 $[M+H]^+$

Example 40

Trans-racemic-2-{[(2R,4S)-1-acryloyl-2-methylpiperidin-4-yl]amino}-N-ethyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

The title compound was prepared and purified according to the method described for **Example 1 Steps 5-7** using trans-racemic-tert-butyl 4-{[7-(ethylcarbamoyl)-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl]amino}-2-methylpiperidine-1-carboxylate (**Example 40 Step 4**). The residue was purified using silica gel column chromatography eluting with 0-12% MeOH in DCM.

^1H NMR (400MHz, DMSO-d_6): δ ppm 12.08 (br s, 1H), 8.18-8.15 (m, 1H), 7.88 (s, 1H), 7.68 (m, 1H), 6.93-6.79 (m, 2H), 6.11-6.07 (m, 1H), 5.67-5.64 (m, 1H), 4.91 (br s, 0.5H), 4.49-4.44 (br m, 1H), 4.25-4.17 (m, 1H), 4.05-3.95 (m, 0.5H), 3.42-3.39 (m, 2.5H), 2.95-2.85 (m, 0.5H), 2.11-1.97 (m, 2H), 1.50-1.16 (m, 8H).

The trans-racemic material was separated into its enantiomers using preparative chiral column chromatography according to the conditions described below;

Column: OJ (250x30mm), 20 micron

Mobile phase: 35% MeOH in NH_3/H_2O; Flow rate: 80 mL/min

QC Analytical LCMS Method:

Column: Chiralcel OJ-H (250x4.6mm, 5 micron); Mobile phase: 5-40% MeOH with 0.05% DEA in CO_2; Flow rate: 2.5 mL/min

The two isomers were arbitrarily assigned absolute stereochemistry

First eluting isomer: Example 41

2-{[(2R,4S)-1-acryloyl-2-methylpiperidin-4-yl]amino}-N-ethyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide. Rt = 6.83 minutes MS m/z 357 $[M+H]^+$

Second eluting isomer: Example 42

2-{[(2S,4R)-1-acryloyl-2-methylpiperidin-4-yl]amino}-N-ethyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide. Rt = 7.83 minutes MS m/z 357 $[M+H]^+$

Example 43

Trans-racemic-2-{[(3R,4R)-1-acryloyl-3-methylpiperidin-4-yl]amino}-N-ethyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

The title compound was prepared and purified according to the method described for **Example 1 Steps 5-7** using trans-racemic-tert-butyl 4-{[7-(ethylcarbamoyl)-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl]amino}-3-methylpiperidine-1-carboxylate (**Example 43 Step 4**). The residue was purified using silica gel column chromatography eluting with 7% MeOH in EtOAc followed by preparative HPLC eluting with 25-45% MeCN in water modified with ammonia to pH=10. ^{1}H NMR (400MHz, DMSO-d_6): δ ppm 12.06 (br s, 1H), 8.17-8.15 (m, 1H), 7.87 (s, 1H), 7.81-7.79 (m, 1H), 6.98-6.96 (m, 1H), 6.87-6.81 (m, 1H), 6.13-6.08 (m, 1H), 5.68-5.65 (m, 1H), 4.20-4.10 (m, 1.5H), 3.82-3.78 (m, 1.5H), 3.45-3.16 (m, 4H), 2.33-2.30 (m, 1H), 1.77-1.67 (m, 2H), 1.20-1.17 (m, 3H), 0.85-0.81 (m, 3H).

MS m/z 357 $[M+H]^+$

The trans-racemic material was separated into its enantiomers using preparative chiral column chromatography according to the conditions described below;

Column: OD (250x30mm), 10 micron; Mobile phase: 50% MeOH in NH_3/H_2O

Flow rate: 70 mL/min

QC Analytical LCMS Method:

Column: Chiralcel OD-H (250x4.6mm, 5 micron); Mobile phase: 40% MeOH with 0.05% DEA in CO_2; Flow rate: 2.35 mL/min

The two isomers were arbitrarily assigned absolute stereochemistry

First eluting isomer: Example 44

2-{[(3R,4R)-1-acryloyl-3-methylpiperidin-4-yl]amino}-N-ethyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide. Rt = 4.24 minutes MS m/z 357 $[M+H]^+$

Second eluting isomer: Example 45

2-{[(3S,4S)-1-acryloyl-3-methylpiperidin-4-yl]amino}-N-ethyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide. Rt = 6.76 minutes MS m/z 357 $[M+H]^+$

Example 46

Trans-racemic-2-{[1-acryloyl-3-methylpiperidin-4-yl]oxy}-N-ethyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

The title compound was prepared and purified according to the method described for **Example 1 Steps 5-7** using trans-racemic-tert-butyl 4-{[7-(ethylcarbamoyl)-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl]oxy}-3-methylpiperidine-1-carboxylate (**Example 46 Step 4**). The residue was purified using silica gel column chromatography eluting with 0-30% MeOH in DCM followed by preparative HPLC eluting with 26-46% MeCN in water with ammonia to pH=10. ^{1}H NMR (400MHz,

DMSO-d_6): δ ppm 12.53 (br s, 1H), 8.25 (s, 1H), 8.13 (s, 1H), 7.82-7.79 (m, 1H), 6.93-6.82 (m, 1H), 6.15-6.11 (m, 1H), 5.71-5.68 (m, 1H), 5.00-4.94 (m, 1H), 4.24-4.19 (m, 1H), 4.03-3.99 (m, 1H), 3.47-3.42 (m, 3.5H), 3.17-3.14 (m, 1H), 2.86-2.84 (m, 0.5H), 2.29-2.26 (m, 1H), 2.00-1.80 (m, 1H), 1.60-1.40 (m, 1H), 1.23 (t, 3H), 1.00 (t, 3H). MS m/z 380 $[M+Na]^+$

The trans-racemic material was separated into its enantiomers using preparative chiral column chromatography according to the conditions described below;

Column: Chiralcel-OD (250x30mm), 10 micron; Mobile phase: 35% EtOH in NH_3/H_2O

Flow rate: 70 mL/min

QC Analytical LCMS Method:

Column: Chiralcel OD-3 (150x4.6mm, 5 micron); Mobile phase: 5-40% MeOH with 0.05% DEA in CO_2; Flow rate: 2.5 mL/min

The two enantiomers were arbitrarily assigned absolute stereochemistry

First eluting isomer: Example 47

2-{[(3R,4R)-1-acryloyl-3-methylpiperidin-4-yl]oxy}-N-ethyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide.

Rt = 6.75 minutes MS m/z 380 $[M+Na]^+$

Second eluting isomer: Example 48

2-{[(3S,4S)-1-acryloyl-3-methylpiperidin-4-yl]oxy}-N-ethyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide.

Rt = 7.57 minutes MS m/z 380 $[M+Na]^+$

The following Examples were prepared according to the methods described for **Example 1 Steps 5-7** using the appropriate pyrrolopyrazine. The steps may be carried out in any order to maximize yield.

Prep HPLC Method A: Column: Kromasil Eternity XT C18 250x21.2 mm, 10 micron.

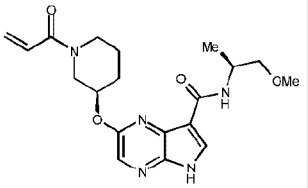
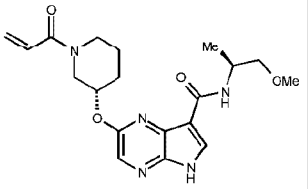
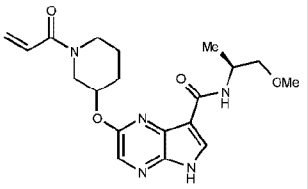
Mobile phase: From 9-29% MeCN in water, both mobile phases modified with 0.05% ammonia

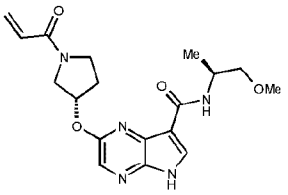
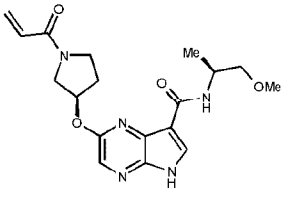
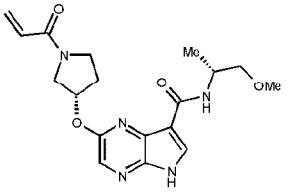
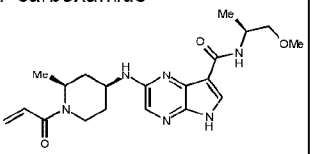
QC Analytical LCMS Method:

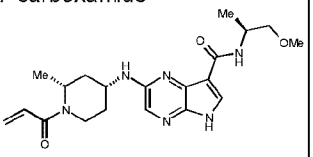
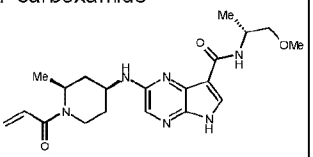
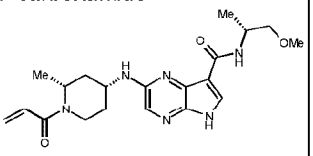
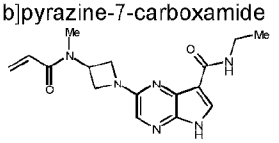
Column: Xterra, 4.6x150 mm, 3.5 micron

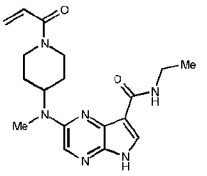
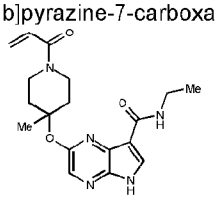
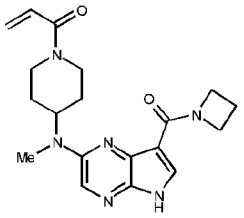
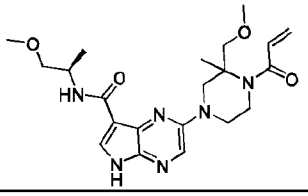
Mobile phase: From 0-60% MeCN in 20 mM ammonium carbonate in water, over 10 minutes, hold at 60% for 5 minutes, flow rate 1 mL/min.

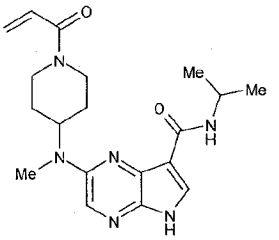
Purification Method B: Silica gel column chromatography eluting with 7% MeOH in EtOAc followed by preparative HPLC eluting with 20-40% MeCN in water modified with ammonia to pH=10.

Example	Name/Structure	SM	Data
49	2-{[(3R)-1-acryloylpiperidin-3-yl]oxy}-N-[(2S)-1-methoxypropan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide 	tert-butyl (R)-3-[(7-[((S)-1-methoxypropan-2-yl)carbamoyl]-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl)oxy]piperidine-1-carboxylate (**Example 49 Step 4**).	^{1}H NMR (400MHz, DMSO-d_6): δ ppm 12.58 (br s, 1H), 8.20 (s, 1H), 8.03-7.92 (m, 2H), 6.87-6.83 (m, 0.5H), 6.55-6.53 (m, 0.5H), 6.09-5.99 (m, 1H), 5.70-5.67 (m, 0.5H), 5.48-5.46 (m, 0.5H), 5.18-5.10 (m, 1H), 4.22-4.19 (m, 2H), 3.99-3.96 (m, 0.5H), 3.80-3.75 (m, 1.5H), 3.75-3.70 (m, 0.5H), 3.42-3.29 (m, 5.5H), 2.12-1.75 (m, 3H), 1.60-1.50 (br m, 1H), 1.20 (d, 3H). 25-45% MeCN in water (with ammonia pH=10). Rt = 3.49 minutes MS m/z 410 $[M+Na]^+$
50	2-{[(3S)-1-acryloylpiperidin-3-yl]oxy}-N-[(2S)-1-methoxypropan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide 	tert-butyl (S)-3-[(7-[((S)-1-methoxypropan-2-yl)carbamoyl]-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl)oxy]piperidine-1-carboxylate (**Example 50 Step 4**).	^{1}H NMR (400MHz, DMSO-d_6): δ ppm 12.58 (br s, 1H), 8.20 (s, 1H), 8.05-7.93 (m, 2H), 6.90-6.86 (m, 0.5H), 6.58-6.57 (m, 0.5H), 6.09-6.00 (m, 1H), 5.70-5.67 (m, 0.5H), 5.50-5.48 (m, 0.5H), 5.14-5.08 (m, 1H), 4.24-4.22 (m, 1H), 4.01-3.96 (m, 1H), 3.80-3.70 (m, 2H), 3.43-3.28 (m, 6H), 2.18-2.12 (m, 1H), 1.95-1.75 (m, 2H), 1.58-1.50 (m, 1H), 1.58-1.50 (br m, 1H), 1.20 (m, 3H). 23-43% MeCN in water (with ammonia pH=10). Rt = 3.53 minutes MS m/z 410 $[M+Na]^+$
51	Racemic-2-[(1-acryloylpiperidin-3-yl)oxy]-N-[(2S)-1-methoxypropan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide 	Racemic-tert-butyl-3-[(7-[((S)-1-methoxypropan-2-yl)carbamoyl]-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl)oxy]piperidine-1-carboxylate (**Example 51 Step 4**).	^{1}H NMR (400MHz, DMSO-d_6): δ ppm 12.59 (br s, 1H), 8.20 (s, 1H), 8.05-7.93 (m, 2H), 6.88-6.87 (m, 0.5H), 6.57-6.55 (m, 0.5H), 6.11-6.00 (m, 1H), 5.70-5.68 (m, 0.5H), 5.48-5.45 (m, 0.5H), 5.15-5.09 (m, 1H), 4.22-4.19 (m, 1H), 3.99-3.70 (m, 4H), 3.42-3.29 (m, 5H), 2.14-1.70 (m, 3H), 1.57-1.50 (m, 1H), 1.20 (d, 3H). Rt = 3.95 minutes MS m/z 410 $[M+Na]^+$

52	2-{[(3S)-1-acryloylpyrrolidin-3-yl]oxy}-N-[(2S)-1-methoxypropan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide 	tert-butyl (S)-3-[(7-[((S)-1-methoxypropan-2-yl)carbamoyl]-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl)oxy]pyrrolidine-1-carboxylate (**Example 52 Step 4**).	^{1}H NMR (400MHz, MeOH-d_4): δ ppm 8.53-8.48 (m, 1H), 8.14 (s, 1H), 7.99 (s, 1H), 6.71-6.57 (m, 1H), 6.32-6.28 (m, 1H), 5.79-5.72 (m, 2H), 4.40-4.30 (m, 1H), 4.10-3.75 (m, 4H), 3.80-3.53 (m, 3H), 3.31 (s, 3H), 2.45-2.37 (m, 2H), 1.34 (d, 3H). 18-38% MeCN in water (with ammonia pH=10). MS m/z 396 $[M+Na]^+$
53	2-{[(3R)-1-acryloylpyrrolidin-3-yl]oxy}-N-[(2S)-1-methoxypropan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide 	tert-butyl (R)-3-[(7-[((S)-1-methoxypropan-2-yl)carbamoyl]-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl)oxy]pyrrolidine-1-carboxylate (**Example 53 Step 4**).	^{1}H NMR (400MHz, MeOH-d_4): δ ppm 8.53-8.48 (m, 1H), 8.16 (s, 1H), 8.01 (s, 1H), 6.73-6.56 (m, 1H), 6.33-6.29 (m, 1H), 5.81-5.72 (m, 2H), 4.40-4.35 (m, 1H), 4.20-4.15 (m, 0.5H), 4.00-3.80 (m, 3.5H), 3.75-3.65 (m, 0.5H), 3.60-3.50 (m, 2.5H), 3.43 (s, 3H), 2.48-2.40 (m, 2H), 1.38 (d, 3H). 18-38% MeCN in water (with ammonia pH=10). MS m/z 396 $[M+Na]^+$
54	2-{[(3S)-1-acryloylpyrrolidin-3-yl]oxy}-N-[(2R)-1-methoxypropan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide 	tert-butyl (S)-3-[(7-[((R)-1-methoxypropan-2-yl)carbamoyl]-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl)oxy]pyrrolidine-1-carboxylate (**Example 54 Step 4**).	^{1}H NMR (400MHz, MeOH-d_4): δ ppm 8.53-8.48 (m, 1H), 8.16 (s, 1H), 8.01 (s, 1H), 6.70-6.58 (m, 1H), 6.34-6.29 (m, 1H), 5.81-5.72 (m, 2H), 4.40-4.30 (m, 1H), 4.20-4.15 (m, 0.5H), 4.00-3.80 (m, 3.5H), 3.75-3.65 (m, 0.5H), 3.60-3.50 (m, 2.5H), 3.43 (s, 3H), 2.50-2.39 (m, 2H), 1.38 (d, 3H). 18-38% MeCN in water (with ammonia pH=10). MS m/z 396 $[M+Na]^+$
55	2-{[(2S,4S)-1-acryloyl-2-methylpiperidin-4-yl]amino}-N-[(2S)-1-methoxypropan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide 	tert-butyl (2S,4S)-4-[(7-[((S)-1-methoxypropan-2-yl)carbamoyl]-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl)amino]-2-methylpiperidine-1-carboxylate (**Example 55 Step 4**).	^{1}H NMR (400MHz, DMSO-d_6): δ ppm 12.09 (br s, 1H), 8.30-8.28 (m, 1H), 7.87 (s, 1H), 7.78 (s, 1H), 7.06-7.04 (m, 1H), 6.81-6.75 (m, 1H), 6.13-6.03 (m, 1H), 5.67-5.64 (m, 1H), 4.41-4.40 (m, 1H), 4.20-3.94 (m, 3H), 3.20-3.15 (m, 6H), 2.10-1.90 (m, 3H), 1.80-1.70 (m, 1H), 1.22-1.14 (m, 6H). 24-44% MeCN in water (with ammonia pH=10). MS m/z 400 $[M+Na]^+$

56	2-{[(2R,4R)-1-acryloyl-2-methylpiperidin-4-yl]amino}-N-[(2S)-1-methoxypropan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide 	tert-butyl (2R,4R)-4-[(7-[((S)-1-methoxypropan-2-yl)carbamoyl]-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl)amino]-2-methylpiperidine-1-carboxylate (**Example 56 Step 4**).	^{1}H NMR (400MHz, DMSO-d_6): δ ppm 12.08 (br s, 1H), 8.39-8.37 (m, 1H), 7.86 (s, 1H), 7.77 (s, 1H), 7.10-7.08 (m, 1H), 6.81-6.75 (m, 1H), 6.13-6.09 (m, 1H), 5.67-5.64 (m, 1H), 4.45-4.40 (m, 1H), 4.20-4.00 (m, 3H), 3.40-3.20 (m, 6H), 2.10-1.70 (m, 4H), 1.21-1.15 (m, 6H). 21-41% MeCN in water (with ammonia pH=10). MS m/z 423 $[M+Na]^+$
57	2-{[(2S,4S)-1-acryloyl-2-methylpiperidin-4-yl]amino}-N-[(2R)-1-methoxypropan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide 	tert-butyl (2S,4S)-4-[(7-[((R)-1-methoxypropan-2-yl)carbamoyl]-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl)amino]-2-methylpiperidine-1-carboxylate (**Example 57 Step 4**).	^{1}H NMR (400MHz, DMSO-d_6): δ ppm 11.94 (br s, 1H), 8.39-8.37 (m, 1H), 7.88 (s, 1H), 7.77 (s, 1H), 7.09-7.07 (m, 1H), 6.81-6.75 (m, 1H), 6.13-6.08 (m, 1H), 5.67-5.64 (m, 1H), 4.45-4.40 (m, 1H), 4.20-3.99 (m, 3H), 3.40-3.20 (m, 6H), 2.04-1.75 (m, 4H), 1.21-1.15 (m, 6H). MS m/z 401 $[M+H]^+$ 100% ee. 25-45% MeCN in water (with ammonia pH=10).
58	2-{[(2R,4R)-1-acryloyl-2-methylpiperidin-4-yl]amino}-N-[(2R)-1-methoxypropan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide 	tert-butyl (2R,4R)-4-[(7-[((R)-1-methoxypropan-2-yl)carbamoyl]-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl)amino]-2-methylpiperidine-1-carboxylate (**Example 58 Step 4**).	^{1}H NMR (400MHz, DMSO-d_6): δ ppm 12.02 (br s, 1H), 8.39-8.37 (m, 1H), 7.88 (s, 1H), 7.77 (s, 1H), 7.08-7.07 (m, 1H), 6.81-6.75 (m, 1H), 6.13-6.08 (m, 1H), 5.67-5.64 (m, 1H), 4.45-4.35 (m, 1H), 4.25-4.00 (m, 3H), 3.40-3.25 (m, 6H), 2.10-1.70 (m, 4H), 1.21-1.15 (m, 6H). MS m/z 401 $[M+H]^+$ 98% ee. 22-42% MeCN in water (with ammonia pH=10).
59	2-{3-[acryloyl(methyl)amino]azetidin-1-yl}-N-ethyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide 	tert-butyl {1-[7-(ethylcarbamoyl)-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl]azetidin-3-yl}methylcarbamate (**Example 59 Step 4**).	Rt = 7.50 minutes MS m/z 329 $[M+H]^+$ Using Prep HPLC Method A. ^{1}H NMR (400MHz, DMSO-d_6): δ ppm 12.28 (br s, 1H), 8.15-8.13 (m, 1H), 8.05 (s, 1H), 7.73 (s, 1H), 6.82-6.75 (m, 1H), 6.18-6.09 (m, 1H), 5.75-5.72 (m, 1H), 5.34-5.16 (m, 1H), 4.35-4.34 (m, 2H), 4.21-4.13 (m, 2H), 3.40-3.06 (m, 5H), 1.34 (t, 3H).

60	2-[(1-acryloylpiperidin-4-yl)(methyl)amino]-N-ethyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide 	tert-butyl 4-{[7-(ethylcarbamoyl)-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl](methyl)amino}piperidine-1-carboxylate (**Example 60 Step 4**).	PM B. ^{1}H NMR (400MHz, DMSO-d_6): δ ppm 12.15 (br s, 1H), 8.13-8.11 (m, 1H), 8.03 (s, 1H), 7.99 (s, 1H), 6.89-6.82 (m, 1H), 6.14-6.09 (m, 1H), 5.70-5.67 (m, 1H), 4.63-4.55 (m, 1H), 4.23-4.20 (m, 1H), 3.41-3.33 (m, 2H), 3.21-3.15 (m, 1H), 2.94 (s, 3H), 2.77-2.71 (m, 1H), 1.74-1.64 (m, 4H), 1.21-1.18 (m, 3H). MS m/z 357 $[M+H]^+$
61	2-[(1-acryloyl-4-methylpiperidin-4-yl)oxy]-N-ethyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide 	tert-butyl 4-{[7-(ethylcarbamoyl)-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl]oxy}-4-methylpiperidine-1-carboxylate (**Example 61 Step 4**).	^{1}H NMR (400MHz, DMSO-d_6): δ ppm 12.71 (br s, 1H), 8.20 (s, 1H), 8.01 (s, 1H), 7.73-7.70 (m, 1H), 6.86-6.79 (m, 1H), 6.13-6.08 (m, 1H), 5.69-5.66 (m, 1H), 4.16-4.13 (m, 1H), 3.88-3.85 (m, 1H), 3.31-3.11 (m, 4H), 2.39-2.33 (m, 2H), 1.83-1.68 (m, 5H), 1.22-1.15 (m, 3H). MS m/z 380 $[M+Na]^+$ 31-51% MeCN in water with ammonia to pH=10.
62	1-(4-{[7-(azetidin-1-ylcarbonyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl](methyl)amino}piperidin-1-yl)prop-2-en-1-one 	tert-butyl 4-{[7-(azetidin-1-ylcarbonyl)-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl](methyl)amino}piperidine-1-carboxylate (**Example 62 Step 4**).	^{1}H NMR (400MHz, DMSO-d_6): δ ppm 12.15 (br s, 1H), 7.95-7.94 (m, 2H), 6.90-6.83 (m, 1H), 6.15-6.10 (m, 1H), 5.71-5.68 (m, 1H), 4.70-4.60 (m, 2H), 4.60-4.40 (br m, 2H), 4.22-4.19 (m, 1H), 4.10-3.95 (m, 2H), 3.22-3.18 (m, 1H), 2.91 (s, 3H), 2.80-2.70 (m, 1H), 2.30-2.22 (m, 2H), 1.70-1.63 (m, 4H). MS m/z 369 $[M+H]^+$ 10-30% MeCN in water with ammonia to pH=10, PM A.
63	2-(4-acryloyl-3-(methoxymethyl)-3-methylpiperazin-1-yl)-N-((R)-1-methoxypropan-2-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide 	tert-butyl 2-(methoxymethyl)-4-(7-(((R)-1-methoxypropan-2-yl)carbamoyl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl)-2-methylpiperazine-1-carboxylate (**Example 63 Step 4**).	^{1}H NMR (400MHz, DMSO-d_6): δ ppm 12.18 (br s, 1H), 8.40-8.37 (m, 1H), 8.00 (s, 1H), 7.91 (s, 1H), 6.81-6.75 (m, 1H), 6.06-6.01 (m, 1H), 5.66-5.63 (m, 1H), 4.18-3.62 (m, 9H), 3.44-3.40 (m, 2H), 3.31 (s, 3H), 3.19 (s, 1H), 1.42 (s, 3H), 1.22 (s, 3H). MS m/z 431 $[M+H]^+$ 20-40% MeCN in water with ammonia to pH=10.

64	2-[(1-acryloylpiperidin-4-yl)(methyl)amino]-N-(propan-2-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide 	tert-butyl 4-((7-(isopropylcarbamoyl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl)(methyl)amino)piperidine-1-carboxylate (**Example 64 Step 4**).	^{1}H NMR (400MHz, DMSO-d_6): δ ppm 8.09-8.07 (m, 1H), 8.02 (s, 1H), 7.97 (s, 1H), 6.89-6.82 (m, 1H), 6.14-6.09 (m, 1H), 5.70-5.67 (m, 1H), 4.64-4.56 (m, 2H), 4.24-4.21 (m, 1H), 4.12-4.05 (m, 1H), 3.19-3.16 (m, 1H), 2.92 (s, 3H), 2.74-2.68 (m, 1H), 1.74-1.61 (m, 4H), 1.23 (s, 3H), 1.22 (s, 3H). MS m/z 393 $[M+Na]^+$ 22-42% MeCN in water with ammonia to pH=10.

Example 65

Cis-racemic-2-{[1-acryloyl-6-methylpiperidin-3-yl]amino}-N-[(2S)-1-methoxypropan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

To a solution of cis-racemic-benzyl -5-[(7-[((S)-1-methoxypropan-2-yl)carbamoyl]-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl)amino]-2-methylpiperidine-1-carboxylate (**Example 65 Step 4,** 620 mg, 1.02 mmol) in MeOH (20 mL) was added palladium on carbon (100 mg) and the reaction was stirred at room temperature under a balloon of hydrogen for 18 hours. Further palladium on carbon (200 mg) was added and the reaction continued at 30°C for 4 hours. The reaction was filtered through Celite™ and the filtrate concentrated *in vacuo*. The residue was dissolved in THF/water (20 mL/5 mL) and treated with DIPEA (262 mg, 2.03 mmol) followed by acryloyl chloride (138 mg, 1.52 mmol) at 0°C. The reaction was stirred at this temperature for 4 hours. Additional acryloyl chloride (46 mg) was added and the reaction stirred at room temperature for 3 hours. The reaction was diluted with EtOAc and concentrated *in vacuo*. The residue was purified using silica gel column chromatography eluting with 5% MeOH in DCM before dissolving in DCM (15 mL) and treating with TFA (4 mL). The reaction was stirred at room temperature for 5 hours, concentrated *in vacuo* and dissolved in MeOH. Ammonia(4 mL) was added and the mixture stirred at room temperature for 4 hours. The solution was concentrated *in vacuo* and purified using silica gel column chromatography eluting with 5% MeOH in DCM to afford the title compound as a yellow solid (230 mg, 73%). ^{1}H NMR (400MHz, DMSO-d_6): δ ppm 12.11 (br s, 1H), 8.30-8.10 (br m, 1H), 7.89 (s, 1H), 7.70 (s, 1H), 7.05-7.04 (m, 1H), 6.90-6.60 (m, 1H), 6.11-6.05 (m, 1H), 5.70-5.60 (m, 1H), 4.80-4.60 (m, 1H), 4.50-4.30 (m, 1H), 4.20-3.70 (m, 2H), 3.36-3.22 (m, 3H), 3.00-2.85 (m, 1H), 1.99-1.94 (m, 2H), 1.80-1.55 (m, 4H), 1.30-1.10 (m, 6H). MS m/z 401 $[M+H]^+$

The cis-racemic material was separated into its enantiomers using preparative chiral column chromatography according to the conditions described below;

Column: AD (250x30mm), 5 micron; Mobile phase: 25% MeOH in NH_3/H_2O; Flow rate: 60 mL/min

QC Analytical LCMS Method:

Column: Chiralpak AD-3 (150x4.6mm, 3 micron); Mobile phase: 5-40% MeOH with 0.05% DEA in CO_2; Flow rate: 2.5 mL/min

The two enantiomers were arbitrarily assigned absolute stereochemistry

First eluting isomer: Example 66

2-{[(3R,6S)-1-acryloyl-6-methylpiperidin-3-yl]amino}-N-[(2S)-1-methoxypropan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide. Rt = 4.64 minutes MS m/z 401 $[M+H]^+$

Second eluting isomer: Example 67

2-{[(3S,6R)-1-acryloyl-6-methylpiperidin-3-yl]amino}-N-[(2S)-1-methoxypropan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide. Rt = 4.97 minutes MS m/z 401 $[M+H]^+$

Example 68

Cis-racemic-2-{[1-acryloyl-6-methylpiperidin-3-yl]amino}-N-[(2R)-1-methoxypropan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

The title compound was prepared according to the method described for **Example 65** using cis-racemic-benzyl-5-[(7-[((R)-1-methoxypropan-2-yl)carbamoyl]-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl)amino]-2-methylpiperidine-1-carboxylate (**Example 68 Step 4**).The residue was purified using silica gel column chromatography eluting with 5% MeOH in DCM followed by preparative HPLC (Phenomenex Gemini C18 (250x21.2, 10 micron), gradient time 10 minutes, flow rate 30 mL/min) using a gradient of 27-57% MeCN in water modified with 0.225% formic acid. ^1H NMR (400MHz, DMSO-d_6): δ ppm 8.31-8.24 (br m, 1H), 7.93 (s, 1H), 7.72 (s, 1H), 7.06-7.04 (m, 1H), 6.90-6.65 (br m, 1H), 6.15-6.05 (m, 1H), 5.70-5.60 (m, 1H), 4.85-4.60 (m, 1H), 4.50-4.40 (m, 1H), 4.20-3.60 (m, 3H), 3.22 (s, 3H), 3.05-2.60 (m, 2H), 2.05-1.90 (m, 1H), 1.75-1.55 (m, 3H), 1.25-1.05 (m, 6H). MS m/z 423 $[M+Na]^+$

During the purification of the cis-racemic material, the corresponding cis enantiomers were also isolated: SFC analysis: Chiralcel OD-3, 150x4.6 mm, 3 micron

Mobile phase: 5-40% MeOH with 0.05% DEA in CO_2, flow rate2.5 mL/min.

The two enantiomers were arbitrarily assigned absolute stereochemistry.

First eluting isomer: Example 69

2-{[(3R,6S)-1-acryloyl-6-methylpiperidin-3-yl]amino}-N-[(2R)-1-methoxypropan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

Rt = 7.83 minutes MS m/z 423 $[M+H]^+$

Second eluting isomer: Example 70

2-{[(3S,6R)-1-acryloyl-6-methylpiperidin-3-yl]amino}-N-[(2R)-1-methoxypropan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

Rt = 8.69 minutes. MS m/z 423 $[M+H]^+$

Example 71

Trans-racemic-2-{[1-acryloyl-2-methylpiperidin-4-yl]oxy}-N-[(2S)-1-methoxypropan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

The title compound was prepared according to the method described for **Example 65** using trans-racemic-benzyl-4-[(7-[((S)-1-methoxypropan-2-yl)carbamoyl]-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl)oxy]-2-methylpiperidine-1-carboxylate (**Example 71 Step 4**). The residue was purified using silica gel column chromatography eluting with 0-5% MeOH in DCM followed by preparative HPLC eluting with 25-45% MeCN in water modified with 0.1% TFA. LCMS analysis: Ultimate XB-C-18 (50x3 mm, 3 micron); 1-100% MeCN in water with 0.1% TFA. Rt = 3.46 minutes MS m/z 402 $[M+H]^+$

^{1}H NMR (400MHz, MeOH-d_4): δ ppm 8.13 (s, 1H), 7.91 (s, 1H), 6.85-6.78 (m, 1H), 6.23-6.19 (m, 1H), 5.77-5.74 (m, 1H), 5.57-5.50 (m, 1H), 5.15-5.00 (m, 1H), 4.70-4.55 (m, 1H), 4.45-4.40 (m, 1H), 4.20-4.10 (br m, 0.5H), 3.60-3.50 (m, 2H), 3.40 (s, 3H), 3.15-3.05 (br m, 0.5H), 2.50-2.40 (m, 1H), 2.20-2.10 (m, 1H), 2.00-1.80 (br m, 1H), 1.70-1.55 (br m, 1H), 1.45-1.30 (m, 6H).

The trans-racemic material was separated into its enantiomers using preparative chiral column chromatography according to the conditions described below;

Column: AS (250x30mm), 5 micron; Mobile phase: 25% MeOH in NH_3/H_2O

Flow rate: 50 mL/min

QC Analytical LCMS Method:

Column: Chiralpak AS-H (250x4.6mm, 5 micron); Mobile phase: 5-40% MeOH with 0.05% DEA in CO_2; Flow rate: 2.35 mL/min

The two enantiomers were arbitrarily assigned absolute stereochemistry

First eluting isomer: Example 72

2-{[(2R,4S)-1-acryloyl-2-methylpiperidin-4-yl]oxy}-N-[(2S)-1-methoxypropan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide. Rt = 5.80 minutes. MS m/z 402 $[M+H]^+$

Second eluting isomer: Example 73

2-{[(2S,4R)-1-acryloyl-2-methylpiperidin-4-yl]oxy}-N-[(2S)-1-methoxypropan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide. Rt = 6.10 minutes. MS m/z 402 $[M+H]^+$

Example 74

Cis-racemic-2-{[1-acryloyl-6-methylpiperidin-3-yl]amino}-N-ethyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

The title compound was prepared according to the method described for Example 65, using cis-racemic-benzyl 5-{[7-(ethylcarbamoyl)-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl]amino}-2-methylpiperidine-1-carboxylate (Example 74, Step 4). The residue was purified using silica gel column chromatography eluting with 5% MeOH in DCM followed by preparative HPLC eluting with 21-41% MeCN in water modified with ammonia to pH=10. ^{1}H NMR (400MHz, DMSO-d_6): δ ppm 11.87 (br s, 1H), 8.06 (br s, 1H), 7.86 (s, 1H), 7.74 (s, 1H), 6.78-6.71 (m, 2H), 6.11-6.06 (m, 1H), 5.66-5.63 (m, 1H), 4.55 (br m, 2H), 3.80-3.70 (br m, 1H), 3.50-3.30 (m, 2H), 2.75-2.60 (m, 1H), 2.00-1.90 (m, 1H), 1.78-1.72 (m, 3H), 1.24-1.12 (m, 6H). MS m/z 357 $[M+H]^+$

The cis-racemic material was separated into its enantiomers using preparative chiral column chromatography according to the conditions described below;

Column: OJ (250x30mm), 20 micron; Mobile phase: 40% MeOH in NH_3/H_2O

Flow rate: 80 mL/min

QC Analytical LCMS Method:

Column: Xtimate C18 (5x30mm, 3 µm); Mobile phase: 1% - 100% MeCN/H_2O (0.05% TFA)

Rt = 3.33 min. The two enantiomers were arbitrarily assigned absolute stereochemistry.

First eluting isomer: Example 75

2-{[(3S,6R)-1-acryloyl-6-methylpiperidin-3-yl]amino}-N-ethyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide.

Rt = 5.97 minutes. MS m/z 357 $[M+H]^+$

Second eluting isomer: Example 76

2-{[(3R,6S)-1-acryloyl-6-methylpiperidin-3-yl]amino}-N-ethyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide.

Rt = 6.32 minutes. MS m/z 357 $[M+H]^+$

Example 77

Trans-racemic-2-{[1-acryloyl-2-methylpiperidin-4-yl]oxy}-N-ethyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

The title compound was prepared according to the method described for **Example 65** using trans-racemic-benzyl 4-{[7-(ethylcarbamoyl)-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl]oxy}-2-methylpiperidine-1-carboxylate (**Example 77 Step 4**). The residue was purified using silica gel column chromatography eluting with 10% MeOH in DCM followed by preparative HPLC eluting with 26-46% MeCN in water with ammonia to pH=10.

^1H NMR (400MHz, DMSO-d_6): δ ppm 12.60 (br s, 1H), 8.20 (s, 1H), 7.97 (s, 1H), 7.85-7.82 (m, 1H), 6.87-6.81 (m, 1H), 6.13-6.09 (m, 1H), 5.70-5.67 (m, 1H), 5.56-5.52 (m, 1H), 5.00-4.90 (br m, 1H), 4.60-4.40 (br m, 1H), 4.20-4.00 (br m, 1H), 3.10-2.90 (br m, 1H), 2.30-2.17 (m, 3H), 1.85-1.50 (br m, 2H), 1.32-1.22 (m, 3H), 1.20 (t, 3H). MS m/z 380 $[M+Na]^+$

QC Analytical LCMS Method:

Column: XB-C18, 3um (3x50mm); Mobile phase: 1% - 100% MeCN/H_2O (0.1% TFA)

Rt = 3.50 min

The trans-racemic material was separated into its enantiomers using preparative chiral column chromatography according to the conditions described below;

Prep SFC Method

ChiralPak AS (250x30mm), 5 micron; Mobile phase: 20% MeOH with 0.1% $NH_3.H_2O$ in supercritical CO_2; Flow rate: 60 mL/min

Chiral SFC Analysis Method:

Column: Chiralpak AS-H (250x30mm), 5 micron; Mobile phase: 5-40% MeOH with 0.05% DEA in CO_2; Flow rate: 2.5 mL/min

The two enantiomers were arbitrarily assigned absolute stereochemistry.

First eluting isomer: Example 78

2-{[(2R,4S)-1-acryloyl-2-methylpiperidin-4-yl]oxy}-N-ethyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide.
Rt = 6.22 minutes MS m/z 380 $[M+Na]^+$

Second eluting isomer: Example 79

2-{[(2S,4R)-1-acryloyl-2-methylpiperidin-4-yl]oxy}-N-ethyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide.
Rt = 6.55 minutes MS m/z 380 $[M+Na]^+$

Example 80

Cis-racemic-2-{[1-acryloyl-6-methylpiperidin-3-yl]oxy}-N-[(2S)-1-methoxypropan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

The title compound was prepared according to the method described for **Example 65** using cis-racemic-benzyl 5-[(7-[(1-methoxypropan-2-yl)carbamoyl]-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl)oxy]-2-methylpiperidine-1-carboxylate (**Example 80 Step 4**). The residue was purified using preparative HPLC eluting with 25-45% MeCN in water with 0.05% ammonia. ^1H NMR (400MHz, DMSO-d_6): δ ppm 12.60 (br s, 1H), 8.21 (s, 1H), 8.01 (s, 1H), 7.97-7.85 (m, 1H), 6.90-6.83 (m, 1H), 6.13-6.09 (m, 1H), 5.75-5.60 (m, 1H), 5.10-4.70 (m, 2H), 4.50-4.40 (m, 0.5H), 4.30-4.10 (m, 1.5H), 3.23 (s, 3H), 2.90-2.50 (m, 2H), 2.20-2.10 (m, 1H), 1.90-1.70 (m, 3H), 1.30-1.10 (m, 6H). MS m/z 402 $[M+H]^+$

QC Analytical LCMS Method:

Column: Ultimate XB-C18, 3µm, 3x 50mm; Mobile phase: 1-100% CH_3CN/H2O (0.1% TFA)
Flow rate: 2.35 mL/min. Rt = 3.60 min.

The cis-racemic material was separated into its enantiomers using preparative chiral column chromatography according to the conditions described below;

Column: OJ (250x30mm), 5 micron; Mobile phase: 20% EtOH in $NH_3.H_2O$
Flow rate: 60 mL/min

Chiral SFC Analysis Method:

Column: Chiralpak AS-H (250x30mm), 5 micron; Mobile phase: 5-40% EtOH with 0.05% DEA in CO_2;
Flow rate: 2.35 mL/min

The two enantiomers were arbitrarily assigned absolute stereochemistry.

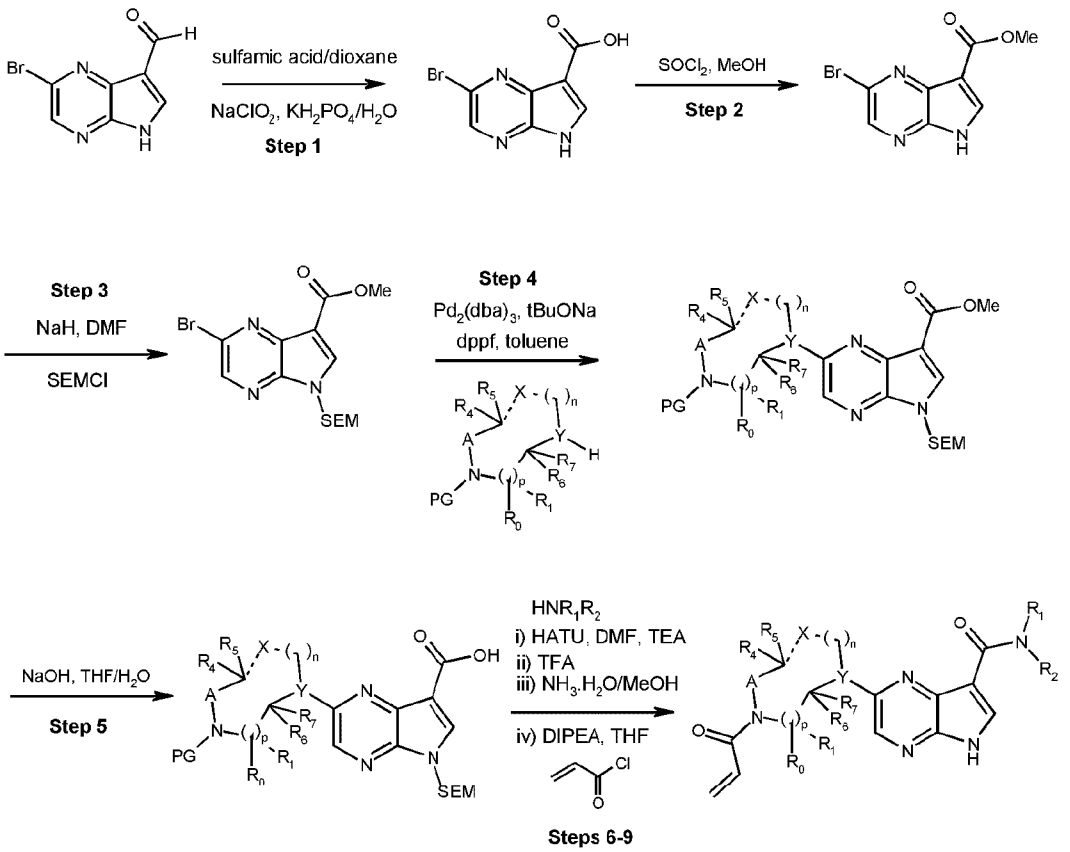
First eluting isomer: Example 81

2-{[(3R,6S)-1-acryloyl-6-methylpiperidin-3-yl]oxy}-N-[(2S)-1-methoxypropan-2-yl]-5Hpyrrolo[2,3-b]pyrazine-7-carboxamide
Rt = 5.74 minutes. MS m/z 402 $[M+H]^+$

Second eluting isomer: Example 82

2-{[(3S,6R)-1-acryloyl-6-methylpiperidin-3-yl]oxy}-N-[(2S)-1-methoxypropan-2-yl]-5Hpyrrolo[2,3-b]pyrazine-7-carboxamide. Rt = 6.78 minutes. MS m/z 402 $[M+H]^+$

Examples 83-87 were prepared as described in the Scheme below:



Example 83 Step 1

2-Bromo-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid

To a solution of 2-bromo-5H-pyrrolo[2,3-b]pyrazine-7-carbaldehyde (75 g, 333 mmol) and sulfamic acid (163 g, 1667 mmol) in dioxane and water (1.5 L, v:v 4:1) was added a solution of $NaClO_2$ (36.4 g, 400 mmol) and KH_2PO_4 (227 g, 1667 mol) in water (0.5 L) dropwise over 40 minutes followed by stirring at room temperature for 18 hours. The reaction was partitioned between EtOAc (2 L) and water (1 L). The aqueous layer was further extracted with EtOAc (1.5 L) and the organic layers were combined, washed with water (1 L), dried over sodium sulphate and concentrated *in vacuo* to afford the title compound as a yellow solid (120 g, 75%).

MS m/z 507 $[2M+Na]^+$

Example 83 Step 2

Methyl 2-bromo-5H-pyrrolo[2,3-b]pyrazine-7-carboxylate

To a suspension of 2-bromo-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid (**Example 83 Step 1**, 145 g, 602 mmol) in MeOH (1.5 L) at 0°C was added thionyl chloride (93 g, 781 mmol) dropwise over 40 minutes. The reaction was heated to reflux for 4 hours before cooling and concentrating *in vacuo*. The

resulting solid was triturated with TBME to afford the title compound as a yellow solid (109 g, 71%) that was taken directly on to the next step.

Example 83 Step 3

Methyl 2-bromo-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxylate

To a suspension of NaH (60% dispersion in oil, 11.9 g, 297 mmol) in DMF (500 mL) at 0°C was added methyl 2-bromo-5H-pyrrolo[2,3-b]pyrazine-7-carboxylate (**Example 83 Step 2**, 55 g, 228 mmol). The reaction was stirred at 0°C for 10 minutes followed by the addition of SEMCl (49.3 g, 251 mmol) and stirring at room temperature for 3 hours. The reaction was poured into ice-water (1.5 L) and extracted into EtOAc (3 x 1.5 L). The combined organic layers were washed with water (2 L), brine (3 x 1.5 L), dried over sodium sulphate and concentrated *in vacuo*. The residue was triturated with TBME to afford the title compound as a white solid (105 g, 60%). ^{1}H NMR (400MHz, DMSO-d_6): δ ppm 8.88 (s, 1H), 8.61 (s, 1H), 5.70 (br s, 2H), 3.86 (br s, 3H), 3.58-3.54 (m, 2H), 0.85-0.81 (m, 2H), -0.09 (s, 9H).

Example 83 Step 4

Methyl 2-(4-(tert-butoxycarbonyl)-3,3-dimethylpiperazin-1-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxylate

To a solution of methyl 2-bromo-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxylate (**Example 83 Step 3**, 4.51 g, 11.7 mmol) and tert-butyl 2,2-dimethylpiperazine-1-carboxylate (5 g, 23.33 mmol) in anhydrous toluene (100 mL) was added dppf (420 mg, 0.758 mmol) followed by cesium carbonate (7.6 g, 23.33 mmol). The reaction was degassed and purged with nitrogen before the addition of $Pd_2(dba)_3$ (534 mg, 0.583 mmol) and heating to 100°C for 12 hours. The reaction was cooled, filtered and the filtrate concentrated *in vacuo*. The residue was purified using silica gel column chromatography eluting with 10-80% EtOAc in petroleum ether to afford the title compound as a red oil (5.24 g, 86%). MS m/z 520 $[M+H]^+$

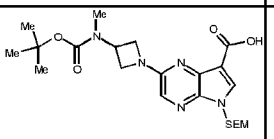
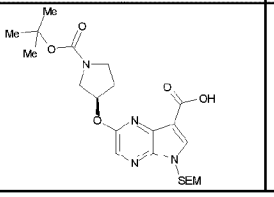
Example 83 Step 5

2-(4-(tert-Butoxycarbonyl)-3,3-dimethylpiperazin-1-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid

To a solution of methyl 2-(4-(tert-butoxycarbonyl)-3,3-dimethylpiperazin-1-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxylate (**Example 83 Step 4**, 5.24 g, 10.08 mmol) in THF (100 mL) and water (30 mL) was added sodium hydroxide (3.23 g, 80.7 mmol) and the reaction was heated to 70°C for 12 hours. Further sodium hydroxide (3.23 g, 80.7 mmol) was added and the reaction continued heating at 70°C for 16 hours followed by heating at 75°C for 60 hours. The reaction was cooled and acidified with 0.5M HCl (100 mL) to pH=5-6. The solution was extracted into EtOAc (2 x 50 mL), the organic layers were combined, washed with brine (100 mL), dried over sodium sulphate and concentrated *in vacuo*. The residue was purified using silica gel column chromatography eluting with 30-80% EtOAc in petroleum ether to afford the title compound as a yellow solid (3.4 g, 67%). ^{1}H NMR (400MHz, DMSO-d_6): δ ppm 12.02 (br s, 1H), 8.34 (s, 1H), 7.96 (s, 1H), 5.58 (s, 2H), 3.83-3.78 (m, 4H), 3.60-3.51 (m, 4H), 1.44 (s, 9H), 1.36 (s, 6H), 0.86-0.80 (m, 2H), -0.09 (s, 9H).

MS m/z 506 $[M+H]^+$

The following Preparations were prepared according to the methods described for **Example 83 Steps 4 and 5** using methyl 2-bromo-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxylate (**Example 83 Step 3**) and the appropriate amine or alcohol.

Prep No.	Name	Structure	Data/SM
84 Steps 4 and 5	2-(3-((tert-butoxycarbon-yl)(methyl)amino)azetidin-1-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid		tert-butyl azetidin-3-yl(methyl)carbamate ^{1}H NMR (400MHz, DMSO-d_6): δ ppm 12.08 (br s, 1H), 8.37 (s, 1H), 7.71 (s, 2H), 4.28-4.24 (m, 2H), 4.10-4.01 (m, 2H), 3.54-3.51 (m, 2H), 2.89 (s, 3H), 1.41 (s, 9H), 0.84-0.80 (m, 2H), -0.08 (s, 9H).ok MS m/z 478 $[M+H]^+$
87 Steps 4 and 5	(R)-2-((1-(tert-butoxycarbonyl)pyrrolidin-3-yl)oxy)-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid		tert-butyl (R)-3-hydroxypyrrolidine-1-carboxylate Taken on directly to the next step.

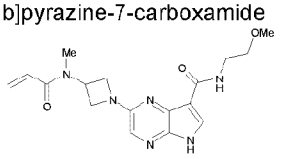
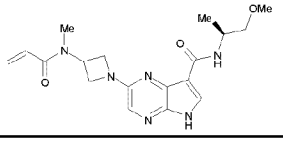
Example 83 Steps 6-9

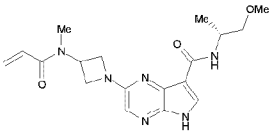
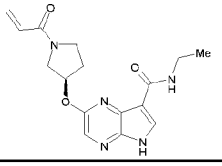
2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-(prop-2-yn-1-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

To a solution of 2-(4-(tert-butoxycarbonyl)-3,3-dimethylpiperazin-1-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid (**Example 83 Steps 4** and **5**, 0.6 g, 1.19 mmol) and 2-propynylamine (196 mg, 3.56 mmol) in DMF (10 mL) was added HATU (0.902 mmol, 2.37 mmol) followed by triethylamine (360 mg, 3.56 mmol). The reaction was stirred at room temperature for 12 hours. The reaction was diluted with water (20 mL) and extracted into EtOAc (3 x 20 mL). The combined organic layers were concentrated *in vacuo* and purified using silica gel column chromatography eluting with 50-100% EtOAc in petroleum ether. The residue was dissolved in DCM (6 mL) and treated with TFA (2 mL) at 0°C. The reaction was stirred at room temperature for 12 hours before concentrating *in vacuo* and azeotroping with MeOH. The residue was dissolved in MeOH (6 mL) and treated with aqueous ammonia (3 mL) at 0°C. The reaction was stirred at room temperature for 2 hours, concentrated *in vacuo* and dissolved in THF (5 mL) and water (5 mL). DIPEA (186 mg, 1.44 mmol) followed by acryloyl chloride (64.8 mg, 0.72 mmol) were added and the reaction stirred at room temperature for 2 hours. Additional DIPEA (186 mg, 1.44 mmol) and acryloyl chloride (64.8 mg, 0.72 mmol) were added and the reaction continued for 6 hours. The reaction was concen-

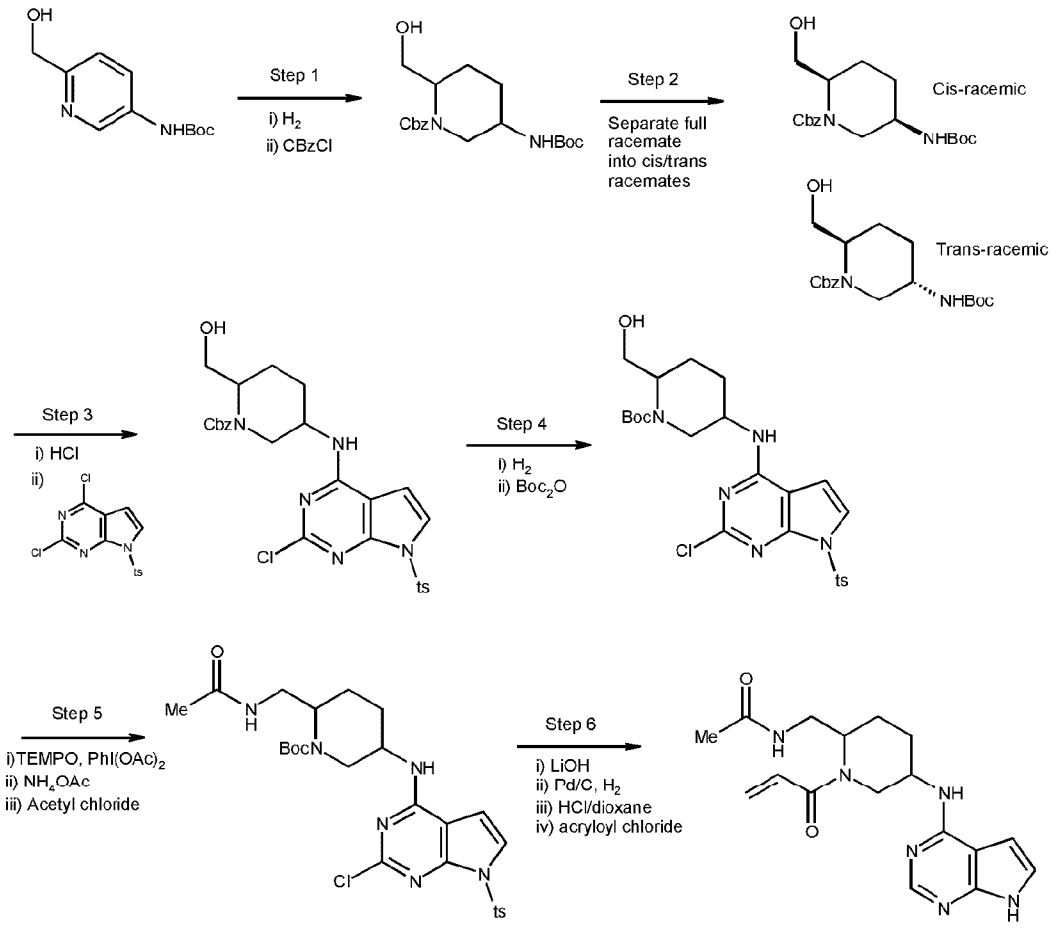
trated *in vacuo* and purified using silica gel column chromatography eluting with 0-20% MeOH in DCM followed by preparative HPLC to afford the title compound as a yellow solid (72 mg, 41%).
Preparative HPLC conditions:
Column: YMC-Actus Triart C18 150x30mmx5µm; Mobile phase: 26-46% MeCN in water modified with 0.225% formic acid. ^{1}H NMR (400MHz, DMSO-d_6): δ ppm 12.31 (br s, 1H), 8.40-8.38 (m, 1H), 8.08 (s, 1H), 7.99 (s, 1H), 6.80-6.73 (m, 1H), 6.06-6.02 (m, 1H), 5.65-5.62 (m, 1H), 4.19-4.18 (m, 2H), 3.96-3.88 (m, 4H), 3.69-3.67 (m, 2H), 3.27 (s, 1H), 1.54 (s, 6H).
MS m/z 389 $[M+Na]^+$

Examples 84-87 were prepared according to the method described for **Example 83 Steps 6-9** using the appropriate acid and amine as described below:
Prep Method A (PM A): Kromasil Eternity XT C18 250x21.2x10 micron, mobile phase: 9-29% MeCN in water modified with ammonia to pH=10.
Prep Method B (PM B): Phenomenex Gemini C18 250x21.2x10 micron, mobile phase 26-46% MeCN in water modified with ammonia to pH=10.

Example	Name/Structure	SM	Data
84	2-{3-[acrylo-yl(methyl)amino]azetidin-1-yl}-N-(2-methoxyethyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide 	2-{3-[(tert-butoxycarbon-yl)(methyl)amino]azetidin-1-yl}-5-{[2-(trimethylsi-lyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid (**Example 84 Steps 4 and 5**) and 2-methoxyethylamine.	PM A ^{1}H NMR (400MHz, DMSO-d_6): δ ppm 12.25 (br s, 1H), 8.42 (br s, 1H), 8.07 (s, 1H), 7.72 (s, 1H), 6.81-6.74 (m, 1H), 6.17-6.13 (m, 1H), 5.74-5.71 (m, 1H), 5.27 (br s, 1H), 4.35-4.33 (m, 2H), 4.19-4.05 (m, 2H), 3.54-3.37 (m, 7H), 3.35-3.16 (m, 3H). MS m/z 359 $[M+H]^+$
85	2-{3-[acrylo-yl(methyl)amino]azetidin-1-yl}-N-[(2S)-1-methoxypropan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide 	2-{3-[(tert-butoxycarbon-yl)(methyl)amino]azetidin-1-yl}-5-{[2-(trimethylsi-lyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid (**Example 85 Steps 4 and 5**) and (S)-1-methoxypropan-2-amine.	PM A with 11-31% MeCN. ^{1}H NMR (400MHz, DMSO-d_6): δ ppm 12.27 (br s, 1H), 8.37-8.35 (m, 1H), 8.04 (s, 1H), 7.71 (s, 1H), 6.80-6.74 (m, 1H), 6.16-6.08 (m, 1H), 5.76-5.71 (m, 1H), 5.30-5.24 (m, 1H), 4.31-4.25 (m, 2H), 4.20-4.05 (m, 3H), 3.44-3.30 (m, 5H), 3.16-3.04 (m, 3H), 1.22-1.18 (m, 3H). MS m/z 373 $[M+H]^+$

86	2-{3-[acryloyl(methyl)amino]azetidin-1-yl}-N-[(2R)-1-methoxypropan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide 	2-{3-[(tert-butoxycarbonyl)(methyl)amino]azetidin-1-yl}-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid (**Example 86 Steps 4 and 5**) and (R)-1-methoxypropan-2-amine	PM B. ^{1}H NMR (400MHz, DMSO-d_6): δ ppm 12.27 (br s, 1H), 8.37-8.35 (m, 1H), 8.04 (s, 1H), 7.71 (s, 1H), 6.80-6.73 (m, 1H), 6.22-6.08 (m, 1H), 5.73-5.71 (m, 1H), 5.30-5.24 (m, 1H), 4.33-4.30 (m, 2H), 4.25-4.05 (m, 3H), 3.41-3.30 (m, 5H), 3.29-3.04 (m, 3H), 1.21-1.18 (m, 3H). MS m/z 373 $[M+H]^+$
87	(R)-2-[(1-acryloylpyrrolidin-3-yl)oxy]-N-ethyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide 	(R)-2-((1-(tert-butoxycarbonyl)pyrrolidin-3-yl)oxy)-5-[(2-(trimethylsilyl)ethoxy)methyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid (**Example 87 Steps 4** and **5**).	^{1}H NMR (400MHz, DMSO-d_6): δ ppm 12.56 (br s, 1H), 8.19 (s, 1H), 8.00 (s, 1H), 7.86-7.82 (m, 1H), 6.63-6.55 (m, 1H), 6.18-6.13 (m, 1H), 5.71-5.64 (m, 2H), 3.98-3.68 (m, 3.5H), 3.50-3.38 (m, 2.5H), 2.36-2.22 (m, 2H), 1.22-1.18 (m, 3H).

Examples 88-90 were prepared as described in the Scheme below:



Example 88 Step 1

Racemic benzyl 5-((tert-butoxycarbonyl)amino)-2-(hydroxymethyl)piperidine-1-carboxylate

To a solution of tert-butyl (6-(hydroxymethyl)pyridin-3-yl)carbamate (25 g, 0.11 mol) in EtOH (200 mL) and acetic acid (25 mL) was added PtO_2 (2.6 g, 11.5 mmol). The reaction was degassed under vacuum and purged with hydrogen three times before stirring under 55 psi of hydrogen at 50°C for 72 hours. The reaction was cooled, filtered, and the filtrate neutralised with saturated aqueous $NaHCO_3$ solution. The solution was concentrated *in vacuo* and the residue extracted into EtOAc (5 x100 mL). The combined organic layers were washed with brine (200 mL), dried over sodium sulphate and concentrated *in vacuo*. Part of the residue (5 g, 0.022 mmol) was dissolved in THF (100 mL) and water (50 mL). $NaHCO_3$ (3.7 g, 0.044 mmol) was added followed by CbzCl (4.4 g, 0.026 mmol) and the reaction was stirred at room temperature for 2 hours. The reaction was concentrated *in vacuo* and extracted into EtOAc (3 x 200 mL). The organic layers were washed with brine (2 x 200 mL) and con-

centrated *in vacuo*. The residue was purified using silica gel column chromatography eluting with 20-30% EtOAc in petroleum ether to afford the title compound as a colorless oil (3 g, 67% over 2 steps). ^{1}H NMR (400MHz, $CDCl_3$): δ ppm 7.27-7.19 (m, 5H), 5.06-5.02 (m, 2H), 4.54-4.52 (m, 1H), 4.25-3.95 (m, 2H), 3.69-3.30 (m, 3H), 3.10-3.05 (m, 1H), 2.65-2.50 (m, 1H), 1.70-1.28 (m, 12H).
MS m/z 751 $[2M+Na]^+$

Example 88 Step 2

Cis-racemic-benzyl 5-((tert-butoxycarbonyl)amino)-2-(hydroxymethyl)piperidine-1-carboxylate and trans-racemic benzyl 5-((tert-butoxycarbonyl)amino)-2-(hydroxymethyl)piperidine-1-carboxylate.

The cis and trans racemic benzyl 5-((tert-butoxycarbonyl)amino)-2-(hydroxymethyl)piperidine-1-carboxylate were separated using preparative HPLC using the conditions below:
Column: Phenomenex Synergi C18 (250x77x10 micron).
Mobile phase: 35-53% MeCN in water modified with 10 mM ammonium carbonate
Gradient time: 25 minutes; Flow rate: 140 mL/min
HPLC QC: WatersXbridge 2.1x50mmx5micron, 0-60% MeCN in water modified with 0.05% ammonia.
The two enantiomers were assigned stereochemistry.
First eluting isomers: trans racemic benzyl 5-((tert-butoxycarbonyl)amino)-2-(hydroxymethyl)piperidine-1-carboxylate. Rt = 3.55 minutes MS m/z 387 $[M+Na]^+$
Second eluting isomers: cis racemic benzyl 5-((tert-butoxycarbonyl)amino)-2-(hydroxymethyl)piperidine-1-carboxylate. Rt = 3.59 minutes MS m/z 387 $[M+Na]^+$

Example 88 Step 3

Cis-racemic-benzyl-5-((2-chloro-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-(hydroxymethyl)piperidine-1-carboxylate

To a solution of cis racemic benzyl 5-((tert-butoxycarbonyl)amino)-2-(hydroxymethyl)piperidine-1-carboxylate (**Example 88 Step 2**, 30 g, 82 mmol) in DCM (200 mL) was added 4M HCl in dioxane (150 mL) at 0°C and the reaction was stirred at this temperature for 2 hours. The reaction was concentrated *in vacuo* and part of the residue (14 g, 46 mmol) was dissolved in n-BuOH (200 mL). DIPEA (13.2 g, 102 mmol) followed by 2,4-dichloro-7-tosyl-7H-pyrrolo[2,3-d]pyrimidine (16 g, 47 mmol) were added and the reaction heated to 50°C for 18 hours. The reaction was cooled, concentrated *in vacuo* and partitioned between EtOAc (200 mL) and water (200 mL). The aqueous layer was backwashed with EtOAc (2 x 200 mL) and the organic layers were combined, washed with brine, dried over sodium sulphate and concentrated *in vacuo*. The residue was purified using preparative HPLC as described below to afford the title compound as a white solid (19 g, 73%).
Column: Gemini 250x50mm x10 micron; Mobile Phase: 53-100% MeCN in water modified with ammonia pH=10. Flow rate: 80 mL/min. MS m/z 570 $[M^{35}Cl+H]^+$

Example 88 Step 4

Cis-racemic-tert-butyl 5-((2-chloro-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-(hydroxymethyl)piperidine-1-carboxylate

To a solution of cis-racemic-benzyl 5-((2-chloro-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-(hydroxymethyl)piperidine-1-carboxylate (**Example 88 Step 3**, 7.91 g, 13.9 mmol) and di-tert-butyl dicarbonate (3.94 g, 18 mmol) in EtOH (100 mL) and THF (100 mL) was added wet palladium on carbon (800 mg). The reaction was stirred under an atmosphere of hydrogen (hydrogen balloon) for 3 hours. The reaction was filtered through Celite™ and the filtrate concentrated *in vacuo*. The residue was purified using silica gel column chromatography eluting with 1:1 petroleum ether and EtOAc to afford the title compound as a white solid (5.6 g, 75%).

^{1}H NMR (400MHz, DMSO-d_6): δ ppm 8.10-8.08 (m, 2H), 7.44-7.43 (m, 1H), 7.34-7.27 (m, 2H), 6.44 (br s, 1H), 5.19 (br s, 1H), 4.32-4.28 (m, 2H), 4.10 (br m, 1H), 3.80-3.79 (m, 1H), 3.67-3.64 (m, 1H), 2.75-2.69 (m, 1H), 2.41 (s, 3H), 2.50-2.30 (m, 1H), 2.05-1.97 (m, 1H), 1.83-1.80 (m, 2H), 1.49-1.44 (m, 1H), 1.44 (s, 9H).

Example 88 Step 5

Cis-racemic-tert-butyl 2-(acetamidomethyl)-5-((2-chloro-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidine-1-carboxylate

To a solution of cis-racemic-tert-butyl 5-((2-chloro-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-(hydroxymethyl)piperidine-1-carboxylate (**Example 88 Step 4**, 4.3 g, 8 mmol) in DCM (85 mL) was added TEMPO (250 mg, 1.6 mmol) and $PhI(OAc)_2$ (2.97 g, 9.2 mmol) and the reaction was stirred at room temperature for 18 hours. The reaction was washed with ether (100 mL), brine (100 mL), dried over sodium sulphate and concentrated *in vacuo*. The residue was purified using silica gel column chromatography eluting with 2-50% EtOAc in petroleum ether to afford the aldehyde intermediate as a white solid (1.81 g, 42%).

The solid was dissolved in MeOH (340 mL) and treated with ammonium acetate (26.13 g, 339 mmol) followed by sodium cyanoborohydride (3.41 g, 54 mmol). The reaction was stirred at room temperature for 18 hours. The reaction was diluted with EtOAc (400 mL) and washed with water (200 mL), saturated aqueous $NaHCO_3$ (200 mL), brine (300 mL) dried over sodium sulphate and concentrated *in vacuo*. The residue was purified using silica gel column chromatography eluting with 0-15% MeOH in DCM to afford the amino intermediate as a white solid (615 mg, 34%).

The solid was dissolved in THF (15 mL) and DCM (15 mL) and treated with triethylamine (363 mg, 3.6 mmol). Acetic anhydride (123 mg, 1.2 mmol) was added and the reaction stirred at room temperature for 2 hours. The reaction was concentrated *in vacuo* to afford the title compound as a yellow solid (700 mg, 100%). MS m/z 577 $[M+H]^+$

Example 88 Step 6

rac-N-(((2R,5R)-5-((7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-1-acryloylpiperidin-2-yl)methyl)acetamide

To a solution of cis-racemic-tert-butyl 2-(acetamidomethyl)-5-((2-chloro-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidine-1-carboxylate (**Example 88 Step 5**, 700 mg, 1.2 mmol) in MeOH

(15 mL) and water (3 mL) was added lithium hydroxide (151 mg, 3.6 mmol) and the reaction was stirred at room temperature for 12 hours. The reaction was concentrated *in vacuo* and the residue purified using 0-15% MeOH in DCM. The residue was dissolved in MeOH (20 mL) and treated with 10% Pd/C (100 mg). The reaction was hydrogenated at 45 psi at 35°C for 16 hours. The reaction was filtered through Celite and the filtrate concentrated *in vacuo*. The residue was dissolved in DCM (5 mL) and treated with 4M HCl in dioxane (5 mL) at 0°C. The reaction was stirred at room temperature for 8 hours. The reaction was concentrated *in vacuo* and dissolved in THF (5 mL) and water (5 mL). DIPEA (464 mg, 3.6 mmol) was added followed by acryloyl chloride at 0°C and the reaction was stirred at 0°C for 2 hours. The reaction was concentrated *in vacuo* and purified using silica gel column chromatography eluting with 10-30% MeOH in DCM to afford the title compound as a white solid (100 mg, 25% over 4 steps).

^{1}H NMR (400MHz, DMSO-d_6): δ ppm 11.52 (br s, 1H), 8.12-8.04 (m, 2H), 7.34-7.32 (m, 1H), 7.09 (s, 1H), 6.76-6.69 (m, 1H), 6.56 (s, 1H), 6.13-6.08 (m, 1H), 5.67-5.64 (m, 1H), 4.61-4.57 (m, 1H), 4.61-4.57 (m, 1H), 4.16-4.06 (m, 2H), 3.29-3.02 (m, 1H), 2.66-2.55 (m, 2H), 1.82-1.59 (m, 7H). LCMS (Ultimate XB-C18 3x50mm x 3 micron); 1-100% MeCN in water modified with 0.1% TFA. Rt = 2.46 minutes MS m/z 343 [M+H]+

The cis-racemic material was separated into its enantiomers using preparative chiral column chromatography according to the conditions described below;

Column: Chiralcel OD-H 21x250 mm, 5uM

Mobile phase:90:10 CO2/MeOH for 10 min, flow rate 75 mL/min.

The two enantiomers were arbitrarily assigned absolute stereochemistry.

First eluting isomer: Example 89

N-{[(2R,5R)-1-acryloyl-5-(7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)piperidin-2-yl]methyl}acetamide

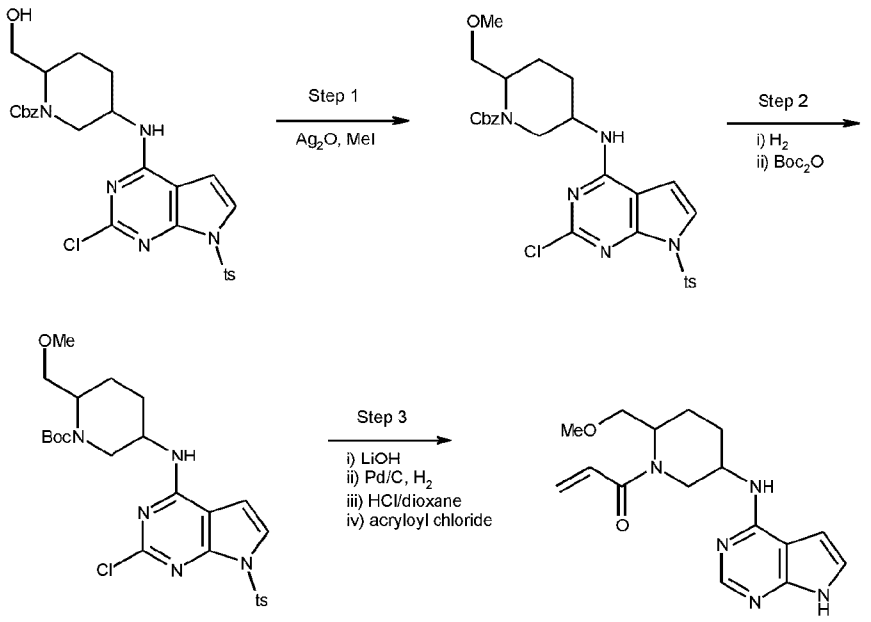
Rt = 5.84 minutes MS m/z 343 $[M+H]^+$

Second eluting isomer: Example 90

N-{[(2S,5S)-1-acryloyl-5-(7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)piperidin-2-yl]methyl}acetamide

Rt = 7.05 minutes MS m/z 343 $[M+H]^{+ok}$

Examples 91-93 were prepared as described in the Scheme below:



Example 91 Step 1

Cis-racemic-benzyl-5-((2-chloro-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-(methoxymethyl)piperidine-1-carboxylate

To a solution of cis-racemic-benzyl 5-((2-chloro-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-(hydroxymethyl)piperidine-1-carboxylate (**Example 88 Step 3**, 1 g, 1.76 mmol) in anhydrous DMF (15 mL) was added Ag_2O (815 mg, 3.51 mmol) followed by methyl iodide (500 mg, 3.51 mmol) and the reaction was stirred at room temperature for 18 hours. Additional methyl iodide (500 mg, 3.51 mmol) was added and the reaction continued for 6 hours. The reaction was concentrated *in vacuo* and purified using silica gel column chromatography eluting with 0-80% EtOAc in petroleum ether to afford the title compound as a white solid (469 mg, 46%).

Taken on directly to the next step.

Example 91 Step 2

Cis-racemic-tert-butyl-5-((2-chloro-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-(methoxymethyl)piperidine-1-carboxylate

The title compound was prepared according to the method described for **Example 88 Step 4** using cis-racemic-benzyl-5-((2-chloro-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-(methoxymethyl)piperidine-1-carboxylate (**Example 91 Step 1**) under 20 psi of hydrogen and taken on directly to the next step.

Example 91 Step 3

Cis-racemic-1-[2-(methoxymethyl)-5-(7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)piperidin-1-yl]prop-2-en-1-one

The title compound was prepared according to **Example 88 Step 6** above using cis-racemic-tert-butyl-5-((2-chloro-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-(methoxymethyl)piperidine-1-carboxylate (**Example 91 Step 2**). MS m/z 316 $[M+H]^+$

The cis-racemic material was separated into its enantiomers using preparative chiral column chromatography according to the conditions described below;

Column: AD 250x30mm, 10 micron; Mobile phase: 45% MeOH in water modified with ammonia.

Flow rate: 80 mL/min. LCMS QC: Chiralpak AD-3 150x4.6mm, 3 micron

Mobile phase: 40% MeOH with 0.05% DEA in CO_2; Flow rate: 2.5 mL/min.

The two enantiomers were arbitrarily assigned absolute stereochemistry.

First eluting isomer: Example 92

1-[(2R,5R)-2-(Methoxymethyl)-5-(7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)piperidin-1-yl]prop-2-en-1-one.

Rt = 2.48 minutes MS m/z 316 $[M+H]^+$

^{1}H NMR (400MHz, DMSO-d_6): δ ppm 11.65 (br s, 1H), 8.10 (s, 1H), 7.14 (s, 1H), 6.85-6.78 (m, 1H), 6.56 (s, 1H), 6.10-6.05 (m, 1H), 5.65-5.62 (m, 1H), 4.90-4.75 (m, 1H), 4.67-4.60 (m, 1.3H), 4.38-4.37 (m, 1H), 4.11-4.09 (m, 0.7H), 3.80-3.50 (m, 1H), 3.45-3.23 (m, 4.3H), 2.93-2.87 (m, 0.7H), 1.98-1.89 (m, 2H), 1.71-1.60 (m, 2H).

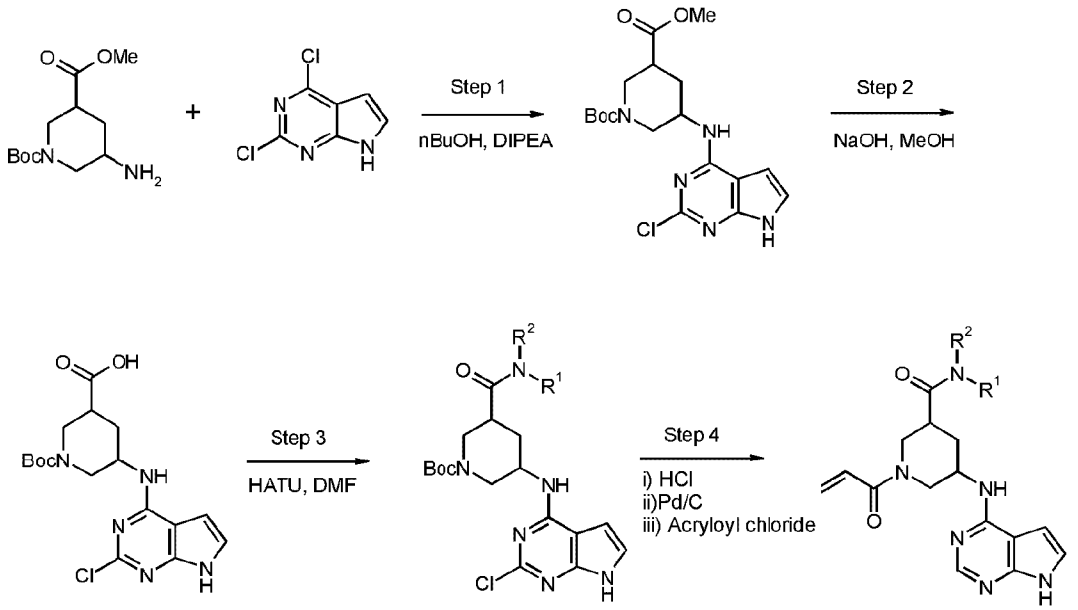
Second eluting isomer: Example 93

1-[(2S,5S)-2-(Methoxymethyl)-5-(7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)piperidin-1-yl]prop-2-en-1-one.

Rt = 3.92 minutes MS m/z 316 $[M+H]^+$

^{1}H NMR (400MHz, DMSO-d_6): δ ppm 11.65 (br s, 1H), 8.10 (s, 1H), 7.14 (s, 1H), 6.85-6.78 (m, 1H), 6.56 (s, 1H), 6.10-6.05 (m, 1H), 5.65-5.62 (m, 1H), 4.90-4.75 (m, 1H), 4.67-4.60 (m, 1.3H), 4.38-4.37 (m, 1H), 4.11-4.09 (m, 0.7H), 3.80-3.50 (m, 1H), 3.45-3.23 (m, 4.3H), 2.93-2.87 (m, 0.7H), 1.98-1.89 (m, 2H), 1.71-1.60 (m, 2H).

Examples 94-96 were prepared according to the following Scheme:



Example 94 Step 1

Cis-racemic-1-(tert-butyl)-3-methyl 5-((2-chloro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidine-1,3-dicarboxylate

To a solution of cis-racemic-1-tert-butyl 3-methyl-5-aminopiperidine-1,3-dicarboxylate (**WO 200906112**, 5 g, 19.3 mmol) in n-BuOH (100 mL) was added 2,4-dichloro-7H-pyrrolo[2,3-d]pyrimidine (4 g, 21.2 mmol) followed by DIPEA (7.47 g, 58 mmol). The reaction was heated to 130°C for 48 hours. The reaction was cooled, concentrated *in vacuo* and partitioned between EtOAc (100 mL) and water (100 mL). The organic layer was collected, washed with water (100 mL), brine (100 mL), dried over sodium sulphate and concentrated *in vacuo*. The residue was purified using silica gel column chromatography eluting with 10-50% EtOAc in petroleum ether to afford the title compound as a white solid (4.4 g, 56%) that was taken directly on to the next step.

Example 94 Step 2

Cis-racemic-1-(tert-butoxycarbonyl)-5-((2-chloro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidine-3-carboxylic acid

To a solution of cis-racemic-1-(tert-butyl) 3-methyl 5-((2-chloro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidine-1,3-dicarboxylate (**Example 94 Step 1**, 4.4 g, 10.73 mmol) in MeOH (50 mL) was added 1M aqueous NaOH solution (43 mL, 43 mmol) dropwise. The reaction was stirred at room temperature for 18 hours before diluting with water (20 mL) and extracting into EtOAc (100 mL). The aqueous phase was acidified with 1M HCl (aq) until pH=5-6. The aqueous layer was extracted into EtOAc (2 x 100 mL), the organic layers combined washed with brine, dried over sodium sulphate and concentrated *in vacuo* to afford the title compound as a white solid (3.7 g, 87%). ^{1}H NMR (400MHz,

DMSO-d_6): δ ppm 11.72 (br s, 1H), 7.79-7.78 (m, 1H), 7.11 (s, 1H), 6.58 (s, 1H), 4.24-4.01 (m, 3H), 2.72-2.22 (m, 4H), 1.65-1.59 (m, 1H), 1.43 (s, 9H).

Example 94 Step 3

Cis-racemic-tert-butyl-3-((2-chloro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-(dimethylcarbamoyl)piperidine-1-carboxylate

To a solution of cis-racemic-1-(tert-butoxycarbonyl)-5-((2-chloro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidine-3-carboxylic acid (**Example 94 Step 2,** 1 g, 2.53 mmol) in DMF (15 mL) was added HATU (1.15 g, 3.04 mmol) and the mixture ws stirred under nitrogen for 30 minutes. Dimethylamine hydrochloride (415 mg, 5.06 mmol) and triethylamine (766 mg, 7.59 mmol) were added and the reaction stirred at room temperature for 18 hours. The reaction was partitioned between EtOAc (20 mL) and water (20 mL). The organic layer was collected, washed with brine, dried over sodium sulphate and concentrated *in vacuo*. The residue was purified using silica gel column chromatography eluting with 5-10% MeOH in DCM to afford the title compound as a white solid (650 mg, 61%). ^{1}H NMR (400MHz, DMSO-d_6): δ ppm 11.71 (br s, 1H), 7.96-7.84 (m, 1H), 7.11 (s, 1H), 6.58 (s, 1H), 4.23-3.96 (m, 3H), 3.17 (s, 3H), 2.95-2.93 (m, 1H), 2.84 (s, 3H), 2.60-2.50 (m, 2H), 2.04-2.00 (m, 1H), 1.80-1.70 (m, 1H), 1.43 (s, 9H).

Example 94 Step 4

Cis-racemic-1-acryloyl-N,N-dimethyl-5-(7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)piperidine-3-carboxamide

To a solution of cis-racemic-tert-butyl 3-((2-chloro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-(dimethylcarbamoyl)piperidine-1-carboxylate (**Example 94 Step 3**, 65 mg, 1.53 mmol) in MeOH (20 mL) was added 10% Pd/C (200 mg). The reaction was purged with argon before hydrogenating at 35 psi at 35°C for 18 hours. The reaction was filtered though Celite™ and concentrated *in vacuo* to give a residue that was dissolved in DCM (15 mL) and treated with 4M HCl in dioxane (4 mL). The reaction was stirred at room temperature for 3 hours before concentrating *in vacuo* and azeotroping with DCM. The residue was dissolved in THF (15 mL) and water (15 mL). DIPEA was added (1.12 g, 8.64 mmol) and the mixture cooled to 0°C. Acryloyl chloride (235 mg, 2.59 mmol) was added and the reaction stirred at 0°C for 1 hour. The reaction was partitioned between water (10 mL) and EtOAc (10 mL). The aqueous layer was collected, concentrated *in vacuo* and purified using preparative HPLC as described below to afford the title compound as a white solid (140 mg, 19% over three steps).

Column: Agela Durashell C18 250x21.2mm x 5 micron

Mobile phase: 2-20% MeCN in water modified with 0.225% formic acid; Flow rate: 30 mL/min.

LCMS QC: HPLC-AE Ultimate XB-C18 3 x 50 mm x 3micron

Mobile phase: 1-100% MeCN in water modified with 0.1% TFA.

Rt = 2.58 minutes MS m/z 343 $[M+H]^+$ ^{1}H NMR (400MHz, DMSO-d_6): δ ppm 11.53 (s, 1H), 8.17-8.10 (m, 1H), 7.43-7.31 (m, 1H), 7.09 (s, 1H), 6.88-6.82 (m, 1H), 6.56 (s, 1H), 6.20-6.14 (m, 1H), 5.76-5.67 (m, 1H), 4.73-4.70 (m, 0.5H), 4.49-4.35 (m, 2.5H), 3.50-3.40 (br m, 1H), 3.08-2.84 (m, 7H), 2.83-2.80 (m, 1H), 2.07-2.04 (m, 1H), 1.89-1.76 (m, 1H).

The cis-racemic material was separated into its enantiomers using preparative chiral column chromatography according to the conditions described below;

Column: AD 250x30mm, 10 micron; Mobile phase: 40% MeOH in water with NH_3:H_2O in supercritical CO_2; Flow rate: 70 mL/min. LCMS QC: Chiralpak AD-3 150x4.6mm, 3 micron

Mobile phase: 40% MeOH with 0.05% DEA in CO_2; Flow rate: 2.5 mL/min.

The two enantiomers were arbitrarily assigned absolute stereochemistry.

First eluting isomer: Example 95

1-[(2R,5R)-2-(Methoxymethyl)-5-(7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)piperidin-1-yl]prop-2-en-1-one;

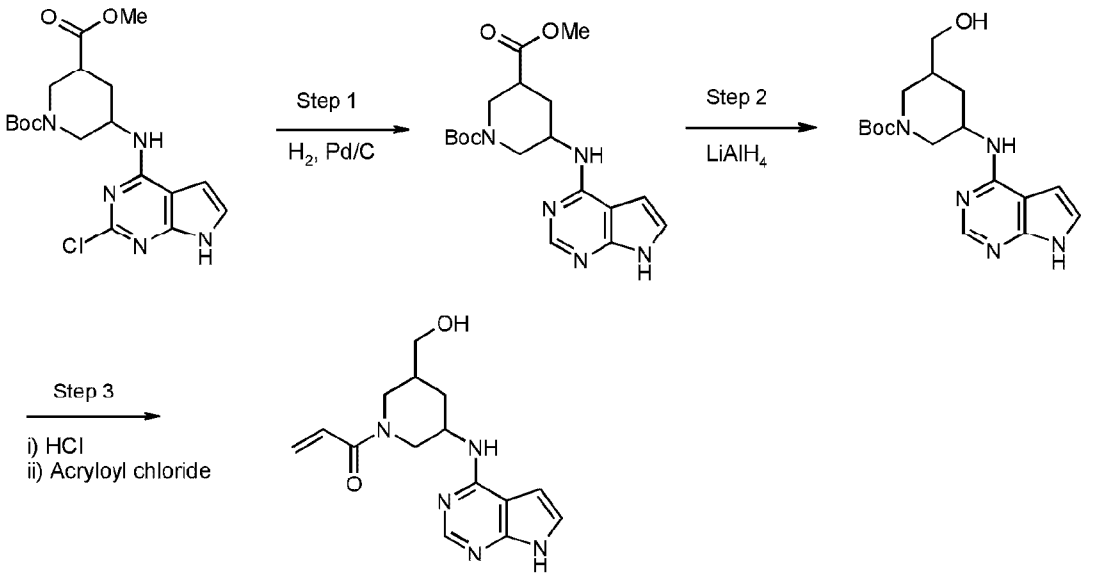
Rt = 1.43 minutes MS m/z 343 $[M+H]^+$

Second eluting isomer: Example 96

1-[(2S,5S)-2-(Methoxymethyl)-5-(7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)piperidin-1-yl]prop-2-en-1-one;

Rt = 2.58 minutes MS m/z 343 $[M+H]^+$

Examples 97-99 were prepared according to the following Scheme:



Example 97 Step 1

Cis-racemic-1-(tert-butyl) 3-methyl 5-((7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidine-1,3-dicarboxylate

The title compound was prepared according to the hydrogenation method described above in **Example 88 Step 4** using cis-racemic-1-(tert-butyl) 3-methyl 5-((2-chloro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidine-1,3-dicarboxylate (**Example 94 Step 1**).

^{1}H NMR (400MHz, DMSO-d_6): δ ppm 12.50 (br s, 1H), 9.10 (m, 1H), 8.33 (s, 1H), 7.36 (s, 1H), 6.93 (s, 1H), 4.25-4.15 (m, 3H), 3.68 (s, 3H), 2.80-2.60 (m, 3H), 2.38-2.35 (m, 1H), 1.71-1.62 (m, 1H), 1.42 (s, 9H).

Example 97 Step 2

Cis-racemic-tert-butyl 3-((7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-(hydroxymethyl)piperidine-1-carboxylate

To a solution of $LiAlH_4$ (388 mg, 10.2 mmol) in anhydrous THF (20 mL), was added a solution of 1-(tert-butyl) 3-methyl 5-((7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidine-1,3-dicarboxylate (**Example 97 Step 1**, 480 mg, 1.28 mmol) in THF (30 mL) dropwise at 0°C under nitrogen. The reaction was stirred at room temperature for 18 hours. The reaction was cooled to 0°C and quenched by the addition of water (0.4 mL) followed by 15% aqueous NaOH solution (0.4 mL). Water was then added (1.2 mL) and the mixture stirred at room temperature for 15 minutes. Anhydrous $MgSO_4$ was added and the reaction stirred for 15 minutes followed by filtration through Celite™. The filtrate was concentrated *in vacuo* to afford the title compound as a colourless solid (120 mg, 27%). MS m/z 348 $[M+H]^+$

Example 97 Step 3

racemic-1-((3R,5S)-3-((7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-(hydroxymethyl)piperidin-1-yl)prop-2-en-1-oneThe title compound was prepared according to the acid deprotection method and acylation method as described in **Example 94 Step 4** above using cis-racemic-tert-butyl 3-((7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-(hydroxymethyl)piperidine-1-carboxylate (**Example 97 Step 2**). ^{1}H NMR (400MHz, DMSO-d_6): δ ppm 11.51 (br s, 1H), 8.13-8.09 (m, 1H), 7.34-7.26 (m, 1H), 7.08 (s, 1H), 6.87-6.81 (m, 1H), 6.57 (s, 1H), 6.15-6.09 (m, 1H), 5.72-5.69 (m, 1H), 4.68-4.59 (m, 1H), 4.37-4.33 (m, 1H), 4.15-4.00 (m, 1H), 3.41-3.39 (m, 2H), 2.79-2.68 (m, 1H), 2.33-2.26 (m, 1H), 2.08-2.02 (m, 1H), 1.75-1.65 (m, 1H), 1.38-1.32 (m, 1H). MS m/z 302 $[M+H]^+$

The cis-racemic material was separated into its enantiomers using preparative chiral column chromatography according to the conditions described below; Column: AD 250x30mm, 5 micron
Mobile phase: 30% MeOH in water with NH_3:H_2O in supercritical CO_2; Flow rate: 60 mL/min.
LCMS QC: Chiralpak AD-3 150x4.6mm, 3 micron; Mobile phase: 5-40% MeOH with 0.05% DEA in CO_2; Flow rate: 2.5 mL/min.

The two enantiomers were arbitrarily assigned absolute stereochemistry.

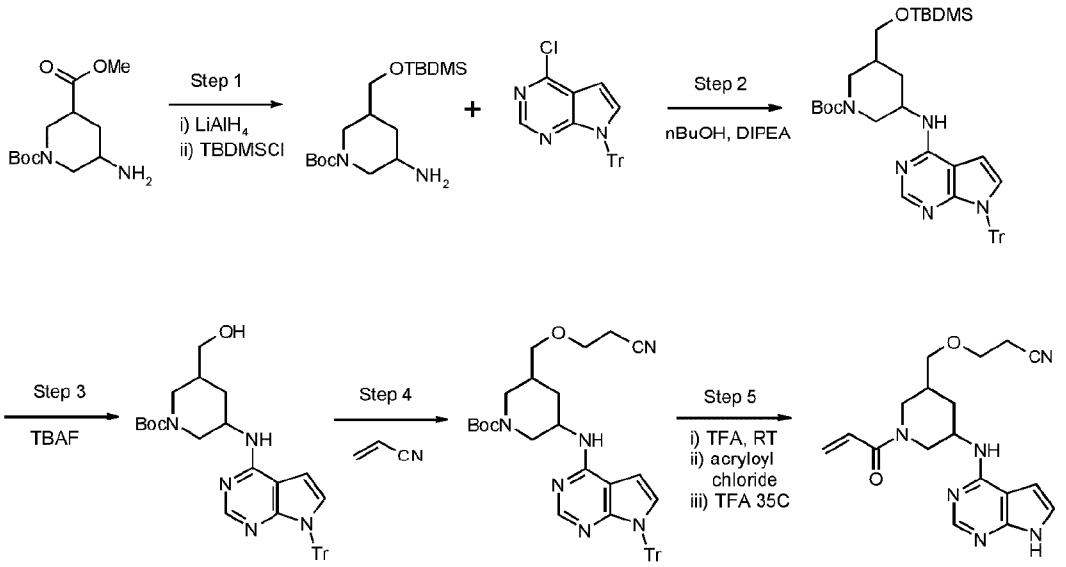
First eluting isomer: Example 98

1-[(3S,5R)-3-(hydroxymethyl)-5-(7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)piperidin-1-yl]prop-2-en-1-one. Rt = 5.05 minutes. MS m/z 302 $[M+H]^+$

Second eluting isomer: Example 99

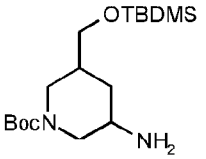
1-[(3R,5S)-3-(hydroxymethyl)-5-(7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)piperidin-1-yl]prop-2-en-1-one. Rt = 5.48 minutes. MS m/z 302 $[M+H]^+$

Examples 100-101 were prepared according to the following Scheme:



Example 100 Step 1

Cis-racemic-tert-butyl 3-amino-5-(((tert-butyldimethylsilyl)oxy)methyl)piperidine-1-carboxylate



To a solution of $LiAlH_4$ (664 mg, 17.5 mmol) in anhydrous THF (60 mL) was added a solution of cis-racemic-1-tert-butyl 3-methyl-5-aminopiperidine-1,3-dicarboxylate (WO200905112, 4.1 g, 16 mmol) in anhydrous THF (10 mL) dropwise at -10°C. The reaction was stirred at this temperature for 30 minutes before the addition of water (0.7 mL), followed by 15% NaOH (aq) solution (0.7 mL) followed by water (2.1 ml). $MgSO_4$ (3 g) was added and the mixture stirred at room temperature for 30 minutes before filtering and concentrating *in vacuo*. The residue was dissolved in THF (100 mL) and treated with imidazole (2.3 g, 34 mmol) followed by TBDMSCl (5 g, 34 mmol). The reaction was stirred at 50°C for 3 hours before concentrating *in vacuo*. The residue was partitioned between EtOAc (200 mL) and water (100 mL). The organic layer was collected, washed with 0.5M HCl (aq) (200 mL), brine (100 mL) and concentrated *in vacuo* to afford the title compound as a yellow oil (5.5 g, 94% over 2 steps) that was taken directly on to the next step.

Example 100 Step 2

Cis-racemic-tert-butyl-3-(((tert-butyldimethylsilyl)oxy)methyl)-5-((1-trityl-1H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidine-1-carboxylate

A solution of cis-racemic-tert-butyl 3-amino-5-(((tert-butyldimethylsilyl)oxy)methyl)piperidine-1-carboxylate (**Example 100 Step 1**, 5.5 g, 16 mmol), DIPEA (6.2 g, 48 mmol) and 4-chloro-1-trityl-1H-

pyrrolo[2,3-d]pyrimidine (see below) , 7 g, 17.6 mmol) in nBuOH (100 mL) was heated to 135°C for 5 days. The reaction was cooled, concentrated *in vacuo* and purified using silica gel column chromatography eluting with 30-60% EtOAc in petroleum ether to afford the title compound as a yellow solid (5.5 g, 65%).

^{1}H NMR (400MHz, DMSO-d_6): δ ppm 7.71 (s, 1H), 7.37-7.26 (m, 10H), 7.10-7.09 (m, 6H), 6.84 (s, 1H), 6.68 (s, 1H), 4.25-4.11 (m, 2H), 3.58-3.54 (m, 1H), 2.37-2.33 (m, 2H), 2.00-1.90 (m, 1H), 1.75-1.65 (m, 1H), 1.39 (s, 9H), 1.25-1.20 (m, 1H), 0.88-0.75 (m, 11H), -0.05 (s, 6H).

The cis-racemic compound was separated into its enantiomers using the following column conditions: Column: 300x50mm, 10 micron. Mobile phase: 25% EtOH with 0.1% $NH_3.H_2O$ in supercritical CO_2; Flow rate: 200 mL/min.

The two enantiomers were arbitrarily assigned absolute stereochemistry:

First eluting isomer: tert-butyl (3S,5R)-3-(((tert-butyldimethylsilyl)oxy)methyl)-5-((1-trityl-1H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidine-1-carboxylate. Rt = 3.77 minutes

Second eluting isomer: tert-butyl (3R,5S)-3-(((tert-butyldimethylsilyl)oxy)methyl)-5-((1-trityl-1H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidine-1-carboxylate. Rt = 4.74 minutes

Preparation of 4-chloro-7-trityl-7H-pyrrolo[2,3-d]pyrimidine

To a stirred solution of 4-chloro-7H-pyrrolo[2,3-d]pyrimidine (25 g,130 mmol) in DMF (1L) was added Cs_2CO_3 (128 g, 390 mmol) and trityl chloride (40g,143.2mmol) in portions. After the addition, the mixture was stirred at 40 °C for 4 hours, TLC (petroleum/ EtOAc = 10:1) indicated the starting material was consumed completely. The reaction was filtered and the filtrate was diluted with water (500 mL) and then extracted with EtOAc (600 mL x 3). The combine organic layers were washed with water (1 Lx 5) and brine (1 L) successively, dried over Na2SO4 and concentrated to dryness. The crude product was triturated with MTBE to give desired product (50g, 75%) as a white solid. ^{1}H NMR (400MHz, $CHCl_3$-d) d = 8.31 (d, J=1.0 Hz, 1H), 7.37 - 7.21 (m, 10H), 7.18 - 7.07 (m, 6H), 6.58 (dd, J=0.8, 3.8 Hz, 1H)

Example 100 Step 3

tert-butyl (3S,5R)-3-(hydroxymethyl)-5-((7-trityl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidine-1-carboxylate

To a solution of tert-butyl (3S,5R)-3-(((tert-butyldimethylsilyl)oxy)methyl)-5-((1-trityl-1H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidine-1-carboxylate (**Example 100 Step 2**, 2.26 g, 3.2 mmol) in THF (50 mL) was added TBAF (1.67 g, 6.4 mmol) dropwise at 45°C followed by stirring at this temperature for 3 hours. The reaction was cooled, washed with water (200 mL) and concentrated *in vacuo*. The residue was purified using silica gel column chromatography eluting with 1:1 EtOAc in petroleum ether to afford the title compound as a white solid (1.9 g, 100%). ^{1}H NMR (400MHz, DMSO-d_6): δ ppm 7.82-7.72 (m, 1H), 7.40-7.22 (m, 10H), 7.10-7.09 (m, 6H), 6.85-6.83 (m, 1H), 6.68-6.67 (m, 1H), 4.64-4.62 (m, 1H), 4.30-4.07 (m, 4H), 3.32-3.19 (m, 1H), 2.34 (br m, 1H), 1.97 (br m, 2H), 1.63 (br m, 1H), 1.40 (s, 9H). MS m/z 590 $[M+H]^+$

Example 101 Step 3

tert-butyl (3R,5S)-3-(hydroxymethyl)-5-((7-trityl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidine-1-carboxylate

The title compound was prepared as described for **Example 100 Step 3** using tert-butyl (3R,5S)-3-(((tert-butyldimethylsilyl)oxy)methyl)-5-((7-trityl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidine-1-carboxylate (**Example 100 Step 2**).

Example 100 Step 4

tert-butyl (3S,5R)-3-((2-cyanoethoxy)methyl)-5-((7-trityl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidine-1-carboxylate

To a solution of tert-butyl (3S,5R)-3-(hydroxymethyl)-5-((7-trityl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidine-1-carboxylate (Step 3(i), 300 mg, 0.5 mmol) in anhydrous THF (5 mL) was added NaH (67 mg, 1.75 mmol) at 0°C under nitrogen and the reaction was stirred at this temperature for 1 hour. Acrylonitrile (93 mg, 1.75 mmol) was added and the reaction stirred at room temperature for 3 hours. The reaction was quenched by the addition of water (2 mL) and concentrated *in vacuo*. The residue was purified using silica gel column chromatography eluting with 20-80% EtOAc in petroleum ether to afford the title compound as a white solid (190 mg, 60%). 1H NMR (400 MHz, DMSO-d6) d ppm 1.21 - 1.29 (m, 1 H) 1.40 (s, 11 H) 1.57 - 1.90 (m, 1 H) 2.77 (t, J=5.90 Hz, 2 H) 3.53 - 3.63 (m, 2 H) 4.10 (br. s., 1 H) 4.19 - 4.29 (m, 1 H) 6.68 (d, J=3.76 Hz, 1 H) 6.84 (d, J=3.76 Hz, 1 H) 7.10 (d, J=7.03 Hz, 7 H) 7.23 - 7.43 (m, 12 H) 7.72 - 7.84 (m, 1 H)

Example 101 Step 4

tert-Butyl-(3R,5S)-3-((2-cyanoethoxy)methyl)-5-((7-trityl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidine-1-carboxylate

The title compound was prepared according to the method described for **Example 100 Step 4** using tert-butyl (3R,5S)-3-(hydroxymethyl)-5-((7-trityl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidine-1-carboxylate (**Example 101 Step 3**).

Example 100 Step 5:

3-{[(3S,5R)-1-Acryloyl-5-(7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)piperidin-3-yl]methoxy}propanenitrile

To a solution of tert-butyl (3S,5R)-3-((2-cyanoethoxy)methyl)-5-((7-trityl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidine-1-carboxylate (**Example 100 Step 4,** 190 mg, 0.32 mmol) in DCM (5 mL) was added TFA (0.3 mL) at 0°C and the reaction was stirred at room temperature for 12 hours. The reaction was concentrated *in vacuo* and dissolved in THF (5 mL) and water (5 mL). The solution was treated with DIPEA (181 mg, 1.4 mmol) followed by acryloyl chloride (63 mg, 0.7 mmol) dropwise at 0°C. The reaction was stirred at 0°C for 2 hours before concentrating *in vacuo* and purifying using silica gel column chromatography eluting with 0-20% MeOH in DCM. The residue was dissolved in TFA (5 mL) and stirred at 35°C for 3 hours. The reaction was concentrated *in vacuo* and purified using preparative HPLC as described below to afford the title compound as an off-white solid (19 mg, 16% over three steps). Column: Phenomenex Gemini C18 250x21.1mm, 24 micron. Mobile phase:

21-41% MeCN in water modified with ammonia to pH=10. ^{1}H NMR (400MHz, DMSO-d_6): δ ppm 11.53 (br s, 1H), 8.13-8.10 (m, 1H), 7.38-7.30 (m, 1H), 7.09 (s, 1H), 6.88-6.80 (m, 1H), 6.58 (s, 1H), 6.16-6.10 (m, 1H), 5.73-5.71 (m, 1H), 4.73-4.58 (m, 1H), 4.35-4.05 (m, 2H), 3.62-3.59 (m, 2H), 3.43-3.40 (m, 2H), 2.80-2.77 (m, 3H), 2.45-2.33 (m, 1H), 2.08-2.05 (m, 1H), 1.87-1.80 (m, 1H), 1.44-1.35 (m, 1H).

MS m/z 355 $[M+H]^+$

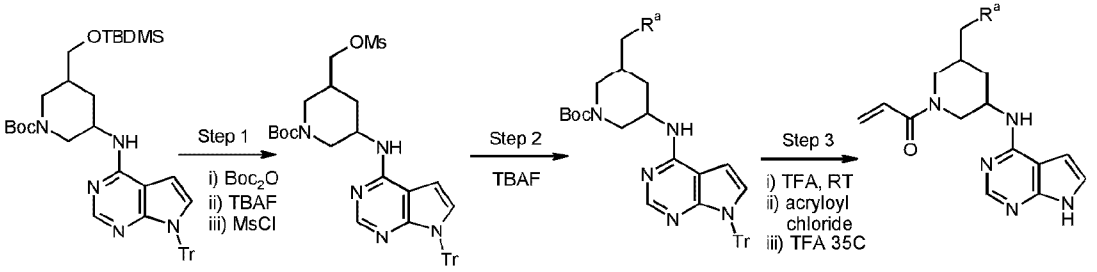
Example 101 Step 5:

3-{[(3R,5S)-1-Acryloyl-5-(7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)piperidin-3-yl]methoxy}propanenitrile

The title compound was prepared according to the method described for **Example 100 Step 5** using tert-butyl (3R,5S)-3-((2-cyanoethoxy)methyl)-5-((7-trityl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidine-1-carboxylate (**Example 101 Step 4**) using 27-47% MeCN in water modified with ammonia to pH=10. ^{1}H NMR (400MHz, DMSO-d_6): δ ppm 11.52 (br s, 1H), 8.13-8.10 (m, 1H), 7.38-7.30 (m, 1H), 7.09 (s, 1H), 6.85-6.81 (m, 1H), 6.57 (s, 1H), 6.16-6.10 (m, 1H), 5.73-5.71 (m, 1H), 4.71-4.58 (m, 1H), 4.35-4.05 (m, 2H), 3.62-3.59 (m, 2H), 3.43-3.40 (m, 2H), 2.80-2.77 (m, 3H), 2.45-2.33 (m, 1H), 2.08-2.05 (m, 1H), 1.87-1.80 (m, 1H), 1.44-1.35 (m, 1H).

MS m/z 355 $[M+H]^+$

Examples 102-107 were prepared according to the following Scheme:



Example 102 Step 1

Cis-racemic-tert-butyl-3-((tert-butoxycarbonyl)(7-trityl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-(((methylsulfonyl)oxy)methyl)piperidine-1-carboxylate

A mixture of cis-racemic-tert-butyl-3-(((tert-butyldimethylsilyl)oxy)methyl)-5-((7-trityl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidine-1-carboxylate (**cis-racemic Example 100 Step 2**, 2 g, 2.84 mmol) in di-tert-butyl dicarbonate (10 mL) was heated to 100°C for 1 hour. The reaction was cooled, concentrated *in vacuo* and purified using silica gel column chromatography eluting with 0-40% EtOAc in petroleum ether. The residue was dissolved in THF (30 mL) and treated with TBAF (1.3 g, 5 mmol). The reaction was stirred at 45°C for 12 hours. The reaction was cooled, washed with brine and concentrated *in vacuo*. The residue was purified using silica gel column chromatography eluting with 30-70% EtOAc in petroleum ether. Part of the residue (1 g, 1.45 mmol) was dissolved in DCM (10 mL) and treated with TEA (440 mg, 4.35 mmol) followed by mesyl chloride (332 mg, 2.90 mmol) at 0°C, and the reaction was stirred at this temperature for 2 hours. The reaction was quenched by the addition of

water (10 mL) and extracted into DCM (20 mL). The organic layer was dried over sodium sulphate, concentrated *in vacuo* to afford the title compound that was used directly in the next step.

Example 102 Step 2

Cis-racemic-tert-butyl-3-((tert-butoxycarbonyl)(7-trityl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-(fluoromethyl)piperidine-1-carboxylate

To a solution of cis-racemic-tert-butyl-3-((tert-butoxycarbonyl)(7-trityl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-(((methylsulfonyl)oxy)methyl)piperidine-1-carboxylate (**Example 102 Step 1**, 1.08 g, 1.4 mmol) in THF (30 mL) was added TBAF (1.47 g, 5.62 mmol).and the reaction was heated at 80°C for 12 hours. The reaction was cooled, concentrated *in vacuo* and purified using silica gel column chromatography eluting with 0-60% EtOAc in petroleum ether to afford the title compound as a white solid (650 mg, 67%). ^{1}H NMR (400MHz, $CDCl_3$): δ ppm 8.38 (s, 1H), 7.28-7.27 (m, 6H), 7.17-7.15 (m, 7H), 6.36-6.35 (m, 1H), 4.34-4.25 (m, 4H), 3.38-3.12 (m, 2H), 2.43-2.40 (m, 1H), 2.17-2.01 (m, 1H), 1.88-1.71 (m, 2H), 1.45 (s, 9H), 1.39 (s, 9H).

Example 102 Step 3:

Cis-racemic-1-[3-(fluoromethyl)-5-(7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)piperidin-1-yl]prop-2-en-1-one

The title compound was prepared according to the method described for **Example 100 Step 5** using cis-racemic-tert-butyl-3-((tert-butoxycarbonyl)(7-trityl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-(fluoromethyl)piperidine-1-carboxylate (**Example 102 Step 2**). The residue was purified using silica gel column chromatography eluting with 0-20% MeOH in DCM followed by preparative HPLC as described below: Column: Phenomenex Gemini C18 250x21.2mm, 10 micron. Mobile phase: 16-36% MeCN in water modified with ammonia to pH=10.

^{1}H NMR (400MHz, DMSO-d_6): δ ppm 11.55 (br s, 1H), 8.13-8.10 (m, 1H), 7.40-7.32 (m, 1H), 7.11-7.10 (m, 1H), 6.89-6.82 (m, 1H), 6.58-6.57 (m, 1H), 6.18-6.10 (m, 1H), 5.75-5.70 (m, 1H), 4.74-4.30 (m, 4H), 4.17-4.05 (m, 1H), 2.89-2.76 (m, 1H), 2.45-2.42 (m, 1H), 2.05-1.99 (m, 2H), 1.51-1.42 (m, 1H). MS m/z 326 $[M+Na]^+$

The cis-racemic material was separated into its enantiomers using preparative chiral column chromatography according to the conditions described below; Column: Chiralcel AD (250x30mm, 10 micron). Mobile phase: 35% MeOH in $NH_3.H_2O$. Flow rate: 80 mL/min

The two enantiomers were arbitrarily assigned absolute stereochemistry

First eluting isomer: Example 103

1-[(3S,5R)-3-(fluoromethyl)-5-(7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)piperidin-1-yl]prop-2-en-1-one. Rt = 7.87 minutes MS m/z 326 $[M+Na]^+$

Second eluting isomer: Example 104

1-[(3R,5S)-3-(fluoromethyl)-5-(7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)piperidin-1-yl]prop-2-en-1-one. Rt = 9.08 minutes MS m/z 326 $[M+Na]^+$

Example 105 Step 2

Cis-racemic-tert-butyl-3-((tert-butoxycarbonyl)(7-trityl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-(cyanomethyl)piperidine-1-carboxylate

To a solution of cis-racemic-tert-butyl-3-((tert-butoxycarbonyl)(7-trityl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-(((methylsulfonyl)oxy)methyl)piperidine-1-carboxylate (**Example 102 Step 1**, 1.8 g, 2.3 mmol) in DMSO (30 mL) was added potassium cyanide (450 mg, 6.9 mmol) and the reaction was heated to 80°C for 12 hours. The reaction was cooled, diluted with water (30 mL) and extracted into EtOAc (50 mL). The organic layer was collected, concentrated *in vacuo* and purified using silica gel column chromatography eluting with 0-50% EtOAc in petroleum ether to afford the title compound as a white solid (1.3 g, 81%).

MS m/z 599 $[M\text{-Boc}+H]^+$

Example 105 Step 3

Cis-racemic-[1-acryloyl-5-(7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)piperidin-3-yl]acetonitrile

The title compound was prepared according to the method described for **Example 100 Step 5** using cis-racemic-tert-butyl 3-((tert-butoxycarbonyl)(7-trityl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-(cyanomethyl)piperidine-1-carboxylate. The residue was purified using silica gel column chromatography eluting with 0-20% MeOH in DCM followed by preparative HPLC as described below: Column: Phenomenex Gemini C18 250x21.2mm, 10 micron

Mobile phase: 12-32% MeCN in water modified with ammonia to pH=10. ^{1}H NMR (400MHz, DMSO-d_6): δ ppm 11.55 (br s, 1H), 8.14-8.10 (m, 1H), 7.43-7.36 (m, 1H), 7.10 (s, 1H), 6.89-6.79 (m, 1H), 6.57 (s, 1H), 6.18-6.12 (m, 1H), 5.75-5.73 (m, 1H), 4.74-4.13 (m, 3H), 2.81-2.68 (m, 4H), 2.41-1.93 (m, 2H), 1.53-1.44 (m, 1H). MS m/z 333 $[M+Na]^+$

The cis-racemic material was separated into its enantiomers using preparative chiral column chromatography according to the conditions described below; Column: AD (250x30mm, 5 micron). Mobile phase: 35% MeOH in $NH_3.H_2O$. Flow rate: 50 mL/min

The two enantiomers were arbitrarily assigned absolute stereochemistry

First eluting isomer: Example 106

[(3R,5R)-1-acryloyl-5-(7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)piperidin-3-yl]acetonitrile

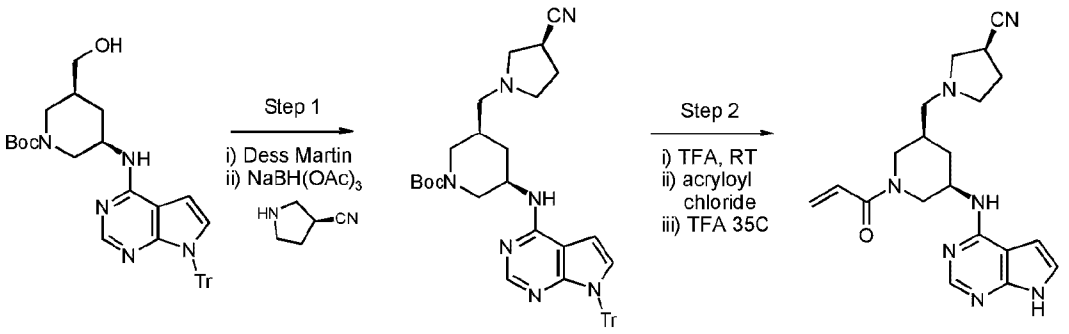
Rt = 7.79 minutes MS m/z 333 $[M+Na]^+$

Second eluting isomer: Example 107

[(3S,5S)-1-acryloyl-5-(7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)piperidin-3-yl]acetonitrile

Rt = 8.35 minutes MS m/z 333 $[M+Na]^+$

Example 108 was prepared according to the following Scheme:



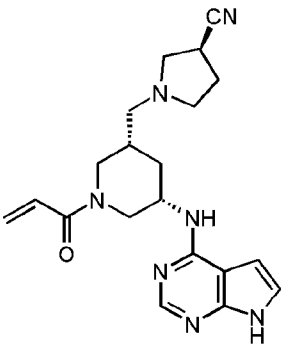
Example 108 Step 1

tert-butyl (3S,5S)-3-(((S)-3-cyanopyrrolidin-1-yl)methyl)-5-((7-trityl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidine-1-carboxylate

To a solution of tert-butyl (3R,5S)-3-(hydroxymethyl)-5-((7-trityl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidine-1-carboxylate (**Example 100 Step 3,** 800 mg, 1.36 mmol), in anhydrous DCM (80 mL) was added Dess-Martin reagent (1.03 g, 2.44 mmol) at 0°C and the reaction was stirred at room temperature for 4 hours. $Na_2S_2O_3$ (300 mg) and saturated aqueous $NaHCO_3$ solution (50 mL) were added and the mixture stirred for 10 minutes. The solution was partitioned between EtOAc (80 mL) and water (50 mL), the organic layer collected, washed with brine, dried over sodium sulphate and concentrated *in vacuo*. The residue was purified using silica gel column chromatography eluting with 0-60% EtOAc in petroleum ether. The residue was dissolved in DCM (30 mL) with (S)-pyrrolidine-3-carbonitrile (147 mg, 1.53 mmol) and treated with $NaBH(OAc)_3$ (162 mg, 0.766 mmol) and AcOH (61 mg, 1 mol) at 0°C. The reaction was stirred at room temperature for 48 hours before the addition of further $NaBH(OAc)_3$ (162 mg, 0.766 mmol) and AcOH (61 mg, 1 mol) at 0°C with further stirring for 5 hours. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ solution (20 mL) and extracted into EtOAc (2 x 30 mL). The combined organic layers were washed with brine, dried over sodium sulphate and concentrated *in vacuo*. The residue was purified using silica gel column chromatography eluting with 0-60% EtOAc in petroleum ether to afford the title compound as an oil (230 mg, 26% over 2 steps). MS m/z 668 $[M+H]^+$

Example 108 Step 2:

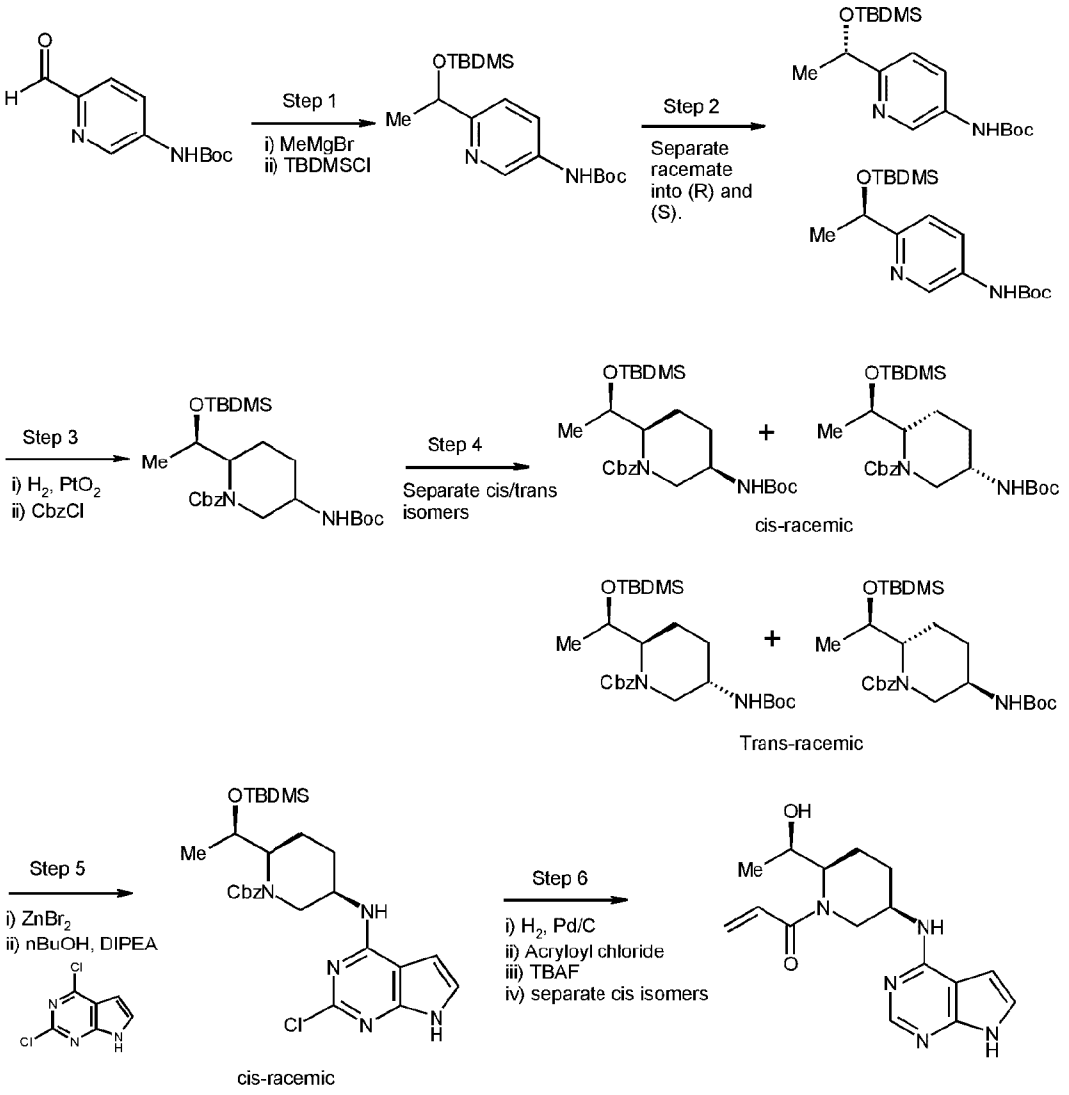
(S)-1-(((3S,5S)-5-((7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-1-acryloylpiperidin-3-yl)methyl)pyrrolidine-3-carbonitrile



The title compound was prepared according to the methods described for **Example 100 Step 5** using tert-butyl (3S,5S)-3-(((S)-3-cyanopyrrolidin-1-yl)methyl)-5-((7-trityl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidine-1-carboxylate (**Example 108 Step 1**).

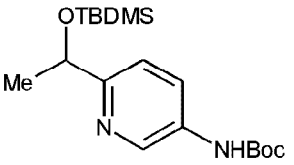
^{1}H NMR (400MHz, DMSO-d_6): δ ppm 11.50 (br s, 1H), 8.12-8.08 (m, 1H), 7.35-7.27 (m, 1H), 7.08 (s, 1H), 6.83-6.80 (m, 1H), 6.56 (s, 1H), 6.16-6.06 (m, 1H), 5.73-5.65 (m, 1H), 4.74-4.57 (m, 1H), 4.37-4.12 (m, 2H), 3.27-3.24 (m, 1H), 2.75-2.70 (m, 5H), 2.62-2.32 (m, 6H), 2.11-1.92 (m, 1H), 1.80-1.70 (m, 1H), 1.31-1.22 (m, 1H). MS m/z 380 $[M+H]^+$

Examples 109-112 were prepared according to the Scheme below:



Example 109 Step 1

Racemic-tert-butyl (6-(1-((tert-butyldimethylsilyl)oxy)ethyl)pyridin-3-yl)carbamate



To a solution of tert-butyl (6-formylpyridin-3-yl)carbamate (8.5 g, 38 mmol) in anhydrous THF (400 mL) was added methyl magnesium bromide (76.5 mL, 229 mmol) at 0°C. The reaction was stirred at room temperature for 18 hours. The reaction was poured into ice-water (1000 mL) and extracted into

EtOAc (3 x 600 mL). The combined organic layers were dried over sodium sulphate and concentrated *in vacuo* to afford a brown solid as the hydroxyl intermediate. To a solution of this hydroxyl intermediate (26.5 g, 0.11 mol) in THF (400 mL) was added imidazole (15.1 g, 0.223 mmol) followed by TBDMSCl (25 g, 0.17 mmol) at 0°C. The reaction was heated to 70°C for 5 hours before pouring into ice-water (200 mL) and extracting with EtOAc (2 x 500 mL). The organic layers were combined, washed with brine (200 mL), dried over sodium sulphate and concentrated *in vacuo*. The residue was purified using silica gel column chromatography eluting with 0-18% EtOAc in petroleum ether to afford the title compound as a white solid (36 g, 92% over 2 steps). ^{1}H NMR (400MHz, DMSO-d_6): δ ppm 9.49 (br s, 1H), 8.49 (s, 1H), 7.86-7.84 (m, 1H), 7.36-7.34 (m, 1H), 4.85-4.80 (m, 1H), 1.41 (s, 9H), 1.35-1.33 (d, 3H), 0.86 (s, 9H), -0.04 (s, 3H), -0.05 (s, 3H).

Example 109 Step 2

The racemate (36 g) was separated into its enantiomers (18 g, and 17.62 g) using the following preparative chiral HPLC: Column: IC (300x50mm, 10 micron. Mobile phase: 20% IPA in NH_3H_2O. Flow rate: 200 mL/min

The two enantiomers were arbitrarily assigned absolute stereochemistry.
to afford (R)-tert-butyl (6-(1-((tert-butyldimethylsilyl)oxy)ethyl)pyridin-3-yl)carbamate and (S)- tert-butyl (6-(1-((tert-butyldimethylsilyl)oxy)ethyl)pyridin-3-yl)carbamate.

Example 109 Steps 3 and 4

Cis/trans-racemic-benzyl-5-((tert-butoxycarbonyl)amino)-2-((R)-1-((tert-butyldimethylsilyl)oxy)ethyl)piperidine-1-carboxylate

To a solution of (R)-tert-butyl (6-(1-((tert-butyldimethylsilyl)oxy)ethyl)pyridin-3-yl)carbamate (**Example 109 Step 2**, 18 g, 51 mmol) in EtOH (260 mL) and AcOH (130 mL) was added 10% PtO_2 and the reaction was hydrogenated under 55 psi at 65°C for 18 hours. The reaction was filtered through Celite and concentrated *in vacuo*. The residue was dissolved in THF (300 mL) and treated with saturated aqueous $NaHCO_3$ solution (300mL). CbzCl (13.3 g, 93 mmol) was added at 0°C and the reaction stirred at this temperature for 1.5 hours. The reaction was extracted with EtOAc (3 x 300 mL), the organic layers were combined, dried over sodium sulfate and concentrated *in vacuo* to afford the title compound that was separated into its cis-racemic and trans-racemic isomers using silica gel column chromatography eluting with 0-10% MeOH in DCM:

Cis-racemic-benzyl-5-((tert-butoxycarbonyl)amino)-2-((R)-1-((tert-butyldimethylsilyl)oxy)ethyl)piperidine-1-carboxylate (7.9 g). ^{1}H NMR (400MHz, DMSO-d_6): δ ppm 7.35-7.21 (m, 5H), 6.85-6.84 (m, 1H), 5.17-4.96 (m, 2H), 4.49-4.48 (m, 2H), 4.06-3.89 (m, 3H), 3.26-3.24 (m, 0.5H), 1.67-1.47 (m, 2.5H), 1.36-1.34 (m, 9H), 1.18-1.08 (m, 4H), 0.84 (s, 9H), 0.04- -0.01 (m, 6H).

Trans-racemic-benzyl-5-((tert-butoxycarbonyl)amino)-2-((R)-1-((tert-butyldimethylsilyl)oxy)ethyl)piperidine-1-carboxylate (6 g). ^{1}H NMR (400MHz, DMSO-d_6): δ ppm 7.34-7.30 (m, 5H), 6.81-6.79 (m, 1H), 5.16-4.97 (m, 2H), 4.06-3.99 (m, 3H), 3.80-3.74 (m, 1H), 3.25-3.15 (m, 0.5), 2.41-2.32 (m, 0.5H), 1.81-1.52 (m, 3H), 1.37-1.33 (m, 10H), 1.00-0.83 (m, 3H), 0.83 (s, 9H), 0.06- -0.02 (m, 6H).

Example 112 Steps 3 and 4

Cis/trans-racemic-benzyl-5-((tert-butoxycarbonyl)amino)-2-((S)-1-((tert-butyldimethylsilyl)oxy)ethyl)piperidine-1-carboxylate

The title compounds were prepared according to the method described for **Example 109 Steps 3 and 4** using (R)-tert-butyl (6-(1-((tert-butyldimethylsilyl)oxy)ethyl)pyridin-3-yl)carbamate (**Example 109 Step 2**). The title compound that was separated into its cis-racemic and trans-racemic isomers using silica gel column chromatography eluting with 0-10% MeOH in DCM:

Cis-racemic-benzyl-5-((tert-butoxycarbonyl)amino)-2-((S)-1-((tert-butyldimethylsilyl)oxy)ethyl)piperidine-1-carboxylate. ^{1}H NMR (400MHz, DMSO-d_6): δ ppm 7.35-7.21 (m, 5H), 6.85-6.84 (m, 1H), 5.17-4.96 (m, 2H), 4.49-4.48 (m, 2H), 4.06-3.89 (m, 3H), 3.26-3.24 (m, 0.5H), 1.67-1.47 (m, 2.5H), 1.36-1.34 (m, 9H), 1.18-1.08 (m, 4H), 0.84 (s, 9H), 0.04- -0.01 (m, 6H).

Trans-racemic-benzyl-5-((tert-butoxycarbonyl)amino)-2-((S)-1-((tert-butyldimethylsilyl)oxy)ethyl)piperidine-1-carboxylate. ^{1}H NMR (400MHz, DMSO-d_6): δ ppm 7.34-7.30 (m, 5H), 6.81-6.79 (m, 1H), 5.14-4.97 (m, 2H), 4.06-3.99 (m, 3H), 3.80-3.74 (m, 1H), 3.25-3.15 (m, 0.5), 2.41-2.32 (m, 0.5H), 1.81-1.52 (m, 3H), 1.37-1.33 (m, 10H), 1.00-0.83 (m, 3H), 0.83 (s, 9H), 0.06- -0.02 (m, 6H).

Example 109 Step 5

Trans-racemic-benzyl 2-((R)-1-((tert-butyldimethylsilyl)oxy)ethyl)-5-((2-chloro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidine-1-carboxylate

To a solution of trans-racemic-benzyl 5-((tert-butoxycarbonyl)amino)-2-((R)-1-((tert-butyldimethylsilyl)oxy)ethyl)piperidine-1-carboxylate (**Example 109 Step 3 and 4**, 7.0 g, 14.2 mmol) in DCM (400 mL) was added zinc bromide (18.1.g, 81 mmol) at 0°C and the reaction was stirred at room temperature for 4 hours. The reaction was poured into ice and saturated aqueous $NaHCO_3$ solution (160 mL) and extracted into DCM (4 x 500 mL). The organic layers were combined, dried over sodium sulphate and concentrated *in vacuo*. The residue was purified using silica gel column chromatography using 0-15% MeOH with ammonia in DCM. The residue (2.5 g, 6.3 mmol) was dissolved in nBuOH (60 mL) and treated with DIPEA (4.13 g, 32 mmol). 2,4-dichloro-7H-pyrrolo[2,3-d]pyrimidine (1.26 g, 6.7 mmol) was added and the reaction heated to 130°C for 24 hours. The reaction was cooled, concentrated *in vacuo* and partitioned between EtOAc (150 mL) and water (100 mL). The organic layer was washed with brine, dried over sodium sulphate and concentrated *in vacuo*. The residue was purified using silica gel column chromatography eluting with 10-20% EtOAc in petroleum ether to afford the title compound as a white solid (2.2 g, 64% over 2 steps). ^{1}H NMR (400MHz, $CDCl_3$): δ ppm 10.33 (br s, 1H), 7.39-7.02 (m, 7H), 5.23-5.01 (m, 2.5H), 4.59-4.00 (m, 4.5H), 3.50-3.39 (m, 1H), 2.75-2.60 (m, 0.5H), 2.30-1.90 (m, 1.5H), 1.75-1.60 (m, 1.5H), 1.28-1.14 (m, 3.5H), 0.90 (s, 9H), 0.09-0.04 (m, 6H).

Example 112 Step 5

Cis-racemic-benzyl 2-((S)-1-((tert-butyldimethylsilyl)oxy)ethyl)-5-((2-chloro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidine-1-carboxylate

The title compound was prepared according to the method described for **Example 109 Step 5** using Cis/trans-racemic-benzyl-5-((tert-butoxycarbonyl)amino)-2-((S)-1-((tert-butyldimethylsilyl)oxy)ethyl)piperidine-1-carboxylate(**Example 112 Steps 3 and 4**). ^{1}H NMR (400MHz, DMSO-d_6): δ ppm 11.75 (br s, 1H), 7.74-7.73 (m, 1H), 7.38-7.25 (m, 4H), 7.12-7.10 (m, 1H), 6.67-6.55 (m, 1H), 5.10-4.98 (m, 2H), 4.30-4.00 (m, 5H), 2.77-2.68 (m, 1H), 1.75-1.50 (m, 2H), 1.20-1.16 (m, 4H), 0.82 (s, 9H), 0.07-0.01 (m, 6H).

Example 109 Step 6

Trans-racemic-1-[2-[(1R)-1-hydroxyethyl]-5-(7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)piperidin-1-yl]prop-2-en-1-one

To a solution of trans-racemic-benzyl 2-((R)-1-((tert-butyldimethylsilyl)oxy)ethyl)-5-((2-chloro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidine-1-carboxylate (**Example 109 Step 5**, 2.9 g, 5.34 mmol) in MeOH (100 mL) was added 10% Pd/C (600 mg) and the reaction was hydrogenated under 45 psi hydrogen at 40°C for 4 days. The reaction was filtered and concentrated *in vacuo* to afford a white solid (1.9 g, 95%). The intermediate (1 g, 2.66 mol) was dissolved in THF (25 mL) and water (25 mL) and treated with DIPEA (1.38 g) dropwise. To the reaction was added acryloyl chloride with stirring at 0°C for 3 hours. The reaction was extracted into EtOAc (2 x 20 mL), the organic layers combined, dried over sodium sulphate and concentrated *in vacuo*. The residue was purified using silica gel column chromatography eluting with 1-10% MeOH in DCM to afford a white solid (600 mg, 53%). This intermediate (380 mg, 0.884 mmol) was dissolved in THF (15 mL) and treated with TBAF (463 mg, 1.77 mmol) and stirred at 45°C for 18 hours. The reaction was concentrated *in vacuo* and purified using silica gel column chromatography eluting with 1-10% MeOH in DCM (280 mg, 50% over three steps).

^{1}H NMR (400MHz, DMSO-d_6): δ ppm 11.52-11.48 (br m, 1H), 8.13-8.09 (m, 1H), 7.31-7.23 (m, 1H), 7.09-7.06 (m, 1H), 6.86-6.54 (m, 2H), 6.25-6.09 (m, 1H), 5.83-5.69 (m, 1H), 4.32-4.04 (m, 4H), 2.86-2.80 (m, 1H), 2.34-1.55 (m, 4H), 1.00-0.99 (m, 3H). MS m/z 316 $[M+H]^+$

The cis-racemic material was separated into its enantiomers using preparative chiral column chromatography according to the conditions described below; Column: YMC-Actus Triart C18 150x30mm, 5 micron. Mobile phase: 2-22% MeCN in water modified with 0.225% formic acid.

QC Analytical LCMS Method:

Column: Chiralcel OJ-H (250x4.6mm, 5 micron); Mobile phase: 5-40% MeOH with 0.05% DEA in CO_2; Flow rate: 2.35 mL/min

The two enantiomers were arbitrarily assigned absolute stereochemistry

First eluting isomer: Example 110

1-[(2S,5R)-2-[(1R)-1-Hydroxyethyl]-5-(7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)piperidin-1-yl]prop-2-en-1-one. Rt = 4.64 minutes MS m/z 316 $[M+H]^+$

Second eluting isomer: Example 111

1-[(2R,5S)-2-[(1R)-1-Hydroxyethyl]-5-(7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)piperidin-1-yl]prop-2-en-1-one. Rt = 5.19 minutes MS m/z 316 $[M+H]^+$

Example 112 Step 6

Cis-racemic-1-[2-[(1S)-1-hydroxyethyl]-5-(7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)piperidin-1-yl]prop-2-en-1-one

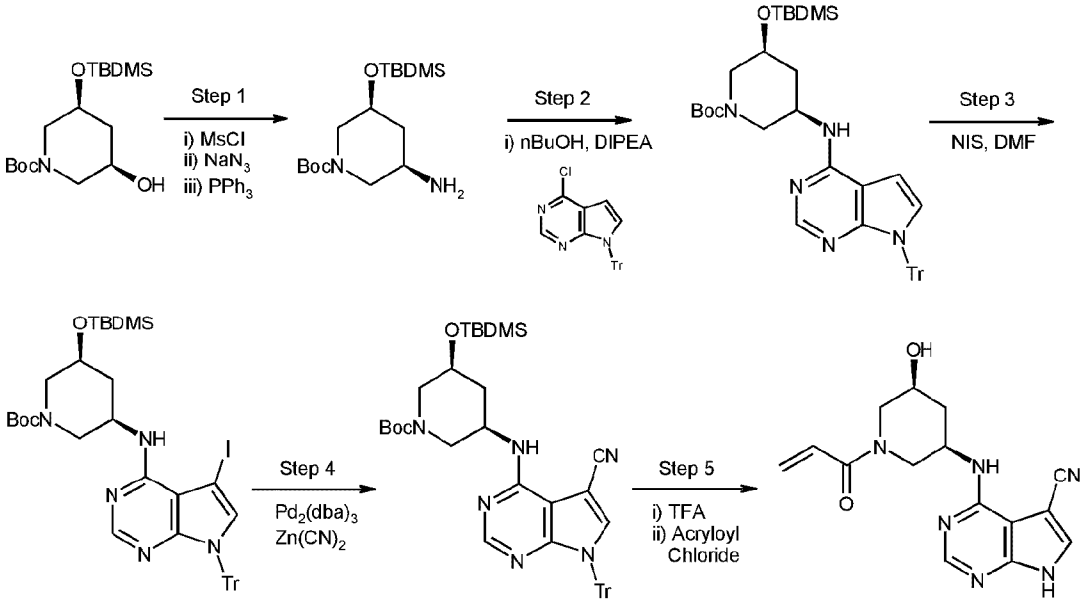
The title compound was prepared according to the method described for **Example 109 Step 6** using cis-racemic-benzyl 2-((S)-1-((tert-butyldimethylsilyl)oxy)ethyl)-5-((2-chloro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidine-1-carboxylate (**Example 112 Step 5**). The residue was purified using silica gel column chromatography eluting with 20-100% EtOAc in petroleum ether followed by preparative HPLC as described below:

Column: Phenomenex Gemini C18 250x21.2mm, 8 micron

Mobile phase: 0-20% MeCN in water modified with ammonia to pH=10.

^{1}H NMR (400MHz, DMSO-d_6): δ ppm 11.52 (br s, 1H), 8.15-8.09 (m, 1H), 7.28-7.26 (m, 1H), 7.09-7.08 (m, 1H), 6.84-6.80 (m, 1H), 6.54 (br s, 1H), 6.07-6.02 (m, 1H), 5.61-5.58 (m, 1H), 4.64-4.60 (m, 2H), 4.12-4.04 (m, 2H), 3.75-3.70 (m, 1H), 3.20-3.10 (m, 1H), 2.66-2.60 (m, 1H), 1.85-1.81 (m, 2H), 1.65-1.63 (m, 1H), 1.16-1.13 (m, 3H). MS m/z 316 $[M+H]^+$

Example 113 was prepared according to the Scheme below:



Example 113 Step 1

tert-Butyl (3R, 5S)-3-amino-5-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate

To a solution of (3S, 5R)-tert-butyl 3-((tert-butyldimethylsilyl)oxy)-5-hydroxypiperidine-1-carboxylate (**WO2011029046**, 3.5 g, 10.55 mmol) in DCM (25 mL) was added TEA (4 4 mL, 31.6 mmol) followed by mesyl chloride (1.06 mL, 13.72 mmol) at 0°C. The reaction was stirred at room temperature for 4 hours before quenching with water and extracting into DCM (2 x 75 mL). The organic layers were

combined, dried over sodium sulphate and concentrated *in vacuo*. The residue was dissolved in DMF (35 mL) and treated with sodium azide (2.05 g, 31.63 mmol). The reaction was heated to 100°C for 16 hours before cooling and concentrating *in vacuo*. The residue was dissolved in EtOAc (200 mL) and washed with water (3 x 50 mL), dried over sodium sulphate and concentrated *in vacuo*. The residue was purified using silica gel column chromatography eluting with 0-20% EtOAc in heptanes to afford the azide intermediate (1.9 g, 51%). The azide intermediate was dissolved in THF (100 mL) and treated with water (0.67 mL) followed by triphenylphosphine (2.01 g, 7.9 mmol). The reaction was heated to reflux for 16 hours, cooled and concentrated *in vacuo*. The residue was purified using silica gel column chromatography eluting with 0-5% MeOH in DCM to afford the title compound as a light yellow oil (1.52 g, 86%). MS m/z 331 $[M+H]^+$

Example 113 Step 2

tert-butyl (3S, 5R)-3-((tert-butyldimethylsilyl)oxy)-5-((7-trityl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidine-1-carboxylate

To a solution of tert-butyl (3R, 5S)-3-amino-5-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate (**Example 113 Step 1**, 9 g, 27.23 mmol) in n-BuOH (140 mL) was added 4-chloro-7-trityl-7H-pyrrolo[2,3-d]pyrimidine (16.17 g, 41 mmol) followed by DIPEA (10.54 g, 82 mmol). The reaction was heated to 120°C for 72 hours. The reaction was cooled and concentrated *in vacuo*. The residue was partitioned between EtOAc (200 mL) and brine (200 mL), the organic layer was collected, washed with further brine (200 mL), dried over sodium sulphate and concentrated *in vacuo*. The residue was purified using silica gel column chromatography eluting with 10-30% EtOAc in petroleum ether to afford the title compound as a yellow solid (18 g, 95%) that was taken on directly to the next step.

Example 113 Step 3

tert-Butyl (3S, 5R)-3-((tert-butyldimethylsilyl)oxy)-5-((5-iodo-7-trityl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidine-1-carboxylate

To a solution of tert-butyl (3S, 5R)-3-((tert-butyldimethylsilyl)oxy)-5-((7-trityl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidine-1-carboxylate (**Example 113 Step 2**, 1.6 g 2.3 mmol) in DMF (30 mL) was added NIS (1.05 g, 4.6 mmol) and the reaction was stirred at room temperature for 2 hours. The reaction was filtered and the filtrate washed with water (20 mL) and concentrated *in vacuo*. The residue was purified using silica gel column chromatography eluting with 20-80% EtOAc in petroleum ether to afford the title compound as a yellow solid (1.2 g, 64%).

MS m/z 816 $[M+H]^+$

Example 113 Step 4

tert-butyl (3S,5R)-3-((tert-butyldimethylsilyl)oxy)-5-((5-cyano-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidine-1-carboxylate

To a solution of tert-butyl (3S, 5R)-3-((tert-butyldimethylsilyl)oxy)-5-((5-iodo-7-trityl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidine-1-carboxylate (**Example 113 Step 3**, 500 mg, 0.6 mmol) in anhydrous DMF (10 mL) was added zinc cyanide (80 mg, 0.72 mmol) followed by dppf (66 mg, 0.12

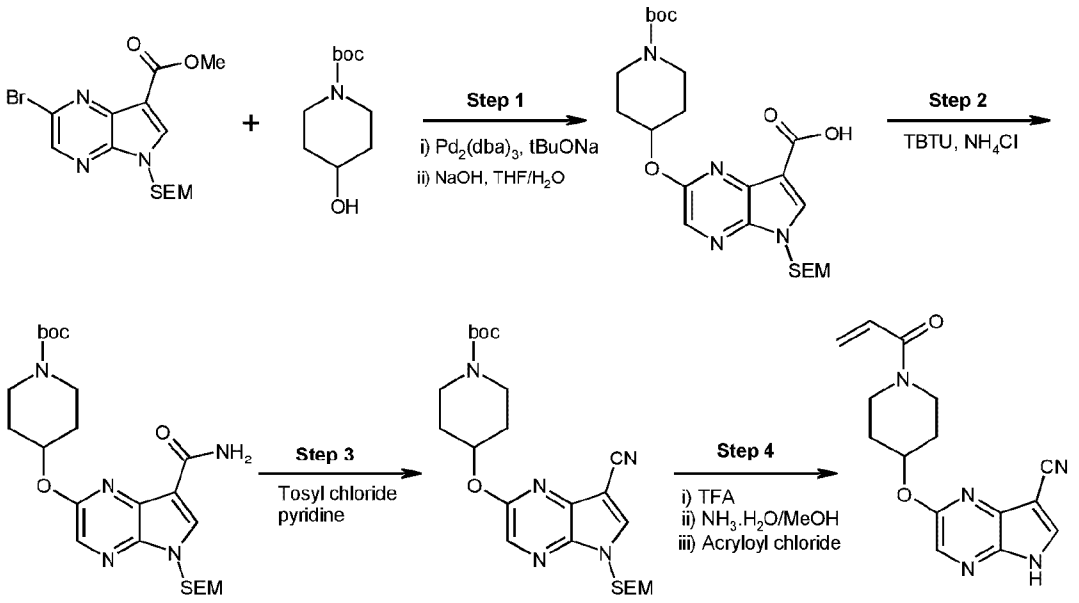
mmol). The reaction was degassed under argon and purged with nitrogen. To the reaction was added $Pd_2(dba)_3$ (55 mg, 0.06 mmol) and the reaction heated to 130°C for 18 hours. The reaction was cooled, concentrated *in vacuo* and purified using silica gel column chromatography eluting with 20-80% EtOAc in petroleum ether to afford the title compound as a brown solid (130 mg, 45%). ^{1}H NMR (400MHz, DMSO-d_6): δ ppm 12.76 (br s, 1H), 8.29 (s, 1H), 8.17 (s, 1H), 6.31-6.26 (m, 1H), 4.30-4.25 (m, 1H), 4.00-3.60 (m, 4H), 3.10-2.90 (m, 1H), 2.15-2.08 (m, 1H), 1.77-1.70 (m, 1H), 1.41-1.20 (m, 9H), 0.88 (s, 9H), 0.107-0.04 (m, 6H).

Example 113 Step 5

4-{[(3R,5S)-1-Acryloyl-5-hydroxypiperidin-3-yl]amino}-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile

To a solution of tert-butyl (3S,5R)-3-((tert-butyldimethylsilyl)oxy)-5-((5-cyano-7-trityl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidine-1-carboxylate (**Example 113 Step 4**, 130 mg, 0.28 mmol) in DCM (5 mL) was added TFA (1 mL) and the reaction was stirred at room temperature for 4 hours. The reaction was concentrated *in vacuo* and dissolved in THF (5 mL) and water (5 mL). To the solution was added DIPEA (108 mg, 0.84 mmol) followed by acryloyl chloride (51 mg, 0.56 mmol) at 0°C. The reaction was stirred at 0°C for 2 hours, then additional water was added (5 mL). The reaction was purified using preparative HPLC as described below to afford the title compound as a yellow solid (15 mg, 18%). Column: Phenomenex Gemini C18 250x21.2mm, 24 micron. Mobile phase: 5-25% MeCN in water modified with ammonia to pH=10. ^{1}H NMR (400MHz, DMSO-d_6): δ ppm 12.59 (br s, 1H), 8.30-8.27 (m, 1H), 8.14-8.10 (m, 1H), 7.23-7.11 (m, 1H), 6.82-6.78 (m, 0.5H), 6.46-6.42 (m, 0.5H), 6.01-5.90 (m, 1H), 5.65-5.40 (m, 2H), 4.47-4.23 (m, 1.5H), 3.88-3.72 (m, 3H), 3.68-3.50 (m, 0.5H), 3.10-2.90 (br m, 1H), 2.12-2.04 (m, 1H), 1.85-1.76 (m, 1H). MS m/z 335 $[M+Na]^+$

Example 114 was prepared as described in the Scheme below:



Example 114 Step 1

2-{[1-(tert-Butoxycarbonyl)piperidin-4-yl]oxy}-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid

The title compound was prepared according to the method described for **Example 83 Step 4** to afford methyl 2-{[1-(tert-butoxycarbonyl)piperidin-4-yl]oxy}-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazine-7-carboxylate using methyl 2-bromo-5-((2-(trimethyl-silyl)ethoxy)methyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxylate (**Example 83 Step 3**) and tert-butyl 4-hydroxypiperidine-1-carboxylate followed by the method described for **Example 83 Step 5.** ^{1}H NMR (400MHz, DMSO-d_6): δ ppm 12.26 (br s, 1H), 8.48 (s, 1H), 8.00 (s, 1H), 5.62 (s, 2H), 5.30-5.27 (m, 1H), 3.66-3.63 (m, 2H), 3.54-3.50 (t, 2H), 3.34-3.26 (m, 2H), 2.02-1.98 (m, 2H), 1.66-1.60 (m, 2H), 1.41 (s, 9H), 0.82-0.78 (t, 2H), -0.11 (s, 9H). MS m/z 515 $[M+Na]^+$

Example 114 Step 2

tert-Butyl 4-[(7-carbamoyl-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl)oxy]piperidine-1-carboxylate

To a solution of 2-{[1-(tert-butoxycarbonyl)piperidin-4-yl]oxy}-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid (**Example 114 Step 1**, 1 g, 2 mmol) and TBTU (785 mg, 2.4 mmol) in DMF (10 mL) was added DIPEA (1 g, 8 mmol) followed by ammonium chloride (573 mg, 10 mmol) and the reaction was stirred at room temperature for 3 hours. The reaction was partitioned between EtOAc (20 mL) and water (20 mL), the organic layer collected, washed with brine (50 mL), dried over sodium sulphate and concentrated *in vacuo*. The residue was purified using silica gel col-

umn chromatography eluting with 5-15% MeOH in DCM to afford the title compound (832 mg, 83%) that was taken directly on to the next step.

Example 114 Step 3

tert-Butyl 4-[(7-cyano-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl)oxy]piperidine-1-carboxylate

A mixture of tert-butyl 4-[(7-carbamoyl-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl)oxy]piperidine-1-carboxylate (**Example 114 Step 2**, 300 mg, 0.61 mmol) and tosyl chloride (350 mg, 1.83 mmol) in pyridine (5 mL) was stirred at room temperature for 4 hours. The reaction was partitioned between EtOAc (20 mL) and water (20 mL). The organic layer was collected, concentrated *in vacuo* and purified using silica gel column chromatography eluting with 20-80% EtOAc in petroleum ether to afford the title compound as a white solid (645 mg, 81%). MS m/z 496 $[M+Na]^+$

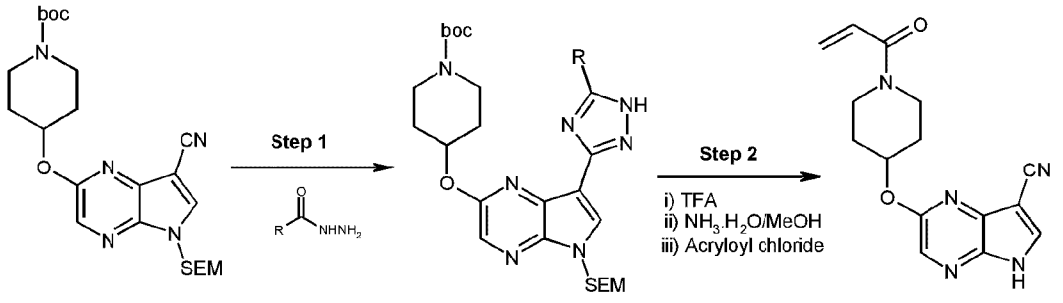
Example 114 Step 4

2-[(1-Acryloylpiperidin-4-yl)oxy]-5H-pyrrolo[2,3-b]pyrazine-7-carbonitrile

The title compound was prepared according to the method described for **Example 1 Steps 5-7** using tert-butyl 4-[(7-cyano-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl)oxy]piperidine-1-carboxylate (**Example 114 Step 3**). The residue was purified using silica gel column chromatography eluting with 2-15% MeOH in DCM followed by preparative HPLC as described below: Column: Phenomenex Gemini C18 250x21.2mm, 24 micron

Mobile phase: 17-37% MeCN in water modified with 0.225% formic acid. ^{1}H NMR (400MHz, DMSO-d_6): δ ppm 8.55 (s, 1H), 8.07 (s, 1H), 6.88-6.82 (m, 1H), 6.15-6.10 (m, 1H), 5.71-5.68 (m, 1H), 5.36-5.34 (m, 1H), 4.00-3.80 (m, 3H), 3.60-3.40 (m, 3H), 2.10-2.00 (m, 2H), 1.75-1.65 (m, 2H). MS m/z 320 $[M+Na]^+$

Examples 115-116 were prepared as described in the Scheme below:



Example 115 Step 1

tert-Butyl 4-{[7-(5-methyl-1H-1,2,4-triazol-3-yl)-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl]oxy}piperidine-1-carboxylate

To a solution of tert-butyl 4-[(7-cyano-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl)oxy]piperidine-1-carboxylate (**Example 114 Step 3**, 500 mg, 1.06 mmol) in nBuOH (15 mL) was

added acetohydrazide (258 mg, 3.48 mmol) and potassium carbonate (292 mg, 2.11 mmol). The reaction was heated to 130°C for 48 hours. The reaction was cooled, concentrated *in vacuo* and purified using silica gel column chromatography eluting with 50-100% EtOAc in petroleum ether to afford the title compound as a yellow solid (270 mg, 48%) that was taken directly on to the next step.

Example 115 Step 2

1-(4-{[7-(5-Methyl-1H-1,2,4-triazol-3-yl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]oxy}piperidin-1-yl)prop-2-en-1-one

The title compound was prepared according to the method described for **Example 1 Steps 5-7** using tert-butyl 4-{[7-(5-methyl-1H-1,2,4-triazol-3-yl)-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl]oxy}piperidine-1-carboxylate (**Example 115 Step 1**). The residue was purified using silica gel column chromatography eluting with 0-10% MeOH in DCM followed by preparative HPLC as described below: Column: Phenomenex Gemini C18 250x21.2mm, 24 micron. Mobile phase: 17-37% MeCN in water modified with ammonia to pH=10.

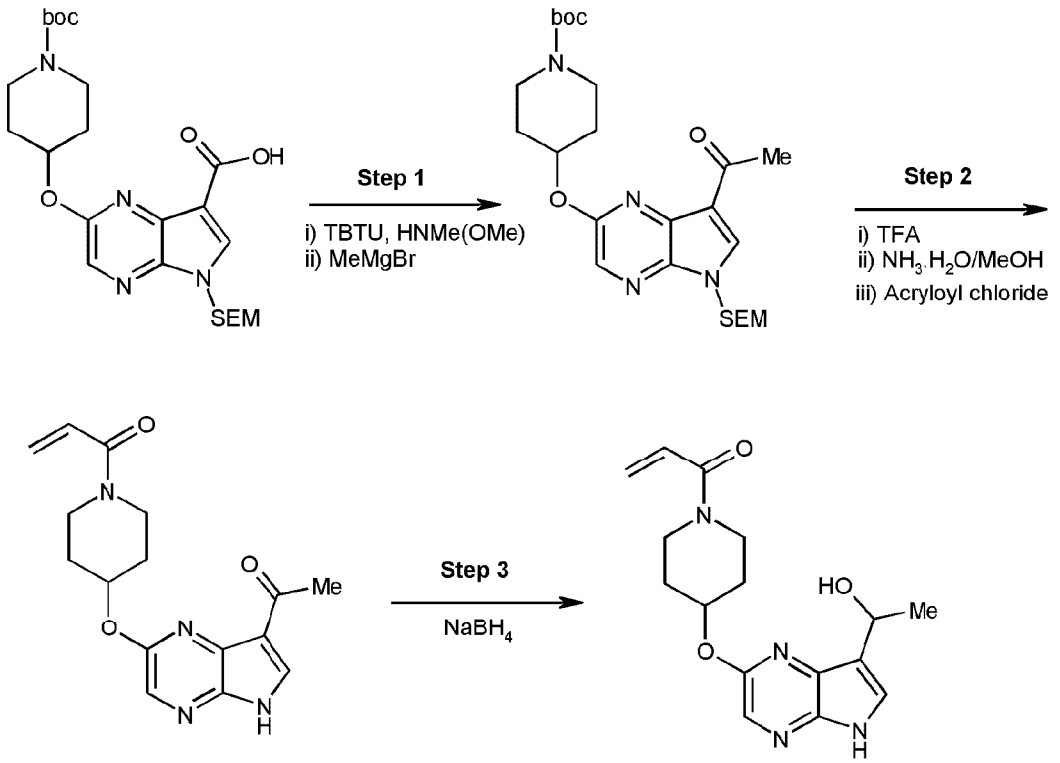
^{1}H NMR (400MHz, DMSO-d_6): δ ppm 13.24 (br m, 1H), 12.46 (br m, 1H), 8.30-7.90 (m, 2H), 6.90-6.80 (m, 1H), 6.15-6.05 (m, 1H), 5.74-5.39 (m, 3H), 4.00-3.80 (m, 1H), 3.56-3.45 (m, 2H), 2.40 (s, 3H), 2.10-2.00 (m, 2H), 1.80-1.60 (m, 2H).

Example 116 Steps 1 and 2

1-[4-({7-[5-(Propan-2-yl)-1H-1,2,4-triazol-3-yl]-5H-pyrrolo[2,3-b]pyrazin-2-yl}oxy)piperidin-1-yl]prop-2-en-1-one

The title compound was prepared according to the method described for **Example 115 Step 1 and Step 2** using isobutyrohydrazide. The residue was purified using silica gel column chromatography eluting with 0-10% MeOH in DCM followed by preparative HPLC as described below: Column: Phenomenex Gemini C18 250x21.2mm, 24 micron. Mobile phase: 21-41% MeCN in water modified with ammonia to pH=10. ^{1}H NMR (400MHz, DMSO-d_6): δ ppm 13.43-13.16 (br m, 1H), 12.45-12.34 (br m, 1H), 8.22 (br s, 1H), 7.96 (s, 1H), 6.90-6.83 (m, 1H), 6.14-6.10 (m, 1H), 5.78-5.67 (m, 2H), 3.97-3.89 (m, 2H), 3.55-3.41 (m, 2H), 3.05-3.00 (m, 1H), 2.10-2.00 (m, 2H), 1.80-1.60 (br m, 2H), 1.32-1.30 (d, 6H). MS m/z 382 $[M+H]^+$

Examples 117-119 were prepared as described in the Scheme below:



Example 117 Step 1

tert-Butyl 4-[(7-acetyl-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl)oxy]piperidine-1-carboxylate

To a solution of 2-{[1-(tert-butoxycarbonyl)piperidin-4-yl]oxy}-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid (**Example 114 Step 1**, 520 mg, 1.06 mmol), and TBTU (407 mg, 1.27 mmol) in DMF (30 mL) was added DIPEA (409 mg, 3.17 mmol) followed by N,O-dimethylhydroxylamine (206 mg, 3.17 mmol) at 0°C. The reaction was stirred at room temperature for 2 hours, quenched by the addition of water and extracted into EtOAc. The organic layer was collected, washed with brine, dried over sodium sulphate and concentrated *in vacuo*. The residue was purified using silica gel column chromatography eluting with 1-30% EtOAc in petroleum ether. The residue (600 mg, 1.12 mmol) was dissolved in THF (20 mL) and treated with methyl magnesium bromide (3M solution in THF, 0.75 mL, 2.24 mmol) at 0°C under nitrogen. The reaction was stirred for 2 hours before quenching with water and extracting into EtOAc. The organic layer was collected, washed with brine, dried over sodium sulphate and concentrated *in vacuo*. The residue was purified using silica gel column chromatography eluting with 1-20% EtOAc in petroleum ether to afford the title compound as a colourless oil (350 mg, 64%). MS m/z 513 $[M+Na]^+$

Example 117 Step 2

1-{4-[(7-Acetyl-5H-pyrrolo[2,3-b]pyrazin-2-yl)oxy]piperidin-1-yl}prop-2-en-1-one

The title compound was prepared according to the method described for **Example 1 Steps 5-7** using tert-butyl 4-[(7-acetyl-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl)oxy]piperidine-1-carboxylate (**Example 117 Step 1**). The residue was purified using silica gel column chromatography eluting with 5% MeOH in DCM. MS m/z 315 $[M+H]^+$

Example 117 Step 3

Racemic-1-(4-{[7-(1-hydroxyethyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]oxy}piperidin-1-yl)prop-2-en-1-one

To a solution of 1-{4-[(7-acetyl-5H-pyrrolo[2,3-b]pyrazin-2-yl)oxy]piperidin-1-yl}prop-2-en-1-one (**Example 117 Step 2**, 220 mg, 0.7 mmol) in MeOH (30 mL) was added sodium borohydride (106 mg, 2.8 mmol) at 0°C and the reaction was stirred for 2 hours. The reaction was concentrated *in vacuo* and purified using silica gel column chromatography eluting with 5-10% MeOH in DCM followed by preparative HPLC as described below to afford the title compound as a white solid (100 mg, 45%).

Column: Phenomenex Gemini C18 250x21.2mm, 10 micron

Mobile phase: 17-37% MeCN in water modified with ammonia to pH=10. ^{1}H NMR (400MHz, DMSO-d_6): δ ppm 11.65 (br s, 1H), 7.84 (s, 1H), 7.55 (s, 1H), 6.89-6.82 (m, 1H), 6.14-6.10 (m, 1H), 5.70-5.67 (m, 1H), 5.26-5.24 (m, 1H), 5.04-5.02 (m, 1H), 4.95-4.94 (m, 1H), 4.00-3.80 (m, 2H), 3.52-3.41 (m, 2H), 2.05-1.95 (m, 2H), 1.69-1.65 (m, 2H), 1.54-1.52 (d, 3H). MS m/z 339 $[M+Na]^+$

The racemate was separated into its enantiomers using the following chiral chromatography:

Column: Chiral Pak AD 250x30mm, 5 micron; Mobile phase A: 35% MeOH with 0.1% $NH_3.H_2O$ in supercritical CO_2.; Flow rate: 50 mL/min. LCMS QC: Column: Chiralpak AD-H 250x4.6mm, 5 micron.

Mobile phase: 5-40% MeOH with 0.05% DEA in supercritical CO_2

Flow rate: 2.35 mL/min

The enantiomers were assigned arbitrarily:

First eluting isomer: Example 118

1-[4-({7-[(1S)-1-hydroxyethyl]-5H-pyrrolo[2,3-b]pyrazin-2-yl}oxy)piperidin-1-yl]prop-2-en-1-one.

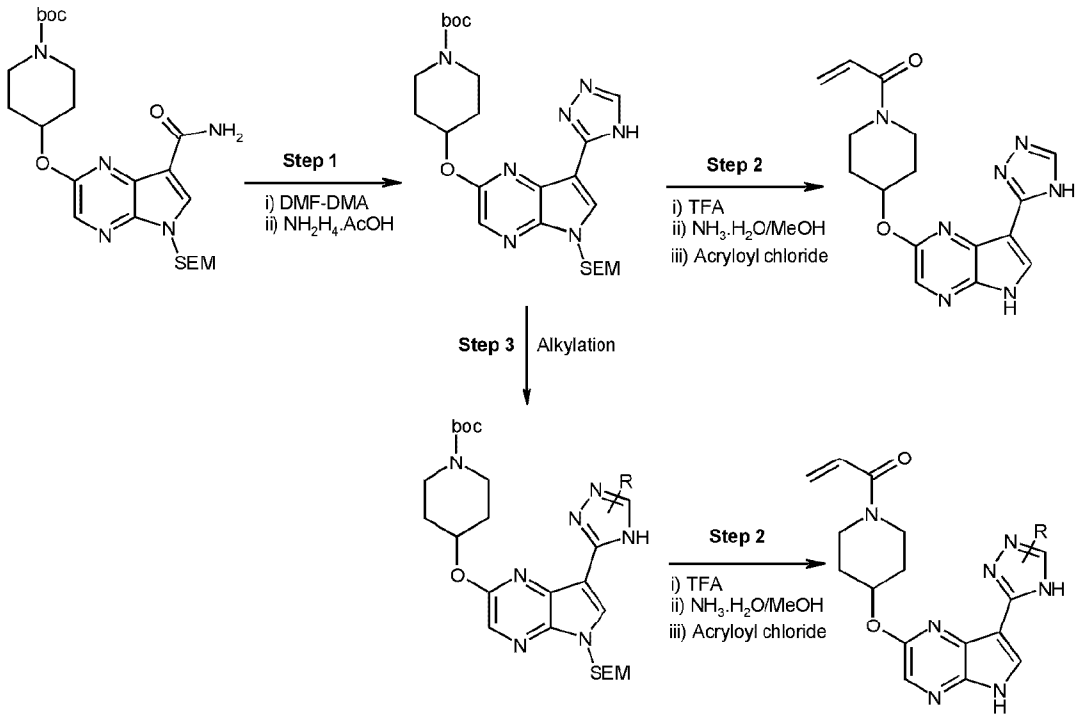
Rt = 8.35 minutes MS m/z 339 $[M+H]^+$

Second eluting isomer: Example 119

1-[4-({7-[(1R)-1-hydroxyethyl]-5H-pyrrolo[2,3-b]pyrazin-2-yl}oxy)piperidin-1-yl]prop-2-en-1-one.

Rt = 8.68 minutes MS m/z 339 $[M+H]^+$

Examples 120-470 were prepared as described in the Scheme:



Example 120 Step 1

tert-Butyl 4-{[7-(4H-1,2,4-triazol-3-yl)-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl]oxy}piperidine-1-carboxylate

A solution of tert-butyl 4-[(7-carbamoyl-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl)oxy]piperidine-1-carboxylate (**Example 114 Step 2**, 800 mg, 1.63 mmol) in DMF-DMA (10 mL) was heated to 80°C for 1 hour. The reaction was cooled and concentrated *in vacuo*. The residue was dissolved in AcOH (20 mL) and treated with hydrazine acetate (1.35 g, 14.65 mmol) the solution was heated to 95°C for 40 minutes before cooling, concentrating *in vacuo* and neutralising to pH=6-7 with saturated aqueous $NaHCO_3$ solution. The mixture was extracted into EtOAc (2 x 30 mL), the organic layers combined, washed with brine, dried over sodium sulphate and concentrated *in vacuo*. The residue was purified using silica gel column chromatography eluting with 0-12% MeOH in DCM to afford the title compound as an oil (500 mg, 68%).

MS m/z 538 $[M+Na]^+$

Example 120 Step 2

1-(4-{[7-(4H-1,2,4-Triazol-3-yl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]oxy}piperidin-1-yl)prop-2-en-1-one

The title compound was prepared according to the method described for **Example 1 Steps 5-7** using tert-butyl 4-{[7-(4H-1,2,4-triazol-3-yl)-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl]oxy}piperidine-1-carboxylate (**Example 120 Step 1**). The residue was purified using preparative HPLC. Column: Phenomenex Gemini C18 25x21.2mm*8uM. Mobile Phase: 10%-30% MeCN in water with 0.05% ammonia. ^1H NMR (400MHz, DMSO-d_6): δ ppm 8.22 (s, 1H), 8.12 (s, 1H), 7.96 (s, 1H),

6.88-6.81 (m, 1H), 6.14-6.09 (m, 1H), 5.69-5.66 (m, 2H), 4.00-3.86 (m, 2H), 3.60-3.40 (m, 4H), 2.10-1.95 (m, 2H), 1.75-1.55 (m, 2H). MS m/z 362 [M+Na]+

Example 121 Step 3

tert-Butyl 4-{[7-(1-ethyl-1H-1,2,4-triazol-5-yl)-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl]oxy}piperidine-1-carboxylate

To a solution of tert-butyl 4-{[7-(4H-1,2,4-triazol-3-yl)-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl]oxy}piperidine-1-carboxylate (**Example 120 Step 1**, 500 mg, 0.97 mmol) in anhydrous DMF (15 mL) was added sodium hydride (77 mg, 1.94 mmol) at 0°C. Ethyl iodide (227 mg, 1.45 mmol) was added and the reaction stirred at room temperature for 18 hours. The reaction was poured into ice-water (30 mL) and extracted into EtOAc (2 x 30 mL). The combined organic layers were washed with brine (30 mL), dried over sodium sulphate and concentrated *in vacuo*. The residue was purified using silica gel column chromatography eluting with 0-5% MeOH in DCM to afford the title compound as an oil (230 mg, 44%).

Example 121 Step 2

1-(4-((7-(1-ethyl-1H-1,2,4-triazol-5-yl)-5H-pyrrolo[2,3-b]pyrazin-2-yl)oxy)piperidin-1-yl)prop-2-en-1-one

The title compound was prepared according to the method described for **Example 1 Steps 5-7** using tert-butyl 4-{[7-(1-ethyl-1H-1,2,4-triazol-5-yl)-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl]oxy}piperidine-1-carboxylate (**Example 120 Step 3**). The residue was purified using silica gel column chromatography eluting with 2-10% MeOH in DCM followed by preparative HPLC as described below: Column: Phenomenex Gemini C18 250x21.2 mm, 8 micron. Mobile phase: 15-35% MeOH in water modified with 0.05% ammonia. ^{1}H NMR (400MHz, DMSO-d_6): δ ppm 8.87 (br s, 1H), 8.26 (s, 1H), 8.02 (s, 1H), 8.00 (s, 1H), 6.88-6.84 (m, 1H), 6.14-6.09 (m, 1H), 5.70-5.67 (m, 1H), 5.30-5.26 (m, 1H), 4.55-4.50 (m, 2H), 4.00-3.88 (m, 2H), 3.50-3.40 (m, 2H), 2.10-1.95 (m, 2H), 1.75-1.60 (m, 2H), 1.43-1.39 (t, 3H).

MS m/z 390 $[M+Na]^+$

HMBC NMR confirms no coupling from ethyl CH_2 to the outer carbon of the triazole.

Example 122 Step 3 (ii)

tert-Butyl 4-{[7-(1-methyl-1H-1,2,4-triazol-5-yl)-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl]oxy}piperidine-1-carboxylate

The title compound was prepared according to the method described for **Example 121 Step 3** using methyl iodide. NOe and HMBC confirm the 1-isomer was isolated.

Example 122 Step 2

1-(4-{[7-(1-Methyl-1H-1,2,4-triazol-5-yl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]oxy}piperidin-1-yl)prop-2-en-1-one

The title compound was prepared according to the method described for **Example 1 Step 5-7** using tert-butyl 4-{[7-(1-methyl-1H-1,2,4-triazol-5-yl)-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl]oxy}piperidine-1-carboxylate (**Example 122 Step 3**). The residue was purified using silica gel column chromatography eluting with 2-10% MeOH in DCM followed by preparative HPLC as

described below: Column: Phenomenex Gemini C18 250x21.2 mm, 8 micron. Mobile phase: 14-34% MeOH in water modified with 0.05% ammonia. ^{1}H NMR (400MHz, DMSO-d_6): δ ppm 12.65 (br s, 1H), 8.19 (s, 1H), 8.02 (s, 1H), 7.98 (s, 1H), 6.88-6.81 (m, 1H), 6.14-6.09 (m, 1H), 5.70-5.67 (m, 1H), 5.31-5.28 (m, 1H), 4.10 (s, 3H), 3.92-3.85 (m, 2H), 3.54-3.42 (m, 2H), 2.05-2.00 (m, 2H), 1.70-1.60 (m, 2H). MS m/z 376 $[M+Na]^+$

Example 123 Step 3

tert-Butyl 4-[(7-[1-(propan-2-yl)-1H-1,2,4-triazol-5-yl]-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl)oxy]piperidine-1-carboxylate and tert-butyl 4-[(7-[1-(propan-2-yl)-1H-1,2,4-triazol-3-yl]-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl)oxy]piperidine-1-carboxylate

The title compounds were prepared according to the method described for **Example 121 Step 3** using isopropyl iodide. The two isomers were separated using silica gel column chromatography eluting with 0-10% MeOH in DCM and structure elucidation was performed using NOe.

tert-butyl-4-[(7-[1-(propan-2-yl)-1H-1,2,4-triazol-5-yl]-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl)oxy]piperidine-1-carboxylate. ^{1}H NMR (400MHz, DMSO-d_6): δ ppm 8.36 (s, 1H), 8.08 (s, 1H), 8.04 (s, 1H), 5.67 (s, 2H), 5.23-5.14 (m, 2H), 3.70-3.67 (m, 2H), 3.58-3.55 (t, 2H), 3.17-3.15 (m, 2H), 2.00-1.97 (m, 2H), 1.65-1.40 (m, 2H), 1.44-1.40 (m, 14H), 0.83-0.80 (t, 2H), -0.11 (s, 9H).

tert-butyl-4-[(7-[1-(propan-2-yl)-1H-1,2,4-triazol-3-yl]-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl)oxy]piperidine-1-carboxylate

^{1}H NMR (400MHz, DMSO-d_6): δ ppm 8.55 (s, 1H), 8.30 (s, 1H), 8.04 (s, 1H), 5.67 (s, 1H), 5.23-5.19 (m, 1H), 4.67-4.60 (m, 1H), 3.78-3.74 (m, 2H), 3.54-3.50 (m, 2H), 3.25-3.10 (m, 2H), 2.15-2.10 (m, 2H), 1.75-1.60 (m, 2H), 1.51 (d, 6H), 1.41 (s, 9H), 0.84-0.80 (t, 2H), -0.11 (s, 9H).

Example 123 Step 2

1-[4-({7-[1-(Propan-2-yl)-1H-1,2,4-triazol-5-yl]-5H-pyrrolo[2,3-b]pyrazin-2-yl}oxy)piperidin-1-yl]prop-2-en-1-one

The title compound was prepared according to the method described for **Example 1 Step 5-7** using tert-butyl 4-[(7-[1-(propan-2-yl)-1H-1,2,4-triazol-5-yl]-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl)oxy]piperidine-1-carboxylate (**Example 123 Step 3**). The residue was purified by preparative HPLC as described below: Column: Phenomenex Gemini C18 250x21.2 mm, 8 micron. Mobile phase: 27-47% MeOH in water modified with 0.05% ammonia

NOe and HMBC confirm the title isomer was isolated. ^{1}H NMR (400MHz, DMSO-d_6): δ ppm 12.61 (br s, 1H), 8.15 (s, 1H), 8.01 (s, 1H), 8.00 (s, 1H), 6.88-6.80 (m, 1H), 6.13-6.08 (m, 1H), 5.69-5.65 (m, 1H), 5.29-5.18 (m, 2H), 3.95-3.90 (m, 2H), 3.50-3.43 (m, 2H), 2.00-1.90 (m, 2H), 1.70-1.60 (m, 2H), 1.44-1.43 (m, 6H). MS m/z 382 $[M+H]^{+ok}$

Example 124 Step 2

1-[4-({7-[1-(Propan-2-yl)-1H-1,2,4-triazol-3-yl]-5H-pyrrolo[2,3-b]pyrazin-2-yl}oxy)piperidin-1-yl]prop-2-en-1-one

The title compound was prepared according to the method described for **Example 1 Steps 5-7** using tert-butyl 4-[(7-[1-(propan-2-yl)-1H-1,2,4-triazol-3-yl]-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl)oxy]piperidine-1-carboxylate (**Example 123 Step 3**). The residue was purified by preparative HPLC as described below:

Column: Phenomenex Gemini C18 250x21.2 mm, 8 micron

Mobile phase: 19-39% MeOH in water modified with 0.05% ammonia

^{1}H NMR (400MHz, DMSO-d_6): δ ppm 8.53 (s, 1H), 8.09 (s, 1H), 7.93 (s, 1H), 6.90-6.83 (m, 1H), 6.14-6.10 (m, 1H), 5.70-5.67 (m, 1H), 5.29-5.25 (m, 1H), 4.65-4.60 (m, 1H), 4.05-3.92 (m, 2H), 3.49-3.43 (m, 2H), 2.19-2.17 (m, 2H), 1.70-1.65 (m, 2H), 1.52-1.50 (d, 6H). MS m/z 382 $[M+H]^+$**Example 125 Step 3**

tert-Butyl 4-{[7-(1-ethyl-1H-1,2,4-triazol-3-yl)-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl]oxy}piperidine-1-carboxylate

To a solution of tert-butyl 4-{[7-(4H-1,2,4-triazol-3-yl)-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl]oxy}piperidine-1-carboxylate (**Example 120 Step 1**, 300 mg, 0.582 mmol) in anhydrous THF (10 mL) was added LiHMDS (1M in THF, 2.33 mL, 2.33 mmol). The reaction was stirred at room temperature for 30 minutes before the addition of ethyl iodide (272 mg, 1.75 mmol) and stirring at room temperature for 18 hours. Additional LiHMDS (1.16 mL, 1.16 mmol) was added followed by ethyl iodide (136 mg, 0.873 mmol) and the reaction was stirred at room temperature for 18 hours. Further equivalents of LiHMDS (1.16 mL, 1.16 mmol) followed by ethyl iodide (136 mg, 0.873 mmol) were added and the reaction was stirred at room temperature for 18 hours.

The reaction was poured onto ice-water (20 mL) and extracted into EtOAc (2 x 20 mL). The organic layers were combined, washed with brine (20 mL), dried over sodium sulphate and concentrated *in vacuo*. The residue was purified using silica gel column chromatography eluting with 20-100% EtOAc in petroleum ether to afford the title compound (60 mg, 22%).

Example 125 Step 2

1-(4-{[7-(1-Ethyl-1H-1,2,4-triazol-3-yl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]oxy}piperidin-1-yl)prop-2-en-1-one

The title compound was prepared according to the method described for **Example 1 Step 5-7** using tert-butyl 4-{[7-(1-ethyl-1H-1,2,4-triazol-3-yl)-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl]oxy}piperidine-1-carboxylate (**Example 125 Step 3**The residue was purified by preparative HPLC as described below: Column: Phenomenex Gemini C18 250x21.2 mm, 8 micron. Mobile phase: 12-42% MeOH in water modified with 0.05% ammonia

HMBC confirms the title isomer was isolated. (CH_2 of ethyl signals with C in triazole).

^{1}H NMR (400MHz, DMSO-d_6): δ ppm 12.28 (br s, 1H), 8.50 (s, 1H), 8.23 (s, 1H), 7.93 (s, 1H), 6.89-6.82 (m, 1H), 6.14-6.09 (m, 1H), 5.70-5.67 (m, 1H), 5.31-5.28 (m, 1H), 4.26-4.21 (m, 2H), 4.00-3.80 (m, 2H), 3.50-3.46 (m, 2H), 2.10-2.00 (m, 2H), 1.80-1.60 (m, 2H), 1.31-1.29 (t, 3H).

MS m/z 390 $[M+Na]^+$

Example 121 Step 3

tert-Butyl 4-{[7-(1-methyl-1H-1,2,4-triazol-3-yl)-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl]oxy}piperidine-1-carboxylate

The title compound was prepared according to the method described for **Example 125 Step 3** using methyl iodide and taken on directly to the next step.

Example 126 Step 2

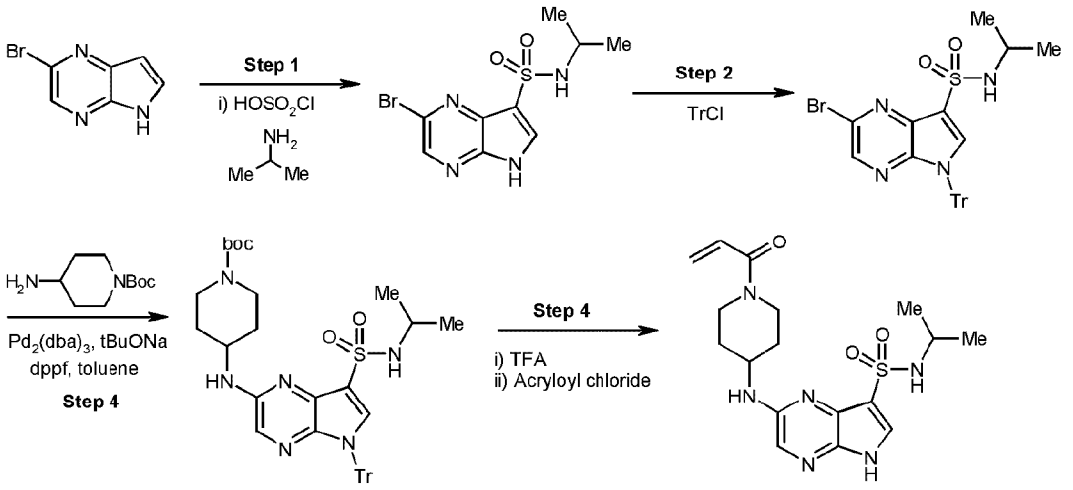
1-(4-{[7-(1-Methyl-1H-1,2,4-triazol-3-yl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]oxy}piperidin-1-yl)prop-2-en-1-one

The title compound was prepared according to the method described for **Example 1 Steps 5-7** using tert-butyl 4-{[7-(1-methyl-1H-1,2,4-triazol-3-yl)-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazin-2-yl]oxy}piperidine-1-carboxylate (**Example 126 Step 3**). The residue was purified by preparative HPLC as described below: Column: Phenomenex Gemini C18 250x21.2 mm, 8 micron. Mobile phase: 10-40% MeOH in water modified with 0.05% ammonia

HMBC and NOe confirms the title isomer was isolated. (CH_3 of methyl signals with C in triazole).

^{1}H NMR (400MHz, DMSO-d_6): δ ppm 8.45 (s, 1H), 8.10 (s, 1H), 7.93 (s, 1H), 6.89-6.82 (m, 1H), 6.14-6.10 (m, 1H), 5.70-5.67 (m, 1H), 5.34-5.32 (m, 1H), 3.91-3.80 (m, 5H), 3.60-3.50 (br m, 2H), 2.20-2.00 (m, 2H), 1.75-1.60 (m, 2H). MS m/z 376 $[M+Na]^+$

Example 127 was prepared as described in the following Scheme:



Example 127 Step 1

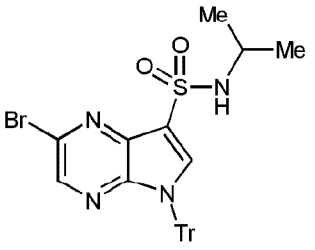
2-Bromo-N-isopropyl-5H-pyrrolo[2,3-b]pyrazine-7-sulfonamide

2-bromo-5H-pyrrolo[2,3-b]pyrazine (5 g, 25 mmol) was added to chlorosulfonic acid (20 mL) at 0°C. The reaction was heated to 100-120°C for 2.5 hours before cooling and pouring into ice-water (80 mL). The solution was extracted into EtOAc (2 x 100 mL), the organic layers combined, washed with brine, dried over sodium sulphate and concentrated *in vacuo*. The residue was added to a solution of

isopropylamine (881 mg, 15 mmol) and triethylamine (2.66 g, 26 mmol) in DCM (60 mL) at 0°C. The reaction was stirred at 0°C for 3 hours, diluted with water (50 mL) and extracted into EtOAc (2 x 80 mL). The organic layers were combined, washed with brine, dried over sodium sulphate and concentrated *in vacuo*. The solid was triturated with TBME to afford the title compound (2 g, 49% over 2 steps) as a brown solid that was used directly in the next step.

Example 127 Step 2

2-Bromo-N-isopropyl-5-trityl-5H-pyrrolo[2,3-b]pyrazine-7-sulfonamide



To a solution of 2-bromo-N-isopropyl-5H-pyrrolo[2,3-b]pyrazine-7-sulfonamide (**Example 127 Step 1**, 1.7 g, 5.33 mmol) and cesium carbonate (5.21 g, 16 mmol) in anhydrous DMF (45 mL) was added trityl chloride (1.51 g, 5.43 mmol) at room temperature and the reaction was stirred at 40°C for 18 hours. The reaction was diluted with water (30 mL) and extracted into EtOAc (2 x 30 mL). The organic layers were combined, washed with brine, dried over sodium sulphate and concentrated *in vacuo*. The residue was purified using silica gel column chromatography eluting with 0-30% EtOAc in petroleum ether to afford the title compound as an off-yellow solid (2.8 g, 94%) that was taken on directly to the next step.

Example 127 Step 3

tert-Butyl 4-((7-(N-isopropylsulfamoyl)-5-trityl-5H-pyrrolo[2,3-b]pyrazin-2-yl)amino)piperidine-1-carboxylate

A suspension of 2-bromo-N-isopropyl-5-trityl-5H-pyrrolo[2,3-b]pyrazine-7-sulfonamide (**Example 127 Step 2**, 500 mg, 0.89 mmol), tert-butyl 4-aminopiperidine-1-carboxylate (357 mg, 1.78 mmol) and cesium carbonate (580 mg, 1.78 mmol) in toluene (20 mL) was purged with nitrogen 4 times. Dppf (99 mg, 0.178 mmol) and $Pd_2(dba)_3$ (163 mg, 0.178 mmol) was added and the reaction was heated at 110°C for 18 hours. The reaction was concentrated *in vacuo* and purified using silica gel column chromatography eluting with 0-100% EtOAc in petroleum ether to afford the title compound as a brown solid (500 mg, 83%). ^{1}H NMR (400MHz, DMSO-d_6): δ ppm 7.40-7.30 (m, 11H), 7.14-6.90 (m, 8H), 3.90-3.81 (m, 4H), 3.00-2.80 (br m, 2H), 1.89-1.86 (m, 2H), 1.39 (s, 9H), 1.31-1.23 (m, 2H), 0.98-0.97 (d, 6H).

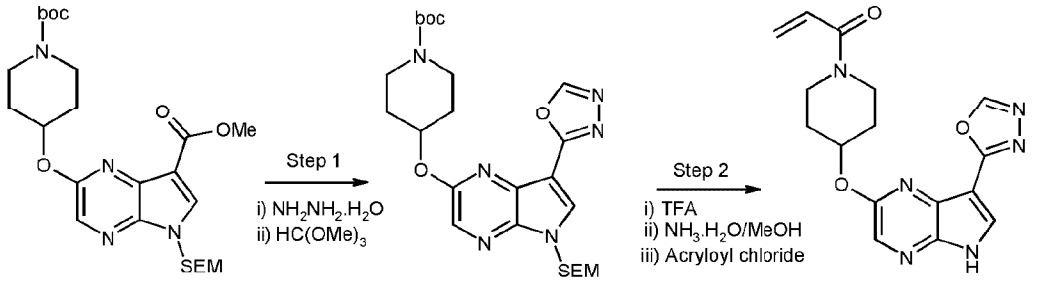
Example 127 Step 4

2-[(1-Acryloylpiperidin-4-yl)amino]-N-(propan-2-yl)-5H-pyrrolo[2,3-b]pyrazine-7-sulfonamide

tert-butyl 4-((7-(N-isopropylsulfamoyl)-5-trityl-5H-pyrrolo[2,3-b]pyrazin-2-yl)amino)piperidine-1-carboxylate (**Example 127 Step 3**, 400 mg, 0.587 mmol) was dissolved in DCM (32 mL) and treated

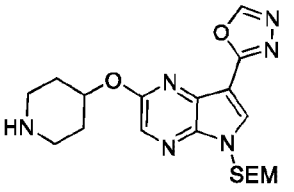
with TFA (10 mL) at 0°C. The reaction was stirred at room temperature for 18 hours and concentrated *in vacuo*. The residue was dissolved in THF (20 mL) and water (20 mL) and treated with DIPEA (229 mg, 1.77 mmol) followed by acryloyl chloride (91 mg, 1 mmol) at 0°C. The reaction was stirred at 0°C for 2 hours and then extracted into EtOAc three times. The organic layers were combined, washed with brine, dried over sodium sulphate and concentrated *in vacuo*. The residue was purified using silica gel column chromatography eluting with 0-10% MeOH in DCM followed by preparative HPLC to afford the title compound as a yellow solid (110 mg, 47%). Column: Phenomenex Gemini C18*21.2mm*8µm; Mobile Phase: 24%-44% MeCN/ H2O (0.05 % ammonia). ^{1}H NMR (400MHz, DMSO-d_6): δ ppm 12.20 (br s, 1H), 7.80 (s, 1H), 7.70 (s, 1H), 6.96 -6.82 (m, 3H), 6.12-6.08 (m, 1H), 5.68-5.65 (m, 1H), 4.30-4.27 (m, 1H), 4.10-4.01 (m, 2H), 3.81-3.76 (m, 1H), 3.25-3.20 (m, 1H), 2.96-2.90 (m, 1H), 2.00-1.90 (m, 2H), 1.40-1.30 (m, 2H), 1.01-1.00 (d, 6H). MS m/z 415 $[M+Na]^+$

Example 128 was prepared as described in the following Scheme:



Example 128 Step 1

2-(2-(piperidin-4-yloxy)-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-b]pyrazin-7-yl)-1,3,4-oxadiazole



To a solution of methyl 2-{[1-(tert-butoxycarbonyl)piperidin-4-yl]oxy}-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazine-7-carboxylate (**Example 108 Step 1 intermediate**, 500 mg, 0.66 mol) in EtOH (6 mL) was added hydrazine hydrate (414 mg, 6.61 mmol) and the reaction was heated to 110°C under microwave irradiation for 1 hour. The reaction was cooled, concentrated *in vacuo* and dissolved in $CH(OMe)_3$ (8 mL). To the solution was added p-toluenesulfonic acid (22.6 mg, 0.119 mmol) and the reaction was heated to 140°C under microwave irradiation for 1 hour. The reaction was cooled, concentrated *in vacuo* and purified using silica gel column chromatography eluting with 12-50% EtOAc in petroleum ether to afford the title compound as a yellow oil (90% over 2 steps).

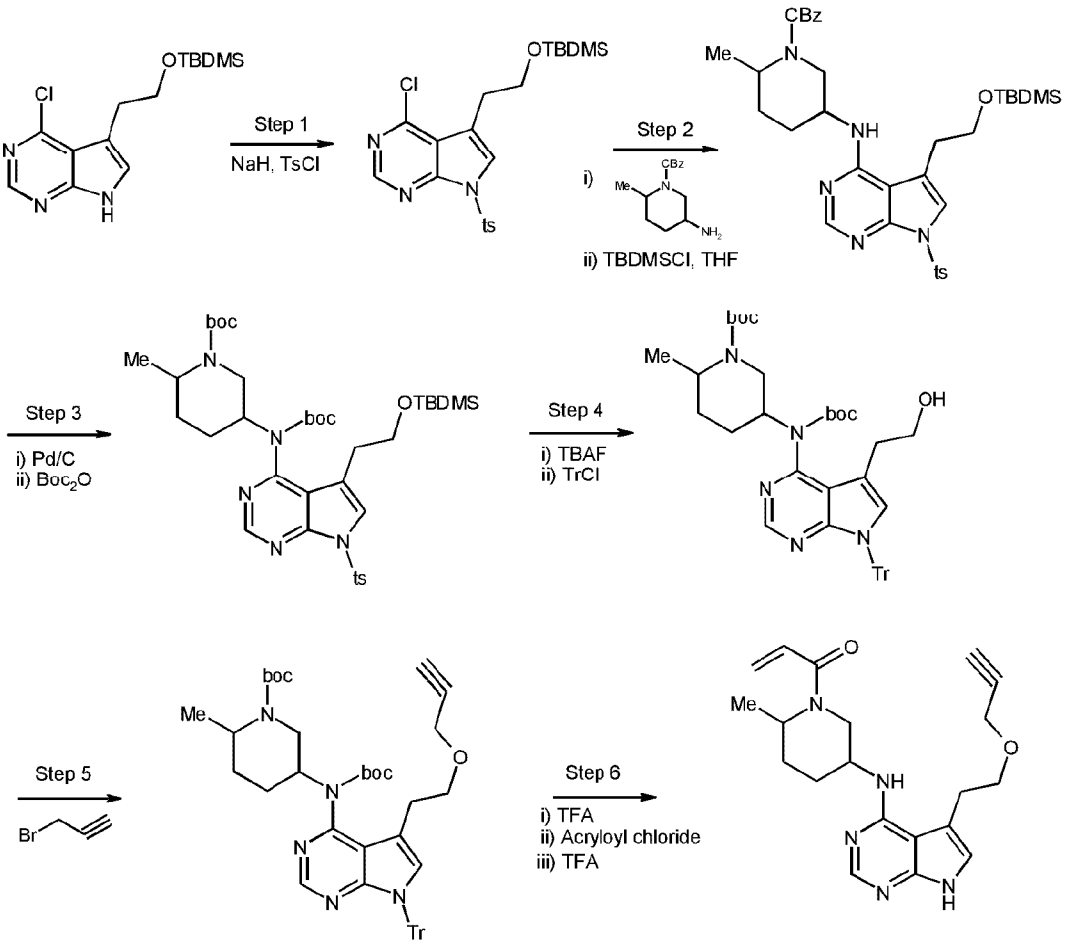
MS m/z 417 $[M+H]^+$

Example 128 Step 2

1-(4-{[7-(1,3,4-Oxadiazol-2-yl)-5H-pyrrolo[2,3-b]pyrazin-2-yl]oxy}piperidin-1-yl)prop-2-en-1-one

The title compound was prepared according to the method described for **Example 127 Step 4** using 2-(2-(piperidin-4-yloxy)-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-b]pyrazin-7-yl)-1,3,4-oxadiazole (**Example 128 Step 1**). The residue was purified using silica gel column chromatography eluting with 0-8% MeOH in DCM followed by preparative HPLC as described below: Column: Phenomenex Gemini C18 250x21.2 mm, 8 micron. Mobile phase: 16-36% MeCN in water modified with 0.05% ammonia. ^{1}H NMR (400MHz, DMSO-d_6): δ ppm 12.86 (br s, 1H), 9.26 (s, 1H), 8.50 (s, 1H), 8.05 (s, 1H), 6.90-6.80 (m, 1H), 6.14-6.10 (m, 1H), 5.70-5.67 (m, 1H), 5.40-5.30 (m, 1H), 4.00-3.80 (br m, 2H), 3.55-3.45 (m, 2H), 2.10-2.00 (m, 2H), 1.80-1.60 (m, 2H). MS m/z 363 $[M+Na]^+$

Examples 129-131 were prepared as described in the following Scheme:



Example 129 Step 1

5-(2-((tert-Butyldimethylsilyl)oxy)ethyl)-4-chloro-7-tosyl-7H-pyrrolo[2,3-d]pyrimidine

To a solution of 5-(2-{[tert-butyl(dimethyl)silyl]oxy}ethyl)-4-chloro-7H-pyrrolo[2,3-d]pyrimidine (**WO 2005021568**, 6 g, 19.24 mmol) in DMF (50 mL) at 0°C was added sodium hydride (769 mg, 19.2 mmol) and the reaction was stirred at 0°C for 10 minutes. Tosyl chloride (3.67 g, 19.2 mmol) was added and the reaction stirred at room temperature for 3 hours. The reaction was quenched by the addition of ice-water (100 mL) and extracted into EtOAc (2 x 100 mL). The combined organic layers were washed with brine (200 mL), dried over sodium sulphate and concentrated *in vacuo*. The residue was purified using silica gel column chromatography eluting with 5-35% EtOAc in petroleum ether to afford the title compound as a colourless oil (7.3 g, 81%). MS m/z 466 $[M+H]^+$

Example 129 Step 2

Benzyl (2S,5R)-5-((5-(2-((tert-butyldimethylsilyl)oxy)ethyl)-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-methylpiperidine-1-carboxylate

To a solution of 5-(2-((tert-butyldimethylsilyl)oxy)ethyl)-4-chloro-7-tosyl-7H-pyrrolo[2,3-d]pyrimidine (**Example 129 Step 1**, 2.25 g, 4.83 mmol) in nBuOH (30 mL) was added benzyl (2S,5R)-5-amino-2-methylpiperidine-1-carboxylate (1 g, 4.02 mmol) followed by DIPEA (1 g, 16.1 mmol). The reaction was heated at 135°C for 96 hours. The reaction was cooled and partitioned between EtOAc (30 mL) and water (20 mL). The aqueous layer was extracted with EtOAc (30 mL) and the organic layers were combined, washed with water and brine (30 mL), dried over sodium sulphate and concentrated *in vacuo*. The residue was purified using silica gel column chromatography eluting with 30-100% EtOAc in petroleum ether to afford benzyl 5-((5-(2-hydroxyethyl)-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-methylpiperidine-1-carboxylate. The intermediate (900 mg, 1.6 mmol) was re-protected by dissolving in THF (10 mL) and treating with imidazole (217 mg, 3.19 mmol) followed by TBDMSCl (479 mg, 3.19 mmol) and the reaction was stirred at room temperature for 24 hours. The reaction was concentrated *in vacuo* and partitioned between EtOAc (20 mL) and water (10 mL). The organic layer was washed with 0.5M HCl (aq), brine (100 mL) and concentrated *in vacuo*. The residue was purified using silica gel column chromatography eluting with 0-50% EtOAc in petroleum ether to afford the title compound as a colourless oil (900 mg, 60% over 2 steps) that was taken on directly to the next step.

Example 129 Step 3

tert-butyl (2S,5R)-5-((5-(2-((tert-butyldimethylsilyl)oxy)ethyl)-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-methylpiperidine-1-carboxylate

The title compound was prepared according to the method described for **Example 91 Step 2** using tert-butyl (2S,5R)-5-((5-(2-((tert-butyldimethylsilyl)oxy)ethyl)-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-methylpiperidine-1-carboxylate (**Example 129 Step 2**).

MS m/z 644 $[M\text{-Boc}+H]^+$

Example 129 Step 4

tert-Butyl (2S,5R)-5-((tert-butoxycarbonyl)(5-(2-hydroxyethyl)-7-trityl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-methylpiperidine-1-carboxylate

To a solution of tert-butyl (2S,5R)-5-((5-(2-((tert-butyldimethylsilyl)oxy)ethyl)-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-methylpiperidine-1-carboxylate (**Example 129 Step 3**, 450 mg, 0.6 mmol)

in THF (10 mL) was added TBAF (316 mg, 1.21 mmol) dropwise at 35°C. The reaction was stirred at this temperature for 12 hours before being washed with brine (2 x 30 mL) and concentrating *in vacuo*. The residue was purified using silica gel column chromatography eluting with 30-70% EtOAc in petroleum ether. The residue was dissolved in DMF (5 mL) and treated with cesium carbonate (452 mg, 1.39 mmol) followed by trityl chloride (155 mg, 0.55 mmol). The reaction was stirred at room temperature for 12 hours and filtered. The filtrate was partitioned between water (20 mL) and EtOAc (20 mL). The aqueous layer was washed with EtOAc (2 x 30 mL), the organic layers were combined, washed with brine (50 mL), dried over sodium sulphate and concentrated *in vacuo*. The residue was purified using silica gel column chromatography eluting with 0-20% MeOH in DCM to afford the title compound as a yellow solid (350 mg, 80% over 2 steps). MS m/z 717 $[M+H]^+$

Example 129 Step 5

tert-Butyl (2S,5R)-5-((tert-butoxycarbonyl)(5-(2-(prop-2-yn-1-yloxy)ethyl)-7-trityl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-methylpiperidine-1-carboxylate

To a solution of tert-butyl (2S,5R)-5-((tert-butoxycarbonyl)(5-(2-hydroxyethyl)-7-trityl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-methylpiperidine-1-carboxylate (Example 473 Step 4, 300 mg, 0.418 mmol) in anhydrous THF (10 mL) was added sodium hydride (60% dispersion in oil, 50 mg, 1.25 mmol) at 0°C. The reaction was stirred at this temperature for 30 minutes before the addition of propargyl bromide (99 mg, 0.84 mmol). The reaction was stirred at room temperature for 12 hours. The reaction was quenched with water (2 mL), concentrated *in vacuo* and purified using silica gel column chromatography eluting with 0-80% EtOAc in petroleum ether to afford the title compound as a yellow solid (160 mg, 51%). MS m/z 756 $[M+H]^+$

Example 129 Step 6

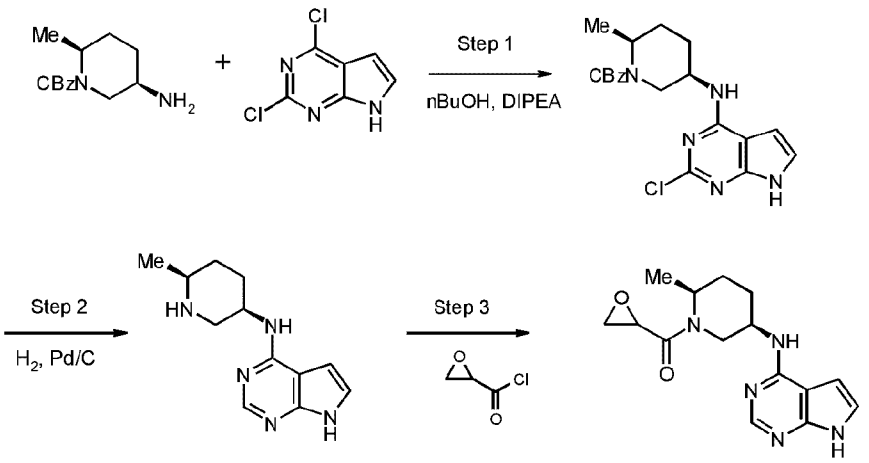
1-((2S,5R)-2-Methyl-5-((5-(2-(prop-2-yn-1-yloxy)ethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidin-1-yl)prop-2-en-1-one

The title compound was prepared according to the method described for **Example 100 Step 5** using tert-butyl (2S,5R)-5-((tert-butoxycarbonyl)(5-(2-(prop-2-yn-1-yloxy)ethyl)-7-trityl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-methylpiperidine-1-carboxylate (**Example 129 Step 5**). The residue was purified using silica gel column chromatography eluting with 0-10% MeOH in DCM.

Example 131

1-[(2S,5R)-2-Methyl-5-({5-[2-(prop-2-yn-1-yloxy)ethyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)piperidin-1-yl]prop-2-en-1-one. ^{1}H NMR (400 MHz, DMSO-d_6) d ppm 1.22 (br. s., 3 H) 1.56 - 1.98 (m, 4 H) 2.68 (br. s., 1 H) 3.05 (br. s., 2 H) 3.41 - 3.51 (m, 1 H) 3.70 (t, *J*=6.27 Hz, 2 H) 4.07 (br. s., 1 H) 4.22 - 4.24 (m, 2 H) 4.34 - 4.90 (m, 2 H) 5.68 (d, *J*=8.53 Hz, 1 H) 6.10 (dd, *J*=16.81, 2.26 Hz, 1 H) 6.27 (br. s., 1 H) 6.80 (br. s., 1 H) 6.94 (s, 1 H) 8.09 (br. s., 1 H) 11.37 (br. s., 1 H). Rt = 3.12 minutes (HPLC) MS m/z 390 $[M+Na]^+$; Rt = 4.28 (Chiral-SFC)

Example 132 was prepared as described in the following Scheme:



Example 132 Step 1

Benzyl (2S,5R)-5-((2-chloro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-methylpiperidine-1-carb-oxylate

The title compound was prepared according to the method described for **Example 94 Step 1** using benzyl (2S,5R)-5-amino-2-methylpiperidine-1-carboxylate (**WO2010016005**). The residue was triturated with TBME and taken on directly to the next step.

Example 132 Step 2

N-((3R,6S)-6-Methylpiperidin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine (example 5, step 7

To a solution of benzyl (2S,5R)-5-((2-chloro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-methylpiperidine-1-carboxylate (**Example 132 Step 1**, 39 g, 0.097 mol) in MeOH (1 L) and THF (300 mL) was added Pd/C (8 g) and the reaction was hydrogenated under 50 psi at 35°C for 5 days. The reaction was filtered through Celite™ and re-hydrogenated with further Pd/C (8 g) under 5o psi at 35°C for 5 days. The reaction was filtered through Celite™ and concentrated *in vacuo* to afford the title compound as a white solid (31 g, 90%). ^{1}H NMR (400MHz, D_2O): δ ppm 7.93 (s, 1H), 7.05-7.04 (m, 1H), 6.45-6.40 (m, 1H), 4.21-4.19 (m, 1H), 3.55-3.51 (m, 1H), 3.29-3.14 (m, 2H), 1.93-1.73 (m, 4H), 1.24-1.23 (d, 3H).

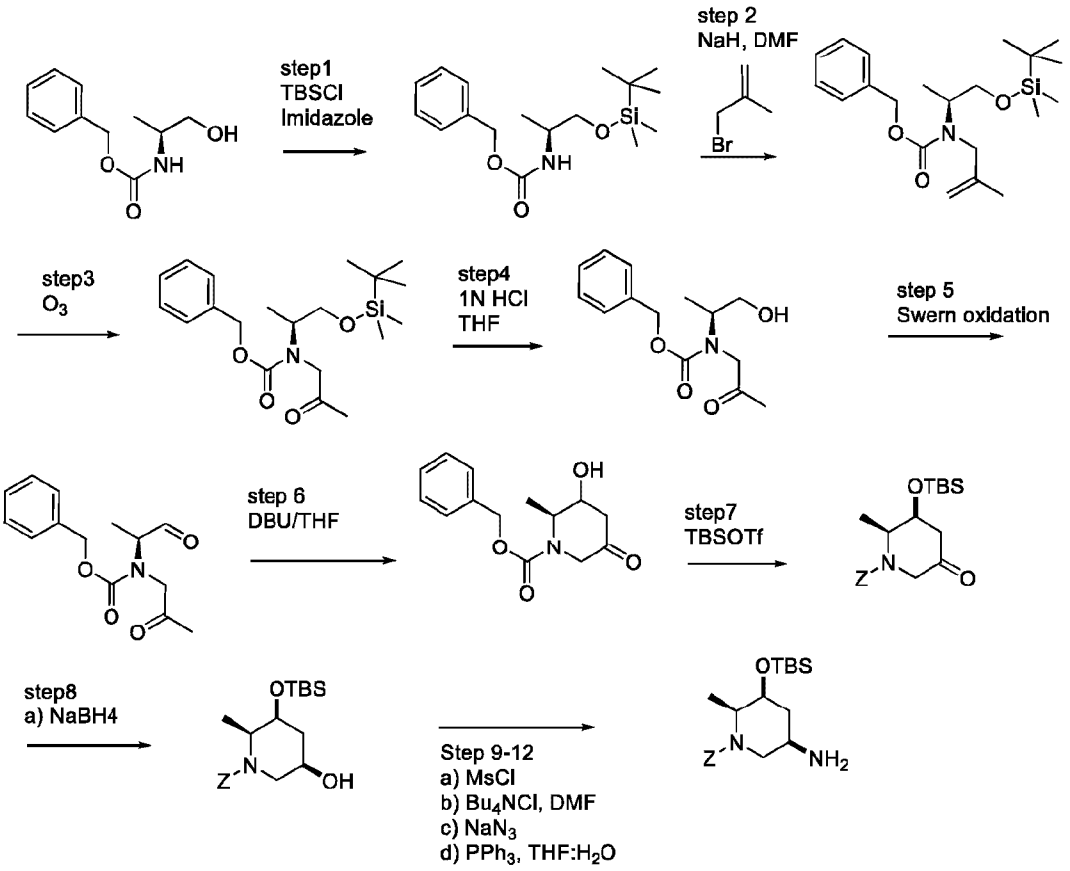
Example 132 Step 3

Racemic-[(2S,5R)-2-methyl-5-(7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)piperidin-1-yl](oxiran-2-yl)methanone

To a solution of racemic oxirane-2-carboxylic acid (114 mg, 0.89 mmol) in DCM (5 mL) was added a solution of oxalyl chloride (0.45 mL, 0.90 mmol) in DCM (2 mL) followed by DMF (1 drop). The reaction was stirred at room temperature for 30 minutes before the addition of a solution of N-((3R,6S)-6-methylpiperidin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine (see **Example 132; Step 2**, 200 mg, 0.86 mmol) and DIPEA (0.6 mL, 3.46 mmol) in DCM (2 mL). The reaction was stirred at room temperature for 1 hour before pouring into saturated aqueous $NaHCO_3$ solution and DCM. The organic layer was collected, dried over sodium sulphate and concentrated *in vacuo*. The residue was purified using silica gel column chromatography eluting with 5-30% MeOH in DCM to afford the title compound (60 mg,

23%). ^{1}H NMR (400 MHz, DMSO-d_6) d ppm 1.13 - 1.37 (m, 3 H) 1.59 - 1.95 (m, 3 H) 2.57 - 3.06 (m, 3 H) 3.74 - 3.97 (m, 1 H) 3.99 - 4.30 (m, 2 H) 4.47 (br. s., 1 H) 4.72 (br. s., 1 H) 6.56 (d, *J*=6.63 Hz, 1 H) 7.10 (d, *J*=2.73 Hz, 1 H) 7.20 - 7.39 (m, 1 H) 7.98 - 8.18 (m, 1 H) 11.52 (br. s., 1 H). MS m/z 302 $[M+H]^+$

Example 133 was prepared as described in the following Scheme:



Example 133 Step 1

Benzyl (S)-(1-((tert-butyldimethylsilyl)oxy)propan-2-yl)carbamate

To a round bottom flask containing (benzyl (S)-(1-hydroxypropan-2-yl)carbamate (5g, 23.9 mmol) dissolved in 50 mL of DCM was added imidazole (1.79 g, 26.3 mmol) and TBDMS-Cl (3.7 g, 23.9 mmol). The reaction was stirred at room temperature overnight. LCMS indicated the reaction was complete. The reaction was diluted with water (100mL) and the mixture separated. The organic layer was collected and concentrated to give the desired product as a clear oil (8.2 g, 100%). ^{1}H NMR ($CDCl_3$): d 7.33-7.30 (5H, m), 5.06 (2H, s), 3.80-3.71(1H, m), 3.59-3.47(2H, m), 1.12(2H, d), 0.85 (9H, s), 0.00(s, 6H). Rt = 1.14 minutes MS m/z 324.3 $[M+H]^+$

Example 133 Step 2

Benzyl (S)-(1-((tert-butyldimethylsilyl)oxy)propan-2-yl)(2-methylallyl)carbamate

To a round bottom flask containing (**Example 133**, **Step 1**, 7.7 g, 23.8 mmol) in DMF (100 mL) at 0 °C was added NaH (60% in mineral oil, 1.9 g, 47.6 mmol) in portions. After 30 min, 3-bromo-2-methyl-propene (6.6 g, 47.6 mmol) was added. After stirring for 1.5 h, NH_4Cl (10%, 100 mL) was added and the aqueous mixture was extracted with EtOAc (3x). The combined organic extracts were washed with brine, dried (Na_2SO_4) and solvent removed to give crude product (9 g). The crude material was purified by chromatography (silica gel (combiflash, 80g gold column, 0 to 10% EA in Hept) to give 6.1 g (68 %) of desired product. ^1H NMR ($CDCl_3$) ,d 7.33-7.30 (5H, m), 5.15-5.05 (2H, m)4.79 (2H, s), 4.0-3.43(5H, m), 1.74-1.62 (3H, m), 1.21-1.09(2H, m), 0.85 (9H, s), 0.00(s, 6H). LCMS = 378.4 $[M+H]^+$ (1.28 minutes)

Example 133 Step 3

Benzyl (S)-(1-((tert-butyldimethylsilyl)oxy)propan-2-yl)(2-oxopropyl)carbamate

To a round bottom flask containing (**Example 133, Step 2,** 6.1 g, 16.2 mmol) in DCM/MeOH (50 mL:50 mL) at -78 ◦C was bubbled O_3. After 5.5 hr, the solution became a light blue color and then Me_2S (3.6 mL, 48.5 mmol) was added and the mixture allowed to warm to room temperature overnight. The solvent was removed in vacuo to give the crude product (7 g, 110%) which was taken directly to the next step. LC/MS: Rt = 1.14 min; MS m/z 380.4 [M+H]+

Example 133 Step 4

Benzyl (S)-(1-hydroxypropan-2-yl)(2-oxopropyl)carbamate

To a solution of (**Example 133, Step 3**, 9.95 g, 26.21 mmol) in THF (400 mL) was added HCl (1N, 105 mL, 105mmol, 4 eq). The reaction was stirred for 3 hrs and then concentrated in vacuo. The aqueous mixture was extracted with DCM (3x). The organic extracts were collected and washed with $NaHCO_3$ (aq), dried (Na_2SO_4) and filtered. The filtrate was concentrated to give 4.3 g of crude alcohol, which was purified by combiflash (40 g gold column, 10 to 50% EA in Hept) to give 3.6 g (51%) of desired product as an oil. LC/MS: Rt = 0.71 minutes. MS m/z 288.34 $[M+Na]^+$, GCMS: Rt = 3.91 MS m/z 265 [M+1]

Example 133 Step 5

Benzyl (S)-(1-oxopropan-2-yl)(2-oxopropyl)carbamate

To a solution of DMSO (5.02 ml, 70 mmol) in anhydrous DCM (100 mL) was added dropwise (at -78 °C.) oxalyl chloride (2.61 ml, 30.1 mmol) under an atmosphere of nitrogen. The resulting mixture was stirred for 15 minutes. A solution of (**Example 133, Step 4**, 6.95 g, 26.22 mmol) in DCM (10 ml) was then added dropwise over a period of 30 minutes. After 2 h, triethylamine (18 mL, 130 mmol) was added slowly. The reaction was stirred at -78 °C for 30 minutes, then the acetone-dry ice bath was removed. The reaction mixture was cooled with an ice bath for 30 min. The ice bath was removed and the reaction was stirred for 60 min. The reaction was then quenched with water. The aqueous mixture was extracted (DCM, 3x) and the organic extracts collected, dried (Na_2SO_4) and the solvent

removed in vacuo. The residue was dissolved in ethyl acetate and the solution was washed with 10% NH_4Cl x2, 50% brine x 3, brine and dried over Na_2SO_4. The solution was concentrated to give 6.9 g desired product as a yellow oil, which was taken on to next step without purification. GCMS: m/z= 263 [M] (4.39min).

Example 133 Step 6

Benzyl (2S,3S)-3-hydroxy-2-methyl-5-oxopiperidine-1-carboxylate

To a solution of (**Example 133, Step 5**, 6900 mg, 26.21 mmol) in THF (250mL) at 0 °C was added DBU. After 48 hr the reaction mixture was treated with 10% NH_4Cl (100 mL). The organic layer was separated. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with 10% NH_4Cl, water, dried (Na_2SO_4) and the solvent removed to give 6 g of crude product. The crude product was purified by combiflash (80g gold column, 10 to 50 to 100% EA in hept) to give 1.8g (25%) of desired product. 1H NMR ($CDCl_3$) , 7.43-7.27 (5H, m), 5.18 (2H, s) 4.56-4.31 (3H, m), 4.30-4.13(2H, m), 3.9 (1H, d,), 2.73-2.58 (2H, m), 1.33 (3H, d,), GCMS, m/z =263.1[M+1](5.010 min)

Example 133 Step 7

Benzyl (2S,3S)-3-((tert-butyldimethylsilyl)oxy)-2-methyl-5-oxopiperidine-1-carboxylate

To a flask containing (**Example 133, Step 6**, 870 mg, 3.30 mmol) and DCM (30 mL) at 0 °C was added 2,6-lutidine (673 mg, 6.15) followed by TBDMSOTf (1.22 g, 4.61 mmol). After 3.5 hr, the TLC indicated the reaction was complete. The reaction was treated with Na_2CO_3(aq) and the mixture separated. The ice bath was removed after 15 min. The mixture was stirred an additional 30 min. before the organic layer was separated and concentrated in vacuo. The residue was purified by combiflash (40 g gold column, 5 to 20% EA in Hept) to give 800 mg desired product. 1H NMR ($CDCl_3$) d 7.35-7.22 (5H, m), 5.18-5.00 (2H, m) 4.56-4.31 (1H, m), 4.30-4.13(2H, m), 3.65-3.46 (1H, m), 2.54-2.45 (2H, m), 1.19 (3H, s), 0.81 (9H, s), 0.00(6H, s). GCMS,m/z =320.2 [M-t-Bu] (5.58min)

Example 133 Step 8

Benzyl (2S,3S,5R)-3-((tert-butyldimethylsilyl)oxy)-5-hydroxy-2-methylpiperidine-1-carboxylate

To a stirred solution of (**Example 133, Step 7,** 430 mg, 1.14 mmol) in 20 mL of MeOH at 0 °C, was added $NaBH_4$ ((129 mg, 3.42 mmol) in 3 portions over 10 min. After 30 min. the solvent was removed and the residue dissolved in ethyl acetate. The organic mixture was washed with Na_2CO_3(aq) , dried (Na_2SO_4) and the solvent removed to give the desired product (420 mg, 97%). ^1H NMR ($CDCl_3$) , 7.33-7.23 (5H, m), 5.07 (2H, q, 11.32Hz), 4.29 (1H, br), 4.11-4.02(1H, m), 3.70-3.63 (1H, m), 3.62-3.53 (1H, m), 2.58 (1H, dd,), 1.97-1.91(1h, m), 1.51 (1H, q,), 1.05 (3H, d,), 0.82 (9H, s), 0.00(6H, s). GCMS, m/z=322.2 [M-t-Bu] (5.657min)

Example 133, Step 9/ 10

Benzyl (2S,3S,5S)-3-((tert-butyldimethylsilyl)oxy)-5-chloro-2-methylpiperidine-1-carboxylate

To a solution of (**Example 133, Step 8,** 430mg, 1.23 mmol) in 20 mL of dichloromethane at 0 °C was added triethylamine (3 eq) and methanesulfonyl chloride (0.13 ml, 1.7 mmol, 1.5 eq). The reaction mixture was allowed to stir at room temperature for 2 hours. The reaction mixture was diluted with 30

mL of EtOAc, washed with sodium carbonate, brine and then dried over anhydrous $MgSO_4$. The organic extracts were filtered and concentrated in vacuo to give 550 mg of mesylate. The oil was dissolved in DMF (20 mL) and Bu_4NCl (3.5 g, 11.3 mmol, 10eq) was added. The reaction was heated to 90 °C for 5 hr and then stirred overnight at room temperature. The reaction was then diluted with 15 mL of ethyl acetate, washed with brine, dried (Na_2SO_4), and the solvent removed to give an oil (406 mg, 90 %). GCMS, m/z =397 [M](5.59min)

Example 133, Step 11

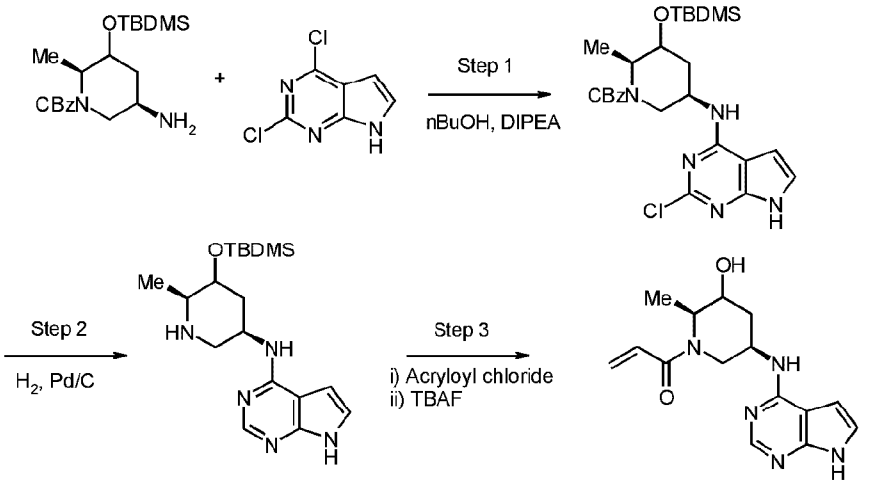
Benzyl (2S,3S,5R)-5-azido-3-((tert-butyldimethylsilyl)oxy)-2-methylpiperidine-1-carboxylate

To a solution of (**Example 133, Step 9/10**, 400 mg, 1.0 mmol) in 20 mL of DMSO at room temperature was added NaN_3. The reaction mixture was then heated to 90 °C over the weekend. The reaction was then allowed to cool to room temperature and diluted with 15 mL of ethyl acetate. The solution was washed with brine, dried (Na_2SO_4) and the solvent removed to give the crude product, which was purified by combiflash (12g gold column 0 to 10% ethyl acetate in heptane) to give 170 mg of desired product (42% yield) . ^{1}H NMR ($CDCl_3$) , 7.35-7.24 (5H, m), 5.17-5.01 (2H, m), 4.39 (0.5H, t,) 4.28(0.5H, t,), 4.18 (0.5H, dd,)), 4.03 (0.5H, dd,), 2.26 (1H, q,), 1.99-1.89 (1H, m) 1.56(1H, q,), 1.05 (3H, d,), 0.83 (9H, s), 0.00(6H, d,). LCMS, m/z=377.5 [M-N_2] (1.27min)

Example 133, Step 12

Benzyl (2S,3S,5R)-5-amino-3-((tert-butyldimethylsilyl)oxy)-2-methylpiperidine-1-carboxylate

To a flask containing (example 477, step 11, 170 mg, 0.42 mmol) was added THF:H_2O (10:1, 5 mL) and PPh_3 (124 mg, 0.462 mmol). The reaction was heated to 50 °C overnight and then allowed to cool to room temperature. The solvent was removed in vacuo to give a white solid, which was taken directly to the next step. MS m/z =379.5 [M+1] (0.76min).



Example 133 Step 13

(2S,3S,5R)-Benzyl 3-(tert-butyldimethylsilyloxy)-5-(2-chloro-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)-2-methylpiperidine-1-carboxylate

The title compound was prepared according to the method described for **Example 94 Step 1** using benzyl (2S,3S,5R)-5-amino-3-((tert-butyldimethylsilyl)oxy)-2-methylpiperidine-1-carboxylate. The residue was purified using silica gel column chromatography eluting with 5-50% EtOAc in heptanes. MS m/z 530 $[M+H]^+$

Example 133 Step 14

N-((3R,5S,6S)-5-(tert-Butyldimethylsilyloxy)-6-methylpiperidin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine

The title compound was prepared according to the method described for **Example 132 Step 2** using benzyl (2S,5R)-3-((tert-butyldimethylsilyl)oxy)-5-((2-chloro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-methylpiperidine-1-carboxylate (**Example 133 Step 1**).

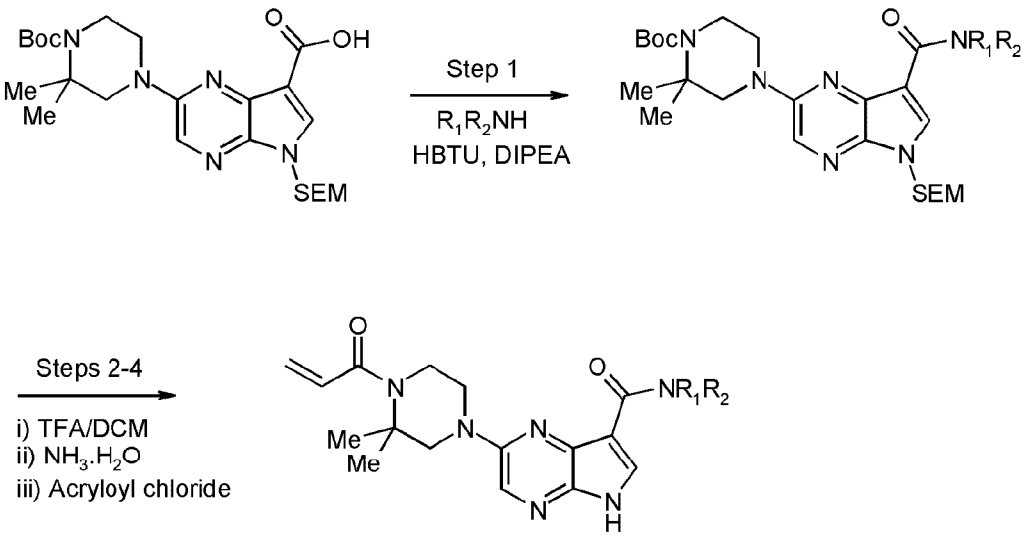
MS m/z 362 $[M+H]^+$

Example 133 Step 15

1-((2S,3S,5R)-5-(7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)-3-hydroxy-2-methylpiperidin-1-yl)prop-2-en-1-one

To a solution of N-((3R,6S)-5-((tert-butyldimethylsilyl)oxy)-6-methylpiperidin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine (81 mg, 0.22 mmol) in THF (5 mL) and saturated aqueous $NaHCO_3$ solution (5 mL) at 0°C was added acryloyl chloride (0.022 mL, 0.27 mmol) and the reaction was stirred at 0°C for 1 hour. Further acryloyl chloride was added (0.011 mL, 0.14 mmol) with further stirring. The reaction was quenched by the addition of water (20 mL) and extracted into EtOAc (3 x 10 mL). The combined organic layers were washed with brine, dried over sodium sulphate and concentrated *in vacuo*. The residue was purified using silica gel column chromatography eluting with 0-10% MeOH in DCM. The residue was dissolved in THF and treated with a 1M solution of TBAF in THF (0.18 mL, 0.18 mmol) at 0 °C and the reaction was stirred at room temperature for 3 hours. Further TBAF was added (0.2 mL) and the reaction continued for 1.5 hours. The reaction was quenched by the addition of water (10 mL) and extracted into EtOAc (3 x 10 mL). The organic layers were collected, dried over sodium sulphate. The residue was purified by RP-HPLC: Column: Waters Sunfire C18 (19x100, 5µm); CH_3CN:H_2O (0.05% TFA), 95:5 to 70:30 in 8.5 min then 100% CH_3CN to 9 min, hold @100% AcCN for 1 min, flow = 25 mL/min to give (1-[(2S,3S,5R)-3-hydroxy-2-methyl-5-(7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)piperidin-1-yl]prop-2-en-1-one, 27.6 mg). LC/MS: Rt = 1.10, MS m/z 302 $[M+H]^+$; Column:Waters-Atlantis C18 (4.6x50mm, 5µm), 95:5 to 5:95 H_2O/ CH_3CN (5 min), Flow: 2.0 mL/min

Examples 134-169 were prepared according to **Library Protocol 1** below:



Library Protocol 1

Step 1

To a 0.25M solution of 2-(4-(tert-butoxycarbonyl)-3,3-dimethylpiperazin-1-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid (**Example 83 Step 5**, 400 µL, 100 µmol) in DMF were added amines of formula R_1R_2NH (120 µmol) followed by DIPEA (39 mg, 300 µmol) and a 0.3M solution of HBTU in DMF (400 µL, 120 µmol). The reactions were shaken at 60°C for 16 hours before cooling and concentrating in vacuo. The residues were washed with water (1 mL) and extracted into EtOAc (3 x 1 mL). The combined organic layers were concentrated in vacuo to afford the Step 1 intermediates.

Steps 2-4

To the Step 1 intermediates was added a solution of TFA in DCM (1.2 mL, v:v 1:5) and the reactions were shaken at 30°C for 4 hours before concentrating in vacuo. The residues were treated with ammonium hydroxide in MeOH (1.6 mL, v:v 1:3) and shaken at 30 °C for 2 hours before concentrating in vacuo. The residues were treated with a saturated solution of $NaHCO_3$ in water (1 mL). To the solutions was added EtOAc (1 mL) followed by acryloyl chloride (18 mg, 200 µmol) and the reactions were shaken at 30 °C for 2 hours. The reactions were concentrated in vacuo and purified using preparative HPLC as described below to afford the following Examples:

Preparative HPLC:

Column: Phenomenex Gemini C18 250x21.2 mm, 8 micron; Mobile phase: Acetonitrile:ammonium hydroxide (pH=10); Gradient time: 8 minutes; Hold time: 1 minute at 100% organic; Flow rate: 35 mL/min.

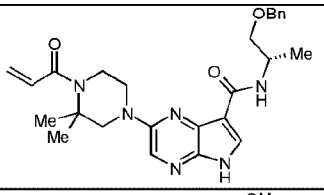
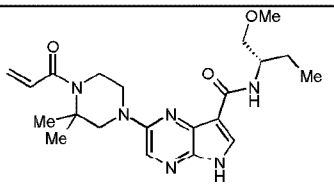
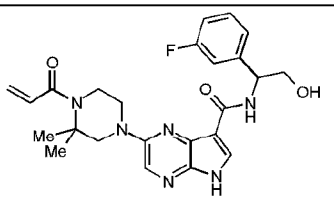
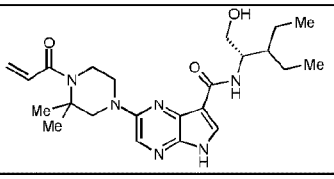
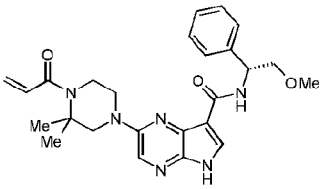
QC Method 1:

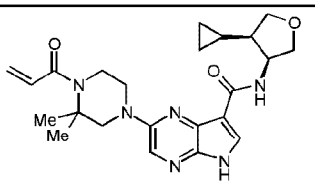
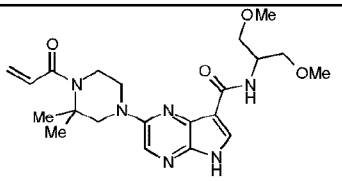
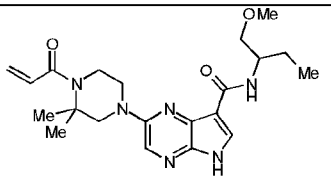
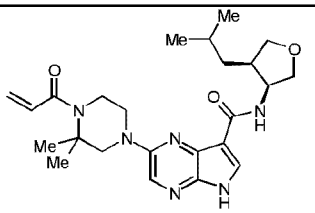
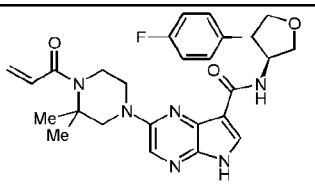
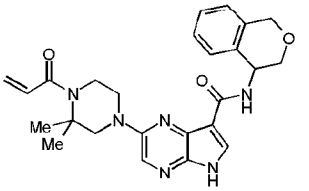
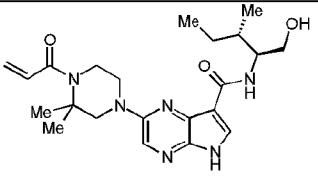
Column: Xbridge C18 2.1x50 mm; 5 micron; Mobile phase A: 0.0375% TFA in water; Mobile phase B: 0.01875% TFA in MeCN. Gradient: initial–1% B; 0.6 minutes–5% B; 4 minutes–100% B; 4.3 minutes–1% B; 4.7 minutes–1% B. Flow rate: 0.8 mL/min

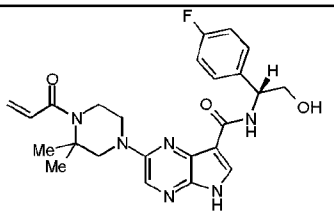
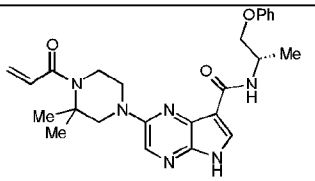
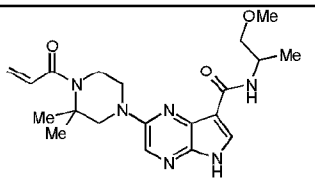
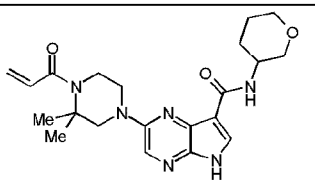
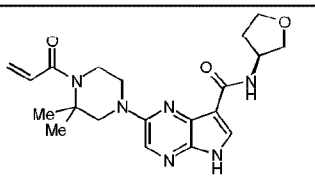
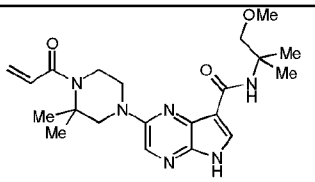
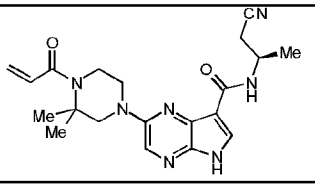
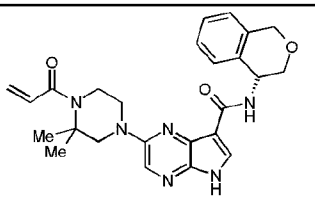
QC Method 2:

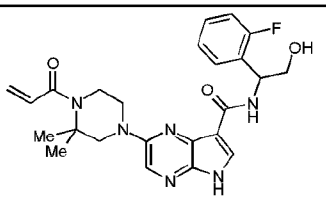
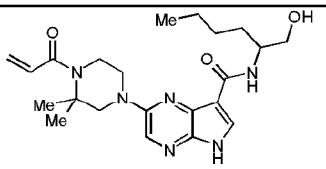
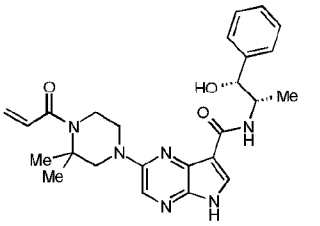
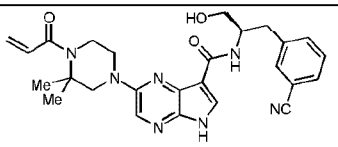
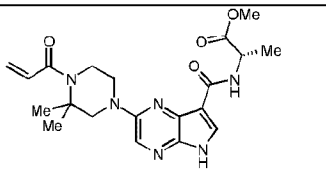
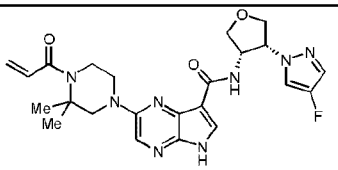
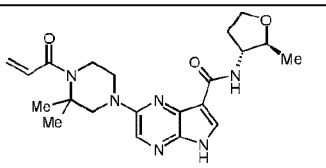
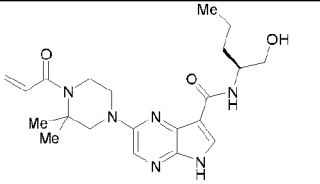
Column: Xbridge C18 2.1x50 mm; 5 micron. Mobile phase A: 0.05% NH_4OH in water; Mobile phase B: 100% MeCN. Gradient: initial–5% B; 0.5 minutes–5% B; 3.4 minutes–100% B; 4.2 minutes–100% B; 4.21 minutes–5% B; 4.7 minutes–5% B.

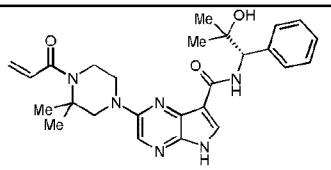
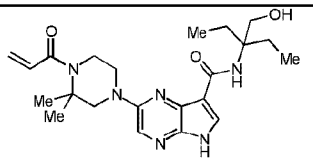
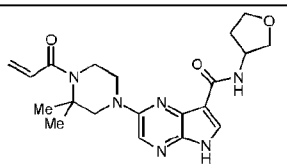
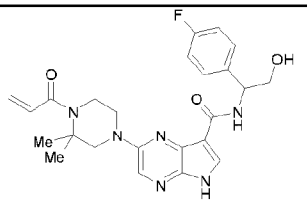
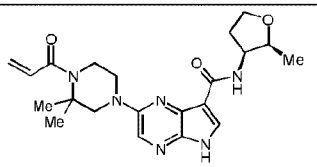
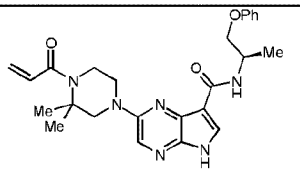
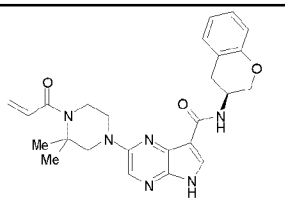
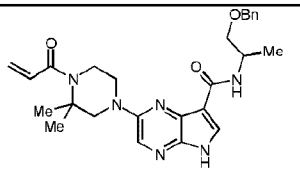
Flow rate: 0.8 mL/min

Ex. No.	Name	Structure	Data/% Organic Eluant
134	2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-[(2S)-1-(benzyloxy)propan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 477 $[M+H]^+$ Rt = 2.87 minutes QC Method 1 Prep HPLC gradient 35-75% organic.
135	2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-[(2S)-1-methoxybutan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 415 $[M+H]^+$ Rt = 2.61 minutes QC Method 1 Prep HPLC gradient 25-65% organic.
136	Racemic-2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-[1-(3-fluorophenyl)-2-hydroxyethyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 467 $[M+H]^+$ Rt = 2.60 minutes QC Method 1 Prep HPLC gradient 25-65% organic.
137	2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-[(2S)-3-ethyl-1-hydroxypentan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 443 $[M+H]^+$ Rt = 2.68 minutes QC Method 1 Prep HPLC gradient 30-70% organic.
138	2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-[(1R)-2-methoxy-1-phenylethyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 463 $[M+H]^+$ Rt = 2.77 minutes QC Method 1 Prep HPLC gradient 30-70% organic.

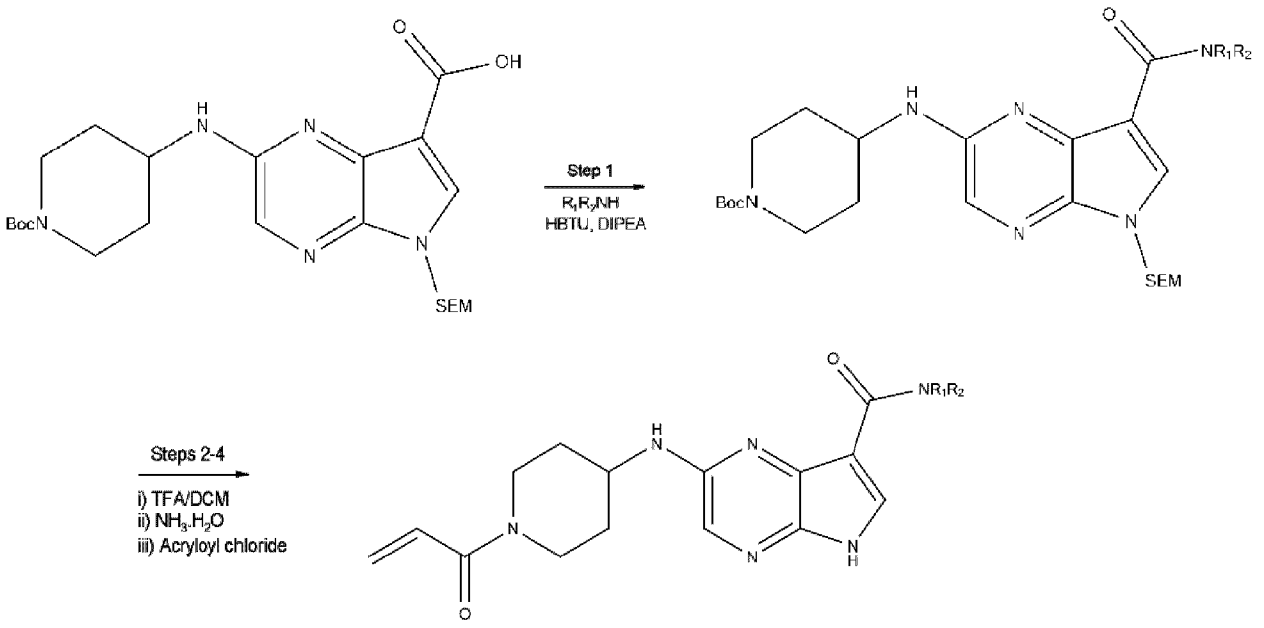
139	2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-[(3S,4R)-4-cyclopropyltetrahydrofuran-3-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 439 $[M+H]^+$ Rt = 2.57 minutes QC Method 1 Prep HPLC gradient 25-65% organic.
140	Racemic-2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-(1,3-dimethoxypropan-2-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 431 $[M+H]^+$ Rt = 2.29 minutes QC Method 2 Prep HPLC gradient 20-60% organic.
141	Racemic-2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-(1-methoxybutan-2-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 415 $[M+H]^+$ Rt = 2.61 minutes QC Method 1 Prep HPLC gradient 25-65% organic.
142	2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-[(3S,4R)-4-(2-methylpropyl)tetrahydrofuran-3-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 455 $[M+H]^+$ Rt = 2.78 minutes QC Method 1 Prep HPLC gradient 30-70% organic.
143	2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-[4-(4-fluorophenyl)tetrahydrofuran-3-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 493 $[M+H]^+$ Rt = 2.68 minutes QC Method 1 Prep HPLC gradient 30-70% organic.
144	Racemic-2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-(3,4-dihydro-1H-isochromen-4-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 461 $[M+H]^+$ Rt = 2.69 minutes QC Method 1 Prep HPLC gradient 30-70% organic.
145	2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-[(2S,3S)-1-hydroxy-3-methylpentan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 429 $[M+H]^+$ Rt = 2.58 minutes QC Method 1 Prep HPLC gradient 25-65% organic.

146	2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-[(1R)-1-(4-fluorophenyl)-2-hydroxyethyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 467 $[M+H]^+$ Rt = 2.56 minutes QC Method 1 Prep HPLC gradient 25-65% organic.
147	2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-[(2S)-1-phenoxypropan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 463 $[M+H]^+$ Rt = 2.88 minutes QC Method 1 Prep HPLC gradient 35-75% organic.
148	Racemic-2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-(1-methoxypropan-2-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 401 $[M+H]^+$ Rt = 2.52 minutes QC Method 1 Prep HPLC gradient 25-65% organic.
149	Racemic-2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-(tetrahydro-2H-pyran-3-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 413 $[M+H]^+$ Rt = 2.28 minutes QC Method 2 Prep HPLC gradient 20-60% organic.
150	2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-[(3S)-tetrahydrofuran-3-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 399 $[M+H]^+$ Rt = 2.18 minutes QC Method 2 Prep HPLC gradient 20-60% organic.
151	2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-(1-methoxy-2-methylpropan-2-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 415 $[M+H]^+$ Rt = 2.65 minutes QC Method 1 Prep HPLC gradient 25-65% organic.
152	2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-[(2R)-1-cyanopropan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 396 $[M+H]^+$ Rt = 2.25 minutes QC Method 2 Prep HPLC gradient 20-60% organic.
153	2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-[(3R)-3,4-dihydro-2H-chromen-3-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 461 $[M+H]^+$ Rt = 2.78 minutes QC Method 1 Prep HPLC gradient 30-70% organic.

154	Racemic-2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-[1-(2-fluorophenyl)-2-hydroxyethyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 467 $[M+H]^+$ Rt = 2.58 minutes QC Method 1 Prep HPLC gradient 25-65% organic.
155	Racemic-2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-(1-hydroxyhexan-2-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 429 $[M+H]^+$ Rt = 2.61 minutes QC Method 1 Prep HPLC gradient 26-66% organic.
156	2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-[(1R,2S)-1-hydroxy-1-phenylpropan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 463 $[M+H]^+$ Rt = 2.66 minutes QC Method 1 Prep HPLC gradient 25-65% organic.
157	2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-[(2R)-1-(3-cyanophenyl)-3-hydroxypropan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 488 $[M+H]^+$ Rt = 2.53 minutes QC Method 1 Prep HPLC gradient 25-65% organic.
158	Methyl N-{[2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]carbonyl}-L-alaninate		MS m/z 415 $[M+H]^+$ Rt = 2.32 minutes QC Method 2 Prep HPLC gradient 25-65% organic.
159	2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-[(3S,4R)-4-(4-fluoro-1H-pyrazol-1-yl)tetrahydrofuran-3-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 483 $[M+H]^+$ Rt = 2.48 minutes QC Method 1 Prep HPLC gradient 20-60% organic.
160	3-({[2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]carbonyl}amino)-2,5-anhydro-1,3,4-trideoxy-D-erythro-pentitol		MS m/z 413 $[M+H]^+$ Rt = 2.45 minutes QC Method 1 Prep HPLC gradient 20-60% organic.
161	2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-[(2S)-1-hydroxypentan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 415 $[M+H]^+$ Rt = 2.50 minutes QC Method 1 Prep HPLC gradient 20-60% organic.

162	2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-[(1S)-2-hydroxy-2-methyl-1-phenylpropyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 477 $[M+H]^+$ Rt = 2.68 minutes QC Method 1 Prep HPLC gradient 30-70% organic.
163	2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-[3-(hydroxymethyl)pentan-3-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 429 $[M+H]^+$ Rt = 2.62 minutes QC Method 1 Prep HPLC gradient 26-66% organic.
164	Racemic-2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-(tetrahydrofuran-3-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 399 $[M+H]^+$ Rt = 2.21 minutes QC Method 2 Prep HPLC gradient 20-60% organic.
165	Racemic-2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-[1-(4-fluorophenyl)-2-hydroxyethyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 467 $[M+H]^+$ Rt = 2.60 minutes QC Method 1 Prep HPLC gradient 25-65% organic.
166	3-({[2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]carbonyl}amino)-2,5-anhydro-1,3,4-trideoxy-L-threo-pentitol		MS m/z 413 $[M+H]^+$ Rt = 2.43 minutes QC Method 1 Prep HPLC gradient 20-60% organic.
167	2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-[(2R)-1-phenoxypropan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 463 $[M+H]^+$ Rt = 2.87 minutes QC Method 1 Prep HPLC gradient 35-75% organic.
168	2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-[(3S)-3,4-dihydro-2H-chromen-3-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 461 $[M+H]^+$ Rt = 2.76 minutes QC Method 1 Prep HPLC gradient 30-70% organic.
169	2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-[(2R)-1-(benzyloxy)propan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 477 $[M+H]^+$ Rt = 2.87 minutes QC Method 1 Prep HPLC gradient 35-75% organic.

Examples 170-196 were prepared according to Library Protocol 2 below:



Library Protocol 2

Step 1

To a 0.25M solution of 2-((1-(tert-butoxycarbonyl)piperidin-4-yl)amino)-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid in DMF **(Prepared in the same way as for Example 83 Steps 4 and 5 using tert-butyl-4-aminopiperidine-1-carboxylate** , 400 µL, 100 µmol) were added amines of formula R_1R_2NH (120 µmol) followed by DIPEA (70 µL, 400 µmol) and a 0.2M solution of HBTU in DMF (600 µL, 120 µmol). The reactions were shaken at 60°C for 16 hours before cooling and concentrating in vacuo to afford the Step 1 intermediates.

Steps 2-4

To the Step 1 intermediates was added a solution of TFA in DCM (1 mL, v:v 1:3) and the reactions were shaken at 30°C for 4 hours before concentrating in vacuo. The residues were treated with ammonium hydroxide in MeOH (1 mL, v:v 1:1) and shaken at 30°C for 16 hours before concentrating in vacuo. The residues were treated with a saturated solution of $NaHCO_3$ in water (1 mL). To the solutions was added EtOAc (1 mL) followed by acryloyl chloride (18 mg, 200 µmol) and the reactions were shaken at 30°C for 2 hours. The reactions were concentrated in vacuo and purified using preparative HPLC as described below to afford the following Examples:

Preparative HPLC:

Column: Phenomenex Gemini C18 250x21.2 mm, 8 micron. Mobile phase: Acetonitrile:ammonium hydroxide (pH=10). Gradient time: 8 minutes; Hold time: 1 minute at 100% organic; Flow rate: 35 mL/min.

QC Method:

Column: Xbridge C18 2.1x50 mm; 5 micron. Mobile phase A: 0.0375% TFA in water; Mobile phase B: 0.01875% TFA in MeCN. Gradient: initial–1% B; 0.6 minutes–5% B; 4 minutes–100% B; 4.3 minutes–1% B; 4.7 minutes–1% B. Flow rate: 0.8 mL/min

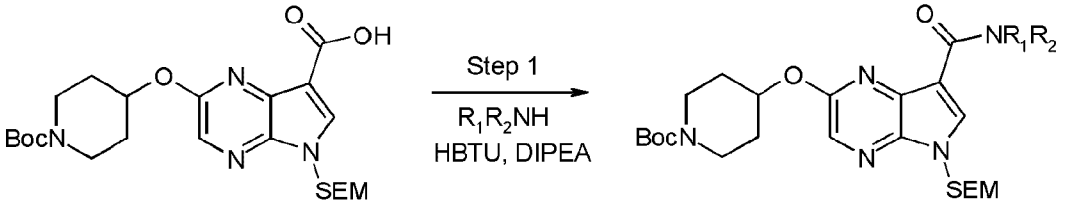
Ex. No.	Name	Structure	Data/% Organic Eluant
170	2-[(1-acryloylpiperidin-4-yl)amino]-N-propyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 357 $[M+H]^+$ Rt = 2.44 minutes Prep HPLC gradient 15-55% organic.
171	2-[(1-acryloylpiperidin-4-yl)amino]-N-{[4-methyl-6-(trifluoromethyl)pyrimidin-2-yl]methyl}-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 489 $[M+H]^+$ Rt = 2.60 minutes Prep HPLC gradient 21-51% organic.
172	2-[(1-acryloylpiperidin-4-yl)amino]-N-(cyclopropylmethyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 369 $[M+H]^+$ Rt = 2.48 minutes Prep HPLC gradient 16-56% organic.
173	2-[(1-acryloylpiperidin-4-yl)amino]-N-[(3-cyclobutyl-1-methyl-1H-pyrazol-5-yl)methyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 463 $[M+H]^+$ Rt = 2.57 minutes Prep HPLC gradient 19-59% organic.
174	2-[(1-acryloylpiperidin-4-yl)amino]-N-(4-fluoro-3-methoxybenzyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 453 $[M+H]^+$ Rt = 2.64 minutes Prep HPLC gradient 19-59% organic.
175	2-[(1-acryloylpiperidin-4-yl)amino]-N-{[3-(propan-2-yl)-1,2-oxazol-5-yl]methyl}-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 438 $[M+H]^+$ Rt = 2.62 minutes Prep HPLC gradient 26-66% organic.
176	2-[(1-acryloylpiperidin-4-yl)amino]-N-(3-fluorobenzyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 423 $[M+H]^+$ Rt = 2.66 minutes Prep HPLC gradient 21-61% organic.

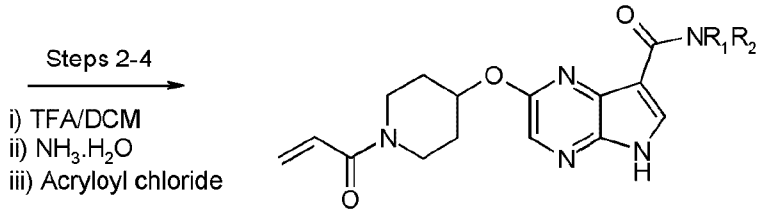
177	2-[(1-acryloylpiperidin-4-yl)amino]-N-[(5-fluoro-1,3-benzoxazol-2-yl)methyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 464 $[M+H]^+$ Rt = 2.65 minutes Prep HPLC gradient 20-60% organic.
178	2-[(1-acryloylpiperidin-4-yl)amino]-N-(2-cyclopropylethyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 383 $[M+H]^+$ Rt = 2.59 minutes Prep HPLC gradient 19-59% organic.
179	2-[(1-acryloylpiperidin-4-yl)amino]-N-(2,2,3,3,3-pentafluoropropyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 447 $[M+H]^+$ Rt = 2.66 minutes Prep HPLC gradient 21-61% organic.
180	2-[(1-acryloylpiperidin-4-yl)amino]-N-{[4-methyl-2-(trifluoromethyl)-1,3-thiazol-5-yl]methyl}-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 494 $[M+H]^+$ Rt = 2.76 minutes Prep HPLC gradient 24-64% organic.
181	2-[(1-acryloylpiperidin-4-yl)amino]-N-[4-(difluoromethoxy)benzyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 471 $[M+H]^+$ Rt = 2.75 minutes Prep HPLC gradient 23-63% organic.
182	2-[(1-acryloylpiperidin-4-yl)amino]-N-[2-(6,7-difluoro-1,3-benzoxazol-2-yl)ethyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 496 $[M+H]^+$ Rt = 2.73 minutes Prep HPLC gradient 23-63% organic.
183	2-[(1-acryloylpiperidin-4-yl)amino]-N-[4-(1H-pyrazol-1-yl)benzyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 471 $[M+H]^+$ Rt = 2.59 minutes Prep HPLC gradient 19-59% organic.

184	2-[(1-acryloylpiperidin-4-yl)amino]-N-[(5-ethyl-6-methylpyridin-2-yl)methyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 448 $[M+H]^+$ Rt = 2.23 minutes Prep HPLC gradient 19-59% organic.
185	2-[(1-acryloylpiperidin-4-yl)amino]-N-{[4-(trifluoromethyl)-1,3-thiazol-5-yl]methyl}-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 480 $[M+H]^+$ Rt = 2.59 minutes Prep HPLC gradient 19-59% organic.
186	2-[(1-acryloylpiperidin-4-yl)amino]-N-[(5-chloropyridin-2-yl)methyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 440 $[M+H]^+$ Rt = 2.53 minutes Prep HPLC gradient 18-58% organic.
187	2-[(1-acryloylpiperidin-4-yl)amino]-N-benzyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 405 $[M+H]^+$ Rt = 2.62 minutes Prep HPLC gradient 20-60% organic.
188	2-[(1-acryloylpiperidin-4-yl)amino]-N-(4-fluorobenzyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 423 $[M+H]^+$ Rt = 2.66 minutes Prep HPLC gradient 21-61% organic.
189	2-[(1-acryloylpiperidin-4-yl)amino]-N-(3-cyano-4-fluorobenzyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 448 $[M+H]^+$ Rt = 2.63 minutes Prep HPLC gradient 20-60% organic.
190	2-[(1-acryloylpiperidin-4-yl)amino]-N-(3-fluoro-4-methoxybenzyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 453 $[M+H]^+$ Rt = 2.63 minutes Prep HPLC gradient 20-60% organic.
191	2-[(1-acryloylpiperidin-4-yl)amino]-N-(4-methoxybenzyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 435 $[M+H]^+$ Rt = 2.60 minutes Prep HPLC gradient 20-60% organic.

192	2-[(1-acryloylpiperidin-4-yl)amino]-N-{[1-(3-fluorophenyl)-1H-pyrazol-4-yl]methyl}-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 489 $[M+H]^+$ Rt = 2.70 minutes Prep HPLC gradient 22-62% organic.
193	2-[(1-acryloylpiperidin-4-yl)amino]-N-(cyclobutylmethyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 383 $[M+H]^+$ Rt = 2.61 minutes Prep HPLC gradient 20-60% organic.
194	2-[(1-acryloylpiperidin-4-yl)amino]-N-[(6-fluoro-1,3-benzoxazol-2-yl)methyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 464 $[M+H]^+$ Rt = 2.65 minutes Prep HPLC gradient 21-61% organic.
195	2-[(1-acryloylpiperidin-4-yl)amino]-N-{[2-methyl-4-(trifluoromethyl)-1,3-thiazol-5-yl]methyl}-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 494 $[M+H]^+$ Rt = 2.65 minutes Prep HPLC gradient 20-60% organic.
196	2-[(1-acryloylpiperidin-4-yl)amino]-N-(2-fluorobenzyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 423 $[M+H]^+$ Rt = 2.65 minutes Prep HPLC gradient 21-61% organic.

Examples 197-230 were prepared according to Library Protocol 3 below:





Library Protocol 3

Step 1

To a 0.1M solution of 2{[1-(tert-butoxycarbonyl)piperidin-4-yl]oxy}-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid in DMF (**Preparation 114 Step 1**, 1.2 mL, 125 µmol) were added amines of formula R_1R_2NH (187 µmol) followed by DIPEA (500 µmol) and HBTU (212 µmol). The reactions were shaken at 30°C for 16 hours before cooling and concentrating in vacuo. To the residues was added saturated aqueous $NaHCO_3$ (1 mL) and the solutions were extracted into EtOAc (3 x 1 mL). The organic layers were collected, dried over sodium sulphate and concentrated in vacuo to afford the Step 1 intermediates.

Steps 2-4

To the Step 1 intermediates was added a solution of TFA in DCM (1.2 mL, v:v 1:4) and the reactions were shaken at 30°C for 4 hours before concentrating in vacuo. The residues were treated with ammonium hydroxide in MeOH (1.2 mL, v:v 1:3) and shaken at 30°C for 16 hours before concentrating in vacuo. The residues were treated with a saturated solution of $NaHCO_3$ in water (800 µL). To the solutions was added EtOAc (800 µL) followed by acryloyl chloride (250 µmol) and the reactions were shaken at 30°C for 2 hours. The reactions were concentrated in vacuo and purified using preparative HPLC as described below to afford the following Examples:

Preparative HPLC:

Column: Phenomenex Gemini C18 250x21.2 mm, 8 micron. Mobile phase: Acetonitrile:ammonium hydroxide (pH=10). Gradient time: 8 minutes; Hold time: 1 minute at 100% organic; Flow rate: 35 mL/min.

QC Method 1:

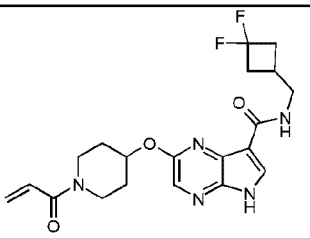
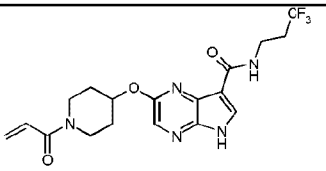
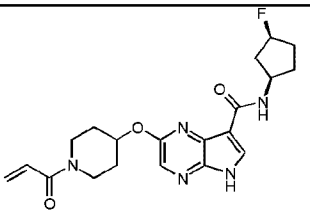
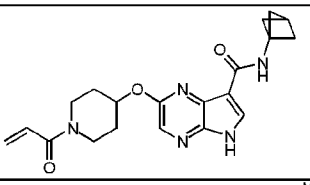
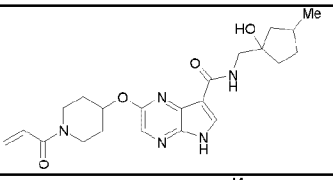
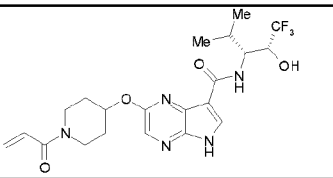
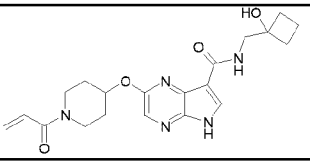
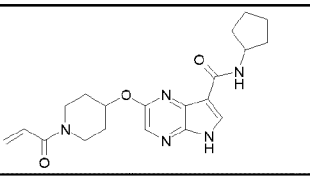
Column: Xbridge C18 2.1x50 mm; 5 micron. Mobile phase A: 0.0375% TFA in water; Mobile phase B: 0.01875% TFA in MeCN. Gradient: initial–1% B; 0.6 minutes–5% B; 4 minutes–100% B; 4.3 minutes–1% B; 4.7 minutes–1% B. Flow rate: 0.8 mL/min

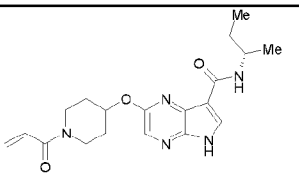
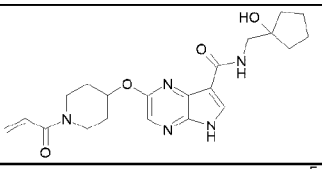
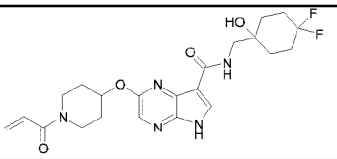
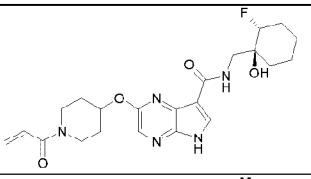
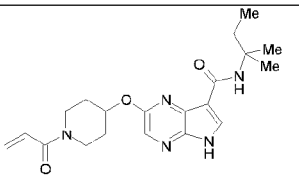
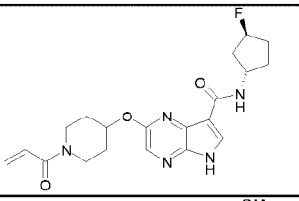
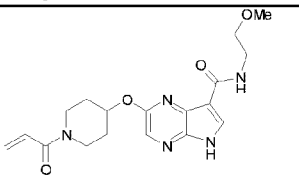
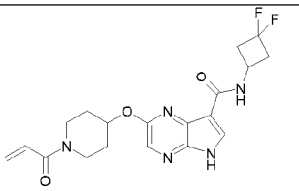
QC Method 2:

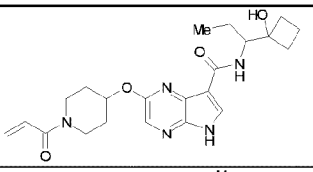
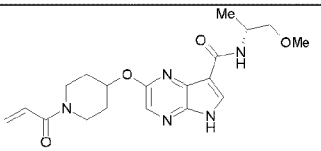
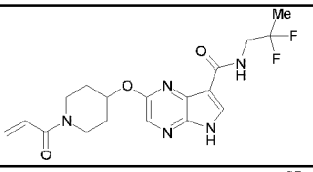
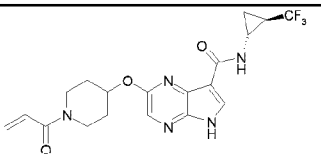
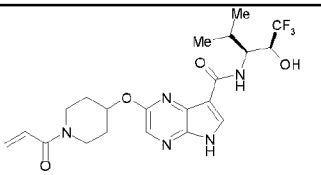
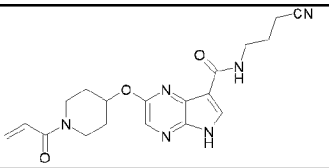
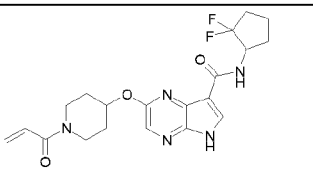
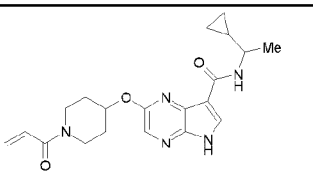
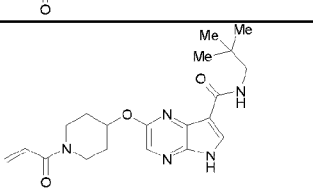
Column: Xbridge C18 2.1x50 mm; 5 micron. Mobile phase A: 0.05% NH_4OH in water; Mobile phase B: 100% MeCN. Gradient: initial–5% B; 0.5 minutes–5% B; 3.4 minutes–100% B; 4.2 minutes–100% B; 4.21 minutes–5% B; 4.7 minutes–5% B. Flow rate: 0.8 mL/min

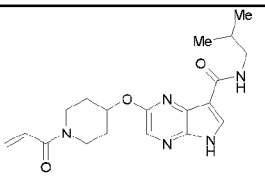
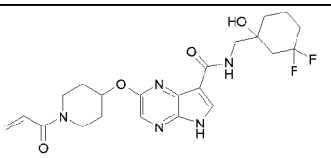
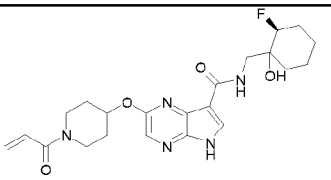
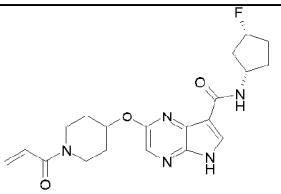
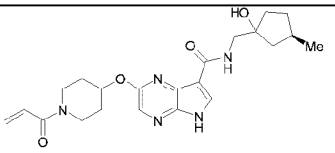
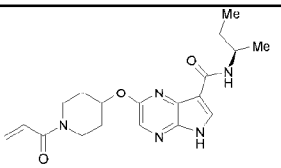
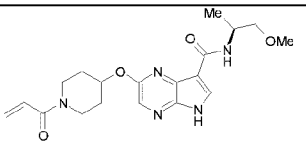
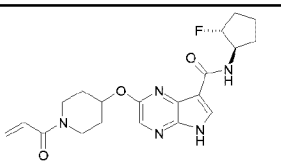
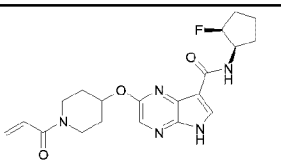
QC Method 1 was used unless otherwise specified:

Ex. No.	Name	Structure	Data/% Organic Eluant/QC Method

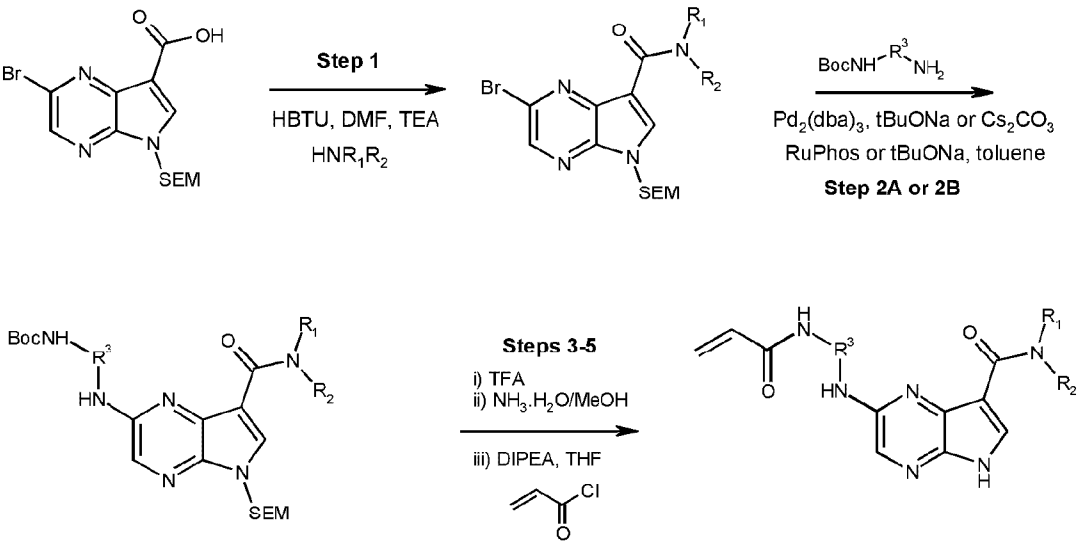
197	2-[(1-acryloylpiperidin-4-yl)oxy]-N-[(3,3-difluorocyclobutyl)methyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 420 $[M+H]^+$ Rt = 2.75 minutes Prep HPLC gradient 21-61% organic.
198	2-[(1-acryloylpiperidin-4-yl)oxy]-N-(3,3,3-trifluoropropyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 412 $[M+H]^+$ Rt = 2.71 minutes Prep HPLC gradient 21-61% organic.
199	2-[(1-acryloylpiperidin-4-yl)oxy]-N-[(1R,3S)-3-fluorocyclopentyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 402 $[M+H]^+$ Rt = 2.64 minutes Prep HPLC gradient 18-58% organic.
200	2-[(1-acryloylpiperidin-4-yl)oxy]-N-(bicyclo[1.1.1]pent-1-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 382 $[M+H]^+$ Rt = 2.79 minutes Prep HPLC gradient 32-72% organic.
201	Racemic-2-[(1-acryloylpiperidin-4-yl)oxy]-N-[(1-hydroxy-3-methylcyclopentyl)methyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 428 $[M+H]^+$ Rt = 2.71 minutes Prep HPLC gradient 20-60% organic.
202	2-[(1-acryloylpiperidin-4-yl)oxy]-N-[(2R,3R)-1,1,1-trifluoro-2-hydroxy-4-methylpentan-3-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 470 $[M+H]^+$ Rt = 2.78 minutes Prep HPLC gradient 21-61% organic.
203	2-[(1-acryloylpiperidin-4-yl)oxy]-N-[(1-hydroxycyclobutyl)methyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 400 $[M+H]^+$ Rt = 2.24 minutes Prep HPLC gradient 23-63% organic. Method 2.
204	Racemic-2-[(1-acryloylpiperidin-4-yl)oxy]-N-cyclopentyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 384 $[M+H]^+$ Rt = 2.74 minutes Prep HPLC gradient 31-71% organic.

205	2-[(1-acryloylpiperidin-4-yl)oxy]-N-[(2S)-butan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 372 $[M+H]^+$ Rt = 2.71 minutes Prep HPLC gradient 30-70% organic.
206	Racemic-2-[(1-acryloylpiperidin-4-yl)oxy]-N-[(1-hydroxycyclopentyl)methyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 414 $[M+H]^+$ Rt = 2.59 minutes Prep HPLC gradient 14-44% organic.
207	2-[(1-acryloylpiperidin-4-yl)oxy]-N-[(4,4-difluoro-1-hydroxycyclohexyl)methyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 464 $[M+H]^+$ Rt = 2.70 minutes Prep HPLC gradient 30-70% organic.
208	2-[(1-acryloylpiperidin-4-yl)oxy]-N-{[(2R)-2-fluoro-1-hydroxycyclohexyl]methyl}-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 446 $[M+H]^+$ Rt = 2.64 minutes Prep HPLC gradient 28-68% organic.
209	2-[(1-acryloylpiperidin-4-yl)oxy]-N-(2-methylbutan-2-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 386 $[M+H]^+$ Rt = 2.85 minutes Prep HPLC gradient 34-74% organic.
210	2-[(1-acryloylpiperidin-4-yl)oxy]-N-[(1S,3S)-3-fluorocyclopentyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 402 $[M+H]^+$ Rt = 2.66 minutes Prep HPLC gradient 29-69% organic.
211	2-[(1-acryloylpiperidin-4-yl)oxy]-N-(2-methoxyethyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 374 $[M+H]^+$ Rt = 2.71 minutes Prep HPLC gradient 21-61% organic. Method 2.
212	2-[(1-acryloylpiperidin-4-yl)oxy]-N-(3,3-difluorocyclobutyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 406 $[M+H]^+$ Rt = 2.43 minutes Prep HPLC gradient 29-69% organic. Method 2.

213	Racemic-2-[(1-acryloylpiperidin-4-yl)oxy]-N-[1-(1-hydroxycyclobutyl)propyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 428 $[M+H]^+$ Rt = 2.61 minutes Prep HPLC gradient 28-68% organic.
214	2-[(1-acryloylpiperidin-4-yl)oxy]-N-[(2R)-1-methoxypropan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 388 $[M+H]^+$ Rt = 2.32 minutes Prep HPLC gradient 26-66% organic. Method 2.
215	2-[(1-acryloylpiperidin-4-yl)oxy]-N-(2,2-difluoropropyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 394 $[M+H]^+$ Rt = 2.65 minutes Prep HPLC gradient 28-68% organic.
216	2-[(1-acryloylpiperidin-4-yl)oxy]-N-[(1R,2R)-2-(trifluoromethyl)cyclopropyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 424 $[M+H]^+$ Rt = 2.80 minutes Prep HPLC gradient 32-72% organic.
217	2-[(1-acryloylpiperidin-4-yl)oxy]-N-[(2S,3S)-1,1,1-trifluoro-2-hydroxy-4-methylpentan-3-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 470 $[M+H]^+$ Rt = 2.76 minutes Prep HPLC gradient 29-69% organic.
218	2-[(1-acryloylpiperidin-4-yl)oxy]-N-(3-cyanopropyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 383 $[M+H]^+$ Rt = 2.23 minutes Prep HPLC gradient 23-63% organic. Method 2.
219	2-[(1-acryloylpiperidin-4-yl)oxy]-N-(2,2-difluorocyclopentyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 420 $[M+H]^+$ Rt = 2.75 minutes Prep HPLC gradient 31-71% organic.
220	Racemic-2-[(1-acryloylpiperidin-4-yl)oxy]-N-(1-cyclopropylethyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 384 $[M+H]^+$ Rt = 2.74 minutes Prep HPLC gradient 31-71% organic.
221	2-[(1-acryloylpiperidin-4-yl)oxy]-N-(2,2-dimethylpropyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 386 $[M+H]^+$ Rt = 2.82 minutes Prep HPLC gradient 33-73% organic.

222	2-[(1-acryloylpiperidin-4-yl)oxy]-N-(2-methylpropyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 372 $[M+H]^+$ Rt = 2.71 minutes Prep HPLC gradient 30-70% organic.
223	Racemic-2-[(1-acryloylpiperidin-4-yl)oxy]-N-[(3,3-difluoro-1-hydroxycyclohexyl)methyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 464 $[M+H]^+$ Rt = 2.65 minutes Prep HPLC gradient 29-69% organic.
224	Racemic-2-[(1-acryloylpiperidin-4-yl)oxy]-N-{[(2S)-2-fluoro-1-hydroxycyclohexyl]methyl}-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 446 $[M+H]^+$ Rt = 2.71 minutes Prep HPLC gradient 30-70% organic.
225	2-[(1-acryloylpiperidin-4-yl)oxy]-N-[(1S,3R)-3-fluorocyclopentyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 402 $[M+H]^+$ Rt = 2.63 minutes Prep HPLC gradient 28-68% organic.
226	Racemic-2-[(1-acryloylpiperidin-4-yl)oxy]-N-{[(3R)-1-hydroxy-3-methylcyclopentyl]methyl}-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 428 $[M+H]^+$ Rt = 2.71 minutes Prep HPLC gradient 20-60% organic.
227	2-[(1-acryloylpiperidin-4-yl)oxy]-N-[(2R)-butan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 372 $[M+H]^+$ Rt = 2.71 minutes Prep HPLC gradient 30-70% organic.
228	2-[(1-acryloylpiperidin-4-yl)oxy]-N-[(2S)-1-methoxypropan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 388 $[M+H]^+$ Rt = 2.33 minutes Prep HPLC gradient 26-66% organic. Method 2.
229	2-[(1-acryloylpiperidin-4-yl)oxy]-N-[(1R,2R)-2-fluorocyclopentyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 402 $[M+H]^+$ Rt = 2.75 minutes Prep HPLC gradient 30-70% organic.
230	2-[(1-acryloylpiperidin-4-yl)oxy]-N-[(1R,2S)-2-fluorocyclopentyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 402 $[M+H]^+$ Rt = 2.72 minutes Prep HPLC gradient 31-71% organic.

Examples 231-264were prepared according to Library Protocol 4 below:



Library Protocol 4

Step 1

To a 0.2M solution of 2-bromo-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid in DMF (**Example 1 Step 2**, 1 mL, 200 µmol) was added the appropriate amine (300 µmol) followed by DIPEA (77.4 mg, 600 µmol) and a 0.22M solution of HBTU in DMF (1 mL, 220 µmol). The reactions were shaken at 60°C for 16 hours before cooling and concentrating in vacuo. The residues were purified using preparative TLC to afford the Step 1 amide intermediate.

Either step 2A or Step 2B was employed for the Buchwald step:

Step 2A

To the Step 1 amide intermediate (100 µmol) was added cesium carbonate (65 mg, 200 µmol), a 0.25M solution of the appropriate Boc-protected amine in toluene (800 µL, 200 µmol), Pd_2dba_3 (4.6 mg, 5 µmol) and Ruphos (2.8 mg, 6 µmol) under nitrogen. The reactions were capped and shaken at 100°C for 16 hours before cooling and concentrating in vacuo. The residue was washed with water (1 mL) and extracted into EtOAc (3 x 1 mL). The organic layers were collected and concentrated in vacuo to afford the Step 2 intermediate.

Step 2B

To the amide intermediate (100 µmol) was added sodium tert-butoxide (19.2 mg, 200 µmol), a 0.25M solution of the appropriate Boc-protected amine in toluene (800 µL, 200 µmol), Pd_2dba_3 (4.6 mg, 5 µmol) and Ruphos (2.8 mg, 6 µmol) under nitrogen. The reactions were capped and shaken at 65°C for 40 hours before cooling and concentrating in vacuo. The residue was washed with water (1 mL)

and extracted into EtOAc (3 x 1 mL). The organic layers were collected and concentrated in vacuo to afford the step 2 intermediate.

Steps 3-5

To the Step 2 intermediates was added a solution of TFA in DCM (1 mL, v:v 1:6) and the reactions were shaken at 30°C for 16 hours before concentrating in vacuo. The residues were treated with ammonium hydroxide in MeOH (1.5 mL, v:v 1:4) and shaken at 30°C for 2 hours before concentrating in vacuo. The residues were treated with a saturated solution of $NaHCO_3$ in water (1 mL). To the solutions was added EtOAc (1 mL) followed by acryloyl chloride (200 µmol) and the reactions were shaken at 30°C for 2 hours. The reactions were concentrated in vacuo and purified using preparative HPLC as described below to afford the following Examples:

Preparative HPLC:

Column: Phenomenex Gemini C18 250x21.2 mm, 8 micron. Mobile phase: Acetonitrile:ammonium hydroxide (pH=10). Gradient time: 8 minutes; Hold time: 1 minute at 100% organic; Flow rate: 35 mL/min.

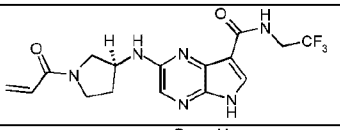
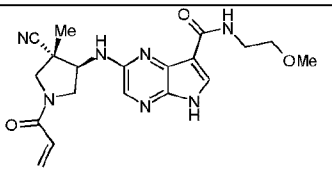
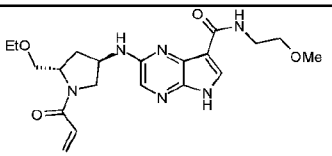
QC Method 1:

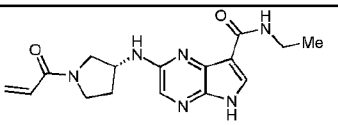
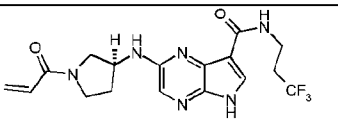
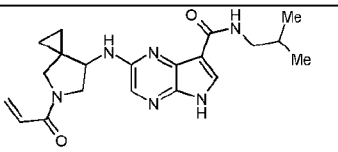
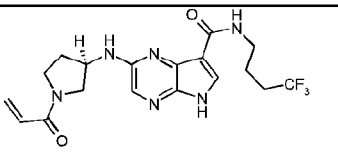
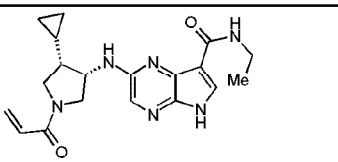
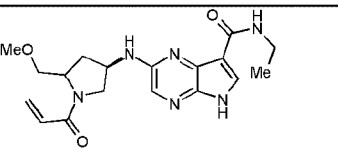
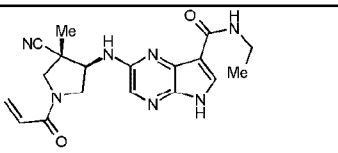
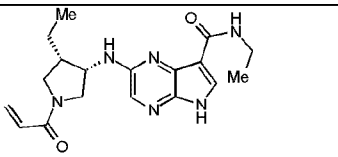
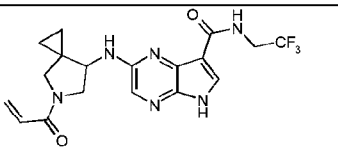
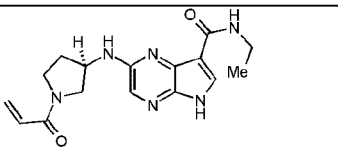
Column: Xbridge C18 2.1x50 mm; 5 micron. Mobile phase A: 0.0375% TFA in water; Mobile phase B: 0.01875% TFA in MeCN. Gradient: initial–1% B; 0.6 minutes–5% B; 4 minutes–100% B; 4.3 minutes–1% B; 4.7 minutes–1% B. Flow rate: 0.8 mL/min

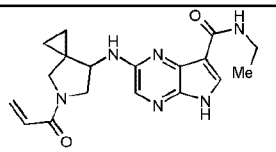
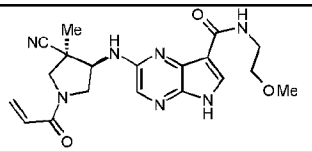
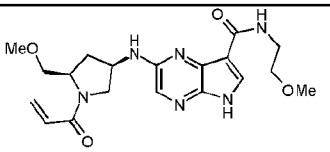
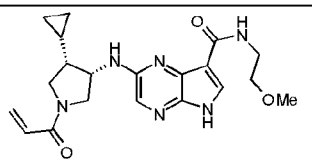
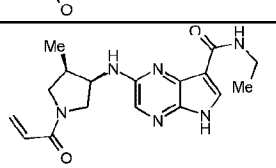
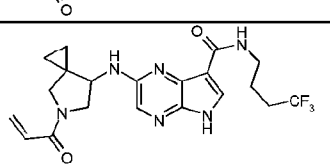
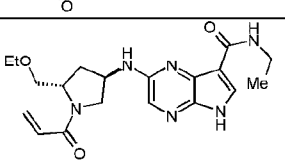
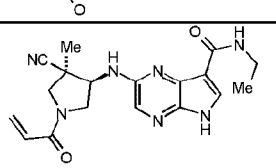
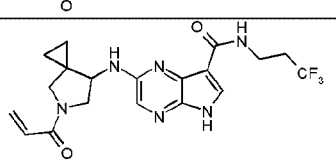
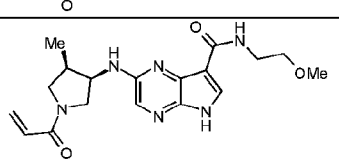
QC Method 2:

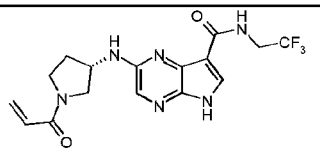
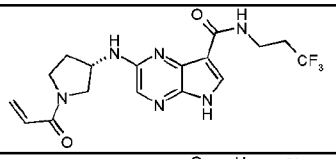
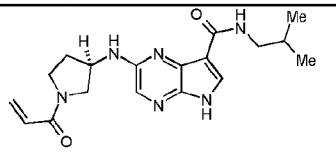
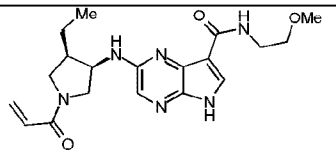
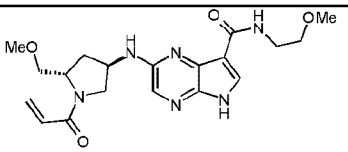
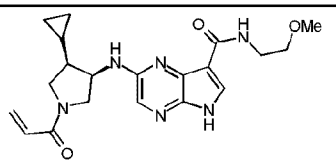
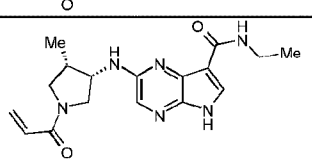
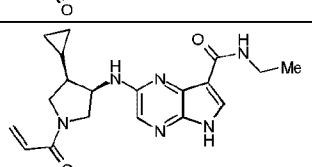
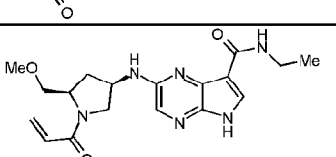
Column: Xbridge C18 2.1x50 mm; 5 micron. Mobile phase A: 0.05% NH_4OH in water; Mobile phase B: 100% MeCN. Gradient: initial–5% B; 0.5 minutes–5% B; 3.4 minutes–100% B; 4.2 minutes–100% B; 4.21 minutes–5% B; 4.7 minutes–5% B. Flow rate: 0.8 mL/min

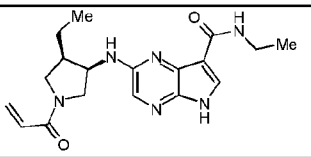
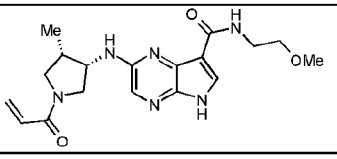
QC Method 1 was used unless otherwise specified:

Ex. No.	Name	Structure	Data/% Organic Eluant/QC Method
231	2-{[(3S)-1-acryloylpyrrolidin-3-yl]amino}-N-(2,2,2-trifluoroethyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 383 $[M+H]^+$ Rt = 2.55 minutes Prep HPLC gradient 18-58% organic.
232	2-{[(3R,4S)-1-acryloyl-4-cyano-4-methylpyrrolidin-3-yl]amino}-N-(2-methoxyethyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 398 $[M+H]^+$ Rt = 2.33 minutes Prep HPLC gradient 5-45% organic.
233	2-{[(3R,5S)-1-acryloyl-5-(ethoxymethyl)pyrrolidin-3-yl]amino}-N-(2-methoxyethyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 417 $[M+H]^+$ Rt = 2.54 minutes Prep HPLC gradient 18-58% organic.

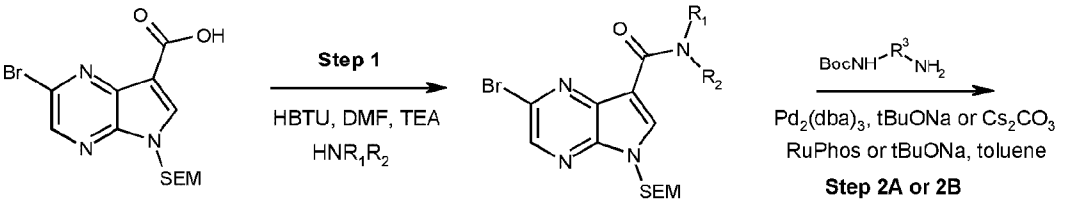
234	2-{[(3R)-1-acryloylpyrrolidin-3-yl]amino}-N-ethyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 329 $[M+H]^+$ Rt = 2.33 minutes Prep HPLC gradient 5-45% organic.
235	2-{[(3S)-1-acryloylpyrrolidin-3-yl]amino}-N-(3,3,3-trifluoropropyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 397 $[M+H]^+$ Rt = 2.55 minutes Prep HPLC gradient 18-58% organic.
236	2-[(5-acryloyl-5-azaspiro[2.4]hept-7-yl)amino]-N-(2-methylpropyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 383 $[M+H]^+$ Rt = 2.72 minutes Prep HPLC gradient 16-56% organic.
237	2-{[(3S)-1-acryloylpyrrolidin-3-yl]amino}-N-(4,4,4-trifluorobutyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 411 $[M+H]^+$ Rt = 2.64 minutes Prep HPLC gradient 21-61% organic.
238	2-{[(3S,4S)-1-acryloyl-4-cyclopropylpyrrolidin-3-yl]amino}-N-ethyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 369 $[M+H]^+$ Rt = 2.58 minutes Prep HPLC gradient 12-52% organic.
239	2-{[(3R,5S)-1-acryloyl-5-(methoxymethyl)pyrrolidin-3-yl]amino}-N-ethyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 373 $[M+H]^+$ Rt = 2.44 minutes Prep HPLC gradient 8-48% organic.
240	2-{[(3R,4S)-1-acryloyl-4-cyano-4-methylpyrrolidin-3-yl]amino}-N-ethyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 368 $[M+H]^+$ Rt = 2.37 minutes Prep HPLC gradient 6-46% organic.
241	2-{[(3S,4S)-1-acryloyl-4-ethylpyrrolidin-3-yl]amino}-N-ethyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 357 $[M+H]^+$ Rt = 2.58 minutes Prep HPLC gradient 12-52% organic.
242	2-[(5-acryloyl-5-azaspiro[2.4]hept-7-yl)amino]-N-(2,2,2-trifluoroethyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 409 $[M+H]^+$ Rt = 2.71 minutes Prep HPLC gradient 15-55% organic.
243	2-{[(3S)-1-acryloylpyrrolidin-3-yl]amino}-N-ethyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 329 $[M+H]^+$ Rt = 2.34 minutes Prep HPLC gradient 4-44% organic.

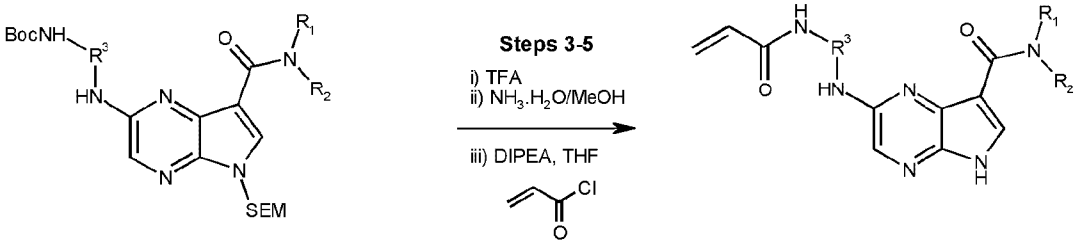
244	2-[(5-acryloyl-5-azaspiro[2.4]hept-7-yl)amino]-N-ethyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 355 $[M+H]^+$ Rt = 2.49 minutes Prep HPLC gradient 9-49% organic.
245	2-{[(3R,4R)-1-acryloyl-4-cyano-4-methylpyrrolidin-3-yl]amino}-N-(2-methoxyethyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 398 $[M+H]^+$ Rt = 2.36 minutes Prep HPLC gradient 5-45% organic.
246	2-{[(3R,5R)-1-acryloyl-5-(methoxymethyl)pyrrolidin-3-yl]amino}-N-(2-methoxyethyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 403 $[M+H]^+$ Rt = 2.16 minutes Prep HPLC gradient 6-46% organic. Method 2.
247	2-{[(3S,4S)-1-acryloyl-4-cyclopropylpyrrolidin-3-yl]amino}-N-(2-methoxyethyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 399 $[M+H]^+$ Rt = 2.54 minutes Prep HPLC gradient 11-51% organic.
248	2-[(1-acryloyl-4-methylpyrrolidin-3-yl)amino]-N-ethyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 343 $[M+H]^+$ Rt = 2.45 minutes Prep HPLC gradient 8-48% organic.
249	2-[(5-acryloyl-5-azaspiro[2.4]hept-7-yl)amino]-N-(4,4,4-trifluorobutyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 437 $[M+H]^+$ Rt = 2.79 minutes Prep HPLC gradient 8-48% organic.
250	2-{[(3R,5S)-1-acryloyl-5-(ethoxymethyl)pyrrolidin-3-yl]amino}-N-ethyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 387 $[M+H]^+$ Rt = 2.59 minutes Prep HPLC gradient 19-59% organic.
251	2-{[(3R,4R)-1-acryloyl-4-cyano-4-methylpyrrolidin-3-yl]amino}-N-ethyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 368 $[M+H]^+$ Rt = 2.38 minutes Prep HPLC gradient 6-46% organic.
252	2-[(5-acryloyl-5-azaspiro[2.4]hept-7-yl)amino]-N-(3,3,3-trifluoropropyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 423 $[M+H]^+$ Rt = 2.70 minutes Prep HPLC gradient 15-55% organic.
253	2-[(1-acryloyl-4-methylpyrrolidin-3-yl)amino]-N-(2-methoxyethyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 373 $[M+H]^+$ Rt = 2.41 minutes Prep HPLC gradient 7-47% organic.

254	2-{[(3R)-1-acryloylpyrrolidin-3-yl]amino}-N-(2,2,2-trifluoroethyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 383 $[M+H]^+$ Rt = 2.54 minutes Prep HPLC gradient 11-51% organic.
255	2-{[(3R)-1-acryloylpyrrolidin-3-yl]amino}-N-(3,3,3-trifluoropropyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 397 $[M+H]^+$ Rt = 2.54 minutes Prep HPLC gradient 10-50% organic.
256	2-{[(3S)-1-acryloylpyrrolidin-3-yl]amino}-N-(2-methylpropyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 357 $[M+H]^+$ Rt = 2.55 minutes Prep HPLC gradient 11-51% organic.
257	2-{[(3R,4R)-1-acryloyl-4-ethylpyrrolidin-3-yl]amino}-N-(2-methoxyethyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 387 $[M+H]^+$ Rt = 2.54 minutes Prep HPLC gradient 11-51% organic.
258	2-{[(3R,5S)-1-acryloyl-5-(methoxymethyl)pyrrolidin-3-yl]amino}-N-(2-methoxyethyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 403 $[M+H]^+$ Rt = 2.19 minutes Prep HPLC gradient 7-47% organic. Method 2.
259	2-{[(3R,4R)-1-acryloyl-4-cyclopropylpyrrolidin-3-yl]amino}-N-(2-methoxyethyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 399 $[M+H]^+$ Rt = 2.55 minutes Prep HPLC gradient 11-51% organic.
260	2-[(1-acryloyl-4-methylpyrrolidin-3-yl)amino]-N-ethyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 343 $[M+H]^+$ Rt = 2.55 minutes Prep HPLC gradient 11-51% organic.
261	2-{[(3R,4R)-1-acryloyl-4-cyclopropylpyrrolidin-3-yl]amino}-N-ethyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 369 $[M+H]^+$ Rt = 2.56 minutes Prep HPLC gradient 12-52% organic.
262	2-{[(3R,5R)-1-acryloyl-5-(methoxymethyl)pyrrolidin-3-yl]amino}-N-ethyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 373 $[M+H]^+$ Rt = 2.42 minutes Prep HPLC gradient 7-47% organic.

263	2-{[(3R,4R)-1-acryloyl-4-ethylpyrrolidin-3-yl]amino}-N-ethyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 357 $[M+H]^+$ Rt = 2.58 minutes Prep HPLC gradient 12-52% organic.
264	2-{[(3S,4S)-1-acryloyl-4-methylpyrrolidin-3-yl]amino}-N-(2-methoxyethyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 373 $[M+H]^+$ Rt = 2.41 minutes Prep HPLC gradient 7-47% organic.

Examples 265-337 were prepared according to Library Protocol 5 below:





Library Protocol 5

Step 1

To a 0.4M solution of 2-bromo-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid in DMF (**Example 1 Step 2**, 250 µL, 100 µmol) was added the appropriate amine (120 µmol) followed by DIPEA (51 µL, 300 µmol) and a 0.48M solution of HBTU in DMF (250 µL, 120 µmol). The reactions were shaken at 60°C for 16 hours before cooling and concentrating in vacuo. The residues were purified using preparative TLC to afford the Step 1 amide intermediate.

Either step 2A or Step 2B was employed for the Buchwald step:

Step 2A

To a 0.2M solution of the Step 1 amide intermediate in toluene (500 µL, 75 µmol) was added cesium carbonate (65 mg, 200 µmol), the appropriate Boc-protected amine (150 µmol), Pd_2dba_3 (4.6 mg, 5 µmol) and Ruphos (2.8 mg, 6 µmol) under nitrogen. The reactions were capped and shaken at 120°C for 16 hours before cooling and concentrating in vacuo. The residue was washed with water (1 mL)

and extracted into EtOAc (3 x 1 mL). The organic layers were collected and concentrated in vacuo to afford the Step 2 intermediate.

Step 2B

To a 0.2M solution of the amide intermediate in toluene (500 µL, 75 µmol) was added sodium tert-butoxide (19.2 mg, 200 µmol), the appropriate Boc-protected amine (150 µmol), Pd_2dba_3 (4.6 mg, 5 µmol) and Ruphos (2.8 mg, 6 µmol) under nitrogen. The reactions were capped and shaken at 65°C for 48 hours before cooling and concentrating in vacuo. The residue was washed with water (1 mL) and extracted into EtOAc (3 x 1 mL). The organic layers were collected and concentrated in vacuo to afford the step 2 intermediate.

Steps 3-5

To the Step 2 intermediates was added a solution of TFA in DCM (1 mL, v:v 1:5) and the reactions were shaken at 30°C for 4 hours before concentrating in vacuo. The residues were treated with ammonium hydroxide in MeOH (1.5 mL, v:v 1:3) and shaken at 30°C for 2 hours before concentrating in vacuo. The residues were treated with a saturated solution of $NaHCO_3$ in water (1 mL). To the solutions was added EtOAc (1 mL) followed by acryloyl chloride (200 µmol) and the reactions were shaken at 30°C for 2 hours. The reactions were concentrated in vacuo and purified using preparative HPLC as described below to afford the following Examples:

Preparative HPLC Method 1:

Column: Phenomenex Gemini C18 250x21.2 mm, 8 micron

Mobile phase: Acetonitrile:ammonium hydroxide (pH=10) or Acetonitrile:formic acid (0.225%).

Gradient time: 8 minutes; Hold time: 1 minute at 100% organic; Flow rate: 35 mL/min.

Preparative HPLC Method 2:

Column: DIKMA Diamonsil(2) C18 200x20 mm, 5 micron.

Mobile phase: Acetonitrile:formic acid (0.225%)

Gradient time: 8 minutes; Hold time: 1 minute at 100% organic; Flow rate: 35 mL/min.

QC Method 1:

Column: Xbridge C18 2.1x50 mm; 5 micron

Mobile phase A: 0.0375% TFA in water; Mobile phase B: 0.01875% TFA in MeCN.

Gradient: initial–1% B; 0.6 minutes–5% B; 4 minutes–100% B; 4.3 minutes–1% B; 4.7 minutes–1% B.

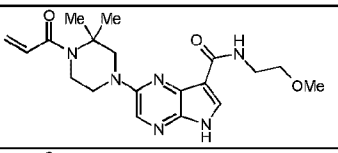
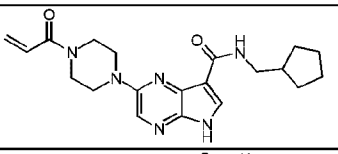
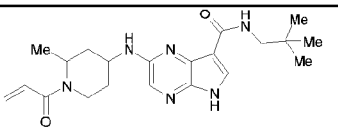
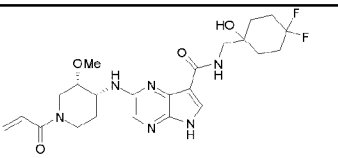
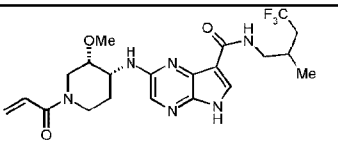
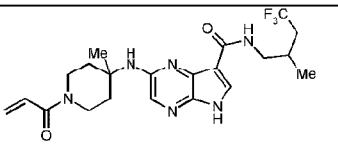
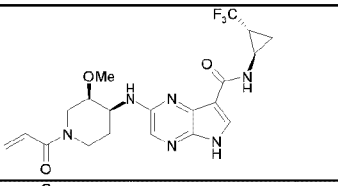
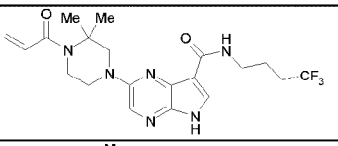
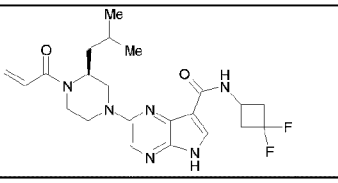
Flow rate: 0.8 mL/min

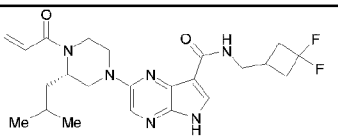
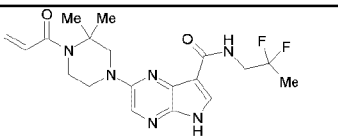
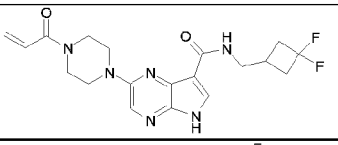
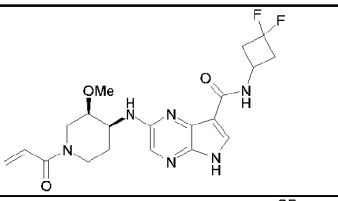
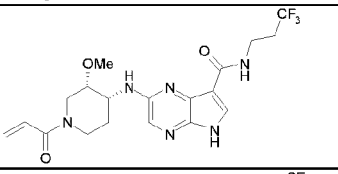
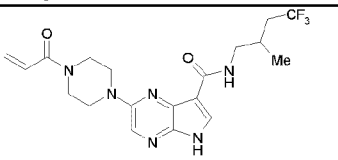
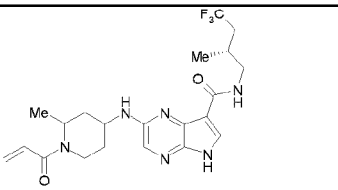
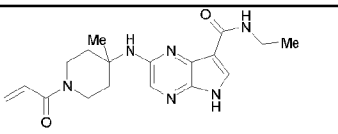
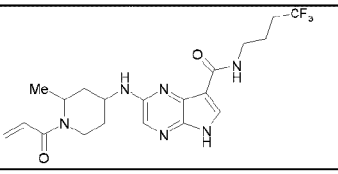
QC Method 2:

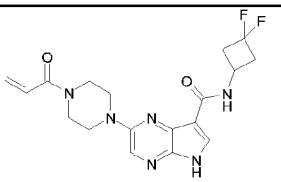
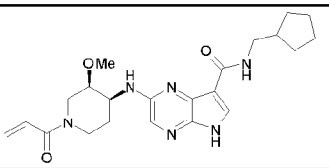
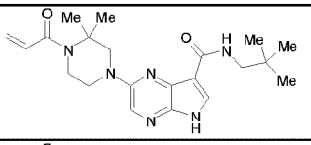
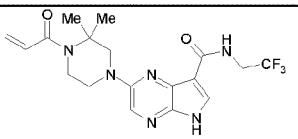
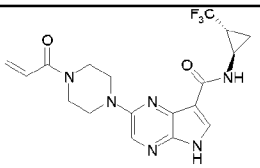
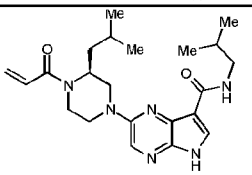
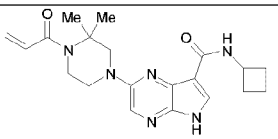
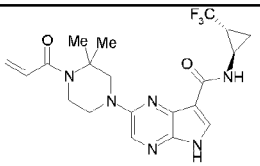
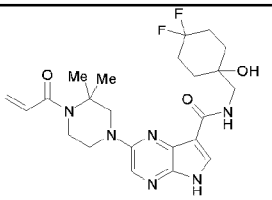
Column: Xbridge C18 2.1x50 mm; 5 micron. Mobile phase A: 0.05% NH_4OH in water; Mobile phase B: 100% MeCN. Gradient: initial–5% B; 0.5 minutes–5% B; 3.4 minutes–100% B; 4.2 minutes–100% B; 4.21 minutes–5% B; 4.7 minutes–5% B. Flow rate: 0.8 mL/min

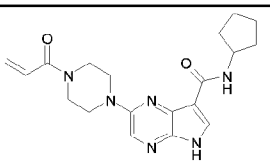
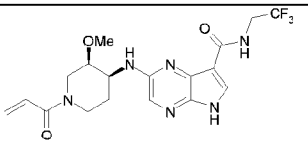
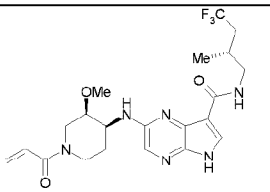
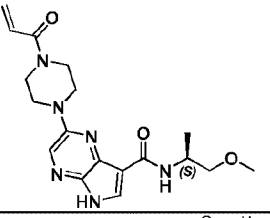
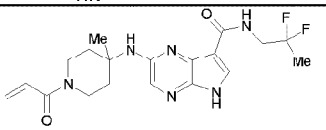
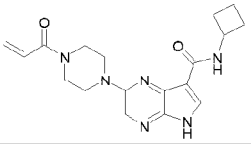
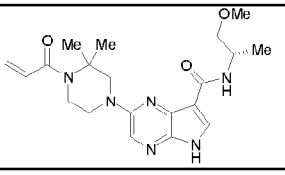
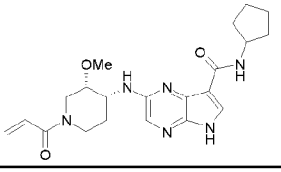
QC Method 1 was used unless otherwise specified:

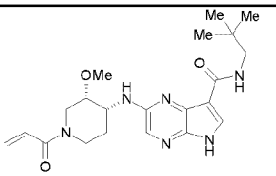
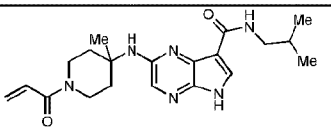
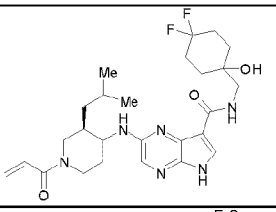
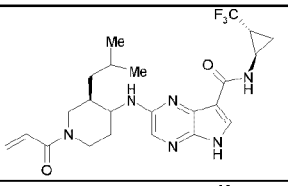
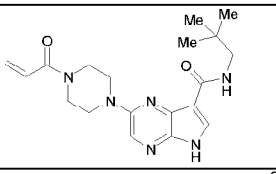
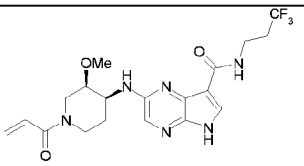
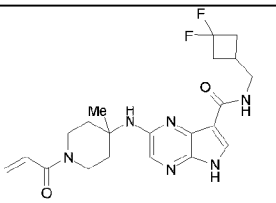
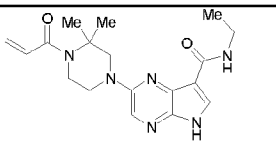
Ex. No.	Name	Structure	Data/% Organic Eluant/QC Method

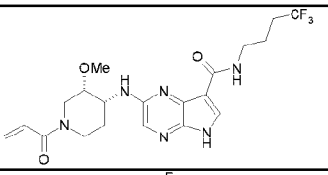
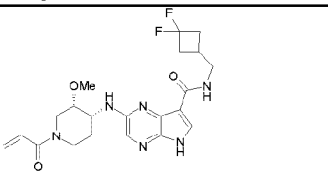
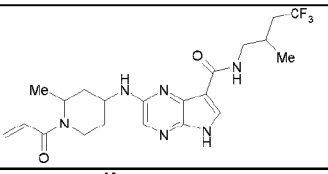
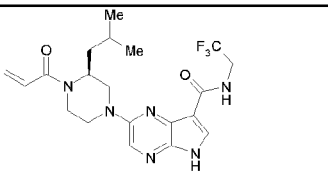
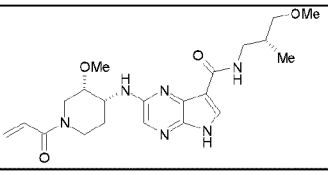
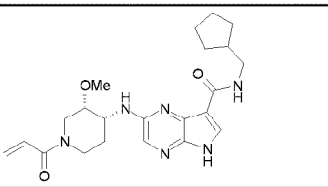
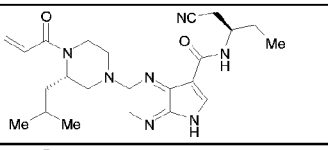
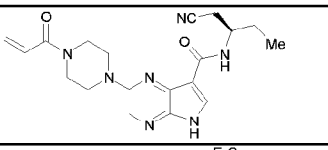
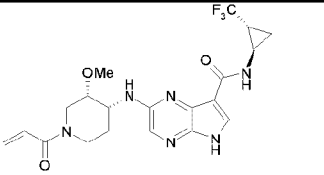
265	2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-(2-methoxyethyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 387 $[M+H]^+$ Rt = 2.58 minutes Prep HPLC gradient 18-58% organic.
266	2-(4-acryloylpiperazin-1-yl)-N-(cyclopentylmethyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 383 $[M+H]^+$ Rt = 2.85 minutes Prep HPLC gradient 28-59% organic.
267	Racemic-2-[(1-acryloyl-2-methylpiperidin-4-yl)amino]-N-(2,2-dimethylpropyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 399 $[M+H]^+$ Rt = 2.82 minutes Prep HPLC gradient 29-69% organic.
268	2-{[(3S,4R)-1-acryloyl-3-methoxypiperidin-4-yl]amino}-N-[(4,4-difluoro-1-hydroxycyclohexyl) methyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 493 $[M+H]^+$ Rt = 2.42 minutes Prep HPLC gradient 13-53% organic. Method 2.
269	Racemic-2-{[(3S,4R)-1-acryloyl-3-methoxypiperidin-4-yl]amino}-N-(4,4,4-trifluoro-2-methylbutyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 469 $[M+H]^+$ Rt = 2.82 minutes Prep HPLC gradient 18-58% organic.
270	Racemic-2-[(1-acryloyl-4-methylpiperidin-4-yl)amino]-N-(4,4,4-trifluoro-2-methylbutyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 453 $[M+H]^+$ Rt = 2.95 minutes Prep HPLC gradient 34-74% organic.
271	2-{[(3R,4S)-1-acryloyl-3-methoxypiperidin-4-yl]amino}-N-[(1R,2R)-2-(trifluoromethyl)cyclopropyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 453 $[M+H]^+$ Rt = 2.50 minutes Prep HPLC gradient 16-56% organic. Method 2.
272	2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-(4,4,4-trifluorobutyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 439 $[M+H]^+$ Rt = 2.64 minutes Prep HPLC gradient 32-72% organic. Method 2.
273	2-[(3S)-4-acryloyl-3-(2-methylpropyl)piperazin-1-yl]-N-(3,3-difluorocyclobutyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 447 $[M+H]^+$ Rt = 3.07 minutes Prep HPLC gradient 36-76% organic.

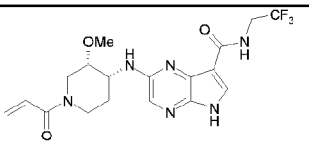
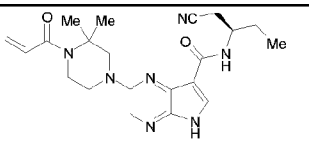
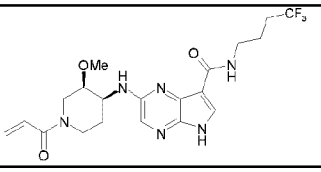
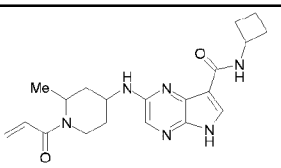
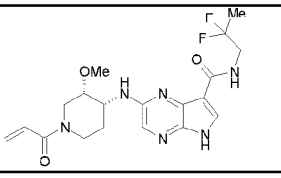
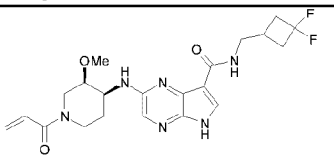
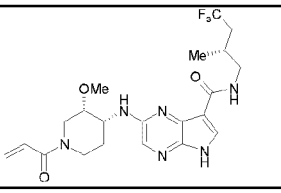
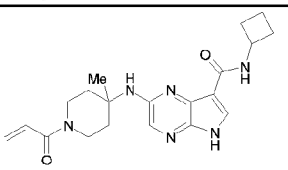
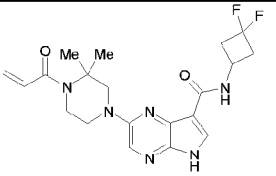
274	2-[(3S)-4-acryloyl-3-(2-methylpropyl)piperazin-1-yl]-N-[(3,3-difluorocyclobutyl)methyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 461 $[M+H]^+$ Rt = 3.12 minutes Prep HPLC gradient 39-79% organic.
275	2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-(2,2-difluoropropyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 407 $[M+H]^+$ Rt = 2.78 minutes Prep HPLC gradient 17-57% organic.
276	2-(4-acryloylpiperazin-1-yl)-N-[(3,3-difluorocyclobutyl)methyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 405 $[M+H]^+$ Rt = 2.71 minutes Prep HPLC gradient 27-67% organic.
277	2-{[(3R,4S)-1-acryloyl-3-methoxypiperidin-4-yl]amino}-N-(3,3-difluorocyclobutyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 435 $[M+H]^+$ Rt = 2.41 minutes Prep HPLC gradient 25-65% organic. Method 2.
278	2-{[(3S,4R)-1-acryloyl-3-methoxypiperidin-4-yl]amino}-N-(3,3,3-trifluoropropyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 441 $[M+H]^+$ Rt = 2.58 minutes Prep HPLC gradient 25-65% organic.
279	Racemic-2-(4-acryloylpiperazin-1-yl)-N-(4,4,4-trifluoro-2-methylbutyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 425 $[M+H]^+$ Rt = 2.85 minutes Prep HPLC gradient 25-55% organic.
280	2-[(1-acryloyl-2-methylpiperidin-4-yl)amino]-N-[(2R)-4,4,4-trifluoro-2-methylbutyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 453 $[M+H]^+$ Rt = 2.89 minutes Prep HPLC gradient 20-60% organic.
281	2-[(1-acryloyl-4-methylpiperidin-4-yl)amino]-N-ethyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 357 $[M+H]^+$ Rt = 2.35 minutes Prep HPLC gradient 10-50% organic. Method 2.
282	Racemic-2-[(1-acryloyl-2-methylpiperidin-4-yl)amino]-N-(4,4,4-trifluorobutyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 439 $[M+H]^+$ Rt = 2.81 minutes Prep HPLC gradient 28-68% organic.

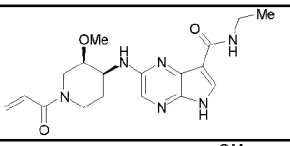
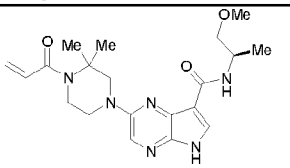
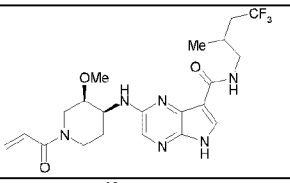
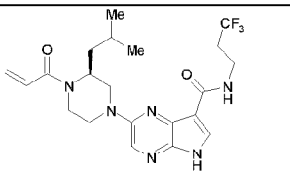
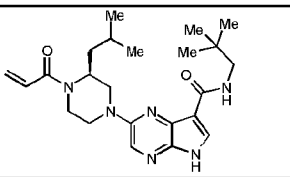
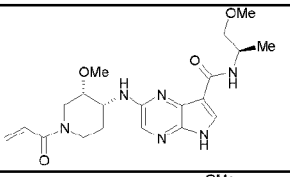
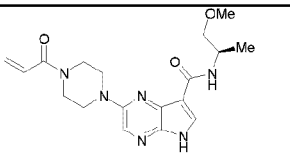
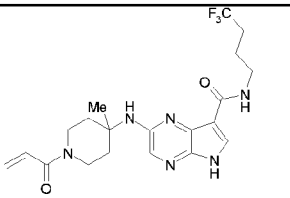
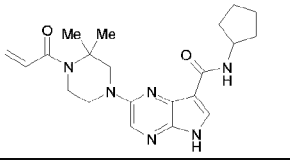
283	2-(4-acryloylpiperazin-1-yl)-N-(3,3-difluorocyclobutyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 391 $[M+H]^+$ Rt = 2.65 minutes Prep HPLC gradient 24-64% organic.
284	2-{[(3R,4S)-1-acryloyl-3-methoxypiperidin-4-yl]amino}-N-(cyclopentylmethyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 427 $[M+H]^+$ Rt = 2.54 minutes Prep HPLC gradient 30-70% organic. Method 2.
285	2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-(2,2-dimethylpropyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 399 $[M+H]^+$ Rt = 2.96 minutes Prep HPLC gradient 22-62% organic.
286	2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-(2,2,2-trifluoroethyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 411 $[M+H]^+$ Rt = 2.58 minutes Prep HPLC gradient 19-59% organic. Method 2.
287	2-(4-acryloylpiperazin-1-yl)-N-[(1R,2R)-2-(trifluoromethyl)cyclopropyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 409 $[M+H]^+$ Rt = 2.52 minutes Prep HPLC gradient 17-57% organic. Method 2.
288	2-[(3S)-4-acryloyl-3-(2-methylpropyl)piperazin-1-yl]-N-(2-methylpropyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 413 $[M+H]^+$ Rt = 3.10 minutes Prep HPLC gradient 39-79% organic.
289	2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-cyclobutyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 383 $[M+H]^+$ Rt = 2.81 minutes Prep HPLC gradient 29-69% organic.
290	2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-[(1R,2R)-2-(trifluoromethyl)cyclopropyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 437 $[M+H]^+$ Rt = 2.95 minutes Prep HPLC gradient 34-74% organic.
291	2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-[(4,4-difluoro-1-hydroxycyclohexyl)methyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 477 $[M+H]^+$ Rt = 2.81 minutes Prep HPLC gradient 29-69% organic.

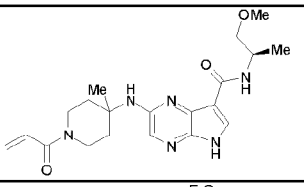
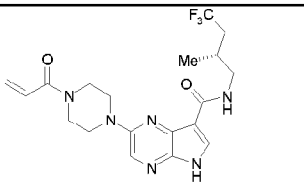
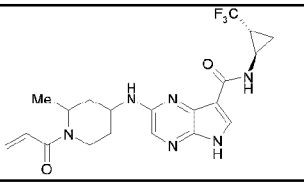
292	Racemic-2-(4-acryloylpiperazin-1-yl)-N-cyclopentyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 369 $[M+H]^+$ Rt = 2.70 minutes Prep HPLC gradient 26-66% organic.
293	2-{[(3R,4S)-1-acryloyl-3-methoxypiperidin-4-yl]amino}-N-(2,2,2-trifluoroethyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 427 $[M+H]^+$ Rt = 2.64 minutes Prep HPLC gradient 25-65% organic.
294	2-[((3R,4S)-1-acryloyl-3-methoxypiperidin-4-yl)amino]-N-([2R]-4,4,4-trifluoro-2-methylbutyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 469 $[M+H]^+$ Rt = 2.83 minutes Prep HPLC gradient 18-58% organic.
295	2-(4-acryloylpiperazin-1-yl)-N-[(2S)-1-methoxypropan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide (worng structure)		MS m/z 373 $[M+H]^+$ Rt = 2.29 minutes Prep HPLC gradient 21-61% organic. Method 2.
296	2-[(1-acryloyl-4-methylpiperidin-4-yl)amino]-N-(2,2-difluoropropyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 407 $[M+H]^+$ Rt = 2.48 minutes Prep HPLC gradient 27-67% organic. Method 2.
297	2-(4-acryloylpiperazin-1-yl)-N-cyclobutyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 355 $[M+H]^+$ Rt = 2.39 minutes Prep HPLC gradient 24-64% organic. Method 2.
298	2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-[(2S)-1-methoxypropan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 401 $[M+H]^+$ Rt = 2.70 minutes Prep HPLC gradient 25-65% organic.
299	Racemic-2-{[(3S,4R)-1-acryloyl-3-methoxypiperidin-4-yl]amino}-N-cyclopentyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 413 $[M+H]^+$ Rt = 2.67 minutes Prep HPLC gradient 25-65% organic.

300	2-{[(3S,4R)-1-acryloyl-3-methoxypiperidin-4-yl]amino}-N-(2,2-dimethylpropyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 415 $[M+H]^+$ Rt = 2.75 minutes Prep HPLC gradient 28-68% organic.
301	2-[(1-acryloyl-4-methylpiperidin-4-yl)amino]-N-(2-methylpropyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 385 $[M+H]^+$ Rt = 2.67 minutes Prep HPLC gradient 23-53% organic.
302	2-[(3S)-4-acryloyl-3-(2-methylpropyl)piperazin-1-yl]-N-[(4,4-difluoro-1-hydroxycyclohexyl)methyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 505 $[M+H]^+$ Rt = 3.04 minutes Prep HPLC gradient 36-76% organic.
303	2-[(3S)-4-acryloyl-3-(2-methylpropyl)piperazin-1-yl]-N-[(1R,2R)-2-(trifluoromethyl)cyclopropyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 465 $[M+H]^+$ Rt = 2.78 minutes Prep HPLC gradient 37-67% organic. Method 2.
304	2-(4-acryloylpiperazin-1-yl)-N-(2,2-dimethylpropyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 371 $[M+H]^+$ Rt = 2.78 minutes Prep HPLC gradient 28-68% organic.
305	2-{[(3R,4S)-1-acryloyl-3-methoxypiperidin-4-yl]amino}-N-(3,3,3-trifluoropropyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 441 $[M+H]^+$ Rt = 2.41 minutes Prep HPLC gradient 25-65% organic. Method 2.
306	2-[(1-acryloyl-4-methylpiperidin-4-yl)amino]-N-[(3,3-difluorocyclobutyl)methyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 433 $[M+H]^+$ Rt = 2.69 minutes Prep HPLC gradient 26-56% organic.
307	2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-ethyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 433 $[M+H]^+$ Rt = 2.64 minutes Prep HPLC gradient 24-64% organic.

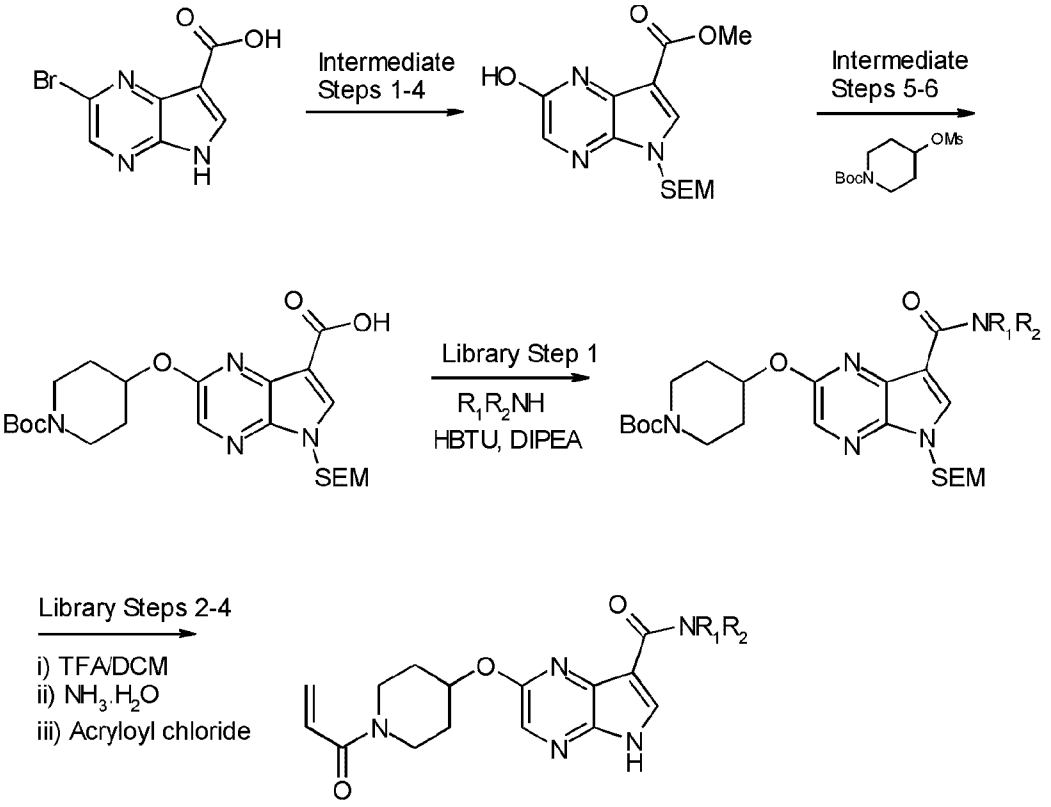
308	2-{[(3S,4R)-1-acryloyl-3-methoxypiperidin-4-yl]amino}-N-(4,4,4-trifluorobutyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 455 $[M+H]^+$ Rt = 2.64 minutes Prep HPLC gradient 24-64% organic.
309	2-{[(3S,4R)-1-acryloyl-3-methoxypiperidin-4-yl]amino}-N-[(3,3-difluorocyclobutyl)methyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 449 $[M+H]^+$ Rt = 2.64 minutes Prep HPLC gradient 23-53% organic.
310	Racemic-2-[(1-acryloyl-2-methylpiperidin-4-yl)amino]-N-(4,4,4-trifluoro-2-methylbutyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 453 $[M+H]^+$ Rt = 2.81 minutes Prep HPLC gradient 29-59% organic.
311	2-[(3S)-4-acryloyl-3-(2-methylpropyl)piperazin-1-yl]-N-(2,2,2-trifluoroethyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 439 $[M+H]^+$ Rt = 3.09 minutes Prep HPLC gradient 26-66% organic.
312	2-{[(3S,4R)-1-acryloyl-3-methoxypiperidin-4-yl]amino}-N-[(2S)-1-methoxypropan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 417 $[M+H]^+$ Rt = 2.16 minutes Prep HPLC gradient 13-53% organic. Method 2.
313	2-{[(3S,4R)-1-acryloyl-3-methoxypiperidin-4-yl]amino}-N-(cyclopentylmethyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 427 $[M+H]^+$ Rt = 2.16 minutes Prep HPLC gradient 13-53% organic.
314	2-[(3S)-4-acryloyl-3-(2-methylpropyl)piperazin-1-yl]-N-[(2R)-1-cyanobutan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 438 $[M+H]^+$ Rt = 2.88 minutes Prep HPLC gradient 28-58% organic.
315	2-(4-acryloylpiperazin-1-yl)-N-[(2R)-1-cyanobutan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 382 $[M+H]^+$ Rt = 2.21 minutes Prep HPLC gradient 16-46% organic. Method 2.
316	2-{[(3S,4R)-1-acryloyl-3-methoxypiperidin-4-yl]amino}-N-[(1R,2R)-2-(trifluoromethyl)cyclopropyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 453 $[M+H]^+$ Rt = 2.64 minutes Prep HPLC gradient 25-55% organic.

317	2-{[(3S,4R)-1-acryloyl-3-methoxypiperidin-4-yl]amino}-N-(2,2,2-trifluoroethyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 427 $[M+H]^+$ Rt = 2.64 minutes Prep HPLC gradient 26-66% organic.
318	2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-[(2R)-1-cyanobutan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 410 $[M+H]^+$ Rt = 2.24 minutes Prep HPLC gradient 21-51% organic.
319	2-{[(3R,4S)-1-acryloyl-3-methoxypiperidin-4-yl]amino}-N-(4,4,4-trifluorobutyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 455 $[M+H]^+$ Rt = 2.64 minutes Prep HPLC gradient 21-51% organic.
320	Racemic-2-[(1-acryloyl-2-methylpiperidin-4-yl)amino]-N-cyclobutyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 383 $[M+H]^+$ Rt = 2.42 minutes Prep HPLC gradient 26-66% organic. Method 2.
321	2-{[(3S,4R)-1-acryloyl-3-methoxypiperidin-4-yl]amino}-N-(2,2-difluoropropyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 423 $[M+H]^+$ Rt = 2.47 minutes Prep HPLC gradient 20-50% organic.
322	2-{[(3R,4S)-1-acryloyl-3-methoxypiperidin-4-yl]amino}-N-[(3,3-difluorocyclobutyl)methyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 449 $[M+H]^+$ Rt = 2.58 minutes Prep HPLC gradient 23-53% organic.
323	2-{[(3S,4R)-1-acryloyl-3-methoxypiperidin-4-yl]amino}-N-[(2R)-4,4,4-trifluoro-2-methylbutyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 469 $[M+H]^+$ Rt = 2.83 minutes Prep HPLC gradient 30-70% organic.
324	2-[(1-acryloyl-4-methylpiperidin-4-yl)amino]-N-cyclobutyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 383 $[M+H]^+$ Rt = 2.61 minutes Prep HPLC gradient 21-51% organic.
325	2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-(3,3-difluorocyclobutyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 419 $[M+H]^+$ Rt = 2.55 minutes Prep HPLC gradient 31-71% organic. Method 2.

326	2-{[(3R,4S)-1-acryloyl-3-methoxypiperidin-4-yl]amino}-N-ethyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 373 $[M+H]^+$ Rt = 2.42 minutes Prep HPLC gradient 18-58% organic.
327	2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-[(2R)-1-methoxypropan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 401 $[M+H]^+$ Rt = 2.59 minutes Prep HPLC gradient 23-53% organic.
328	Racemic-2-{[(3R,4S)-1-acryloyl-3-methoxypiperidin-4-yl]amino}-N-(4,4,4-trifluoro-2-methylbutyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 469 $[M+H]^+$ Rt = 2.73 minutes Prep HPLC gradient 27-57% organic.
329	2-[(3S)-4-acryloyl-3-(2-methylpropyl)piperazin-1-yl]-N-(3,3,3-trifluoropropyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 453 $[M+H]^+$ Rt = 3.09 minutes Prep HPLC gradient 37-77% organic.
330	2-[(3S)-4-acryloyl-3-(2-methylpropyl)piperazin-1-yl]-N-(2,2-dimethylpropyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 427 $[M+H]^+$ Rt = 3.01 minutes Prep HPLC gradient 29-69% organic.
331	2-{[(3S,4R)-1-acryloyl-3-methoxypiperidin-4-yl]amino}-N-[(2R)-1-methoxypropan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 417 $[M+H]^+$ Rt = 2.37 minutes Prep HPLC gradient 17-47% organic.
332	2-(4-acryloylpiperazin-1-yl)-N-[(2R)-1-methoxypropan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 373 $[M+H]^+$ Rt = 2.17 minutes Prep HPLC gradient 14-44% organic. Method 2.
333	2-[(1-acryloyl-4-methylpiperidin-4-yl)amino]-N-(4,4,4-trifluorobutyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 439 $[M+H]^+$ Rt = 2.75 minutes Prep HPLC gradient 24-54% organic.
334	2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-cyclopentyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 397 $[M+H]^+$ Rt = 2.88 minutes Prep HPLC gradient 32-72% organic.

335	2-[(1-acryloyl-4-methylpiperidin-4-yl)amino]-N-[(2R)-1-methoxypropan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 401 $[M+H]^+$ Rt = 2.48 minutes Prep HPLC gradient 17-47% organic.
336	2-(4-acryloylpiperazin-1-yl)-N-[(2R)-4,4,4-trifluoro-2-methylbutyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 425 $[M+H]^+$ Rt = 2.86 minutes Prep HPLC gradient 19-59% organic.
337	Racemic-2-[(1-acryloyl-2-methylpiperidin-4-yl)amino]-N-[(1R,2R)-2-(trifluoromethyl)cyclopropyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide		MS m/z 437 $[M+H]^+$ Rt = 2.83 minutes Prep HPLC gradient 18-58% organic.

Examples 338-348 were prepared according to the synthesis and **Library Protocol 6** below:



Intermediate Steps 1-4

Methyl 5-hydroxy-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxylate

To a solution of 5-bromo-1H-pyrrolo[2,3-b]pyridine-3-carboxylic acid (22 g, 92 mmol) in MeOH (220 mL) was added thionyl chloride (33 mL) and the reaction was heated to 70°C for 18 hours. The reaction was concentrated in vacuo and the residue treated with saturated aqueous $NaHCO_3$ solution (200 mL) to afford a precipitate. The solid was filtered and dried to afford the methyl ester intermediate. A solution of this intermediate (9.1 g, 35 mmol) in DMF (150 mL) was treated with sodium hydride (3.57 g, 89 mmol) and stirred at 0°C for 30 minutes. SEMCl (11.9 g, 71 mmol) was added and the reaction stirred at room temperature for 2 hours. The reaction was quenched by the addition of ice-water (100 mL) and extracted into EtOAc (2 x 100 mL). The combined organic layers were washed with brine, dried over sodium sulphate and concentrated in vacuo. The residue was purified using silica gel column chromatography eluting with 0-30% EtOAc in petroleum ether to afford the SEM protected intermediate. To a solution of this intermediate (4.20 g, 10.9 mmol) in dioxane (100 mL) was added bispinacolatodiborane (3.32 g, 13.1 mmol) and potassium acetate (3.21 g, 32 mmol). The reaction was degassed with nitrogen before the addition of $Pd(dppf)Cl_2$ (798 mg, 1.09 mmol) and heating to 100°C for 18 hours. The reaction was cooled, concentrated in vacuo and purified using silica gel column chromatography eluting with 0-30% EtOAc in petroleum ether. The residue was dissolved in THF (50 mL) and water (50 mL) and treated with $NaBO_3.4H_2O$ (8.36 g, 54 mmol) at 10°C. The reaction was stirred at room temperature for 2 hrs and then partitioned between EtOAc and water. The organic layer was collected, washed with brine, dried over sodium sulphate and concentrated in vacuo to afford the title compound (4 g, 90% over 4 steps) that was taken on directly to the next step.

Intermediate Steps 5-6

5-((1-(tert-butoxycarbonyl)piperidin-4-yl)oxy)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxylic acid

To a solution of methyl 5-hydroxy-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxylate (**Intermediate Steps 1-4**, 4 g, 11 mmol) in DMF (50 mL) was added potassium carbonate (5.41 g, 25 mmol) and the reaction was heated to 110°C for 5 minutes. tert-butyl 4-((methylsulfonyl)oxy)piperidine-1-carboxylate (2.5 g, 12.4 mmol) was added and the reaction was heated at 70°C for 2 hours. Further tert-butyl 4-((methylsulfonyl)oxy)piperidine-1-carboxylate (2.5 g, 12.4 mmol) was added and the reaction heated to 110°C for 18 hours. The reaction was cooled and partitioned between EtOAc (130 mL) and water (120 mL). The aqueous layer was extracted with EtOAc (50 mL) and the organic extracts were combined, dried over sodium sulphate and concentrated in vacuo. The residue was purified using silica gel column chromatography eluting with 0-20% EtOAc in petroleum ether. The residue was dissolved in MeOH (50 mL) and treated with a solution of sodium hydroxide (2.26 g, 56 mmol) in water (30 mL). The reaction was heated to 60°C for 18 hours. The reaction was cooled, concentrated in vacuo, acidified to pH=4-5 with 1N HCl (aq) and extracted into EtOAc (2 x 100 mL). The combined organic layers were washed with brine, dried over sodium sulphate and concentrated in vacuo to afford the title compound as a white solid (4.2 g, 94 over 2 steps).

^{1}H NMR (400MHz, DMSO-d_6):δ ppm 12.34 (br s, 1H), 8.32 (s, 1H), 8.15 (s, 1H), 7.90 (s, 1H), 5.63 (s, 2H), 4.62-4.59 (m, 1H), 3.68-3.65 (m, 2H), 3.56-3.53 (m, 2H), 3.30-3.20 (m, 2H), 1.98-1.90 (m, 2H), 1.61-1.55 (m, 2H), 0.84-0.81 (m, 2H), -0.09 (s, 9H). MS m/z 514 $[M+Na]^+$

Library Protocol 6

Step 1

To a 0.25M solution of 5-((1-(tert-butoxycarbonyl)piperidin-4-yl)oxy)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxylic acid (**Intermediate Steps 5-6**, 400 µL, 100 µmol) in DMF were added amines of formula R_1R_2NH (150 µmol) followed by DIPEA (39 mg, 300 µmol) and a 0.27M solution of HBTU in DMF (400 µL, 110 µmol). The reactions were shaken at 60°C for 16 hours before cooling and concentrating in vacuo. The residues were washed with water (1 mL) and extracted into EtOAc (3 x 1 mL). The combined organic layers were concentrated in vacuo to afford the Step 1 intermediates.

Steps 2-4

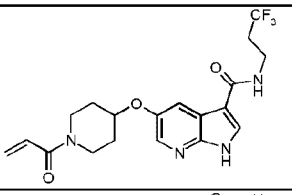
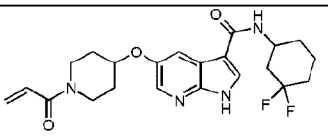
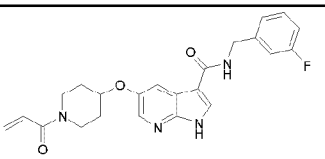
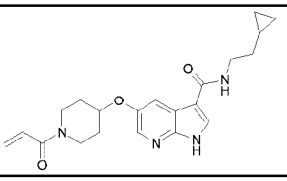
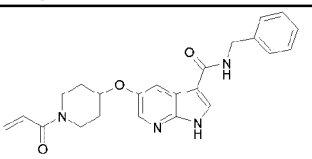
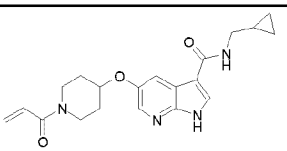
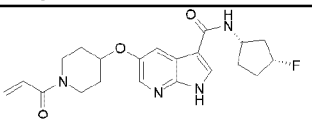
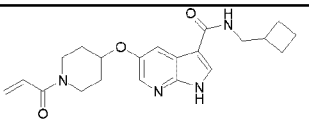
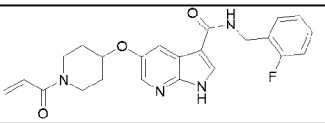
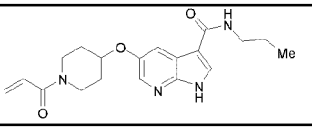
To the Step 1 intermediates was added a solution of TFA in DCM (1.2 mL, v:v 1:5) and the reactions were shaken at 30°C for 4 hours before concentrating in vacuo. The residues were treated with ammonium hydroxide in MeOH (1.6 mL, v:v 1:3) and shaken at 30°C for 6 hours before concentrating in vacuo. The residues were treated with a saturated solution of $NaHCO_3$ in water (1 mL). To the solutions was added EtOAc (1 mL) followed by acryloyl chloride (18 mg, 200 µmol) and the reactions were shaken at 30°C for 2 hours. The reactions were concentrated in vacuo and purified using preparative HPLC as described below to afford the following Examples:

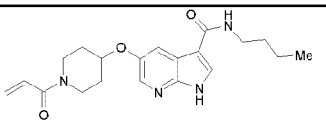
Preparative HPLC:

Column: Phenomenex Gemini C18 250x21.2 mm, 8 micron. Mobile phase: Acetonitrile:ammonium hydroxide (pH=10). Gradient time: 8 minutes; Hold time: 1 minute at 100% organic; Flow rate: 35 mL/min.

QC Method:

Column: Xbridge C18 2.1x50 mm; 5 micron. Mobile phase A: 0.0375% TFA in water; Mobile phase B: 0.01875% TFA in MeCN. Gradient: initial–1% B; 0.6 minutes–5% B; 4 minutes–100% B; 4.3 minutes–1% B; 4.7 minutes–1% B. Flow rate: 0.8 mL/min

Ex. No.	Name	Structure	Data/% Organic Eluant
338	5-[(1-acryloylpiperidin-4-yl)oxy]-N-(3,3,3-trifluoropropyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide		MS m/z 411 $[M+H]^+$ Rt = 2.56 minutes Prep HPLC gradient 22-62% organic.
339	5-[(1-acryloylpiperidin-4-yl)oxy]-N-(3,3-difluorocyclohexyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide		MS m/z 433 $[M+H]^+$ Rt = 2.65 minutes Prep HPLC gradient 25-65% organic.
340	5-[(1-acryloylpiperidin-4-yl)oxy]-N-(3-fluorobenzyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide		MS m/z 423 $[M+H]^+$ Rt = 2.70 minutes Prep HPLC gradient 26-66% organic.
341	5-[(1-acryloylpiperidin-4-yl)oxy]-N-(3,3-difluorocyclohexyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide		MS m/z 423 $[M+H]^+$ Rt = 2.70 minutes Prep HPLC gradient 26-66% organic.
342	5-[(1-acryloylpiperidin-4-yl)oxy]-N-benzyl-1H-pyrrolo[2,3-b]pyridine-3-carboxamide		MS m/z 383 $[M+H]^+$ Rt = 2.59 minutes Prep HPLC gradient 28-68% organic.
343	5-[(1-acryloylpiperidin-4-yl)oxy]-N-(cyclopropylmethyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide		MS m/z 369 $[M+H]^+$ Rt = 2.46 minutes Prep HPLC gradient 19-59% organic.
344	5-[(1-acryloylpiperidin-4-yl)oxy]-N-[(1S,3R)-3-fluorocyclopentyl]-1H-pyrrolo[2,3-b]pyridine-3-carboxamide		MS m/z 401 $[M+H]^+$ Rt = 2.47 minutes Prep HPLC gradient 19-59% organic.
345	5-[(1-acryloylpiperidin-4-yl)oxy]-N-(cyclobutylmethyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide		MS m/z 383 $[M+H]^+$ Rt = 2.62 minutes Prep HPLC gradient 24-64% organic.
346	5-[(1-acryloylpiperidin-4-yl)oxy]-N-(2-fluorobenzyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide		MS m/z 423 $[M+H]^+$ Rt = 2.69 minutes Prep HPLC gradient 26-66% organic.
347	5-[(1-acryloylpiperidin-4-yl)oxy]-N-propyl-1H-pyrrolo[2,3-b]pyridine-3-carboxamide		MS m/z 357 $[M+H]^+$ Rt = 2.41 minutes Prep HPLC gradient 18-58% organic.

348	5-[(1-acryloylpiperidin-4-yl)oxy]-N-butyl-1H-pyrrolo[2,3-b]pyridine-3-carboxamide		MS m/z 371 $[M+H]^+$ Rt = 2.57 minutes Prep HPLC gradient 23-63% organic.

Example 349:

2-(((2S,4S)-1-acryloyl-2-methylpiperidin-4-yl)amino)-N-ethyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide (cis racemic)

The title compound was prepared according to the method described for Example __ using cis-racemic-benzyl 4-amino-2-methylpiperidine-1-carboxylate. The residue was purified using silica gel column chromatography eluting with 5% MeOH in DCM followed by preparative HPLC eluting with 18-38% MeCN in water modified with ammonia to pH=10. ^{1}H NMR (400 MHz, $CHCl_3$-*d*) d ppm 9.69 (br. s., 1 H) 8.15 (br. s., 1 H) 8.04 (br. s., 1 H) 7.60 - 7.75 (m, 1 H) 6.59 (dd, *J*=16.56, 10.54 Hz, 1 H) 6.33 (d, *J*=17.07 Hz, 1 H) 5.72 (d, *J*=11.04 Hz, 1 H) 4.73 (d, *J*=4.52 Hz, 1 H) 4.54 (br. s., 1 H) 4.15 (d, *J*=4.52 Hz, 2 H) 3.44 - 3.65 (m, 2 H) 3.32 (t, *J*=11.54 Hz, 1 H) 2.06 - 2.26 (m, 2 H) 1.93 (d, *J*=13.05 Hz, 2 H) 1.26-1.40 (m, 6 H) MS m/z [M+H]+ = 357.0

QC Analytical LC Method

Column: Xtimate C18 (5x30mm, 3µm). Mobile Phase: 1-100% MeCN/H_2O (0.05% TFA)

Rt =3.19 min. LC/MS = 3.19 min (XTimate C18 5*30 mm, 3 um)

The cis-racemic material was separated into its enantiomers using preparative chiral chromatography according to conditions described below:

Prep Chiral LC Method:

Column: AS-H (21x250mm, 5um); CO_2/EtOH ; 85:15 A/B hold for 15 min, T = 40 °C, flow: 75 mL/min

Chiral LC QC Method:

Column: AS-H (4.6x 100 mm, 5um); CO_2/EtOH ; 80:20 A/B hold for 15 min, T = 40 oC, flow: 1.5 mL/min

The two enantiomers were arbitrarily assigned absolute stereochemistry

First Eluting isomer: Example 350

2-(((2S,4S)-1-Acryloyl-2-methylpiperidin-4-yl)amino)-N-ethyl-5-methyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide. Rt = 5.29 MS m/z 357 [M+H]+

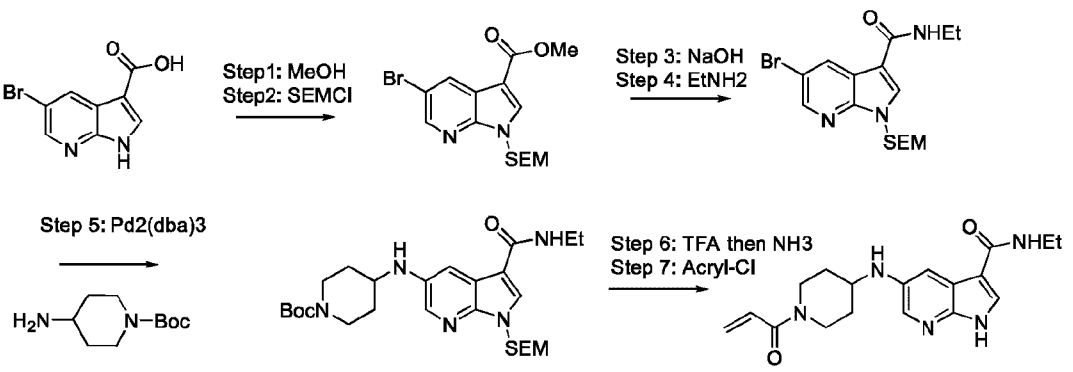
Second eluting isomer: Example 351

2-(((2R,4R)-1-Acryloyl-2-methylpiperidin-4-yl)amino)-N-ethyl-5-methyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide. Rt = 7.43 MS m/z 379 [M+H]+

Example 352

5-((1-Acryloylpiperidin-4-yl)amino)-N-ethyl-1-methyl-1H-pyrrolo[2,3-b]pyridine-3-carboxamide

Prepared according to scheme below



Example 352, Step 1

To a mixture of 5-bromo-1H-pyrrolo[2,3-b]pyridine-3-carboxylic acid (20 g, 82.99 mmol) in MeOH (200 mL) was added $SOCl_2$ (30ml) dropwise at room temperature. After addition, the resulting mixture was heated to 70 °C and stirred overnight. TLC (EtOAc) showed the reaction was completed. The solvent was removed *in vacuo* and then aqueous $NaHCO_3$ (20 mL) was added at which time a precipitate formed. The solid was filtered and dried to give methyl 5-bromo-1H-pyrrolo[2,3-b]pyridine-3-carboxylate (15.3g, 72.3%) as a brown solid.

Example 352 Step 2

To a solution of **Example 352**, step 1 (14.3 g, 56.1 mmol) in DMF (200 mL) at 0 °C was added NaH (5.61g, 140.25 mmol) in portions. After addition, the mixture was stirred at 0 °C for 0.5 then SEM-Cl (18.7g, 112.2 mmol) was added dropwise and the reaction stirred at room temperature for 4 h. TLC (Petroleum ether/ EtOAc=2/1) showed most of the starting material was consumed and the reaction mixture was poured into ice-water and extracted with EtOAc (300 mL*2). The combined organic layers were washed with brine and dried over Na_2SO_4, filtered, and concentrated to give the crude product, which was purified by silica-gel column (eluting with EtOAc/Petroleum ether=5%~10%) to obtain methyl 5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxylate (10.1g, 46.8%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) d ppm 8.33 - 8.61 (m, 3 H) 5.68 (s, 2 H) 3.87 (s, 3 H) 3.56 (t, *J*=8.03 Hz, 2 H) 0.82 (t, *J*=8.03 Hz, 2 H) -0.10 (s, 9 H).

Example 352 Step 3

To a solution of **Example 352, Step 2** (5.0 g, 13.0 mmol) in THF (150 mL) was added a solution of NaOH (2.6 g, 65.0 mmol) in H_2O (50 mL) and the mixture refluxed overnight. TLC (EtOAc/Petroleum ether = 1:2) showed the starting material was consumed completely. The solvent was removed and the residue was diluted with H_2O (30ml), the solution was adjusted to pH=6 with conc'd HCl. The solution was extracted with EtOAc (200mlx2) and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered ,and concentrated to give 5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxylic acid (4.2 g, 87.1%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) d ppm 12.66 (br. s., 1 H) 8.22 - 8.65 (m, 3 H) 5.67 (s, 2 H) 3.55 (t, *J*=8.03 Hz, 2 H) 0.82 (t, *J*=8.03 Hz, 2 H) -0.35 - 0.05 (m, 9 H)

Example 352 Step 4

To a solution of **Example 352, Step 3** (1.1 g, 2.96 mmol) in DMF (20 mL) was added Et_3N (598 mg, 5.92 mmol) and HATU (1.35 g, 3.55 mmol), followed by $EtNH_2$ (267 mg, 5.92 mmol). The mixture was stirred at room temperature overnight. TLC (EtOAc/Petroleum ether = 1:2) showed the starting material was consumed completely. H_2O (30 mL) was added and the mixture was extracted with EtOAc (50 mLx2) and the combined organic layers were washed with H_2O (30 mL), brine (50 mL), dried over Na_2SO_4, filtered, and concentrated to give the crude material, which was purified by silica-gel column eluting with EtOAc/Petroleum ether = 1/12~1/2 to provide 5-bromo-N-ethyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide (1.02 g, 86.6%) as a white solid. 1H NMR (400 MHz, DMSO- d_6) d ppm 8.63 (s, 1 H) 8.44 (s, 1 H) 8.35 (s, 1 H), 8.22-8.19 (m, 1 H), 5.65 (s, 2 H), 3.54-3.51 (m, 2 H) 3.31-3.28 (m, 2 H) 1.16-1.12 (m, 3 H) 0.86-0.82 (m, 2 H) -0.09 (s, 9 H)

Example 352 Step 5

To a stirred solution of **Example 352 Step 4** (700 mg, 1.75 mmol) in toluene (20 mL) was added tert-butyl 4-aminopiperidine-1-carboxylate (700 mg, 3.5 mmol), and t-BuONa (504mg, 5.25 mmol) at room temperature. The resulting mixture was degassed and purged with N_2 twice and then $Pd_2(dba)_3$ (320 mg, 0.35mmol) and X-phos (167 mg, 0.35 mmol) were added. The resulting mixture was degassed and purged with N_2 again and stirred at 100°C overnight under N_2 atmosphere. TLC (EtOAc/Petroleum ether = 1:1) showed the starting material was consumed completely. The solvent was removed and the residue was diluted with H_2O (20 mL) and extracted with EtOAc (40 mLx2). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified via Biotage SP1 (EtOAc/PE from 25% to 100% as eluent) to give tert-butyl 4-((3-(ethylcarbamoyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)amino)piperidine-1-carboxylate (422mg, 46.5%) as yellow oil. MS m/z 518 [M+H]+

Example 352 Step 6/7

To a solution of **Example 352, Step 5** (422 mg, 0.82 mmol) in DCM (4 mL) at 0 ◦C was added TFA (5 mL). The mixture was warmed to room temperature and stirred for 3 hours, after which LCMS showed the reaction was completed. The mixture was evaporated to dryness to give crude product (655 mg, 100%) as a yellow oil which was used in the next step. To the crude product (655 mg, 1.40 mmol) in MeOH (4 mL) at 0 ◦C was added NH_3/H_2O (3 mL). The mixture was stirred at room temperature for 2 hrs, after which LC/MS indicated no starting material remained. The reaction was evaporated to give desired product (400 mg, 99.2%), which was taken directly to the next step. MS m/z 288 [M+H]+

Example 352 Step 8

To a stirred solution of **Example 352**, Step 7 (400 mg, 1.39 mmol,) in THF/H_2O (3 mL/3 mL) was added DIPEA (360 mg, 2.78 mmol), followed by acryloyl chloride (252 mg, 2.78 mmol) dropwise at 0°C carefully. After the addition, the resulting mixture was stirred at 0°C for 2 hours. LCMS showed the start material had been consumed. The mixture was purified via Biotage SP1 (MeOH/DCM from

0~10%) to give 5-((1-acryloylpiperidin-4-yl)amino)-N-ethyl-1H-pyrrolo[2,3-b]pyridine-3-carboxamide (142mg, 35.5%) as a yellow solid, this was further purified by HPLC give desired product.

Prep HPLC

Column: Kromasil Eternity XT C18 250 *21.2* 10µm. Mobile phase: 5% MeCN/H_2O to 25% MeCN/H_2O , pH = 10

QC Analytical HPLC

Column: Ultimate XB-C18, 3 µm, 3*50 mm. Mobile Phase 1% CH_3CN/H_2O to 100% CH_3CN/H_2O (0.1% TFA). Rt = 2.63 min; MS m/z 342 [M+H]+. ^{1}H NMR (400 MHz, DMSO-d_6) d ppm 11.59 (br. s., 1 H) 7.75 - 8.02 (m, 3 H) 7.67 (br. s., 1 H) 6.85 (dd, *J*=16.56, 10.54 Hz, 1 H) 6.11 (d, *J*=16.06 Hz, 1 H) 5.68 (d, *J*=10.04 Hz, 1 H) 5.31 (d, *J*=8.03 Hz, 1 H) 4.30 (d, *J*=12.55 Hz, 1 H) 4.03 (d, *J*=13.05 Hz, 1 H) 3.51 (br. s., 1 H) 3.15 - 3.31 (m, 4 H) 2.95 (t, *J*=11.54 Hz, 1 H) 1.98 (br. s., 2 H) 1.29 (br. s., 2 H) 1.13 (t, *J*=7.03 Hz, 3 H)

Example 353

2-(((2S,4S)-1-Acryloyl-2-methylpiperidin-4-yl)amino)-N-((S)-1-methoxypropan-2-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide (cis-racemic)

The title compound was prepared analogous to the method described for **Example 71**, using cis-racemic benzyl (2S,4S)-4-amino-2-methylpiperidine-1-carboxylate and (S)-2-bromo-N-(1-methoxypropan-2-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide. The residue was purified using silica gel column chromatography eluting with 0 to 10% MeOH in DCM followed by preparative HPLC eluting with 24-44% MeCN in water modified with ammonia to pH=10 (Phenomenex Gemini C18 250*211.2mm*8 um). LCMS analysis: Xtimate C18 5*30mm, 3 um; 1 to 100% MeCN/H_2O in 0.1% TFA. Rt = 3.27 min MS m/z 423 [M+Na]+. ^{1}H NMR (400 MHz, DMSO-d_6) d ppm 12.10 (br. s., 1 H) 8.21 - 8.53 (m, 1 H) 7.88 (s, 1 H) 7.79 (s, 1 H) 7.09 (dd, *J*=14.31, 5.77 Hz, 1 H) 6.80 (dd, *J*=16.81, 10.29 Hz, 1 H) 6.12 (dd, *J*=16.81, 2.26 Hz, 1 H) 5.67 (dd, *J*=10.54, 2.51 Hz, 1 H) 4.41 (br. s., 1 H) 3.81 - 4.29 (m, 3 H) 3.10 - 3.30 (m, 6 H) 1.63 - 2.14 (m, 4 H) 1.05 - 1.37 (m, 6 H)

Example 354

2-(((2S,4S)-1-Acryloyl-2-methylpiperidin-4-yl)amino)-N-((R)-1-methoxypropan-2-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide (cis-racemic)

The title compound was prepared analogous to the method described for **Example 71** using cis-racemic benzyl (2S,4S)-4-amino-2-methylpiperidine-1-carboxylate and (R)-2-bromo-N-(1-methoxypropan-2-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamideThe residue was purified using silica gel column chromatography eluting with 0 to 10% MeOH in DCM followed by preparative HPLC eluting with 24-44% MeCN in water modified with ammonia to pH=10 (Phenomenex Gemini C18 250*211.2mm*8 µm)

LCMS analysis: Xtimate C18 5*30mm, 3 um; 1 to 100% MeCN/H_2O in 0.1% TFA. Rt = 3.25 min MS m/z 423 [M+Na]+. ^{1}H NMR (400 MHz, DMSO-d_6) d ppm 8.20 - 8.44 (m, 1 H) 7.83 - 7.96 (m, 1 H) 7.79 (s, 1 H) 7.03 (dd, *J*=13.55, 5.52 Hz, 1 H) 6.79 (dd, *J*=16.56, 10.54 Hz, 1 H) 6.12 (dd, *J*=16.56, 2.51

Hz, 1 H) 5.67 (dd, *J*=10.54, 2.51 Hz, 1 H) 4.41 (br. s., 1 H) 3.87 - 4.26 (m, 3 H) 3.09 - 3.49 (m, 9 H) 1.88 - 2.15 (m, 3 H) 1.77 (br. s., 1 H) 0.97 - 1.40 (m, 6 H)

Example 355 and Example 356

2-(((3S,4R)-1-Acryloyl-3-methoxypiperidin-4-yl)amino)-N-((S)-1-methoxypropan-2-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

and

2-(((3R,4S)-1-Acryloyl-3-methoxypiperidin-4-yl)amino)-N-((S)-1-methoxypropan-2-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

The title compounds were prepared analogous to the method described **for Example 71**, using cis-racemic tert-butyl (3S,4R)-4-amino-3-methoxypiperidine-1-carboxylate and (S)-2-bromo-N-(1-methoxypropan-2-yl)-5-((2-(trimethylsilyl)ethoxy)methyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide. The residue was purified using silica gel column chromatography eluting with 0 to 10% MeOH in DCM (800 mg, 94%) followed by preparative HPLC eluting with 22-42% MeCN in water modified with ammonia to pH=10 (Phenomenex Gemini C18 250*211.2mm*8 um) to give racemic-cis material (350 mg, 41%).

The rac-cis material was separated by chiral SFC to give the enantiomeric pair, stereochemistry arbitrarily assigned:

Prep SFC Conditions

Column: OD (250mm*30mm, 10 µm); Mobile phase: 35% MeOH, NH_3/H_2O; Flow: 80 mL/min

Peak 1, Example 355

HPLC: Column: UltimateXB-C18, 3µm, 3*50mm; Mobile phase 1-100% CH_3CN/H_2O (0.1% TFA); Rt = 3.71 min

Chiral SFC QC: Column: Chiralcel OD-3, 150*4.6 mm; Mobile phase: $MeOH/CO_2$ (0.05% DEA) 5-40%; flow = 2.5 mL/min, Rt = 7.55 min.

^{1}H NMR (400 MHz, DMSO-d_6) d ppm 12.11 (br. s., 1 H) 8.15 - 8.39 (m, 1 H) 7.63 - 7.99 (m, 2 H) 6.67 - 7.07 (m, 2 H) 6.13 (d, *J*=16.56 Hz, 1 H) 5.69 (dd, *J*=10.29, 2.26 Hz, 1 H) 4.69 (d, *J*=12.55 Hz, 1 H) 3.93 - 4.49 (m, 4 H) 3.55 - 3.79 (m, 1 H) 3.46 (d, *J*=4.52 Hz, 1 H) 3.11 - 3.30 (m, 7 H) 2.67 - 3.02 (m, 1 H) 1.50 - 1.91 (m, 2 H) 1.22 (d, *J*=6.53 Hz, 3 H)

Peak 2, Example 356

HPLC: Column: UltimateXB-C18, 3µm, 3*50mm; Mobile phase 1-100% CH_3CN/H_2O (0.1% TFA); Rt = 3.72 min

Chiral SFC QC: Column: Chiralcel OD-3, 150*4.6 mm; Mobile phase: $MeOH/CO_2$ (0.05% DEA) 5-40%; flow = 2.5 mL/min, Rt = 8.62 min. ^{1}H NMR (400 MHz, DMSO-d_6) d ppm 12.11 (br. s., 1 H) 8.15 - 8.39 (m, 1 H) 7.63 - 7.99 (m, 2 H) 6.67 - 7.07 (m, 2 H) 6.13 (d, *J*=16.56 Hz, 1 H) 5.69 (dd, *J*=10.29, 2.26 Hz, 1 H) 4.69 (d, *J*=12.55 Hz, 1 H) 3.93 - 4.49 (m, 4 H) 3.55 - 3.79 (m, 1 H) 3.46 (d, *J*=4.52 Hz, 1 H) 3.11 - 3.30 (m, 7 H) 2.67 - 3.02 (m, 1 H) 1.50 - 1.91 (m, 2 H) 1.22 (d, *J*=6.53 Hz, 3 H)

Biological Evaluation

JAK Caliper Enzyme Assay at 4 μM or 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 μM. 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 μM 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, 4 μM or 1 mM ATP and 1 μM peptide substrate. The JAK3 assays contained 1 μM of the JAKtide peptide (FITC-KGGEEEEYFELVKK). The assays were initiated by the addition 1 nM JAK3 enzyme and were incubated at room temperature 75 minutes for JAK3. 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.

Stability of JAK3 Covalent Inhibitors in Rat and Human Whole Blood

Rat blood was collected from 3 male Sprague-Dawley rats (200-250g, Charles River Laboratories) and pooled for each study. Human blood was collected from one male and one female healthy subjects at the Occupational Health & Wellness Center at Pfizer, Groton, CT and pooled for each study. Both rat and human blood was collected freshly into K_2-EDTA tubes and kept on ice. An aliquot of the blood was transferred to microtubes and pre-warmed for 10 min at 37°C using a heat block. The test compound was then added (1 μM final concentration) and the incubation was continued for 180 min at 37 °C in duplicates. An aliquot of the incubation mixture was removed at designated time points during the course of the incubation, mixed with an aliquot of acetonitrile containing an internal standard,vortexed and centrifuged. The resulting supernatants were removed and subjected to LC-MS/MS analyses to determine parent compound concentrations. Peak area ratios of the parent compound vs the internal standard were used to determine the % of parent compound remaining vs incubation time.

HWB IL-15 induced STAT5 phosphorylation Assay

After serial dilution of the test compounds 1:2 in DMSO at desired concentration (500X of final), the compounds were further diluted in PBS (by adding 4 μL compound/DMSO in 96 μL PBS, [DMSO]=4%, 20X final). To 96-well polypropylene plates were added 90 μl HWB (heparin treated Human Whole Blood)/well, followed by 5 μl/well 4% DMSO in D-PBS or various concentrations of 20X inhibitor in 4% DMSO in D-PBS (w/o Ca^{+2} or Mg^{+2}) to give 1X in 0.2% DMSO. After mixing and incubating for 45 minutes at 37°C, 5 μl D-PBS (unstimulated control) or 20X stocks of 5μl human IL-15

(final concentration is 50 ng/ml) were added, and mixed three times. After incubating 15 minutes at 37°C, 1X Lyse/Fix Buffer (BD Phosflow 5x Lyse/Fix Buffer) was added to all wells at 1000 µl/well, then incubated for 20 minutes at 37 °C and spun 5 mins at 1200 rpm. After washing in 1000 µl FACS buffer 1X and spinning for 5mins at 1200 rpm, 400 µl ice cold Perm Buffer III were added to each well. After mixing gently (1-2X) and incubating on ice for 30 minutes, spinning for 5 mins at 1200 rpm without interruption, and washing 1X in cold 1000 ml FACS buffer (D-PBS containing 0.1 % BSA and 0.1% sodium azide) 250 µl/well of the desired AlexaFluor647-conjugated anti-phospho STAT5 antibody at 1:125 dilution in FACS buffer was added. Following incubating at 4 °C over night, all the samples were transferred to 96-well polypropylene U-bottom plate, and checked by flow cytometry gated on total lymphocytes. IC_{50} values obtained are listed in the Table.

PBMC IL-15 Induced P-STAT5

Test compounds were serially diluted in DMSO, with further dilution of the compounds in RPMI 1640 medium (Invitrogen #72400) supplemented with 10 mM HEPES, pH 7.4, 1 mM sodium pyruvate, and Penicillin/Streptomycin (by adding 5 µL compound/DMSO in 120 µL Dulbecco's Phosphate-Buffered Saline (D-PBS, 1X), [DMSO]=4%, and mixing the solution by repeated pipetting, 6X). IL-15 was diluted to the concentration at 820 ng/mL in RPMI 1640 medium.

Frozen human PBMC (200-250 million cells/vial) was thawed at 37 °C. The cells were transferred to 10 mL warm medium in a 50-mL conical tube, and centrifuged at 1,200 RPM at room temperature for 5 min. The supernatant was aspirated. Cells were suspended in 3 mL warm human plasma and incubated at 37 °C in a tissue culture incubator for 1.5 to 2 h. After adding 47 ml D-PBS (37 °C) to PBMC/FBS suspension, centrifuging at 1,200 RPM at room temperature for 5 min, and aspirating the supernatant, the cells were resuspended in 20 mL warm RPMI medium. Ninety µL of cell suspension were pipetted per well in a 96-well, deep-well, V-bottom plate, and the plate was incubated at 37 °C for 30 min. Five µL of compound were transferred to each well (final 0.2% DMSO), vortex gently and incubate at 37°C for 15 min; 5 µL 4%DMSO/PBS were added to the control wells. After adding 5 µL 820 ng/mL of human IL-15 (final 41 ng/mL) to each well (5 µL PBS to the control wells), vortexing gently and incubating at 37 °C for 15 min, followed by 0.3 mL 1% paraformaldehyde/PBS (37 °C) to each well, and incubating the plate at room temperature for 15 min, the plates were centrifuged at 1,200 RPM (Beckman GS-6R or Sorvall Legend) at room temperature for 5 min, and the supernatant was aspirated using a 8-channel or 12-channel manifold. After adding 0.8 mL staining buffer per well, the plates were centrifuged at 1,200 RPM (Beckman GS-6R or Sorvall Legend) at room temperature for 5 min, and again the supernatant was aspirated using a 8-channel or 12-channel manifold. The plate was vortexed, and 0.35 mL 90% methanol/10% H_2O (-20°C) was added per well, and the plate incubated on ice for 20 min. After again adding 0.8 mL staining buffer per well, the plates were centrifuged at 1,200 RPM (Beckman GS-6R or Sorvall Legend) at room temperature for 5 min, and again the supernatant was aspirated using a 8-channel or 12-channel manifold, and then 0.8 mL Staining buffer was added per well. After once again adding 0.8 mL staining buffer per well, the

plates were centrifuged at 1,200 RPM (Beckman GS-6R or Sorvall Legend) at room temperature for 5 min, and again the supernatant was aspirated using a 8-channel or 12-channel manifold. Then the plate was vortexed, and 250 µL/well of Alexa Fluor® 647 conjugated anti-STAT5 antibody (1 to 125 dilution; 1 µL antibody per 250 µL staining buffer) was added, and the plate was incubated at 4 °C overnight in the dark. Samples of 250 µL/well were transferred to a 96-well U-bottom plate, and the FACS analysis was performed gating on total lymphocytes. Samples were analyzed using a BD Calibur™ or BD FACSCanto™ flow cytometer equipped with the BD High Throughput Sampler.

Table I. Enzyme Assay and Blood Stability Data.

Ex	JAK3 4 μM ATP IC_{50} (nM)	JAK3 1mM ATP IC_{50} (nM)	PBMC IL15 _pSTAT5_ IC_{50} (nM)	HWB _IL15 pSTAT5 IC_{50} (nM)	Human blood stability $t_{1/2}$ (min)
5	0.408	46			
6	10.102	1,320			
7	1.485	106	403.119		158
8	0.355	46	133.236		>360.000
9	8.862	1,211			
10	2.766	632			
11	1.613	308			207.759
12	5.281	766			
14	54.789	3,008			
15	31.369	3,285			
17	0.319	37	2561.816		189.399
18	0.491	96	5985.753		>360.000
20	5.416	926			
21	4.694	633			
22	1.288	134			
23	3.582	651			
24	1.113	295			
25	1.332	92	1603.173		
26	1.649	99	1926.549		
27	0.468	19	382.483		>360.000
28	13.706	1,159			
29		8307			
30	6.865	865			
31	0.211	47	3866.586		294
32	0.848	138	9099.464		>360.000
33	0.23	34	2812.08		208
34	0.501	105	580.327		>360.000
35	6.768	621			
36	0.875	54	175.991	1092.17	>360.000
37	0.375	51	675.816	1942.711	305
38	0.328	30	204.524	1161.485	263
39	1.014	202	2376.484		>360.000
40	0.384	24	134.246	841.679	243
41	0.159	22	146.605	515.375	225
42	0.4	50	356.609	1059.915	281
43	0.258	50	411.297		223.838
44	0.35	47	315.212	1233.751	256.048

Ex	JAK3 4 µM ATP IC_{50} (nM)	JAK3 1mM ATP IC_{50} (nM)	PBMC IL15 _pSTAT5_ IC_{50} (nM)	HWB _IL15 pSTAT5 IC_{50} (nM)	Human blood stability $t_{1/2}$ (min)
45	0.39	57	459.995		202.192
46	3.381	209	870.704		
47	1.178	87	362.653	3577.789	108
48	49.105	3,061	6689.177		
49	27.087	2,101			196.039
50	1.089	91	430.547		>360.000
51	2.932	212	998.72		158.879
52	1.023	153	626.827		167
53	31.168	4,003			
54	2.486	345	1639.582		
55	2.213	192	2258.051		>360.000
56	0.927	70	1603.309		>360.000
57	4.446	241	3216.686		>360.000
58	2.77	282	4737.71		>360.000
59	6.265	1,196	4868.413		
60	0.448	130	379.473		178.134
61	3.394	564	2172.11		
62	13.47	2,700			
63	2.439	379			
64	0.408	50	227.603	3128.272	265.131
65	1.024	53	585.305		>360.000
66	6.214	412			>360.000
67	0.511	25	439.296		>360.000
68	2.172	247	4571.172		>360.000
69	0.782	137	2607.954		>360.000
70	9.097	1,391			>360.000
71	1.129	54	260.396	931.362	309
72	1.134	80	415.042		166
73	0.971	33	173.619	738.297	>360.000
74	0.995	177	1180.961		>360.000
75	1.599	316	2276.87		>360.000
76	0.566	136	1147.608		>360.000
77	0.702	115	560.626	2450.401	>320.333
78	1.832	314	935.276		>360.000
79	0.608	77	264.358	2711.879	329.878
80	1.32	160	828.951		288.261
81		76.9			>360
83	10.656	1,107			
84	1.666	329	1223.734		
85	2.906	467			83
86	0.515	94	259.72	2917.627	100

Ex	JAK3 4 µM ATP IC_{50} (nM)	JAK3 1mM ATP IC_{50} (nM)	PBMC IL15 _pSTAT5_ IC_{50} (nM)	HWB _IL15 pSTAT5 IC_{50} (nM)	Human blood stability $t_{1/2}$ (min)
87	14.002	1,322	6485.529		>360.000
88	1.5	137	3453	5048	>360.0
89	76.421	7,673			
90	1.038	152	3220.504		
92	20.944	2,436			
93	710.72	>3,160			
94	0.8	148	1078.3		
95	0.466	65	478.942	804.421	188
96	432.968	>10,000			
97	1.713	187	1063.965		
98	1.264	152	932.175		105.768
99	89.202	8,988			
100	76.266	2,661	>10000.000		211
101	0.219	28	226.783	703.427	114
102	1.899	142	236.784	1532.345	121
103	0.424	38	155.243	658.882	137
105	0.408	54	324.218	1069.197	138
106	0.125	25	191.916	287.035	112
107	11.807	1,243	8260.517		
108	0.769	136	3260.465	3483.335	133.832
109	0.713	155	320.415		132.105
110	867.417	>10,000			
111	0.858	77	536.695		172.108
112	1.028	181	1012.124		
113	2.395	589	1942.788		>360.000
114	19.662	3,811			
115	8.315	929			226.018
116	14.665	2,549			
117	11.872	1,493			
118	16.084	1,892			
119	34.246	3,927	9310.19		
120	4.479	725			>360.000
121	6.961	921			160.212
122	8.968	1,465			
123	7.649	1,104	3043.142		146.779
124	5.891	1,102	2430.305		291.809
125	7.816	1,878			
126	14.918	3,527			
127	9.426	1,083			
128	6.667	787			>360.000
129	0.534	24	86.171		267.223

Ex	JAK3 4 µM ATP IC_{50} (nM)	JAK3 1mM ATP IC_{50} (nM)	PBMC IL15 _pSTAT5_ IC_{50} (nM)	HWB _IL15 pSTAT5 IC_{50} (nM)	Human blood stability $t_{1/2}$ (min)
131	0.182	33			
132	1.672	255	523.984		
133	1.111	76	302.319		238
134	12.382	2,528			
135	1.489	168	759.164		
136	5.82	632			
137	28.077	3,024			
138	46.72	4,839			
139	1.57	109	711.345		>360.000
140	2.71	384	1707.879		
141	0.794	103	346.533		
142	60.402	4,432			
143	22.609	1,920			
144	3.318	430			
145	18.372	1,933			
146	12.23	1,367			
147	41.719	3,712			
148	0.773	111	312.169		>360.000
149	0.565	134	163.308	4236.663	
150	8.087	1,115			
151	13.568	1,515			
152	1.973	256	509.756		
153	5.207	538			
154	4.683	590			
155	4.916	721			
156	28.9	4,089			
157	20.627	2,898			
158	3.07	365	888.383		
159	6.307	865			
160	4.33	463			
161	7.348	1,118			
162	6.192	581			
163	1.241	160	408.899		
164	4.338	726			
165	10.683	957			
166	0.667	58	167.842	1205.374	>360.000
167	4.605	599			
168	7.756	769			
169	7.309	845			
170	0.508	4			307.85
171	0.928	55	946.664		

Ex	JAK3 4 µM ATP IC_{50} (nM)	JAK3 1mM ATP IC_{50} (nM)	PBMC IL15 _pSTAT5_ IC_{50} (nM)	HWB _IL15 pSTAT5 IC_{50} (nM)	Human blood stability $t_{1/2}$ (min)
172	0.448	5	81.314	321.705	326
173	0.681	43	1415.742		
174	0.368	13	161.927	1730.052	
175	0.426	8	77.33	1322.928	
176	0.437	3	23.956	318.21	ok291
177	0.626	25	420.375		
178	0.442	6	88.6	360.009	ok334.132
179	0.596	18	94.819	849.931	
180	0.481	12	203.604	944.012	
181	0.379	5	159.433	1815.479	
182	2.444	165	>10000.000		
183	1.034	41	1587.648		
184	1.394	68	1190.05		
185	0.372	6	73.025	541.837	
186	0.485	15	212.715	870.057	
187	0.503	6	54.697	240.33	>360.000ok
188	0.515	6	88.047	913.058	>360.000
189	0.689	6	202.772	1144.319	>360.000
190	0.193	7	96.87	618.953	
191	0.484	9	136.883	777.795	
192	0.627	29	906.631		
193	0.393	5	68.408	637.257	
194	0.993	22			
195	0.494	7	82.676	687.986	
196	0.479	5	54.667	362.206	>360.000
197	0.788	147	706.383		
198	0.361	53	249.879	1404.891	
199	0.414	47	250.141	2020.346	
200	0.411	46	148.58	1520.388	>360.000
201	3.624	411			
202	5.311	697			
203	2.819	370	4462.504		
204	0.272	49	130.142	1390.465	>360.000
205	0.138	16	92.35	513.012	250.221
206	2.788	325	3100.582		
207	4.071	538			
208	6.987	734			
209	0.609	64	206.051	>10000.000	267
210	0.435	54	325.117		
211	0.5	74	395.002	1744.169	
212	0.922	328	1340.35		

Ex	JAK3 4 µM ATP IC_{50} (nM)	JAK3 1mM ATP IC_{50} (nM)	PBMC IL15 _pSTAT5_ IC_{50} (nM)	HWB _IL15 pSTAT5 IC_{50} (nM)	Human blood stability $t_{1/2}$ (min)
213	3.071	343	1724.477		
214	0.209	20	56.941	194.733	ok287.47
215	0.782	97	618.746		
216	3.269	463			
217	1.968	272	2093.153		
218	0.627	105	1202.186		
219	0.363	25	134.493	888.536	243
220	0.211	18	100.287	1074.161	222
221	4.4	713			
222	0.38	53	280.092	1017.369	
223	4.134	344	3334.709		
224	3.542	526			
225	0.233	25	170.257	772.383	236
226	2.116	430			
227	0.279	22	145.723	681.633	270.193
228	0.229	18	93.296	378.222	253.848
229	0.582	60	220.861	2387.609	356
230	0.305	34	155.156	1705.739	351.124
231	0.322	85	353.117		321
232	2.497	606			
233	6.789	1,095			
234	17.916	2,269			
235	0.304	37	207.51		347
236	45.087	6,550			
237	0.25	56	780.068		259
238	9.478	1,358			
239	3.78	757			
240	10.889	4,059			
241	3.795	857			
242	62.118	>10,000			
243	0.586	141	1731.02		>360.000
244	82.347	>10,000			
245	1.775	297	>10000.000		
246	7.792	1,113			
247	3.337	829			
248	48.658	5,334			
249	75.293	>10,000			
250	4.312	798			
251	5.118	1,316			
252	110.446	>10,000			
253	72.015	7,678			

Ex	JAK3 4 µM ATP IC_{50} (nM)	JAK3 1mM ATP IC_{50} (nM)	PBMC IL15 _pSTAT5_ IC_{50} (nM)	HWB _IL15 pSTAT5 IC_{50} (nM)	Human blood stability $t_{1/2}$ (min)
254	17.204	2,544			
255	6.373	846			
256	0.124	23	531.251		275
257	55.343	6,455			
258	6.226	1,048			
259	180.34	>10,000			
260	2.137	676			
261	259.415	>10,000			
262	11.594	2,181			
263	52.389	6,461			
264	2.412	479			
265	4.627	742	2063.272		
266	0.2	22	64.232	528.022	
267	4.986	802			
268	1.434	330	>10000.000		
269	0.888	82	219.991	1385.249	
270	0.526	63	670.261		
271	0.676	144	1144.556		
272	3.825	651			
273	1.587	204	388.534		
274	0.984	157	506.646		
275	3.186	418	1032.718		
276	0.479	111	622.954		
277	0.59	155	2317.882		
278	1.227	70	271.528	2464.465	
279	0.343	31	107.438	765.352	
280	2.494	501			
281	1.021	73	1221.893		
282	2.454	359	3090.779		
283	0.509	97	256.746	1197.298	
284	0.301	42	185.811	819.008	>360.000
285	4.049	515	1793.745		
286	12.435	1,023			
287	2.709	499			
288	0.376	57	150.849	2155.905	>360.000
289	1.292	209	453.834		
290	20.826	2,148			
291	15.468	1,491			
292	0.315	17	27.682	841.226	
293	0.68	51	217.689	817.839	204
294	1.16	62	575.453		

Ex	JAK3 4 µM ATP IC_{50} (nM)	JAK3 1mM ATP IC_{50} (nM)	PBMC IL15 _pSTAT5_ IC_{50} (nM)	HWB _IL15 pSTAT5 IC_{50} (nM)	Human blood stability $t_{1/2}$ (min)
295	0.179	29	71.014	199.062	ok133.207
296	0.519	57	609.211		
297	0.43	45	150.267	718.167	
298	0.485	69	210.494	1282.125	>360.000
299	1.205	57	305.123	913.169	
300	0.69	92	699.748		
301	0.431	44	386.705	3026.667	
302	2.89	385	1186.599		
303	4.808	731			
304	0.194	29	96.793	524.121	
305	0.496	53	277.881	6384.984	
306	0.705	107	1571.655		
307	9.821	1,076	2133.638		
308	0.531	48	305.873	775.119	
309	0.898	59	526.112		
310	2.08	170	1196.196		
311	1.783	223	586.459		
312	1.053	56	310.139	703.955	
313	0.736	46	242.669	986.468	
314	0.24	30	115.347	401.86	186.987
315	0.348	26	74.904	210.675	ok
316	0.643	129	294.486	1454.374	
317	0.979	77	314.798	834.96	
318	0.535	59	214.491	1758.629	
319	0.404	45	210.832	396.387	334
320	2.158	182	1253.422		
321	0.448	46	310.342	999.032	>360.000
322	0.269	47	427.563		
323	0.392	69	430.342		
324	0.418	21	202.933	1267.22	257.921
325	12.797	1,264			
326	0.455	50	329.899	780.409	>360.000
327	0.546	56	260.694	1037.851	>360.000
328	0.578	37	143.2	287.352	251.86
329	0.587	60	246.862	6286.522	
330	0.287	45	122.071	1971.669	
331	0.313	42	288.136	263.22	ok331.235
332	0.262	22	87.738	220.984	144.963
333	0.307	44	773.506		
334	0.703	93	73.642	3916.304	
335	0.262	57	848.914		

Ex	JAK3 4 µM ATP IC_{50} (nM)	JAK3 1mM ATP IC_{50} (nM)	PBMC IL15 _pSTAT5_ IC_{50} (nM)	HWB _IL15 pSTAT5 IC_{50} (nM)	Human blood stability $t_{1/2}$ (min)
336	0.24	26	107.382	372.581	ok
337	14.372	1,845			
338	31.42	2,776			
339	16.469	2,699			
340	29.951	3,469			
341	20.947	2,605			
342	26.446	2,634			
343	75.132	4,879			
344	26.678	2,537			
345	43.652	4,026			
346	40.914	4,439			
347	24.176	3,078			
348	10.239	1,188			
349	2.12	367	2929.437		
350	32.115	4,368			>360.000
351	2.877	838			331
352	52.311	4,497			
353	1.478	123	2203.352		>360.000
354	3.408	261	4518.962		
355	0.327	30			
356	4.074	831			

CLAIMS:

1. A compound selected from the group consisting of:

1-(4-{[7-(azetidin-1-ylcarbonyl)-5H-pyrrolo[2,3-b]pyrazin-2-yl](methyl)amino}piperidin-1-yl)prop-2-en-1-one

2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-(prop-2-yn-1-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-{3-[acryloyl(methyl)amino]azetidin-1-yl}-N-(2-methoxyethyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-{3-[acryloyl(methyl)amino]azetidin-1-yl}-N-[(2S)-1-methoxypropan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-{3-[acryloyl(methyl)amino]azetidin-1-yl}-N-[(2R)-1-methoxypropan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

Cis-racemic-N-{[(1-acryloyl-5-(7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)piperidin-2-yl]methyl}acetamide

N-{[(2R,5R)-1-acryloyl-5-(7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)piperidin-2-yl]methyl}acetamide

N-{[(2S,5S)-1-acryloyl-5-(7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)piperidin-2-yl]methyl}acetamide

Cis-racemic-1-acryloyl-N,N-dimethyl-5-(7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)piperidine-3-carboxamide

3-{[(3S,5R)-1-Acryloyl-5-(7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)piperidin-3-yl]methoxy}propanenitrile

3-{[(3R,5S)-1-Acryloyl-5-(7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)piperidin-3-yl]methoxy}propanenitrile

Cis-racemic-[1-acryloyl-5-(7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)piperidin-3-yl]acetonitrile

[(3R,5R)-1-acryloyl-5-(7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)piperidin-3-yl]acetonitrile

[(3S,5S)-1-acryloyl-5-(7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)piperidin-3-yl]acetonitrile

1-((2S,5R)-2-Methyl-5-((5-(2-(prop-2-yn-1-yloxy)ethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidin-1-yl)prop-2-en-1-one

1-[(2S,5R)-2-Methyl-5-({5-[2-(prop-2-yn-1-yloxy)ethyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl}amino)piperidin-1-yl]prop-2-en-1-one

2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-[(2S)-1-(benzyloxy)propan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

Racemic-2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-[1-(3-fluorophenyl)-2-hydroxyethyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-[(2S)-3-ethyl-1-hydroxypentan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-[(1R)-2-methoxy-1-phenylethyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-[(3S,4R)-4-cyclopropyltetrahydrofuran-3-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-[(3S,4R)-4-(2-methylpropyl)tetrahydrofuran-3-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-[4-(4-fluorophenyl)tetrahydrofuran-3-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

Racemic-2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-(3,4-dihydro-1H-isochromen-4-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-[(1R)-1-(4-fluorophenyl)-2-hydroxyethyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-[(2S)-1-phenoxypropan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

Racemic-2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-(tetrahydro-2H-pyran-3-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-[(3S)-tetrahydrofuran-3-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-[(3R)-3,4-dihydro-2H-chromen-3-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

Racemic-2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-[1-(2-fluorophenyl)-2-hydroxyethyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-[(1R,2S)-1-hydroxy-1-phenylpropan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-[(2R)-1-(3-cyanophenyl)-3-hydroxypropan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

Methyl N-{[2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]carbonyl}-L-alaninate

2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-[(3S,4R)-4-(4-fluoro-1H-pyrazol-1-yl)tetrahydrofuran-3-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

3-({[2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]carbonyl}amino)-2,5-anhydro-1,3,4-trideoxy-D-erythro-pentitol

2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-[(1S)-2-hydroxy-2-methyl-1-phenylpropyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

Racemic-2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-(tetrahydrofuran-3-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

Racemic-2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-[1-(4-fluorophenyl)-2-hydroxyethyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

3-({[2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-5H-pyrrolo[2,3-b]pyrazin-7-yl]carbonyl}amino)-2,5-anhydro-1,3,4-trideoxy-L-threo-pentitol

2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-[(2R)-1-phenoxypropan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-[(3S)-3,4-dihydro-2H-chromen-3-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-[(2R)-1-(benzyloxy)propan-2-yl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-[(1-acryloylpiperidin-4-yl)amino]-N-{[4-methyl-6-(trifluoromethyl)pyrimidin-2-yl]methyl}-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-[(1-acryloylpiperidin-4-yl)amino]-N-[(3-cyclobutyl-1-methyl-1H-pyrazol-5-yl)methyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-[(1-acryloylpiperidin-4-yl)amino]-N-(4-fluoro-3-methoxybenzyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-[(1-acryloylpiperidin-4-yl)amino]-N-{[3-(propan-2-yl)-1,2-oxazol-5-yl]methyl}-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-[(1-acryloylpiperidin-4-yl)amino]-N-(3-fluorobenzyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-[(1-acryloylpiperidin-4-yl)amino]-N-[(5-fluoro-1,3-benzoxazol-2-yl)methyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-[(1-acryloylpiperidin-4-yl)amino]-N-{[4-methyl-2-(trifluoromethyl)-1,3-thiazol-5-yl]methyl}-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-[(1-acryloylpiperidin-4-yl)amino]-N-[4-(difluoromethoxy)benzyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-[(1-acryloylpiperidin-4-yl)amino]-N-[2-(6,7-difluoro-1,3-benzoxazol-2-yl)ethyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-[(1-acryloylpiperidin-4-yl)amino]-N-[4-(1H-pyrazol-1-yl)benzyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-[(1-acryloylpiperidin-4-yl)amino]-N-[(5-ethyl-6-methylpyridin-2-yl)methyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-[(1-acryloylpiperidin-4-yl)amino]-N-{[4-(trifluoromethyl)-1,3-thiazol-5-yl]methyl}-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-[(1-acryloylpiperidin-4-yl)amino]-N-[(5-chloropyridin-2-yl)methyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-[(1-acryloylpiperidin-4-yl)amino]-N-benzyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-[(1-acryloylpiperidin-4-yl)amino]-N-(4-fluorobenzyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-[(1-acryloylpiperidin-4-yl)amino]-N-(3-cyano-4-fluorobenzyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-[(1-acryloylpiperidin-4-yl)amino]-N-(3-fluoro-4-methoxybenzyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-[(1-acryloylpiperidin-4-yl)amino]-N-(4-methoxybenzyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-[(1-acryloylpiperidin-4-yl)amino]-N-{[1-(3-fluorophenyl)-1H-pyrazol-4-yl]methyl}-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-[(1-acryloylpiperidin-4-yl)amino]-N-[(6-fluoro-1,3-benzoxazol-2-yl)methyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-[(1-acryloylpiperidin-4-yl)amino]-N-{[2-methyl-4-(trifluoromethyl)-1,3-thiazol-5-yl]methyl}-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-[(1-acryloylpiperidin-4-yl)amino]-N-(2-fluorobenzyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-[(1-acryloylpiperidin-4-yl)oxy]-N-[(3,3-difluorocyclobutyl)methyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-[(1-acryloylpiperidin-4-yl)oxy]-N-[(1R,3S)-3-fluorocyclopentyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-[(1-acryloylpiperidin-4-yl)oxy]-N-(bicyclo[1.1.1]pent-1-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

Racemic-2-[(1-acryloylpiperidin-4-yl)oxy]-N-[(1-hydroxy-3-methylcyclopentyl)methyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-[(1-acryloylpiperidin-4-yl)oxy]-N-[(1-hydroxycyclobutyl)methyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

Racemic-2-[(1-acryloylpiperidin-4-yl)oxy]-N-cyclopentyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

Racemic-2-[(1-acryloylpiperidin-4-yl)oxy]-N-[(1-hydroxycyclopentyl)methyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-[(1-acryloylpiperidin-4-yl)oxy]-N-[(4,4-difluoro-1-hydroxycyclohexyl)methyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-[(1-acryloylpiperidin-4-yl)oxy]-N-{[(2R)-2-fluoro-1-hydroxycyclohexyl]methyl}-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-[(1-acryloylpiperidin-4-yl)oxy]-N-[(1S,3S)-3-fluorocyclopentyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-[(1-acryloylpiperidin-4-yl)oxy]-N-(3,3-difluorocyclobutyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

Racemic-2-[(1-acryloylpiperidin-4-yl)oxy]-N-[1-(1-hydroxycyclobutyl)propyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-[(1-acryloylpiperidin-4-yl)oxy]-N-[(1R,2R)-2-(trifluoromethyl)cyclopropyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-[(1-acryloylpiperidin-4-yl)oxy]-N-(2,2-difluorocyclopentyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

Racemic-2-[(1-acryloylpiperidin-4-yl)oxy]-N-[(3,3-difluoro-1-hydroxycyclohexyl)methyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

Racemic-2-[(1-acryloylpiperidin-4-yl)oxy]-N-{[(2S)-2-fluoro-1-hydroxycyclohexyl]methyl}-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-[(1-acryloylpiperidin-4-yl)oxy]-N-[(1S,3R)-3-fluorocyclopentyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

Racemic-2-[(1-acryloylpiperidin-4-yl)oxy]-N-{[(3R)-1-hydroxy-3-methylcyclopentyl]methyl}-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-[(1-acryloylpiperidin-4-yl)oxy]-N-[(1R,2R)-2-fluorocyclopentyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-[(1-acryloylpiperidin-4-yl)oxy]-N-[(1R,2S)-2-fluorocyclopentyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-[(5-acryloyl-5-azaspiro[2.4]hept-7-yl)amino]-N-(2-methylpropyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-{[(3S,4S)-1-acryloyl-4-cyclopropylpyrrolidin-3-yl]amino}-N-ethyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-[(5-acryloyl-5-azaspiro[2.4]hept-7-yl)amino]-N-(2,2,2-trifluoroethyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-[(5-acryloyl-5-azaspiro[2.4]hept-7-yl)amino]-N-ethyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-{[(3S,4S)-1-acryloyl-4-cyclopropylpyrrolidin-3-yl]amino}-N-(2-methoxyethyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-[(5-acryloyl-5-azaspiro[2.4]hept-7-yl)amino]-N-(4,4,4-trifluorobutyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-[(5-acryloyl-5-azaspiro[2.4]hept-7-yl)amino]-N-(3,3,3-trifluoropropyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-{[(3R,4R)-1-acryloyl-4-cyclopropylpyrrolidin-3-yl]amino}-N-(2-methoxyethyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-{[(3R,4R)-1-acryloyl-4-cyclopropylpyrrolidin-3-yl]amino}-N-ethyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-{[(3S,4R)-1-acryloyl-3-methoxypiperidin-4-yl]amino}-N-[(4,4-difluoro-1-hydroxycyclohexyl)methyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-{[(3R,4S)-1-acryloyl-3-methoxypiperidin-4-yl]amino}-N-[(1R,2R)-2-(trifluoromethyl)cyclopropyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-[(3S)-4-acryloyl-3-(2-methylpropyl)piperazin-1-yl]-N-(3,3-difluorocyclobutyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-[(3S)-4-acryloyl-3-(2-methylpropyl)piperazin-1-yl]-N-[(3,3-difluorocyclobutyl)methyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-(4-acryloylpiperazin-1-yl)-N-[(3,3-difluorocyclobutyl)methyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-{[(3R,4S)-1-acryloyl-3-methoxypiperidin-4-yl]amino}-N-(3,3-difluorocyclobutyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-(4-acryloylpiperazin-1-yl)-N-(3,3-difluorocyclobutyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-(4-acryloylpiperazin-1-yl)-N-[(1R,2R)-2-(trifluoromethyl)cyclopropyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-cyclobutyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-[(1R,2R)-2-(trifluoromethyl)cyclopropyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-[(4,4-difluoro-1-hydroxycyclohexyl)methyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

Racemic-2-(4-acryloylpiperazin-1-yl)-N-cyclopentyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-(4-acryloylpiperazin-1-yl)-N-cyclobutyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

Racemic-2-{[(3S,4R)-1-acryloyl-3-methoxypiperidin-4-yl]amino}-N-cyclopentyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-[(3S)-4-acryloyl-3-(2-methylpropyl)piperazin-1-yl]-N-[(4,4-difluoro-1-hydroxycyclohexyl)methyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-[(3S)-4-acryloyl-3-(2-methylpropyl)piperazin-1-yl]-N-[(1R,2R)-2-(trifluoromethyl)cyclopropyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-[(1-acryloyl-4-methylpiperidin-4-yl)amino]-N-[(3,3-difluorocyclobutyl)methyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-{[(3S,4R)-1-acryloyl-3-methoxypiperidin-4-yl]amino}-N-[(3,3-difluorocyclobutyl)methyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-{[(3S,4R)-1-acryloyl-3-methoxypiperidin-4-yl]amino}-N-[(1R,2R)-2-(trifluoromethyl)cyclopropyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

Racemic-2-[(1-acryloyl-2-methylpiperidin-4-yl)amino]-N-cyclobutyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-{[(3R,4S)-1-acryloyl-3-methoxypiperidin-4-yl]amino}-N-[(3,3-difluorocyclobutyl)methyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-[(1-acryloyl-4-methylpiperidin-4-yl)amino]-N-cyclobutyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-(3,3-difluorocyclobutyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

2-(4-acryloyl-3,3-dimethylpiperazin-1-yl)-N-cyclopentyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

Racemic-2-[(1-acryloyl-2-methylpiperidin-4-yl)amino]-N-[(1R,2R)-2-(trifluoromethyl)cyclopropyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

5-[(1-acryloylpiperidin-4-yl)oxy]-N-(3,3-difluorocyclohexyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide

5-[(1-acryloylpiperidin-4-yl)oxy]-N-(3-fluorobenzyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide

5-[(1-acryloylpiperidin-4-yl)oxy]-N-(3,3-difluorocyclohexyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide

5-[(1-acryloylpiperidin-4-yl)oxy]-N-benzyl-1H-pyrrolo[2,3-b]pyridine-3-carboxamide

5-[(1-acryloylpiperidin-4-yl)oxy]-N-[(1S,3R)-3-fluorocyclopentyl]-1H-pyrrolo[2,3-b]pyridine-3-carboxamide and

5-[(1-acryloylpiperidin-4-yl)oxy]-N-(2-fluorobenzyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide;
or, a pharmaceutically acceptable salt thereof.

2. The compound of claim 1 wherein the compound is 2-[(1-acryloylpiperidin-4-yl)amino]-N-(3-fluorobenzyl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide; or, a pharmaceutically acceptable salt thereof.

3. The compound of claim 1 wherein the compound is 2-[(1-acryloylpiperidin-4-yl)amino]-N-benzyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide; or, a pharmaceutically acceptable salt thereof.