[19]	INTELLECTUAL PROPERTY PHILIPPINES			
[12]	INVENTION PUBLICATION			
[11]	Publication Number:	12016500938	Document Code:	B1
[22]	Publication Date:	27/6/2016		
[21]	Application Number:	12016500938	Document Code:	A
[22]	Date Filed:	20/5/2016		
[54]	Title:	PYRROLO[2,3-D]PYRIMIDINYL, PYRROLO[2,3-B]PYRAZINYL AND PYRROLO[2,3-D]PYRIDINYL ACRYLAMIDES		
[71]	Applicant(s):	PFIZER		
[72]	Inventor(s):	BROWN MATTHEW FRANK CASIMIRO-GARCIA AGUSTIN CHE YE COE JOTHAM WADSWORTH FLANAGAN MARK EDWARD GILBERT ADAM MATTHEW HAYWARD MATTHEW MERRILL LANGILLE JONATHAN DAVID MONTGOMERY JUSTIN IAN TELLIEZ JEAN-BAPTISTE THORARENSEN ATLI UNWALLA RAYOMAND JAL TRUJILLO JOHN I		
[30]	Priority Data:	5/12/2013 US201361912074P		
[51]	International Class 8:	A61K 31/4375 20060101AFI20181112BHPH; A61P 35/00 20060101ALI20181112BHPH; C07D 471/04 20060101ALI20181112BHPH; C07D 487/04 20060101ALI20181112BHPH;		
[57]	Abstract:	The present invention provides pharmaceutically active pyrrolo[2,3- d]pyrimidinyl and pyrrolo[2,3-d]pyridinyl acrylamides 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.		

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 autoantibodies 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 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 and pyrrolo[2,3-d]pyridinyl acrylamides and analogues thereof. In particular, the present invention is directed to compounds

including pyrrolo[2,3-d]pyrimidinyl and pyrrolo[2,3-d]pyridinyl acrylamides 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. Examples 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.

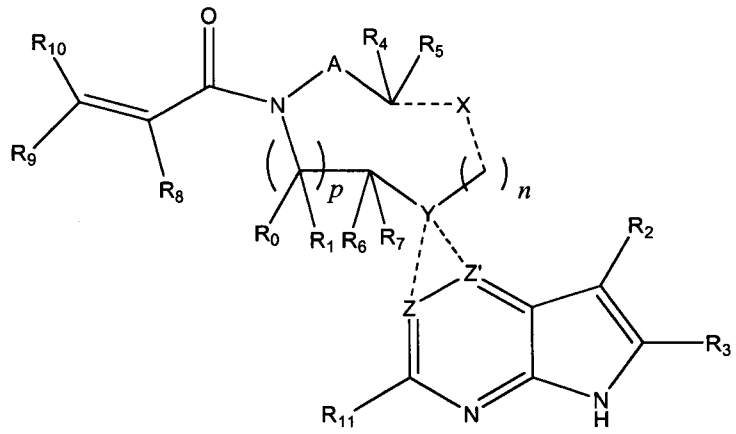
"Pharmaceutically acceptable" means suitable for use in mammals, companion animals or livestock animals.

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 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

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_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_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;

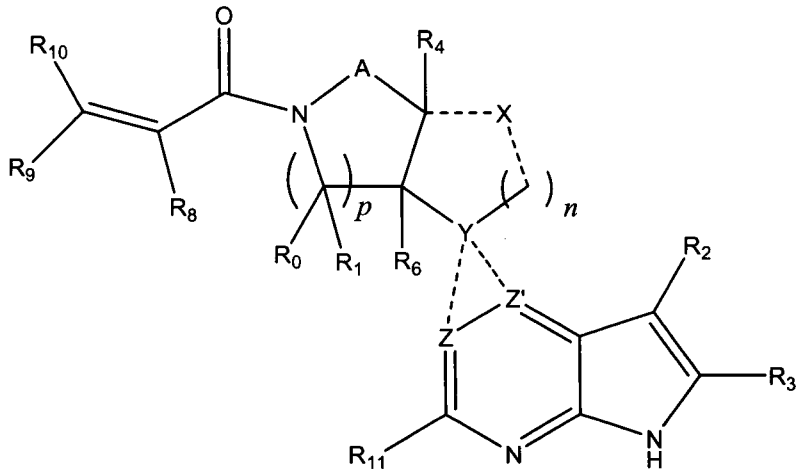
one and only one of the dotted bonds to Z and Z' constitutes a single bond, the other being absent, and either Z is C when the dotted bond to Z is a single bond, and Z' is N or CR_{16}; or, Z is CR_{16} or N when the dotted bond to Z' is a single bond, and Z' is C; where R_{16} is C_1-C_4 alkyl, C_6-C_{10} 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 O or —$(CR_eR_f)_s$—, 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, whereby when *n* is 0, and X is O, said O is bonded to H, and said dotted bond between X and —$(CH_2)_n$— is absent, and when X is —$(CR_eR_f)_s$—, and X is bonded directly to Y; and (b) if X is absent, said dotted bonds are absent and *n* is 0, whereby when Y is N, either (i) said N atom is substituted by H, (ii) Z is C, Z' is C or N, the dotted bond to Z is a single bond, the dotted bond to Z' being absent, or (iii) Z is C or N, Z' is C, the dotted bond to Z' is a single bond, the dotted bond to Z being absent, where said Y being an N atom may 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 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_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, alkyla-

mino, 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_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;

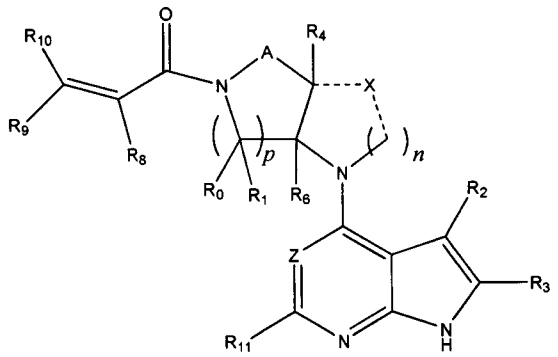
one and only one of the dotted bonds to Z and Z' constitutes a single bond, the other being absent, and either Z is C when the dotted bond to Z is a single bond, and Z' is N or CR_{16}; or, Z is CR_{16} or N when the dotted bond to Z' is a single bond, and Z' is C; where R_{16} is C_1-C_4 alkyl, C_6-C_{10} 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 O or —$(CR_eR_f)_s$—, 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, whereby when *n* is 0, and X is O, said O is bonded to H, and said dotted bond between X and —$(CH_2)_n$— is absent, and when X is —$(CR_eR_f)_s$—, and X is bonded directly to Y; and (b) if X is absent, said dotted bonds are absent and *n* is 0, whereby when Y is N, either (i) said N atom is substituted by H, (ii) Z is C, Z' is C or N, the dotted bond to Z is a single bond, the dotted bond to Z' being absent, or (iii) Z is C or N, Z' is C, the dotted bond to Z' is a

single bond, the dotted bond to Z being absent, where said Y being an N atom may 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, alkyla-

mino, 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;

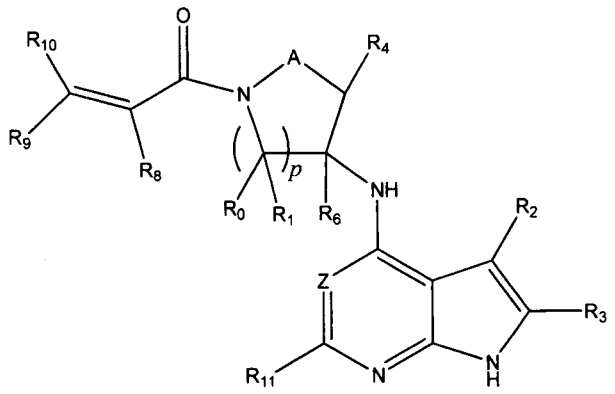
R_{12}, R_{13}, R_{14} and R_{15} are independently selected from hydrogen, C_1-C_6 linear or branched chain alkyl, C_1-C_6 linear or branched chain perfluoroalkyl, C_6-C_{10} aryl, alkylaryl, and (aryl)C_1-C_6 linear or branched chain alkyl;

Z is CR_{16} or N, where R_{16} is 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, X is O or —$(CR_eR_f)_s$—, 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, whereby when *n* is 0, and X is O, said O is bonded to H, and said dotted bond between X and —$(CH_2)_n$— is absent; and (b) if X is absent, said dotted bonds are absent and *n* is 0, whereby either (i) the adjacent N atom is substituted by H, or (ii) said N atom may 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 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_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;

Z is CR_{16} or N, where R_{16} is 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 substi-

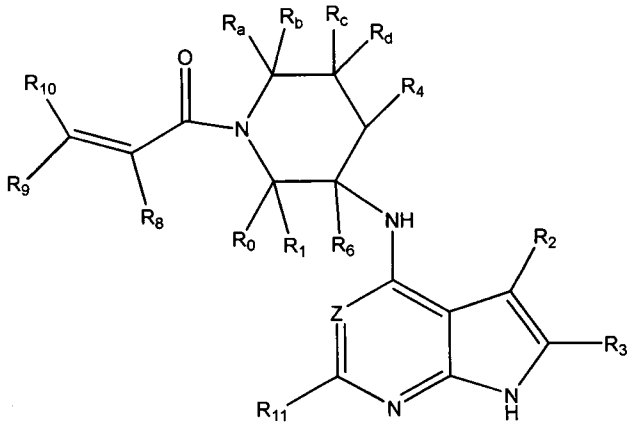
tuted with one or more substituents selected from the group consisting of halo, hydroxy, methoxy, amino, CF_3, and C_3-C_6 cycloalkyl;

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; 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;

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,

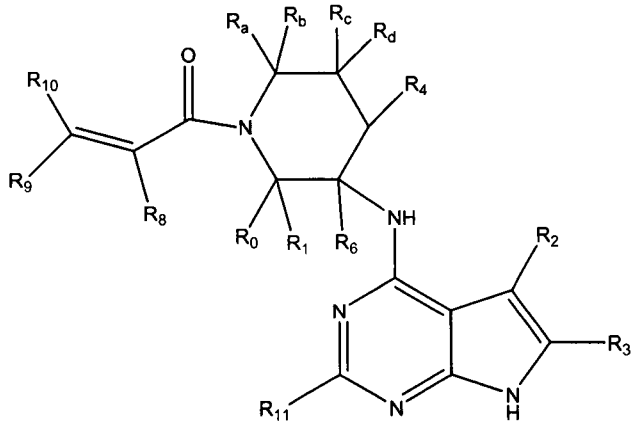
R_b, R_c or R_d, may independently form a bond or a C_1-C_6 linear alkyl chain; and/or, alternatively, R_8 and R_9 may together form a 3-6-membered ring optionally containing one or two O or N atoms;

Z is CR_{16} or N, where R_{16} is 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;

R_{11} is hydrogen or deuterium; and,

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.

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, (heter-

ocyclic)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;

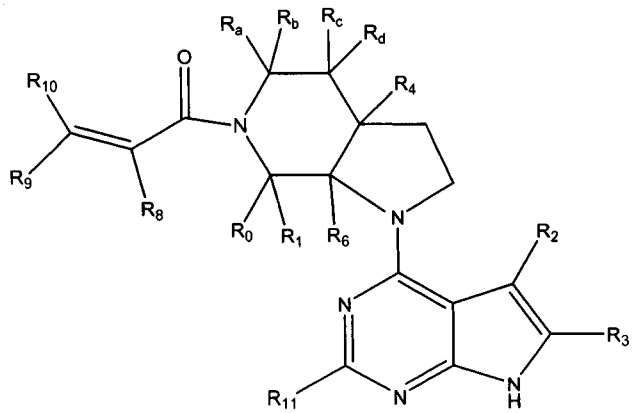
R_0, R_1, R_4, R_6, R_8, R_9 and R_{10} are independently selected from hydrogen, C_1-C_6 linear or branched chain alkyl, C_1-C_6 linear or branched chain perfluoroalkyl, C_6-C_{10} aryl, monocyclic or bicyclic heteroaryl, comprising 5- and/or 6-membered rings, (aryl)C_1-C_6 linear or branched chain 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 al-

kyl)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; and,

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.

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;

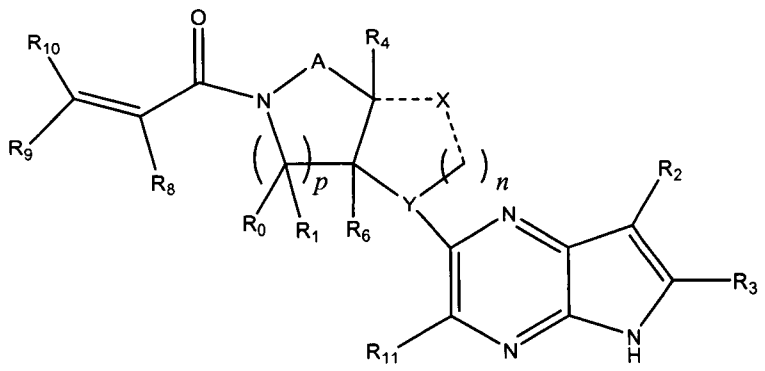
R_0, R_1, R_4, R_6, R_8, R_9 and R_{10} are independently selected from hydrogen, C_1-C_6 linear or branched chain alkyl, C_1-C_6 linear or branched chain perfluoroalkyl, C_6-C_{10} aryl, monocyclic or bicyclic heteroaryl, comprising 5- and/or 6-membered rings, (aryl)C_1-C_6 linear or branched chain 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; and,

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.

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 perfluoroal-

kyl, 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;

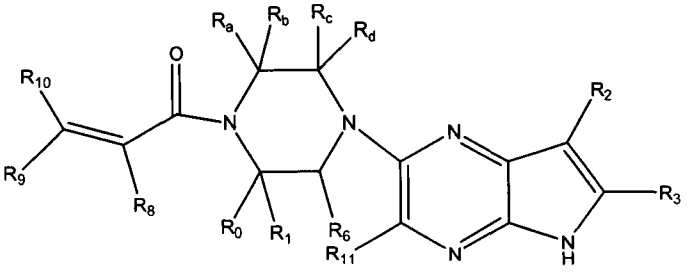
R_{12}, R_{13}, R_{14} and R_{15} are independently selected from hydrogen, C_1-C_6 linear or branched chain alkyl, C_1-C_6 linear or branched chain perfluoroalkyl, C_6-C_{10} aryl, alkylaryl, and (aryl)C_1-C_6 linear or branched chain alkyl;

X and the dotted bonds thereto may be present or absent, whereby, (a) if X is present, Y is N, and X is O or –-(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, whereby when *n* is 0, and X is O, said O is bonded to H, and said dotted bond between X and —$(CH_2)_n$— is absent, and when X is —$(CR_eR_f)_s$—, and X is bonded directly to Y; and (b) if X is absent, said dotted bonds are absent and *n* is 0, whereby when Y is N, either (i) said N atom is substituted by H, or (ii) said N atom may 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 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;

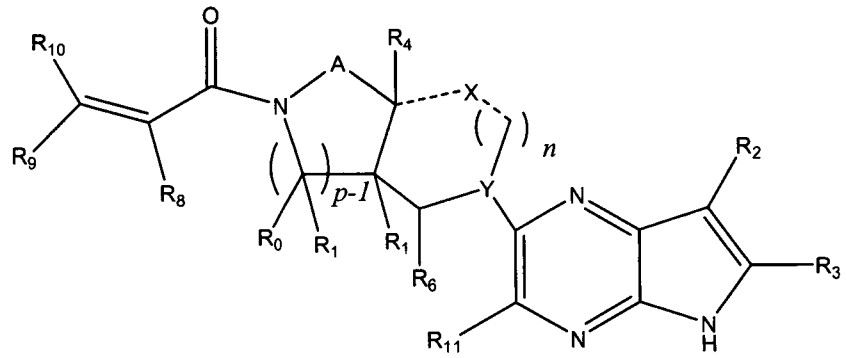
R_3 is selected from the group consisting of hydrogen, deuterium, C_1-C_6 linear or branched chain alkyl, C_1-C_6 linear or branched chain perfluoroalkyl, halogen, and cyano;

R_0, R_1, 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_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, 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 line-

ar 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 cyclo-

alkyl; 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 O or —$(CR_eR_f)_s$—, 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, whereby when *n* is 0, and X is O, said O is bonded to H, and said dotted bond between X and —$(CH_2)_n$— is absent, and when X is —$(CR_eR_f)_s$—, and X is bonded directly to Y; and (b) if X is absent, said dotted bonds are absent and *n* is 0, whereby when Y is N, either (i) said N atom is substituted by H, or (ii) said N atom may 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.

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

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

N-isopropyl-2-(3-(N-methylacrylamido)azetidin-1-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide;
2-((3R,4R)-1-acryloyl-3-hydroxypiperidin-4-ylamino)-N-isopropyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide;
(S)-2-(1-acryloylpyrrolidin-3-ylamino)-N-isopropyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide;
(S)-2-((1-acryloylpyrrolidin-2-yl)methylamino)-N-isopropyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide;
2-((1R,3R)-3-acrylamidocyclobutylamino)-N-isopropyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide; and,
(S)-2-((1-acryloylpyrrolidin-3-yl)methylamino)-N-isopropyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide; or, a pharmaceutically acceptable salt thereof.

The invention further provides additional compounds selected from the group consisting of:
(R)-4-(1-acryloylpiperidin-3-ylamino)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile;
(R)-4-(1-acryloylpiperidin-3-ylamino)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile;
(R)-1-(3-(5-chloro-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)piperidin-1-yl)prop-2-en-1-one;
1-((2S,5R)-5-(7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)-2-methylpiperidin-1-yl)prop-2-en-1-one;
1-((3R,5S)-3-(7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)-5-hydroxypiperidin-1-yl)prop-2-en-1-one;
(R)-1-(3-(5-(2-methoxyethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)piperidin-1-yl)prop-2-en-1-one;
1-(5-(7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)-2-(hydroxymethyl)piperidin-1-yl)prop-2-en-1-one;
1-((3R,5S)-3-(7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)-5-fluoropiperidin-1-yl)prop-2-en-1-one;
1-((3R,4S)-3-(7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)-4-methylpiperidin-1-yl)prop-2-en-1-one;
1-((3S,4R)-3-(7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)-4-fluoropiperidin-1-yl)prop-2-en-1-one;

PYRROLO[2,3-D]PYRIMIDINYL, PYRROLO[2,3-B]PYRAZINYL AND PYRROLO[2,3-D]PYRIDINYL ACRYLAMIDES

FIELD OF THE INVENTION

The present invention provides pharmaceutically active heterocyclic acrylamides, *inter alia,* pyrrolo[2,3-d]pyrimidinyl, pyrrolo[2,3-b]pyrazinyl and pyrrolo[2,3-d]pyridinyl acrylamides 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.

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 which then phosphorylate the cytokine receptor, thereby creating

1-((2S,5R)-5-(7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)-2-ethylpiperidin-1-yl)prop-2-en-1-one;
(R)-1-(3-(7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)piperidin-1-yl)prop-2-en-1-one;
1-((3aS,7aS)-1-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)tetrahydro-1H-pyrrolo[2,3-c]pyridin-6(2H,7H,7aH)-yl)prop-2-en-1-one;
(R)-1-(3-(3-chloro-1H-pyrrolo[2,3-b]pyridin-4-ylamino)piperidin-1-yl)prop-2-en-1-one;
1-((1R,2R,5R)-2-(7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)-8-azabicyclo[3.2.1]octan-8-yl)prop-2-en-1-one;
1-((2R,5R)-5-(7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)-2-(hydroxymethyl)piperidin-1-yl)prop-2-en-1-one;
1-((3R,5R)-3-(7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)-5-fluoropiperidin-1-yl)prop-2-en-1-one;
(R)-1-(3-(5-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)piperidin-1-yl)prop-2-en-1-one;
1-((3R,5S)-3-(7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)-5-methylpiperidin-1-yl)prop-2-en-1-one;
1-((2S,5R)-5-(5-(2-methoxyethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)-2-methylpiperidin-1-yl)prop-2-en-1-one;
1-((3R,5S)-3-(7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)-5-methylpiperidin-1-yl)prop-2-en-1-one;
1-((3R,4S)-3-(7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)-4-methylpiperidin-1-yl)prop-2-en-1-one;
(R)-1-(3-(5-ethyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)piperidin-1-yl)prop-2-en-1-one;
1-((2S,5R)-5-(7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)-2-methylpiperidin-1-yl)prop-2-en-1-one;
(R)-1-(3-(5-fluoro-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)piperidin-1-yl)prop-2-en-1-one;
(R)-4-(1-acryloylpiperidin-3-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile; and,

(3R,5R)-5-(7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)-1-acryloylpiperidine-3-carbonitrile; or, a pharmaceutically acceptable salt thereof.

In particular, the invention provides 2-(1-acryloylpiperidin-4-ylamino)-N-isopropyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide; or, a pharmaceutically acceptable salt thereof; N-isopropyl-2-(3-(N-methylacrylamido)azetidin-1-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide; or, a pharmaceutically acceptable salt thereof; 2-((3R,4R)-1-acryloyl-3-hydroxypiperidin-4-ylamino)-N-isopropyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide; or, a pharmaceutically acceptable salt thereof; (S)-2-(1-acryloylpyrrolidin-3-ylamino)-N-isopropyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide; or, a pharmaceutically acceptable salt thereof; (S)-2-((1-acryloylpyrrolidin-2-yl)methylamino)-N-isopropyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide; or a pharmaceutically acceptable salt thereof; 1-((3aS,7aS)-1-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)tetrahydro-1H-pyrrolo[2,3-c]pyridin-6(2H,7H,7aH)-yl)prop-2-en-1-one; or, a pharmaceutically acceptable salt thereof; 1-((1R,2R,5R)-2-((7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-8-azabicyclo[3.2.1]octan-8-yl)prop-2-en-1-one, or a pharmaceutically acceptable salt thereof; 1-((3R,4S)-3-((7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-4-methylpiperidin-1-yl)prop-2-en-1-one, or a pharmaceutically acceptable salt thereof; 1-((2S,5R)-5-(7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)-2-methylpiperidin-1-yl)prop-2-en-1-one; or, a pharmaceutically acceptable salt thereof; (R)-4-(1-acryloylpiperidin-3-ylamino)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile; or, a pharmaceutically acceptable salt thereof.

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 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 dis-

ease, 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.

In specific embodiments, the invention provides the method of treatment or prevention noted above, wherein the compound is selected from the group consisting of:

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

N-isopropyl-2-(3-(N-methylacrylamido)azetidin-1-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide;

2-((3R,4R)-1-acryloyl-3-hydroxypiperidin-4-ylamino)-N-isopropyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide;

(S)-2-(1-acryloylpyrrolidin-3-ylamino)-N-isopropyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide;

(S)-2-((1-acryloylpyrrolidin-2-yl)methylamino)-N-isopropyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide;

2-((1R,3R)-3-acrylamidocyclobutylamino)-N-isopropyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide;

(S)-2-((1-acryloylpyrrolidin-3-yl)methylamino)-N-isopropyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide;

(R)-4-(1-acryloylpiperidin-3-ylamino)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile;

(R)-4-(1-acryloylpiperidin-3-ylamino)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile;

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

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

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

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

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

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

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

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

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

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

1-((3aS,7aS)-1-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)tetrahydro-1H-pyrrolo[2,3-c]pyridin-6(2H,7H,7aH)-yl)prop-2-en-1-one;

(R)-1-(3-(3-chloro-1H-pyrrolo[2,3-b]pyridin-4-ylamino)piperidin-1-yl)prop-2-en-1-one;

1-((1R,2R,5R)-2-(7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)-8-azabicyclo[3.2.1]octan-8-yl)prop-2-en-1-one;

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

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

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

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

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

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

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

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

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

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

(R)-4-(1-acryloylpiperidin-3-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile; and,

(3R,5R)-5-(7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)-1-acryloylpiperidine-3-carbonitrile; or, a pharmaceutically acceptable salt thereof.

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.

In specific embodiments, the invention provides the method for treating or preventing inflammatory bowel disease, wherein the compound is selected from the group consisting of:

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

N-isopropyl-2-(3-(N-methylacrylamido)azetidin-1-yl)-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide;

2-((3R,4R)-1-acryloyl-3-hydroxypiperidin-4-ylamino)-N-isopropyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide;

(S)-2-(1-acryloylpyrrolidin-3-ylamino)-N-isopropyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide;

(S)-2-((1-acryloylpyrrolidin-2-yl)methylamino)-N-isopropyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide;

2-((1R,3R)-3-acrylamidocyclobutylamino)-N-isopropyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide;

(S)-2-((1-acryloylpyrrolidin-3-yl)methylamino)-N-isopropyl-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide;

(R)-4-(1-acryloylpiperidin-3-ylamino)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile;

(R)-4-(1-acryloylpiperidin-3-ylamino)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile;

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

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

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

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

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

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

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

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

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

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

1-((3aS,7aS)-1-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)tetrahydro-1H-pyrrolo[2,3-c]pyridin-6(2H,7H,7aH)-yl)prop-2-en-1-one;

(R)-1-(3-(3-chloro-1H-pyrrolo[2,3-b]pyridin-4-ylamino)piperidin-1-yl)prop-2-en-1-one;

1-((1R,2R,5R)-2-(7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)-8-azabicyclo[3.2.1]octan-8-yl)prop-2-en-1-one;

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

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

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

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

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

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

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

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

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

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

(R)-4-(1-acryloylpiperidin-3-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile; and,

(3R,5R)-5-(7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)-1-acryloylpiperidine-3-carbonitrile; 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 accord 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 ace-

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 c a compound having the structure:

tate, adipate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulfate/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.

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. Antihis-

tamines 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 (anti-mycobacterial drugs, e.g., 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 (PG) may need to be protected 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 transformations 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 and compounds 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.

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.

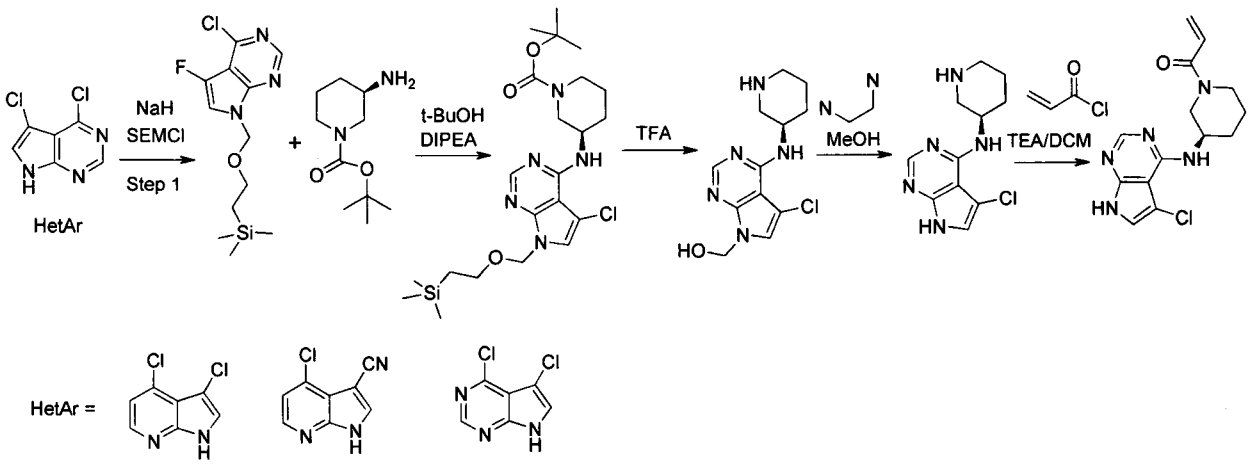
EXPERIMENTAL SECTION

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.

Example 1: (R)-1-(3-((3-chloro-1H-pyrrolo[2,3-b]pyridin-4-yl)amino)piperidin-1-yl)prop-2-en-1-one.

Example 2: (R)-4-((1-acryloylpiperidin-3-yl)amino)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile.

Example 3: (R)-1-(3-((5-chloro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidin-1-yl)prop-2-en-1-one.



Step 1. Halide monomers (300 µmol) were dissolved anhydrous DMF (10 ml/mmol, 3 ml) under argon atmosphere. NaH (60% suspension in mineral oil, 2 equiv, 600 µmol, ~30 mg) was added at 0 °C to each reaction vial. Each reaction vial was stirred at 0 °C for 30 min. SEM chloride (2 equiv, 600 µmol, 106 µL) was added dropwise to the reaction mixture and stirring was continued at 25 °C for 16 hrs. Completion of reaction was monitored by LCMS/TLC and solvents were stripped off using thermo explorer (1 hr, 5 torr, and 45 °C). The residue was purified by column chromatography using 5-10% ethyl acetate-hexane as eluent. For each monomer yield was around 75-80%.

Step 2. The amine template (0.2 M solution) in anhydrous toluene was prepared (solution A). 0.3 M solution of SEM protected halide monomers in anhydrous toluene was prepared (solution B). One ml of solution A (1 equiv, 200 µmol) was added followed by 1 ml of solution B (1.5 equiv, 300 µmol) to each reaction vial under argon purging condition. Anhydrous t-BuONa (3 equiv, 600 µmol, ~60 mg) was added to each reaction vial. $Pd_2(dba)_3$ (0.03 equiv, 6 µmol, ~6 mg) was dispensed under argon flow followed by BINAP (0.06 equiv, 12 µmol, ~7.5 mg). Each reaction vial was stirred at 90°C for 16 hrs. The reaction was checked by LCMS. The reaction mixture was filtered and the solvent was evaporated in thermo explorer (1 hr, 5 torr, and 45°C)

Step 2. (Set 2 monomers) The amine template (0.2 M solution) in t-BuOH was prepared (solution A). 0.3 M solution of SEM protected halide monomers in t-BuOH was prepared (solution B). One ml of solution A (1 equiv, 200

μmol) was added followed by 1 ml of solution B (1.5 equiv, 300 μmol) to each reaction vial. 103 μL (3 equiv, 600 μmol) of DIPEA was dispensed to each vial. Reaction vials were stirred for 16 h at 80°C. The reaction was checked by LC-MS. Solvent was evaporated in thermo explorer (1 hr, 5 torr, and 45°C)

Step 3 and 4 (Boc deprotection and Sem deprotection) Each step 2 residue was treated with 2 ml of TFA at 25 °C for 4 hrs. LCMS monitoring was done to check complete conversion to intermediate hydroxyl methyl derivative. After completion of reaction, solvents were evaporated using thermo explorer (1 hr, 5 torr, and 45°C) and azeotroped with toluene to remove traces of TFA (1 hr, 5 torr, and 45°C). Each residue was dissolved in 2 ml of MeOH and ~70 μL of ethylenediamine was added to each reaction vial and again stirred for 16 hrs at 25°C. Reactions were checked by LC-MS. After completion of reaction, the solvent was evaporated and residue was dissolved in 5 ml ethyl acetate. The organic layer was washed with water (2 ml) and brine (2 ml). The organic extract was dried over anhydrous sodium sulfate and concentrated under reduced pressure.

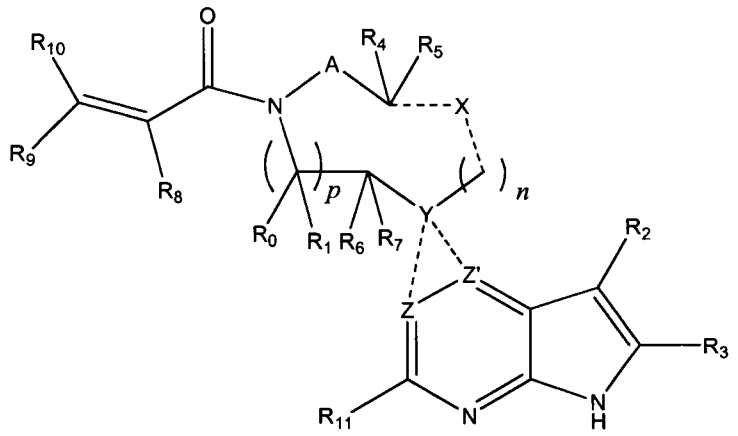
Step 5 (Rxn with acryloyl chloride) All the calculations were done in 100 μmol scale at the final step. Each step 4 residue was dissolved in anhydrous THF (1 ml) under argon atmosphere. 200 μmol (2 equiv, 28 μL) of TEA was added to each reaction mixture. Reaction mixtures were cooled to 0°C and a solution of 0.5 equiv of acryloyl chloride in THF (4 μL in 500 μL THF) was added slowly maintaining ice cold condition during the addition. After stirring for 10 min at 0°C, the solvent was evaporated and the residue was dissolved in 1 ml DMSO. 10 μL of the DMSO solution was diluted to 200 μL with DMSO for QC analysis and remaining amount was submitted for prep-HPLC purification. Purification on Xterra® RP18 (19 x 250 mm, 10 μ, H2O (10mM NH_4OAc): CH_3CN).

Example	LC/MS
1	305.7
2	296.3
3	306.7

Example 4: 1-((3S,4S)-3-((7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-4-fluoropiperidin-1-yl)prop-2-en-1-one.

Step 1. (3S,4S)-Benzyl 4-fluoro-3-((7-trityl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidine-1-carboxylate. To a solution of 4-chloro-7-trityl-7H-pyrrolo[2,3-d]pyrimidine (140 mg, 0.354 mmol) and cesium fluoride (430 mg, 2.83 mmol) in DMSO (2.0 mL) was added (3S,4S)-benzyl 3-amino-4-fluoropiperidine-1-carboxylate (prepared as described in WO2010016005) (100 mg, 0.346 mmol). The reaction mixture was heated to 120 °C for 9 hours. LCMS showed that 4-chloro-7-trityl-7H-pyrrolo[2,3-d]pyrimidine was consumed completely. The reaction mixture was diluted with a 1:1 mixture of DCM/water (200 mL). The organic layer was extracted and the aqueous layer was back extracted with DCM (2 x 50 mL). The organic extracts were combined, washed with brine (2 x 100 mL), dried over sodium sulfate, filtered, and concentrated in vacuo to yield crude product which was dry loaded with Celite® onto a Silicycle 25g HP column and purified via normal phase column chromatography (0-75% EtOAc/heptanes over 15 column volumes) to afford (3S,4S)-benzyl 4-fluoro-3-((7-trityl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidine-1-carboxylate (149.6 mg, 69%) as a colorless solid. ^{1}H NMR (400MHz, DMSO-d_6) 7.74 (s, 1H), 7.58 (d, J = 8.0 Hz, 1H), 7.39-7.18 (m, 15 H), 7.09-7.05 (m, 5H), 6.84 (d, J = 3.8 Hz, 1H), 6.68 (d, J = 3.8 Hz, 1H), 5.05 (s, 2H), 4.84-4.64 (m, 2H), 4.35 -4.24 (m, 1H), 4.15 – 4.05 (m, 1H), 3.95 – 3.85 (m, 1H), 2.25 – 2.13 (m, 1H), 1.70 – 1.58 (m, 1H).

Step 2. N-((3S,4S)-4-Fluoropiperidin-3-yl)-7-trityl-7H-pyrrolo[2,3-d]pyrimidin-4-amine . To a dry hydrogenation bottle, 10% Pd/C (65 mg) was added under nitrogen atmosphere. Then a solution of (3S,4S)-benzyl 4-fluoro-3-((7-trityl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidine-1-carboxylate (150 mg, 0.245 mmol) in anhydrous ethanol (5.0 mL) was added and the resulting mixture was hydrogenated under 50 psi of H_2 at ambient temperature for 3 hours. LCMS showed the starting material was consumed completely. The reaction mixture was filtered through a thin pad of Celite® and the filter cake was washed with ethanol. The combined filtrate was evaporated, azeotroped with



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

toluene (5 x) at 75°C to afford compound N-((3S,4S)-4-fluoropiperidin-3-yl)-7-trityl-7H-pyrrolo[2,3-d]pyrimidin-4-amine (104 mg, 89%) as a colorless solid, which was used directly in the next step without further purification.

Step 3. 1-((3S,4S)-4-Fluoro-3-((7-trityl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidin-1-yl)prop-2-en-1-one. To a solution of N-((3S,4S)-4-fluoropiperidin-3-yl)-7-trityl-7H-pyrrolo[2,3-d]pyrimidin-4-amine (102 mg, 0.214 mmol) in anhydrous d-$CHCl_3$ (5.0 mL) is added Hunig's base (0.2 mL, 1.0 mmol). The reaction mixture was cooled to 2° C then treated, dropwise, with a solution of acrylic chloride (0.017 mL, 0.214 mmol) in anhydrous d-$CHCl_3$ (1.0 mL). The reaction mixture was allowed to warm to ambient temperature and after 30 minutes, LCMS showed compound N-((3S,4S)-4-fluoropiperidin-3-yl)-7-trityl-7H-pyrrolo[2,3-d]pyrimidin-4-amine was consumed completely. The reaction mixture was cooled to 2° C and quenched with 10% aqueous sodium bicarbonate (5 mL). The organic layer was extracted and the aqueous layer was back extracted with chloroform (2 x 2 mL). The organic extracts were combined, dried over magnesium sulfate, filtered, and concentrated in vacuo to yield crude product which was dry loaded with Celite® onto a Silicycle 12 g HP column and purified via normal phase column chromatography (50-80% EtOAc/heptanes over 10 column volumes) to afford 1-((3S,4S)-4-fluoro-3-((7-trityl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidin-1-yl)prop-2-en-1-one (79.0 mg, 69%) as a colorless solid. LCMS (M+H) 532.64.

Step 4. Preparation of 1-((3S,4S)-3-((7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-4-fluoropiperidin-1-yl)prop-2-en-1-one. A solution of 1-((3S,4S)-4-fluoro-3-((7-trityl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidin-1-yl)prop-2-en-1-one (79.0 mg, 0.150 mmol) in trifluoroacetic acid (1.15 mL) was allowed to stir at ambient temperature for 16 hours. The reaction mixture was concentrated in vacuo and dry loaded with Celite® onto a Silicycle® 12 g HP column and purified via normal phase column chromatography (0-20% MeOH/DCM over 10 column volumes) to afford 1-((3S,4S)-3-((7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-4-fluoropiperidin-1-yl)prop-2-en-1-one (37.6 mg, 87%) as a colorless solid. LCMS (M+H) 290.48. HPLC 1.330 min. ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.20 (s, 1H), 7.23-7.10 (m, 1H), 6.90-6.62 (m, 2H), 6.21 (t, J = 20

Hz, 1 H), 5.82-5.66 (m, 1H), 4.93 – 4.71 (m, 1H), 4.62 – 4.03 (m, 3H), 3.44 – 3.04 (m, 2H), 2.36 -2.24 (m, 1H), 1.89-1.74 (m, 1H).

Example 5: 1-((2S,5R)-5-((7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-methylpiperidin-1-yl)prop-2-en-1-one.

Step 1. tert-Butyl (6-methylpyridin-3-yl)carbamate. To a solution of 6-methylpyridin-3-amine (25 g, 231. mmol)) in EtOH (100 mL) at 0 °C was added $(Boc)_2O$ (55.5 g, 298 mmol) dropwise slowly. After the addition, the solution was stirred at room temperature overnight. TLC (petroleum ether/EtOAc, 2:1) showed 6-methylpyridin-3-amine was consumed completely. The reaction mixture was filtered and the filter cake was washed with EtOH (30 mLx3). The combined filtrate was concentrated in vacuo to afford a yellow residual, which was purified by chromatography (petroleum ether/EtOAc, 4:1 to 1:1) to give tert-butyl (6-methylpyridin-3-yl)carbamate (32.5 g, 67.4%) as a white solid. ^1H NMR (400MHz, $CDCl_3$) 8.30 (d, J=2.0 Hz, 1H), 7.86 (br s, 1H), 7.10 (d, J=8.5 Hz, 1H), 6.57 (br s, 1H), 2.49 (s, 3H), 1.51 (s, 9H)

Step 2. rac-cis/trans- tert-Butyl (6-methylpiperidin-3-yl)carbamate. To a dry hydrogenation bottle, PtO_2 (2.5 g) was added under Ar atmosphere. Then a solution of tert-butyl (6-methylpyridin-3-yl)carbamate (33 g, 158.5 mmol) in HOAc (300 mL) was added and the resulting mixture was hydrogenated under 55 psi of H_2 at 50 °C for 30 hours. TLC (petroleum ether/EtOAc, 2:1) showed the starting material was consumed completely. The reaction mixture was filtered and the filter cake was washed with MeOH (50 mLx2). The combined filtrate was evaporated to give tert-butyl (6-methylpiperidin-3-yl)carbamate (34 g, 100%) as a yellow oil (~2:1 cis/trans), which was used directly to next step without further purification. LC/MS (M+H) 215.2.

Step 3. rac-cis/trans-Benzyl 5-((tert-butoxycarbonyl)amino)-2-methylpiperidine-1-carboxylate. To a stirred solution of tert-butyl (6-methylpiperidin-3-yl)carbamate (27.0 g, 126 mmol) and $NaHCO_3$ (74.2 g, 883 mmol) in THF (350 mL)/H_2O (350 mL) was added CbzCl (32.17 g, 189 mmol) dropwise at room temperature. After the addition, the resulting mixture was

stirred at room temperature for 2 hours. TLC (CH_2Cl_2/MeOH, 10:1) showed the starting material was consumed completely. The reaction mixture was extracted with EtOAc (300 mLx2). The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated to give crude product. The crude product was further purified by chromatography (PE/EA, 30:1-10:1) to give rac-cis/trans benzyl 5-((tert-butoxycarbonyl)amino)-2-methylpiperidine-1-carboxylate (44.0 g, 100%) as a colorless oil. (^{1}H NMR showed ~ 1mol of BnOH.) ^{1}H NMR (400MHz, $CDCl_3$) δ 7.35 - 7.19 (m, 9 H), 5.14 - 4.99 (m, 2H), 4.82 (d, J=6.0 Hz, 1H), 4.67 - 4.59 (m, 2H), 4.48 - 4.28 (m, 2H), 4.17 (d, J=9.8 Hz, 1H), 3.97 (d, J=13.8 Hz, 1H), 3.73 (br s, 1H), 3.39 (br s, 1H), 3.02 (d, J=14.1 Hz, 1H), 2.49 (t, J=12.0 Hz, 1H), 1.89 - 1.59 (m, 3H), 1.48 (dd, J=1.5, 13.8 Hz, 1H), 1.39 - 1.32 (m, 8H), 1.11 - 1.01 (m, 3H).

Step 4. rac-(2S,5R)-Benzyl 5-((tert-butoxycarbonyl)amino)-2-methylpiperidine-1-carboxylate and rac- (2S,5S)-benzyl 5-((tert-butoxycarbonyl)amino)-2-methylpiperidine-1-carboxylate. The rac-cis/trans benzyl 5-((tert-butoxycarbonyl)amino)-2-methylpiperidine-1-carboxylate (44 g) was separated by chiral SFC to give rac-cis - (2S,5R)-benzyl 5-((tert-butoxycarbonyl)amino)-2-methylpiperidine-1-carboxylate (Peak 2, 24.5 g, 55.68%) and rac-trans - (2S,5S)-benzyl 5-((tert-butoxycarbonyl)amino)-2-methylpiperidine-1-carboxylate (Peak 1, 12.3 g, 27.95%). Peak 2, cis material was carried on to Boc removal. Prep SFC Column : ChiralCel OD 300mmx50mm, 10 μm; Mobile phase: A: Supercritical CO2 , B: IPA (0.1%NH_3H_2O), A:B =85:15 at 180ml/min; Column Temp: 38 °C; Nozzle Pressure: 100Bar; Nozzle Temp: 60 °C; Evaporator Temp: 20 °C; Trimmer Temp: 25 °C; Wavelength: 220nm

Peak 1 (trans): ^{1}H NMR (400MHz, $CDCl_3$) δ 7.44 - 7.28 (m, 5H), 5.23 - 5.06 (m, 2H), 4.55 - 4.35 (m, 2H), 4.25 (d, J=10.0 Hz, 1H), 3.58 - 3.25 (m, 1H), 2.58 (t, J=12.0 Hz, 1H), 1.87 (d, J=11.0 Hz, 1H), 1.82 - 1.69 (m, 2H), 1.56 (d, J=13.8 Hz, 1H), 1.50 - 1.36 (m, 9H), 1.21 (d, J=6.3 Hz, 3H).

Peak 2 (cis): ^{1}H NMR (400MHz, $CDCl_3$) δ 7.42 - 7.29 (m, 5H), 5.20 - 5.08 (m, 2H), 4.89 (br s, 1H), 4.47 (br s, 1H), 4.05 (d, J=14.1 Hz, 1H), 3.81 (br s, 1H), 3.11 (d, J=13.8 Hz, 1H), 1.93 - 1.68 (m, 4H), 1.43 (s, 9H), 1.20 - 1.13 (m, 3H).

Step 5. Racemic (2S,5R)-benzyl 5-amino-2-methylpiperidine-1-carboxylate. To a solution of rac-cis - (2S,5R)-benzyl 5-((tert-butoxycarbonyl)amino)-2-methylpiperidine-1-carboxylate (pk 2, 40.0 g, 115.6 mmol) in CH_2Cl_2 (60 mL) at 0 °C was added (4M HCl (g)/dioxane (200 mL) dropwise. After the addition, the solution was stirred at room temperature for 4hrs. TLC (petroleum ether/EtOAc, 2:1) showed the starting material was consumed completely. The reaction mixture was concentrated to give racemic (2S,5R)-benzyl 5-amino-2-methylpiperidine-1-carboxylate (31.0 g, 94.8%) as a white solid (HCl salt). ^{1}H NMR (400MHz, DMSO-d_6) δ 8.37 (br s, 3H), 7.24 - 7.49 (m, 5H), 5.09 (s, 2H), 4.32 (m, 1H), 4.16 (d, J=8.28Hz, 1H), 3.00 (br s, 2H), 1.83 (m, 2H), 1.59 (m, 2H), 1.11 (d, J=7.03Hz, 3H).

Step 6. Racemic (2S,5R)-benzyl 5-((2-chloro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-methylpiperidine-1-carboxylate. A mixture of 2,4-dichloro-7H-pyrrolo[2,3-d]pyrimidine (21.8 g, 0.116 mol), DIPEA (67.7 g, 0.525 mol) and racemic (2S,5R)-benzyl 5-amino-2-methylpiperidine-1-carboxylate (30 g, 0.105 mol) in n-BuOH (300 mL) was heated to 140 °C overnight. LC-MS indicated the reaction was completed. The reaction mixture was cooled to room temperature and evaporated to dryness; the residue was partitioned with EtOAc (500 mL) and water (500 mL). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated to give crude product, which was triturated with MTBE to give racemic (2S,5R)-benzyl 5-((2-chloro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-methylpiperidine-1-carboxylate (36 g, 86 %) as a yellow solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 11.70 (br s, 1H), 7.71 (d, J=7.8 Hz, 1H), 7.46 - 7.25 (m, 5H), 7.10 (br s, 1H), 6.56 (br s, 1H), 5.18 - 5.00 (m, 2H), 4.38 (d, J=6.8 Hz, 1H), 4.16 (br s, 1H), 4.03 (q, J=7.3 Hz, 2H), 2.76 (t, J=11.8 Hz, 1H), 1.87 - 1.68 (m, 2H), 1.63 (d, J=7.3 Hz, 1H), 1.19 - 1.12 (m, 3H).

Step 7. rac-N-((3R,6S)-6-Methylpiperidin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine. To a dry hydrogenation bottle, 10% dry Pd/C (7 g) was added under Ar atmosphere. Subsequently, a solution of racemic (2S,5R)-benzyl 5-((2-chloro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-methylpiperidine-1-carboxylate (36 g, 0.09 mol) in MeOH (1500 mL) and THF (250 mL) was add-

ed and the resulting mixture was shaken on a Parr apparatus (45 psi of H_2 at 25 °C for 48 hours). LC-MS indicated the Cbz was removed completely, but ~30% of chloride remained. The reaction mixture was filtered and the filtrate was subjected to the reaction conditions again with 5 g of 10% dry Pd/C under 50 psi of H_2 at 45 °C for 12 h. LC-MS showed the reaction was completed. The reaction mixture was filtered through a pad of Celite® and the cake was washed with MeOH three times. The combined filtrates were concentrated to give rac -N-((3R,6S)-6-methylpiperidin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine (23 g, 94.6%) as a white solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 11.53 (br s, 1H), 8.11 (d, J=12.5 Hz, 1H), 7.30 (dd, J=6.5, 18.6 Hz, 1H), 7.10 (br s, 1H), 6.90 - 6.73 (m, 1H), 6.59 - 6.52 (m, 1H), 6.10 (dd, J=1.5, 17.1 Hz, 1H), 5.68 (d, J=10.5 Hz, 1H), 4.86 - 4.51 (m, 1H), 4.41 - 3.97 (m, 2H), 3.02 - 2.55 (m, 1H), 1.89 - 1.59 (m, 3H), 1.28 - 1.10 (m, 3H).

Step 8. rac-1-((2S,5R)-5-((7H-Pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-methylpiperidin-1-yl)prop-2-en-1-one. To a stirred solution of rac-N-((3R,6S)-6-methylpiperidin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine HCl salt (5.00 g, 18.5 mmol) in THF (250 mL) and saturated aq. $NaHCO_3$ solution (250 mL) was added acryloyl chloride (2.02 g, 22.2 mmol) dropwise at 0 °C carefully. After addition, the resulting mixture was stirred at 0 °C for 4 hours. TLC (DCM/MeOH/NH_4OH, 10:1:1) showed rac-N-((3R,6S)-6-methylpiperidin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine was consumed completely. The reaction mixture was diluted with H_2O (125 mL) and extracted with EtOAc (125 mLx3); the combined organic layer was washed with brine, and dried over Na_2SO_4. The most volatile components were removed in vacuum. The crude product was purified by column chromatography on silica gel (DCM/MeOH, 10:1) to give pure product. The product was triturated with EtOAc (150 mL) and filtered to give rac-1-((2S,5R)-5-((7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-methylpiperidin-1-yl)prop-2-en-1-one (2.0 g, 38% yield) as a white solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 11.53 (br s, 1H), 8.12 (d, J=12.8 Hz, 1H), 7.30 (dd, J=6.8, 18.8 Hz, 1H), 7.10 (br s, 1H), 6.89-6.71 (m, 1H), 6.56 (d, J=1.8 Hz, 1H), 6.10 (dd, J=2.1, 16.7 Hz, 1H), 5.72-5.61 (m, 1H), 4.81 (br s, 0.5H), 4.56 (d, J=10.3 Hz, 0.5H), 4.37 (br s, 0.5H), 4.20 - 3.95 (m, 1.5H), 2.96 (t,

J=11.9Hz, 0.5H), 2.60 (t, J=12.0 Hz, 0.5H), 1.92 - 1.59 (m, 4H), 1.30 - 1.07 (m, 3H).

Step 9. Preparation of (+)-1-((2R,5S)-5-((7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-methylpiperidin-1-yl)prop-2-en-1-one (pk 1) and (-) 1-((2S,5R)-5-((7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-methylpiperidin-1-yl)prop-2-en-1-one (pk 2). The racemic compound : rac-1-((2S,5R)-5-((7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-methylpiperidin-1-yl)prop-2-en-1-one (from Step 8) was purified by chiral SFC to give pure enantiomers. Peak 1 (4.63 g, +) and peak 2 (4.42 g, -) SFC conditions: Column: ChiralPak IC (300 mm*50 mm, 10 µm); Mobile phase: 40% ethanol (0.05% NH_3 in H_2O) in CO_2; Flow rate: 200 mL/min; wave-length: 220nm.

The absolute stereochemistry was assigned based on X-ray crystallographic analysis.

Peak 1: (+) 1-((2R,5S)-5-((7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-methylpiperidin-1-yl)prop-2-en-1-one ^{1}H NMR (400MHz, DMSO-d_6) δ 11.53 (br s, 1H), 8.12 (d, J=12.8 Hz, 1H), 7.30 (dd, J=6.8, 18.8Hz, 1H), 7.10 (br s, 1H), 6.89 - 6.71 (m, 1H), 6.56 (d, J=1.8 Hz, 1H), 6.10 (dd, J=2.1, 16.7 Hz, 1H), 5.72-5.61 (m, 1H), 4.81 (br s, 0.5H), 4.56 (d, J=10.3 Hz, 0.5H), 4.37 (br s, 0.5H), 4.20 - 3.95 (m, 1.5H), 2.96 (t, J=11.9, Hz, 0.5H), 2.60 (t, J=12.0 Hz, 0.5H), 1.92 - 1.59 (m, 4H), 1.30 - 1.07 (m, 3H). LC/MS (M+H) 286.2. OR = $[a]_D^{20}$ = +0.34 (c = 0.6, MeOH).

Peak 2: (-) 1-((2S,5R)-5-((7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-methylpiperidin-1-yl)prop-2-en-1-one ^{1}H NMR (400MHz, DMSO-d_6) δ 11.53 (br s, 1H), 8.12 (d, J=12.8 Hz, 1H), 7.30 (dd, J=6.8, 18.8 Hz, 1H), 7.10 (br s, 1H), 6.89 - 6.71 (m, 1H), 6.56 (d, J=1.8 Hz, 1H), 6.10 (dd, J=2.1, 16.7 Hz, 1H), 5.72-5.61 (m, 1H), 4.81 (br s, 0.5H), 4.56 (d, J=10.3 Hz, 0.5H), 4.37 (br s, 0.5H), 4.20 - 3.95 (m, 1.5H), 2.96 (t, J=11.9, Hz, 0.5H), 2.60 (t, J=12.0 Hz, 0.5H), 1.92 - 1.59

(m, 4H), 1.30 - 1.07 (m, 3H). LC/MS (M+H) 286.2. OR $[a]_D^{20}$ = -0.36 (c = 0.6, MeOH).

Example 6: (3R,5R)-5-((7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-1-acryloylpiperidine-3-carbonitrile.

Step 1. Preparation of N-((3R,5R)-1-benzyl-5-((tert-butyldimethylsilyl)oxy)piperidin-3-yl)-7-trityl-7H-pyrrolo[2,3-d]pyrimidin-4-amine. To a mixture of 4-chloro-7-trityl-7H-pyrrolo[2,3-d]pyrimidine (16.3 g, 41.18 mmol) and compound (3R,5R)-1-benzyl-5-((tert-butyldimethylsilyl)oxy)piperidin-3-amine (prepared as described in *Eur. J. Org. Chem.* **2012**, *10*, 2023. (12 g, 37.44 mmol) in n-BuOH (250 mL) at rt was added DIPEA (14.5 g, 112.32 mmol). The reaction mixture was heated to 110 °C for 3 days. TLC (DCM/MeOH, 10:1) showed most of amine was consumed. The reaction mixture was cooled to room temperature and evaporated to dryness via oil pump at 45°C; the residue was partitioned with EtOAc (800 mL) and water (500 mL). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated to give crude product, which was purified by chromatography (EtOAc/PE from 0% to 30%) to give N-((3R,5R)-1-benzyl-5-((tert-butyldimethylsilyl)oxy)piperidin-3-yl)-7-trityl-7H-pyrrolo[2,3-d]pyrimidin-4-amine (15 g, 65%) as a yellow solid. LC/MS (M+H) 679.4. ^{1}H NMR (400 MHz, $CDCl_3$) δ -0.03 (d, *J*=2.01 Hz, 6 H) 0.82 (s, 9 H) 1.50 (d, *J*=12.55 Hz, 1 H) 2.31 (d, *J*=11.54 Hz, 2 H) 2.74 (d, *J*=12.55 Hz, 1 H) 2.96 (br s, 1 H) 3.40 - 3.73 (m, 2 H) 3.99 (br s, 1 H) 4.50 (br s, 1 H) 5.58 (br s, 1 H) 6.32 (d, *J*=4.02 Hz, 1 H) 6.90 (d, *J*=3.51 Hz, 1 H) 7.13 - 7.38 (m, 20 H) 8.00 (s, 1 H).

Step 2. (3R,5R)-tert-Butyl 3-((tert-butyldimethylsilyl)oxy)-5-((7-trityl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidine-1-carboxylate. To a dry hydrogenation bottle, 10% dry Pd/C (1.5 g) was added. Then a solution of N-((3R,5R)-1-benzyl-5-((tert-butyldimethylsilyl)oxy)piperidin-3-yl)-7-trityl-7H-pyrrolo[2,3-d]pyrimidin-4-amine (14.8 g, 21.76 mmol) and $(Boc)_2O$ (5.22 g, 23.94 mmol) in MeOH (300 mL) was added and the resulting mixture was hydrogenated under 50 psi of H_2 at 40 °C for 12 hours. TLC (PE/EtOAc 4:1)

showed the reaction was complete. The reaction solution was filtered through a pad of Celite® and the cake was washed with MeOH three times. The combined filtrate was concentrated to give (3R,5R)-tert-butyl 3-((tert-butyldimethylsilyl)oxy)-5-((7-trityl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino) piperidine-1-carboxylate (14.8 g, ~100%) as a yellow solid, which was used directly to next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.06 (br s, 6 H) 0.72 - 0.94 (m, 9 H) 1.16 - 1.43 (m, 4 H) 1.49 (br s, 9 H) 1.57 - 2.40 (m, 3 H) 2.93 - 3.13 (m, 1 H) 3.37 - 4.01 (m, 3 H) 4.45 (br s, 1 H) 4.72 - 5.38 (m, 1 H) 6.30 (br s, 1 H) 6.90 (br s, 1 H) 7.08 - 7.36 (m, 16 H) 8.01 (s, 1 H).

Step 3. (3R,5R)-tert-Butyl 3-hydroxy-5-((7-trityl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidine-1-carboxylate. To a solution of (3R,5R)-tert-butyl 3-((tert-butyldimethylsilyl)oxy)-5-((7-trityl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidine-1-carboxylate (15 g, 21.74 mmol) in anhydrous THF (300 mL) was added n-Bu_4NF (11.38 g, 43.47 mmol). The reaction mixture was then heated to 40 °C overnight. TLC (PE/EtOAc 4:1) indicated the reaction was complete. The reaction solution was diluted with water (300 mL) and then extracted with EtOAc (2x200 mL). The combined organic layers were washed with water, brine and dried over Na_2SO_4, which after concentration gave (3R,5R)-tert-butyl 3-hydroxy-5-((7-trityl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidine-1-carboxylate (14.6 g, ~100%), which was used directly in the next step without further purification. 1H NMR (400MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.37 - 7.08 (m, 17H), 6.91 (d, J=3.5 Hz, 1H), 6.30 (br s, 1H), 4.48 (d, J=3.5 Hz, 1H), 4.05 (br s, 1H), 3.83 - 3.51 (m, 4H), 3.23 (br s, 1H), 1.58 - 1.29 (m, 10H).

Step 4. (R)-tert-Butyl 3-oxo-5-((7-trityl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidine-1-carboxylate. To a solution of compound (3R,5R)-tert-butyl 3-hydroxy-5-((7-trityl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidine-1-carboxylate (5.0 g, 8.68 mmol) in DCM (100 mL) was added Dess-Martin periodinane (4.0 g, 9.55 mmol). The mixture was stirred at room temperature for 18 hours. TLC (DCM/MeOH, 10:1) showed starting material was consumed completely. The reaction mixture was concentrated to give crude product (7.8g) as yellow solid, which was purified by prep-HPLC to give (R)-

tert-butyl 3-oxo-5-((7-trityl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidine-1-carboxylate (3.7 g, 74 %) as a white solid. LC/MS (M+H) = 574.3. ^{1}H NMR (400 MHz, DMSO-d_6) d ppm 1.24 (s, 9 H) 2.20 - 2.45 (m, 2 H) 3.04 - 3.36 (m, 2 H) 3.92 - 4.27 (m, 3 H) 6.88 - 7.46 (m, 16 H) 8.29 - 8.57 (m, 2 H) 10.46 - 10.71 (m, 1 H).

Step 5. (5R)-tert-Butyl 3-cyano-5-((7-trityl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidine-1-carboxylate (mixture of isomers). To a mixture of (R)-tert-butyl 3-oxo-5-((7-trityl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidine-1-carboxylate (1.0 g, 1.74 mmol) and TOSMIC (693.7 mg, 3.83 mmol) in DME (30 ml) at 0 °C was added t-BuOK (624.4 mg, 5.58 mmol) and EtOH (176.3 mg, 3.83 mmol) in portions. The resulting mixture was stirred at 0 °C for 0.5 hour. The mixture was allowed to warm to room temperature and stirred for 2 hours. TLC (DCM/MeOH, 10:1) showed the reaction was complete. The reaction solution was filtered, and the filtrate was concentrated to dryness and purified by preparative TLC (petroleum ether /EtOAC, 2:1) to afford (5R)-5-((7-trityl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino) piperidine-3-carbonitrile (mixture of isomers, 200 mg, 20%) as a yellow solid. LC/MS (M+H) 585.3.

Step 6. Preparation of (5R)-5-((7-trityl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidine-3-carbonitrile (mixture of isomers). To a solution of (5R)-tert-butyl 3-cyano-5-((7-trityl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidine-1-carboxylate (235 mg, 0.41 mmol) in DCM (1.5 ml) at 0 °C was added TFA (229.0 mg, 2.0 mmol). The reaction mixture was then stirred at room temperature for 12 hours. TLC (petroleum ether /EtOAC, 1:1) showed the reaction was complete. The reaction mixture was concentrated in vacuo to give (5R)-5-((7-trityl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidine-3-carbonitrile (mixture of isomers) (235 mg, 100%) as a yellow solid. LC/MS (M+H) 485.0.

Step 7. Preparation of (5R)-1-acryloyl-5-((7-trityl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidine-3-carbonitrile (mixture of isomers). To a stirred solution of (5R)-5-((7-trityl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidine-3-carbonitrile (100 mg, 0.206 mmol) in THF (3 mL) :aq. $NaHCO_3$ solution (2.5 mL) at 0 °C was added acryloyl chloride (22.4 mg, 0.247 mmol) dropwise. After addition, the resulting mixture was stirred at 0 °C for 2 hours. TLC (DCM/MeOH, 20:1)

showed the reaction was completely. The reaction mixture was diluted with H_2O (20 mL) and extracted with EtOAc (30 mL×2), the combined organic layer were washed with brine, dried over Na_2SO_4 and concentrated to give crude product, which was further purified by preparative TLC (petroleum ether /EtOAC, 1:1) to give (5R)-1-acryloyl-5-((7-trityl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidine-3-carbonitrile and *trans isomer* (80 mg, 72 %) as yellow solid. LC/MS (M+H) 539.1.

Step 8. Preparation of (3S,5R)-5-((7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-1-acryloylpiperidine-3-carbonitrile and (3R,5R)-5-((7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-1-acryloylpiperidine-3-carbonitrile.

To a round bottom flask containing (5R)-1-acryloyl-5-((7-trityl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino) piperidine-3-carbonitrile and compound 5-1 (80 mg, 0.272 mmol) was added TFA (1 mL). The mixture was stirred at room temperature for 12 hours. TLC (petroleum ether /EtOAC, 1:1) showed 20% starting material remained. The reaction was heated to 30 °C for another 5h. LCMS indicated completion. The reaction mixture was concentrated to give crude product, which was further purified by prep. TLC (Petroleum ether /EtOAC, 1:1) to give a mixture of (3S,5R)-5-((7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-1-acryloylpiperidine-3-carbonitrile and (3R,5R)-5-((7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-1-acryloylpiperidine-3-carbonitrile (12 mg, 10 % for 3 steps) as a white solid. Chiral HPLC showed it was a mixture of trans/cis, which was purified further by chiral SFC. After chiral SFC, 1.4 mg of peak 1 and 3.3 mg of peak 2 was obtained. Peak 1: (3S,5R)-5-((7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-1-acryloyl piperidine-3-carbonitrile and Peak 2: (3R,5R)-5-((7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-1-acryloylpiperidine-3-carbonitrile. SFC separation conditions: Column: ChiralPak AD (250mmx30mm, 20 μm); Mobile phase: 50% EtOH+NH_3/H_2O 80mL/min; Column: Chiralpak AD-H 250×4.6mm I.D., 5 μm; Mobile phase: ethanol (0.05% DEA) in CO_2 from 5% to 40%; Flow rate: 2.35mL/min; Wavelength: 220nm; Peak 1: ^{1}H NMR (400MHz, CD_3OD) δ 8.16 (br s, 1H), 7.10 (d, J=3.5 Hz, 1H), 6.85 (dd, J=10.4, 16.7 Hz, 1H), 6.57 (d, J=3.5 Hz, 1H), 6.27 (dd, J=1.8, 16.8 Hz, 1H), 5.80 (d, J=9.5 Hz, 1H), 4.85 - 4.77 (m, 1H), 4.63 (s, 1H), 4.43 (d,

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_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_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;

J=11.8 Hz, 1H), 4.28 - 4.19 (m, 1H), 3.14 - 2.97 (m, 2H), 2.55 (d, J=12.5 Hz, 1H), 2.00 (d, J=14.6 Hz, 1H). Peak 2: ^{1}H NMR (400MHz, CD_3OD) δ 8.20 (br s, 1H), 7.09 (d, J=3.5 Hz, 1H), 6.90 - 6.54 (m, 2H), 6.32 - 6.07 (m, 1H), 5.90 - 5.57 (m, 1H), 4.71 - 4.41 (m, 2H), 4.40 - 4.01 (m, 2H), 3.71 - 3.40 (m, 2H), 2.39 (br s, 1H), 2.17 (d, J=9.0 Hz, 1H).

Example 7: 1-((2R,5R)-5-((7H-Pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-(hydroxymethyl)piperidin-1-yl)prop-2-en-1-one.

Step 1. Methyl 5-aminopicolinate. To a stirred solution of 5-aminopicolinic acid (170g, 1.23mol) in MeOH (1700 ml) was added $SOCl_2$ (178.6 ml, 2.47mol) at 0°C. The reaction mixture was then refluxed for 72 h. The mixture was then cooled to 0°C and additional $SOCl_2$ was added (40 ml, 0.55mol). The mixture was then refluxed for 24h. The excess $SOCl_2$ was removed under reduced pressure and the crude material was neutralized with aq. $NaHCO_3$. The mixture was filtered and the filter cake dried at 40-50°C overnight. The solid was collected to give methyl 5-aminopicolinate (350g). The filtrate was further extracted with DCM (3x2 L). The organic extract was washed with brine, dried (Na_2SO_4) and concentrated to dryness to afford crude compound (200g). All of solids were collected to give methyl 5-aminopicolinate (550g from 680 g of compound **1**, 73%) as a white solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 8.12 (d, J=2.5 Hz, 1H), 7.93 (d, J=8.5 Hz, 1H), 6.97 (dd, J=2.8, 8.5 Hz, 1H), 4.24 (br s, 2H), 3.93 (s, 3H).

Step 2. Methyl 5-((tert-butoxycarbonyl)amino)picolinate. Methyl 5-aminopicolinate (110g, 0.723mol) was dissolved in DCM (2000 ml) at 20°C under N_2. To the reaction mixture, Boc-anhydride (173.6g, 0.80mol) and DMAP (8.8 g, 0.0723 mol) were added. The reaction mixture was stirred at 20°C for 20 h. TLC (PE/EA, 2:1) showed that the starting material was consumed completely. The reaction mixture was filtered and washed with DCM (4x3000ml). H_2O (2000 ml) was added and layers were separated. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give crude product. The crude compound

was washed with petroleum ether (4000mL) and stirred for 1.0 hour. Filtration and evaporation in vacuo afforded methyl 5-((tert-butoxycarbonyl)amino) picolinate (750g from 550 g of methyl 5-aminopicolinate, 82.3%) as a white solid for next step without further purification. LC/MS (M+H) = 253.1.

Step 3. tert-Butyl (6-(hydroxymethyl)pyridin-3-yl)carbamate. LAH powder (36 g, 0.96mol) was suspended in dry THF (1000 ml) under N_2 atmosphere and cooled to 0°C. To the mixture was added compound **3** (150g, 0.60mol) in dry THF (1000 ml) slowly at 0°C. The reaction mixture was gradually warmed to room temperature and stirred for 12h. TLC(PE/EA, 1:1) showed that the reaction was complete, and the reaction was quenched with dropwise addition of THF-Water (9:1, 400 mL) followed by 90 ml 15% NaOH aqueous and 50 ml of water at 0°C, stirred for 0.5h at room temperature, and filtered through a pad of Celite®, and then washed with THF (4 x 1000ml). The filtrate was concentrated under reduced pressure to give the crude which was purified by column chromatography over silica gel eluting with PE/EA (2:1~1:2). The desired fraction was concentrated to afford tert-butyl (6-(hydroxymethyl)pyridin-3-yl)carbamate (450g, 67%) as a white solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 9.58 - 9.40 (m, 1H), 8.59 - 8.45 (m, 1H), 7.95 - 7.78 (m, 1H), 7.42 - 7.22 (m, 1H), 5.42 - 5.21 (m, 1H), 4.58 - 4.40 (m, 2H), 1.48 (s, 9H).

Step 4. tert-Butyl (6-(hydroxymethyl)piperidin-3-yl)carbamate. To a solution of tert-butyl (6-(hydroxymethyl)pyridin-3-yl)carbamate (30g, 0.134mol) in EtOH (300ml) and HOAc (20ml) was added PtO_2 (3.0g, 0.0223mol) under N_2. The mixture was hydrogenated at 65°C/55 psi of H_2 for 72 hours. The mixture was filtered through a pad of Celite® and the filter cake was washed with EtOH (3x2000ml). The filtrate was concentrated under reduced pressure to remove EtOH and HOAc. Saturated aqueous $NaHCO_3$ was added to adjust pH to 6~7 and the aqueous layer was extracted with EtOAc (3x2000ml). The combined organic layer were washed with brine, dried over Na_2SO_4 and concentrated to dryness to give the crude product, which was triturated with PE/EA (1:1) for 2 hours and filtered to give recovered tert-butyl (6-(hydroxymethyl)pyridin-3-yl)carbamate (90g, 50%) as a white solid. The aqueous layer was evaporated to remove most of the water to give a mixture

of tert-butyl (6-(hydroxymethyl)piperidin-3-yl)carbamate (90g, 50%) in aq.$NaHCO_3$, which was directly used for next step without further purification. LC/MS (M+H) = 231.2.

Step 5. Benzyl 5-((tert-butoxycarbonyl)amino)-2-(hydroxymethyl)piperidine-1-carboxylate. To a stirred solution of tert-Butyl (6-(hydroxymethyl)piperidin-3-yl)carbamate (45g, 0.20mol) in THF (600 ml) and H_2O (300 ml) was added $NaHCO_3$ (33.6 g, 0.40mol). To this mixture was added Cbz-Cl (41g, 0.24mol) dropwise at 0°C and the resultant mixture was allowed to come to room temperature and stirred for 12 h. TLC (5% MeOH in DCM) was checked to show starting material was consumed completely. Volatiles were removed under reduced pressure, water (500ml) was added, and the aqueous mixture was extracted with EtOAc (2x600 ml). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated to dryness to afford the crude product, which was purified by column chromatography (silica gel eluted with DCM/EA (4:1~2:1) to give benzyl 5-((tert-butoxycarbonyl)amino)-2-(hydroxymethyl)piperidine-1-carboxylate (90 g ,63%) as a gum.
^1H NMR (400MHz, DMSO-d_6) δ 7.37 (s, 5H), 7.05 - 6.76 (m, 1H), 5.20 - 4.99 (m, 2H), 4.89 - 4.67 (m, 1H), 4.24 - 3.92 (m, 2H), 3.62 - 3.40 (m, 2H), 3.34-2.88 (m, 1H), 2.18 - 1.62 (m, 2H), 1.55 - 1.13 (m, 12H).

Step 6. (2R,5R)-Benzyl 5-((2-chloro-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-(hydroxymethyl) piperidine-1-carboxylate. To a round bottom flask was added 2,4-dichloro-7-tosyl-7H-pyrrolo[2,3-d]pyrimidine (6.03 g, 17.6 mmol), DIPEA (6.8 mL, 2.2 eq), benzyl 5-((tert-butoxycarbonyl)amino)-2-(hydroxymethyl)piperidine-1-carboxylate (5.6 g, 1.0 eq) and n-butanol (50 mL). The reaction mixture was heated to 50 °C overnight. The reaction mixture was poured into ethyl acetate/water and the layers separated. The aqueous layer was extracted (2 x EtOAc). The organic extracts were collected, washed with brine, dried (Na_2SO_4) and the solvent removed to give an oil, which after chromatography (silica, ethyl acetate/heptanes) gave two major peaks with equivalent mass. Pk 1 = 2.5 g (trans material); Pk 2 = 3.3 g (cis material): Peak 1 (trans): (2S,5R)-benzyl 2-(hydroxymethyl)-5-((7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidine-1-carboxylate. LC/MS (M+H)

570.1 ^{1}H NMR (400 MHz, MeOH-d_4) δ ppm 1.63 - 1.81 (m, 2 H) 1.99 - 2.18 (m, 2 H) 2.43 (s, 3 H) 3.19 (d, *J*=12.49 Hz, 1 H) 3.65 - 3.82 (m, 2 H) 4.16 - 4.48 (m, 4 H) 6.85 (d, *J*=3.90 Hz, 1 H) 6.90 - 7.20 (m, 5 H) 7.29 - 7.44 (m, 2 H) 7.50 (d, *J*=3.90 Hz, 1 H) 8.06 (d, *J*=8.20 Hz, 2 H)

Peak 2 (cis): (2R,5R)-benzyl 5-((2-chloro-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-(hydroxymethyl)piperidine-1-carboxylate. LC/MS (M+H) 570.1. ^{1}H NMR (400 MHz, MeOH-d_4) δ 1.63 - 2.02 (m, 4 H) 2.42 (s, 3 H) 2.71 - 2.84 (m, 1 H) 3.61 - 3.81 (m, 3 H) 4.30 - 4.41 (m, 2 H) 5.08 - 5.23 (m, 2 H) 6.74 (d, *J*=3.90 Hz, 1 H) 7.26 - 7.44 (m, 7 H) 7.49 (br s, 1 H) 8.03 (d, *J*=8.20 Hz, 2 H)

Step 7. (2R,5R)-Benzyl 5-((2-chloro-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-(hydroxymethyl) piperidine-1-carboxylate and (2S,5S)-benzyl 5-((2-chloro-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-(hydroxymethyl)piperidine-1-carboxylate. Racemic –cis-(2R,5R)-benzyl 5-((2-chloro-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-(hydroxymethyl)piperidine-1-carboxylate (3.31 g) was separated by chiral SFC-Chiral (Lux Cellulose-3 250 mm x 21.2 mm, 5 µm, CO_2/MeOH, 80 mL/min) to give two peaks, absolute stereochemistry arbitrarily assigned: pk1 (1.5 g) (2R,5R)-benzyl 5-((2-chloro-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-(hydroxymethyl)piperidine-1-carboxylate. OR $a_{[D]}^{20}$ = -0.10 (c = 0.5, MeOH). Pk2 (1.5 g) (2S,5S)-benzyl 5-((2-chloro-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-(hydroxymethyl)piperidine-1-carboxylate. OR $a_{[D]}^{20}$ = +0.12 (c = 0.5, MeOH).

Step 8. ((2R,5R)-5-((2-Chloro-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidin-2-yl)methanol. To a Parr hydrogenation bottle was added (2R,5R)-benzyl 5-((2-chloro-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-(hydroxymethyl)piperidine-1-carboxylate (in 100 mL of EtOH) and $Pd(OH)_2$ (1.2 g). The reaction was shaken on a Parr shaker apparatus at 20 psi H_2 for 4 hr at room temperature. The reaction mixture was then filtered through a pad of Celite® and the solvent removed in vacuo to give ((2R,5R)-5-((2-chloro-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidin-2-yl)methanol (1.73 g, 91%). LC/MS (M+H) = 436.1. ^{1}H NMR (400 MHz, MeOH-d_4) δ 1.33 - 1.65 (m, 2 H) 1.84 (dd, *J*=13.07, 2.93 Hz, 1 H) 2.13 (d, *J*=12.10 Hz, 1 H) 2.46

(m, 3 H) 2.52 (t, *J*=11.32 Hz, 1 H) 2.66 - 2.80 (m, 1 H) 3.39 - 3.64 (m, 3 H) 4.21-4.26 (m, 1 H) 6.76 (d, *J*=3.90 Hz, 1 H) 7.33 - 7.44 (m, 2 H) 7.49 (d, *J*=3.90 Hz, 1 H) 8.02 (d, *J*=8.20 Hz, 2 H).

Step 9. ((2R,5R)-5-((2-Chloro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidin-2-yl)methanol. To a round bottom flask containing (2R,5R)-5-((2-chloro-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidin-2-yl)methanol (1.1 g, 2.52 mmol) was added MeOH (10 mL) and K_2CO_3 (767 mg, 2.2 eq). The reaction was stirred at room temperature overnight and then poured into water. The aqueous mixture was extracted with n-BuOH. The organic extracts were dried (Na_2SO_4) and the solvent removed to give the crude product, which was purified by chromatography (silica, DCM/MeOH (10:1, MeOH:NH_4OH) to give the desired product (610 mg, 86%). LC/MS (M+H) 282.1. ^{1}H NMR (400 MHz, MeOH-d_4) δ 1.19 - 1.67 (m, 2 H) 1.84 (dd, *J*=13.07, 2.93 Hz, 1 H) 2.18 (d, *J*=12.88 Hz, 1 H) 2.67 (dd, *J*=7.22, 4.10 Hz, 1 H) 3.40 - 3.61 (m, 3 H) 3.94 - 4.09 (m, 1 H) 4.26 (t, *J*=11.32 Hz, 1 H) 6.58 (d, *J*=3.51 Hz, 1 H) 6.95 - 7.06 (m, 1 H).

Step 10. ((2R,5R)-5-((7H-Pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidin-2-yl)methanol. To a round bottom flask containing (2R,5R)-5-((2-chloro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidin-2-yl)methanol (202 mg, 0.72 mmol) in ethanol (20 mL) was added 10% Pd/C (100 mg) and ammonium formate (233 mg, 5 eq). The reaction mixture was heated to reflux overnight and then filtered through a pad of Celite®. The solvent was removed in vacuo to provide ((2R,5R)-5-((7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidin-2-yl)methanol (110 mg, 62%). LC/MS (M+H) 248.1. ^{1}H NMR (400 MHz, MeOH-d_4) δ 1.80 - 2.24 (m, 4 H) 3.35-3.39 (m, 2 H) 3.66 - 3.89 (m, 3 H) 4.49 (t, *J*=4.10 Hz, 1 H) 6.70 (d, *J*=3.51 Hz, 1 H) 7.15 (d, *J*=3.51 Hz, 1 H) 8.11 - 8.28 (m, 1 H).

Step 11. 1-((2R,5R)-5-((7H-Pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-(hydroxymethyl)piperidin-1-yl)prop-2-en-1-one. To a solution of ((2R,5R)-5-((7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidin-2-yl)methanol (172 mg, 0.69 mmol) in DCM/$CHCl_3$/CF_3CH_2OH (3:1:0.5 mL) was added TEA (0.19 mL, 2.0 eq). The reaction mixture was cooled to 0 °C. After 30 min, acryloyl chloride

(in DCM, 1 mL) was added dropwise. After 2 hrs, the reaction mixture was poured into water/DCM and the layers separated. The organic layer was collected, dried (Na_2SO_4) and the solvent removed to give the crude product (224 mg). A portion of the crude product (50 mg) was purified by RP-HPLC to give 1-((2R,5R)-5-((7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-(hydroxymethyl)piperidin-1-yl)prop-2-en-1-one (4.4 mg). LC/MS (M+H) 302.2. ^{1}H NMR (400 MHz, MeOH-d_4) δ ppm 1.72 - 2.22 (m, 4 H) 2.81 - 2.99 (m, 1 H) 3.65 - 3.85 (m, 2 H) 3.88 - 4.17 (m, 2 H) 4.25 - 4.45 (m, 1 H) 5.80 (d, *J*=12.10 Hz, 1 H) 6.26 (d, *J*=16.78 Hz, 1 H) 6.80 - 6.99 (m, 2 H) 7.39 (br s, 1 H) 8.21 - 8.40 (m, 1 H).

Example 8: 1-((3aS,7aS)-1-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)hexahydro-1H-pyrrolo[2,3-c]pyridin-6(2H)-yl)prop-2-en-1-one.

Step 1. tert-Butyl 1H-pyrrolo[2,3-c]pyridine-1-carboxylate. To a solution of 1H-pyrrolo[2,3-c]pyridine (250 g, 2.12 mol) in CH_3CN (2L) was added K_2CO_3 (584 g, 4.23 mol) and DMAP (12.9 g, 0.11 mol). After 10 min, $(Boc)_2O$ (508.7 g, 2.33 mol) was added over a period of 40 min. After the addition, the resulting mixture was stirred at room temperature for 3 hour. TLC (petroleum ether: ethyl acetate, 1:1) indicated starting material was consumed completely. The mixture was filtered, and the filtrate was evaporated to dryness, and then partitioned between EtOAc (4 L) and water (2 L). The organic layer was washed with brine (1 L), dried over Na_2SO_4 and concentrated to give tert-butyl 1H-pyrrolo[2,3-c]pyridine-1-carboxylate (830 g, 90%) as a white solid. ^{1}H NMR (400 MHz, CDCl3) δ 9.3 (bs, 1 H) 8.32 (d, 1 H), 7.65 (bs, 1 H), 7.41-7.39 (m, 1 H), 6.50 (d, 1 H), 1.62 (s, 9 H).

Step 2. (3aS,7aR)-tert-Butyl octahydro-1H-pyrrolo[2,3-c]pyridine-1-carboxylate. To a dry hydrogenation bottle, PtO_2 (13 g) was added under Ar atmosphere. A solution of tert-butyl 1H-pyrrolo[2,3-c]pyridine-1-carboxylate (135 g, 0.62 mol) in EtOH (3 L) was added and the resulting mixture was hydrogenated at 50 psi H_2 at 80 °C for 48 hours. TLC (petroleum ether/EtOAc, 1:1) showed starting material was consumed completely. The reaction mix-

ture was filtered, and the filtrate was concentrated to give (3aS,7aR)-tert-butyl octahydro-1H-pyrrolo[2,3-c]pyridine-1-carboxylate (810 g, 96.4%) as a colorless oil. ^{1}H NMR (400 MHz, MeOH-d_4) δ 1.27 - 1.43 (m, 9 H) 1.49 - 1.95 (m, 4 H) 2.18 - 2.48 (m, 2 H) 2.53 - 2.77 (m, 2 H) 3.09 (d, *J*=5.02 Hz, 1 H) 3.19 - 3.42 (m, 2 H) 3.62 (br s, 1 H).

Step 3. (3aR,7aR)-Benzyl hexahydro-1H-pyrrolo[2,3-c]pyridine-6(2H)-carboxylate. To a stirred solution of (3aS,7aR)-tert-butyl octahydro-1H-pyrrolo[2,3-c]pyridine-1-carboxylate (200 g, 0.885 mol) and DIPEA (251 g, 1.95 mol) in DCM (2L) at 0 °C was added dropwise Cbz-Cl (181 g, 1.06 mol) over a period of 45 min. After the addition, the resulting mixture was stirred at room temperature for 16 hours. TLC (DCM/MeOH, 10:1) showed the starting material was consumed completely. The reaction mixture was evaporated to dryness, and then partitioned between EtOAc (8L) and water (3 L); the organic layer was washed with water (3 L) and brine (3 L), dried over anhydrous Na_2SO_4 and concentrated to give (3aS,7aR)-tert-butyl octahydro-1H-pyrrolo[2,3-c]pyridine-1-carboxylate (1147 g, 90%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 - 1.48 (m, 9 H) 1.51 - 1.65 (m, 1 H) 1.68 - 1.90 (m, 2 H) 2.32 (br s, 1 H) 2.72 (t, *J*=11.04 Hz, 1 H) 2.97 (br s, 1 H) 3.13 - 3.56 (m, 3 H) 3.73 (s, 2 H) 3.85 - 4.28 (m, 1 H) 4.91 - 5.14 (m, 2 H) 7.12 - 7.38 (m, 5 H).

Step 4, 5 and 6. (3aR,7aR)-Benzyl hexahydro-1H-pyrrolo[2,3-c]pyridine-6(2H)-carboxylate and (3aS,7aS)-benzyl hexahydro-1H-pyrrolo[2,3-c]pyridine-6(2H)-carboxylate. To a 0 °C stirred solution of (3aS,7aR)-tert-butyl octahydro-1H-pyrrolo[2,3-c]pyridine-1-carboxylate (280 g, 0.68 mol) in DCM (600 mL) was added dropwise 4M HCl in dioxane (2.5 L) over a period of 1 hour. The reaction mixture was stirred at room temperature for 15 hours. TLC (petroleum ether/EtOAc, 2:1) showed the starting material was consumed completely. The reaction mixture was evaporated to dryness, and then partitioned between MTBE (6L) and water H_2O (4 L), the aqueous phase was then basified to pH 9~10 and extracted with DCM (3 L*4). The combined organic layers were concentrated to give rac-(3aR,7aR)-benzyl hexahydro-1H-pyrrolo[2,3-c]pyridine-6(2H)-carboxylate (687 g, 85%), which was separated

by SFC to give (3aS,7aS)-benzyl hexahydro-1H-pyrrolo[2,3-c]pyridine-6(2H)-carboxylate (280 g, 42.2%) and (3aR,7aR)-benzyl hexahydro-1H-pyrrolo[2,3-c]pyridine-6(2H)-carboxylate (270, 39.3%) as yellow oil. (Peak 1 was(3aR,7aR)-benzyl hexahydro-1H-pyrrolo[2,3-c]pyridine-6(2H)-carboxylate, RT = 9.81; peak 2 was (3aS,7aS)-benzyl hexahydro-1H-pyrrolo[2,3-c]pyridine-6(2H)-carboxylate, RT = 10.63). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 - 1.63 (m, 3 H) 1.68 - 1.90 (m, 2 H) 1.97 - 2.09 (m, 1 H) 2.71 - 3.19 (m, 4 H) 3.26 - 3.43 (m, 1 H) 3.55 - 3.77 (m, 2 H) 5.02 (br s, 2 H) 7.10 - 7.35 (m, 5 H). Separation conditions: Instrument: SFC 350; Column: AS 250mmx50mm,10 μm; Mobile phase: A: Supercritical CO_2 , B: EtOH (0.05%DEA) , A:B =65:35 at 240ml/min; Column Temp: 38 °C; Nozzle Pressure: 100Bar; Nozzle Temp: 60 °C; Evaporator Temp: 20 °C; Trimmer Temp: 25 °C; Wavelength: 220nm.

Step 7. (3aS,7aS)-Benzyl 1-(2-chloro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)hexahydro-1H-pyrrolo[2,3-c]pyridine-6(2H)-carboxylate. A mixture of (3aS,7aS)-benzyl hexahydro-1H-pyrrolo[2,3-c]pyridine-6(2H)-carboxylate, peak 2(135 g, 0.52 mol), DIPEA (268 g, 2.1 mol) and 2,4-dichloro-7H-pyrrolo[2,3-d]pyrimidine (88.7 g, 0.47 mol) in n-BuOH (1L) was heated to 80 °C for 3 hours, TLC (Petroleum ether/ether, 2:1) showed 2,4-dichloro-7H-pyrrolo[2,3-d]pyrimidine was consumed completely. The reaction mixture was cooled to room temperature and evaporated to dryness via oil pump at 45 °C. The residue was partitioned between DCM (2L) and water (1.5 L); the organic layer was washed with water (1 L) and brine (1 L), dried over Na_2SO_4 and concentrated to give (3aS,7aS)-benzyl 1-(2-chloro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)hexahydro-1H-pyrrolo[2,3-c]pyridine-6(2H)-carboxylate (310 g, 80%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.58 - 2.35 (m, 5 H) 2.90 - 3.28 (m, 2 H) 3.58 - 4.07 (m, 3 H) 4.35 (br s, 2 H) 5.16 (br s, 2 H) 6.46 - 6.85 (m, 1 H) 7.12 - 7.57 (m, 6 H) 11.87 (br s, 1 H).

Step 8. 4-((3aR,7aS)-Octahydro-1H-pyrrolo[2,3-c]pyridin-1-yl)-7H-pyrrolo[2,3-d]pyrimidine. To a dry Parr hydrogenation bottle, Pd/C (12 g) was added under Ar atmosphere. Then a solution of (3aS,7aS)-benzyl 1-(2-chloro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)hexahydro-1H-pyrrolo[2,3-c]pyridine-6(2H)-carboxylate (62 g, 0.15 mol) in EtOH (1.2 L) was added and the resulting mix-

ture was hydrogenated under 50 psi of H_2 at 65 °C for 48 hours, TLC (Petroleum ether/EtOAc, 1:1) showed the starting material was consumed completely; the reaction mixture was filtered and the filter cake was washed with warm MeOH and water (v/v 1:1, 500 mLx2); the combined filtrate was evaporated to give 4-((3aR,7aS)-octahydro-1H-pyrrolo[2,3-c]pyridin-1-yl)-7H-pyrrolo[2,3-d]pyrimidine (190 g, 90%) as a white solid.

Step 9. 1-((3aS,7aS)-1-(7H-Pyrrolo[2,3-d]pyrimidin-4-yl)hexahydro-1H-pyrrolo[2,3-c]pyridin-6(2H)-yl)prop-2-en-1-one. To a solution of 4-((3aR,7aS)-octahydro-1H-pyrrolo[2,3-c]pyridin-1-yl)-7H-pyrrolo[2,3-d]pyrimidine (150 g, 0.54 mol) in aq $NaHCO_3$ (150 g, 1.79 mol) in H_2O (1.5 L) at 0 °C was added dropwise a solution of acryloyl chloride (53.3 g, 0.59 mol) in MeCN (150 mL) carefully. After the addition, the resulting mixture was stirred at room temperature for 2 hours. TLC (DCM/MeOH, 5:1) showed 4-((3aR,7aS)-octahydro-1H-pyrrolo[2,3-c]pyridin-1-yl)-7H-pyrrolo[2,3-d]pyrimidine was consumed completely. The reaction mixture was extracted with DCM (500 mL*4) and the combined organic layers were concentrated to give the crude product, which was purified by column chromatography to give 1-((3aS,7aS)-1-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)hexahydro-1H-pyrrolo[2,3-c]pyridin-6(2H)-yl)prop-2-en-1-one (130 g, 81%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.58 (s, 1H) 8.09-8.07 (d, J=9.2Hz, 1H) 7.115(s, 1H), 6.82-6.78 (m, 1H), 6.51 (m, 1H), 6.05-6.01 (m, 1H), 5.69-5.85 (m, 1H), 4.69-4.68 (m, 0.5H), 4.27 (s, 1H), 3.90-3.74 (m, 3H), 3.13-3.24 (m, 2H), 2.74-2.71 (m, 0.5H), 2.19-1.74 (m, 4.5 H).

Example 9: 1-((2S,5R)-5-((7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-ethylpiperidin-1-yl)prop-2-en-1-one.

The racemic 5-((tert-butoxycarbonyl)amino)-2-ethylpiperidine-1-carboxylate was prepared using a process similar to the methyl intermediate. The racemic intermediate contained the cis-isomers as the major component as was the case for the methyl intermediate. The racemic mixture was separated into four optically pure isomers via chiral SFC, and the two cis-isomers were ob-

tained as peak 3 and 4. SFC preparative separation conditions: Column: Chiralcel OJ-H 30×250mm; Mobile phase: 95/5 CO_2/methanol; Flow rate: 120mL/min; Wavelength: 210nm; SFC analytical condition: Column: Chiralcel OJ-H 4.6×25mm; Mobile phase: 5-60% CO_2/methanol; Flow rate: 3mL/min; Wavelength: 210nm.

Preparation of final analogs using the enantiomerically pure benzyl 5-((tert-butoxycarbonyl)amino)-2-ethylpiperidine-1-carboxylate followed protocols similar to other analogs (see Example 5) . Thus 1-((2S,5R)-5-((7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-ethylpiperidin-1-yl)prop-2-en-1-one was prepared from peak 3 of the chiral separation of the racemic 5-((tert-butoxycarbonyl)amino)-2-ethylpiperidine-1-carboxylate. ^{1}H NMR (400MHz, DMSO-d_6) δ 11.51 (br s, 1H), 8.11 (d, J=13.6 Hz, 1H), 7.26 (dd, J=6.6, 21.4 Hz, 1H), 7.08 (br s, 1H), 6.9 - 6.7 (m, 1H), 6.53 (s, 1H), 6.10 (d, J=16.8 Hz, 1H), 5.7 - 5.6 (m, 1H), 4.57 (br s, 1H), 4.07 (m, 2H), 2.90 (t, J=12.1 Hz, 1H), 1.92 - 1.5 (m, 6H), 0.81 (m, 3H). LCMS (acid, 3 min run): RT 0.76 min. LC/MS (M+H) = 300.25.

Example 10: 1-((3R,5R)-3-((7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-fluoropiperidin-1-yl)prop-2-en-1-one

Step 1. N-((3R,5R)-1-Benzyl-5-fluoropiperidin-3-yl)-2-chloro-7H-pyrrolo[2,3-d]pyrimidin-4-amine. A mixture of (3R,5R)-1-benzyl-5-fluoropiperidin-3-amine (prepared as described in *Eur. J. Org. Chem.* **2012**, 10, 2023 and *Org. Lett.* **2011**, 13, 4442) (500 mg, 2.4 mmol), DIPEA (1.55 g, 12 mmol) and 2,4-dichloro-7H-pyrrolo[2,3-d]pyrimidine (495 mg, 2.64 mmol) in n-BuOH (35 mL) was heated to 130-140 °C overnight. LC-MS showed the reaction was completed. TLC (PE/EtOAc, 1:1) showed the starting material was consumed completely and the desired product was formed. The reaction mixture was cooled to room temperature and evaporated to dryness in vacuo at 45 °C. The residue was treated with water (20 mL) and extracted with EtOAc (30 mL×2). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated to give crude product, which was purified via chro-

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 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 O or —$(CR_eR_f)_s$—, 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, whereby when *n* is 0, and X is O, said O is bonded to H, and said dotted bond between X and —$(CH_2)_n$— is absent, and when X is —$(CR_eR_f)_s$—, and X is bonded directly to Y; and (b) if X is absent, said dotted bonds are absent and *n* is 0, whereby when Y is N, either (i) said N atom is substituted by H, (ii) Z is C, Z' is C or N, the dotted bond to Z is a single bond, the dotted bond to Z' being absent, or (iii) Z is C or N, Z' is C, the dotted bond to Z' is a single bond, the dotted bond to Z being absent, where said Y being an N atom may 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:

matography to give N-((3R,5R)-1-benzyl-5-fluoropiperidin-3-yl)-2-chloro-7H-pyrrolo[2,3-d]pyrimidin-4-amine (760 mg, 88.0 %) as an oil. LC/MS (M+H) 360.2.

Step 2. N-((3R,5R)-5-Fluoropiperidin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine. To a dry Parr hydrogenation bottle, 10% dry Pd/C (160 mg) was added under Ar atmosphere followed by a solution of N-((3R,5R)-1-benzyl-5-fluoropiperidin-3-yl)-2-chloro-7H-pyrrolo[2,3-d]pyrimidin-4-amine (940 mg, 2.61 mmol) in MeOH (30 mL) and THF (6 mL). The resulting mixture was hydrogenated under 50 psi of H_2 at 35 °C for 72 hours. LC-MS showed most of the starting material was consumed completely and the desired product was formed. The reaction solution was filtered through a pad of Celite®, and the filter cake was washed with MeOH three times. The combined filtrate was concentrated to give N-((3R,5R)-5-fluoropiperidin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine (600 mg, 97.5%) as a white solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 11.61 (br s, 1H), 9.50 (br s, 1H), 8.22 - 8.11 (m, 1H), 7.60 (d, J=7.8 Hz, 1H), 7.23 - 7.03 (m, 1H), 6.61 (d, J=1.8 Hz, 1H), 5.32 - 5.13 (m, 1H), 4.80 - 4.64 (m, 1H), 3.32 - 3.24 (m, 1H), 3.22 - 3.12 (m, 1H), 2.84 (t, J=11.5 Hz, 1H), 2.32 (br s, 1H), 2.05 - 1.85 (m, 1H), 1.37 - 0.82 (m, 1H).

Step 3. 1-((3R,5R)-3-((7H-Pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-fluoropiperidin-1-yl)prop-2-en-1-one.

To a stirred solution of N-((3R,5R)-5-fluoropiperidin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine (200 mg, 0.85 mmol) in THF (12 mL) and aq. $NaHCO_3$ solution (12 mL) at 0 °C was added acryl-Cl (85 mg, 0.93 mmol) dropwise. The resulting mixture was stirred at 0 °C for 2 hours. TLC (DCM/MeOH, 10:1) showed starting material was consumed completely. The reaction mixture was diluted with H_2O (20 mL) and extracted with EtOAc (30 mL×2); the combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated to give crude product, which was further purified by column chromatography on silica gel (MeOH: DCM, 0-8%) to give 1-((3R,5R)-3-((7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-fluoropiperidin-1-yl)prop-2-en-1-one (130 mg, 53.0%) as a white solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 11.55 (br s, 1H), 8.13 (d, J=18.8 Hz, 1H), 7.41 - 7.27 (m, 1H), 7.10 (br s, 1H), 6.80 (dd,

J=10.5, 16.8 Hz, 1H), 6.55 (br s, 1H), 6.13 (dd, J=2.3, 16.6 Hz, 1H), 5.70 (d, J=10.3 Hz, 1H), 5.17 - 4.91 (m, 1H), 4.71 - 4.18 (m, 3H), 3.40 (d, J=15.1 Hz, 0.5H), 3.19 - 2.98 (m, 1H), 2.61 (t, J=11.5 Hz, 0.5H), 2.29 (d, J=6.0 Hz, 1H), 2.05 - 1.74 (m, 1H).

Example 11: 1-((3R,4S)-3-((7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-4-methylpiperidin-1-yl)prop-2-en-1-one

Step 1. rac-(3R,4S)-tert-Butyl 3-((2-chloro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-4-methylpiperidine-1-carboxylate. To a solution of rac-(3R,4S)-tert-butyl 3-amino-4-methylpiperidine-1-carboxylate (prepared as described in WO2011029046) (500 mg, 2.333 mmol) and 2,4-dichloro-7H-pyrrolo[2,3-d]pyrimidine (483 mg, 2.566 mmol, 1.1 eq.) in n-BuOH (15 mL) was added DIPEA (903 mg, 6.999 mmol, 3.0 eq.) at room temperature, and heated to 140 °C overnight. After LCMS indicated the reaction was complete, the reaction mixture was concentrated to dryness in vacuo. The residue was dissolved in EtOAc (50 mL) and diluted with water (50 mL). The layers were separated and the aqueous layer was extracted with EtOAc (50 mL×1), and the combined organic layers were washed with brine, dried with sodium sulfate. The solvent was removed under reduced pressure. The residue was purified by column chromatography (EtOAc/PE = 8% ~ 50%) to give rac-(3R,4S)-tert-butyl 3-((2-chloro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-4-methylpiperidine-1-carboxylate (rac-trans, 563 mg, 66 %) as a yellow solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 11.92 (br s, 1H), 7.14 (br s, 1H), 6.46 (br s, 1H), 4.40 (d, J=9.3 Hz, 1H), 4.08-3.65 (m, 2H), 2.98 - 2.63 (m, 2H), 1.90 - 1.60 (m, 3H), 1.52-1.38 (m, 1H), 1.48 (s, 9H), 1.11 - 1.05 (m, 3H).

Step 2. Rac-(3R,4S)-tert-Butyl 3-((7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-4-methylpiperidine-1-carboxylate. To a dry Parr hydrogenation bottle, dry Pd/C (100 mg) was added under N_2 atmosphere. A solution of rac-(3R,4S)-tert-butyl 3-((2-chloro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-4-methylpiperidine-1-carboxylate (560 mg, 1.531 mmol) in MeOH /THF (30 mL/10 mL) was added, and the resulting mixture was heated to 40 °C under 50 psi of H_2 for 2 days.

After LCMS showed the reaction to be complete, the reaction mixture was filtered, and the filter cake was washed with MeOH. The combined filtrate was evaporated to give rac-(3R,4S)-tert-butyl 3-((7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-4-methylpiperidine-1-carboxylate (520 mg, 93 %) as a yellow solid. LC/MS (M+H) = 332.2.

Step 3. Rac-N-((3R,4S)-4-Methylpiperidin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine. To a solution of rac-(3R,4S)-tert-butyl 3-((7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-4-methylpiperidine-1-carboxylate (520 mg, 1.531 mmol) in DCM (15 mL) at 0 °C was added 4.0 M HCl/ dioxane (15 mL). The reaction mixture was allowed to warm to room temperature and stirred for 3 hours. After LCMS showed the reaction to be complete, the reaction mixture was concentrated to give rac-N-((3R,4S)-4-methylpiperidin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine (410 mg, 100 %) as a solid. LC/MS (M+H) = 232.2.

Step 4. rac-1-((3R,4S)-3-((7H-Pyrrolo[2,3-d]pyrimidin-4-yl)amino)-4-methylpiperidin-1-yl)prop-2-en-1-one.

To a solution of rac- N-((3R,4S)-4-methylpiperidin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine (410 mg, 1.530 mmol) in THF (20 mL) and saturated.$NaHCO_3$ (15 mL) at 0 °C was added acryloyl chloride (152 mg, 1.683 mmol, 1.1 eq.). The reaction mixture was stirred at 0 °C for 2 hours. After TLC (EtOAc/MeOH, 10:1) showed the reaction to be complete, the reaction mixture was diluted with water (50 mL), and extracted with EtOAc (50 mL×2). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (MeOH/EtOAc, 2%~10%) and lyophilized to give rac-1-((3R,4S)-3-((7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-4-methylpiperidin-1-yl)prop-2-en-1-one (150 mg, 34 %) as a white solid. ^1H NMR (400MHz, DMSO-d_6) δ 11.53 (br s, 1H), 8.08 (d,J=15.1 Hz, 1H), 7.32 - 7.20 (m, 1H), 7.08 (br s, 1H), 6.81 (dt, J=10.5, 17.3 Hz, 1H), 6.59 (br s, 1H), 6.12 (d, J=14.8 Hz, 1H), 5.69 (d, J=10.3 Hz, 1H), 4.65 - 4.39 (m, 1H), 4.27 - 4.04 (m, 1H), 3.94 - 3.71 (m, 1H),

3.08 - 2.96 (m, 0.5H), 2.89 - 2.77 (m, 0.5H), 2.71 - 2.60 (m, 0.5H), 2.46 - 2.28 (m, 0.5H), 1.82 (d, J=12.3 Hz, 2H), 1.29 - 1.12 (m, 1H), 0.94 (dd, J=6.0, 12.3 Hz, 3H). LCMS (M+H) = 286.1.

Step 5. 1-((3R,4S)-3-((7H-Pyrrolo[2,3-d]pyrimidin-4-yl)amino)-4-methylpiperidin-1-yl)prop-2-en-1-one (pk 1) and 1-((3S,4R)-3-((7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-4-methylpiperidin-1-yl)prop-2-en-1-one (pk 2). rac-1-((3R,4S)-3-((7H-Pyrrolo[2,3-d]pyrimidin-4-yl)amino)-4-methylpiperidin-1-yl)prop-2-en-1-one (120 mg) was separated by chiral SFC (Chiral Pak-AD (250 x 30 mm, 5um), 30% EtOH (0.05% NH3 in H2O) in CO2) to give the pair of enantiomers, (peak 1, 47.8 mg) and (peak 2, 48.2 mg) as white solids, absolute stereochemistry arbitrarily assigned.

Peak 1 data: ^{1}H NMR (400MHz, DMSO-d_6) δ 11.53 (br s, 1H), 8.08 (d, J=15.1 Hz, 1H), 7.32 - 7.20 (m, 1H), 7.08 (br s, 1H), 6.81 (dt, J=10.5, 17.3 Hz, 1H), 6.59 (br s, 1H), 6.12 (d, J=14.8 Hz, 1H), 5.69 (d, J=10.3 Hz, 1H), 4.65 - 4.39 (m, 1H), 4.27 - 4.04 (m, 1H), 3.94 - 3.71 (m, 1H), 3.08 - 2.96 (m, 0.5H), 2.89 - 2.77 (m, 0.5H), 2.71 - 2.60 (m, 0.5H), 2.46 - 2.28 (m, 0.5H), 1.82 (d, J=12.3 Hz, 2H), 1.29 - 1.12 (m, 1H), 0.94 (dd, J=6.0, 12.3 Hz, 3H). LCMS (M+H) = 285.9. Peak 2 data: ^{1}H NMR (400MHz, DMSO-d_6) δ 11.53 (br s, 1H), 8.08 (d, J=15.1 Hz, 1H), 7.32 - 7.20 (m, 1H), 7.08 (br s, 1H), 6.81 (dt, J=10.5, 17.3 Hz, 1H), 6.59 (br s, 1H), 6.12 (d, J=14.8 Hz, 1H), 5.69 (d, J=10.3 Hz, 1H), 4.65 - 4.39 (m, 1H), 4.27 - 4.04 (m, 1H), 3.94 - 3.71 (m, 1H), 3.08 - 2.96 (m, 0.5H), 2.89 - 2.77 (m, 0.5H), 2.71 - 2.60 (m, 0.5H), 2.46 - 2.28 (m, 0.5H), 1.82 (d, J=12.3 Hz, 2H), 1.29 - 1.12 (m, 1H), 0.94 (dd, J=6.0, 12.3 Hz, 3H). LCMS (M+H) = 285.9.

Example 12: (R)-1-(3-((7H-Pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidin-1-yl)prop-2-en-1-one

Step 1. (R)-tert-Butyl 3-((7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidine-1-carboxylate. To a stirred solution of 4-chloro-7-tosyl-7H-pyrrolo[2,3-d]pyrimidine (8.73 g, 28.4 mmol) in n-Butanol (100 mL) was added DIPEA (6.0 mL, 1.2 eq) and (R)-3-amino piperidine-1-carboxylic acid

tert-butyl ester (6.82 g, 1.2 eq). The reaction mixture was heated at 70°C for overnight. The solvent was removed under reduced pressure and the crude residue was purified by column chromatography (100-200 mesh silica, 0-3% MeOH in DCM) to obtain (R)-tert-butyl 3-((7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidine-1-carboxylate (5.6 g, 42%). LC/MS (M+H) = 472.2. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.09 - 1.30 (m, 4 H) 1.33 (br s, 9 H) 1.49 - 1.94 (m, 2 H) 2.34 (s, 3 H) 3.37 (br s, 2 H) 3.67 (d, *J*=12.88 Hz, 1 H) 4.09 - 4.21 (m, 1 H) 6.39 (d, *J*=4.10 Hz, 1 H) 7.10 - 7.29 (m, 2 H) 7.42 (d, *J*=4.10 Hz, 1 H) 7.92 - 8.07 (m, 2 H) 8.39 (s, 1 H).

Step 2. (R)-tert-Butyl 3-((7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidine-1-carboxylate. To a stirred solution of (R)-tert-butyl 3-((7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidine-1-carboxylate (29.4g, 62mmol) in MeOH (96 mL), THF (96 mL) and water (96mL) was added $LiOH{\cdot}H_2O$ (2.99g, 125 mmol, 2 eq). The mixture was heated at 60°C for 1 hour. After the reaction mixture was cooled to room temperature, the organic solvent evaporated in vacuo. The aqueous mixture was made slightly acidic and then extracted with ethyl acetate (4 x 150 mL). The organic fractions were combined and washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by column chromatography (100-200 mesh silica, 0-2% MeOH in DCM) to provide 8.5g (70%) of (R)-tert-butyl 3-((7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidine-1-carboxylate as an off white solid. LC/MS(M+H) 318.2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (br s, 9 H) 1.58 - 1.87 (m, 3 H) 2.04 (dd, *J*=8.39, 4.10 Hz, 1 H) 3.35 - 3.56 (m, 2 H) 3.75 - 3.91 (m, 2 H) 4.22 - 4.38 (m, 1 H) 5.18 (br s, 1 H) 6.33 - 6.47 (m, 1 H) 7.11 (d, *J*=2.34 Hz, 1 H) 8.39 (s, 1 H) 10.19 (br s, 1 H).

Step 3. (R)-N-(Piperidin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine. To a stirred solution of (R)-tert-butyl 3-((7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidine-1-carboxylate in dioxane (40 mL) was added 4M HCl in dioxane (60 mL) dropwise. The reaction was stirred for ~1hr and then diluted with diethyl ether to form a solid, which was filtered and collected. The solid was dried on high vacuum to give (R)-N-(piperidin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine HCl salt (4.6 g, 92%). LC/MS (M+H) = 218.2. ^{1}H NMR

(400 MHz, D_2O) δ 1.70 - 2.31 (m, 4 H) 2.94 - 3.18 (m, 2 H) 3.32 - 3.45 (m, 1 H) 3.64 (dd, *J*=12.68, 4.10 Hz, 1 H) 4.31 - 4.47 (m, 1 H) 6.78 (d, *J*=3.51 Hz, 1 H) 7.35 (d, *J*=3.90 Hz, 1 H) 8.24 - 8.35 (m, 1 H).

Step 4. (R)-1-(3-((7H-Pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidin-1-yl)prop-2-en-1-one. To a round bottom flask containing (R)-N-(piperidin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine HCl salt (1.0 g, 3.44 mmol) was added DCM (30 mL), EtOH (3 mL) and TEA (2.11 mL, 4.4 eq). After 30 min, acrylolyl chloride in 20 ml of DCM was added dropwise and the reaction stirred at rt for 2 hrs. The mixture was poured into water and the layers separated. The organic layer was dried (Na_2SO_4) and the solvent removed to give crude product (~900 mg). The material was purified by chromatography (silica, DCM/MEOH) to give (R)-1-(3-((7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidin-1-yl)prop-2-en-1-one (310 mg, 33%). LC/MS (M+H) = 272.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.40 - 2.12 (m, 3 H) 2.61 - 2.76 (m, 1 H) 2.89 - 3.18 (m, 2 H) 3.92 - 4.22 (m, 2 H) 4.55 (d, *J*=12.10 Hz, 1 H) 5.47 - 5.75 (m, 1 H) 5.97 - 6.20 (m, 1 H) 6.60 (br s, 1 H) 6.65 - 6.90 (m, 1 H) 7.00 - 7.13 (m, 1 H) 7.25 (d, *J*=6.63 Hz, 1 H) 8.12 (d, *J*=14.44 Hz, 1 H) 11.50 (br s, 1 H).

Example 13: 1-((2S,5R)-5-((5-(2-Methoxyethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-methylpiperidin-1-yl)prop-2-en-1-one

Step 1. (+)-(2S,5R)-Benzyl 5-amino-2-methylpiperidine-1-carboxylate and (-)-(2R,5S)-benzyl 5-amino-2-methylpiperidine-1-carboxylate. Racemic (2S,5R)-benzyl 5-amino-2-methylpiperidine-1-carboxylate (Example 5, step 5, 10 g) was purified by chiral SFC (cellulose-2; CO_2/MeOH-0.2% NH_3/EtOH) to give pk 1: (2R,5S)-benzyl 5-amino-2-methylpiperidine-1-carboxylate, [a]d20 = -7.09 (c = 1.1, MeOH). ^{1}H NMR (400MHz, DMSO-d_6) δ 8.37 (br s, 3H), 7.24 - 7.49 (m, 5H), 5.09 (s, 2H), 4.32 (m, 1H), 4.16 (d, J=8.28Hz, 1H), 3.00 (br s, 2H), 1.83 (m, 2H), 1.59 (m, 2H), 1.11 (d, J=7.03Hz, 3H). pk2 : (2S,5R)-benzyl 5-amino-2-methylpiperidine-1-carboxylate, [a]d20 = +7.09 (c = 1.1, MeOH). ^{1}H NMR (400MHz, DMSO-d_6) δ 8.37 (br s, 3H), 7.24 - 7.49 (m, 5H), 5.09 (s, 2H),

4.32 (m, 1H), 4.16 (d, J=8.28Hz, 1H), 3.00 (br s, 2H), 1.83 (m, 2H), 1.59 (m, 2H), 1.11 (d, J=7.03Hz, 3H).

Step 2. (2S,5R)-Benzyl 5-((5-(2-methoxyethyl)-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-methylpiperidine-1-carboxylate. A mixture of 4-chloro-5-(2-methoxyethyl)-7-tosyl-7H-pyrrolo[2,3-d]pyrimidine, (+)-(2S,5R)-benzyl 5-amino-2-methylpiperidine-1-carboxylate and Hunig's base in n-BuOH were combined and heated to 90 °C overnight.. The mixture was removed from heat and concentrated. The residue was purified by CombiFlash® (24g gold column, 0 to 50% EA in Hept) to give 264 mg of (2S,5R)-benzyl 5-((5-(2-methoxyethyl)-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-methylpiperidine-1-carboxylate. LC/MS (M+H) 578.5.

Step 3. 5-(2-Methoxyethyl)-N-((3R,6S)-6-methylpiperidin-3-yl)-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine. To a Parr reactor bottle was added (2S,5R)-benzyl 5-((5-(2-methoxyethyl)-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-methylpiperidine-1-carboxylate (in 10 mL of EtOH) and $Pd(OH)_2$ (126 mg). The reaction was stirred at 25 psi H_2 overnight at rt. The mixture was filtered through Celite® and the solvent removed to give 190 mg 5-(2-methoxyethyl)-N-((3R,6S)-6-methylpiperidin-3-yl)-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine as a white foam. LC/MS (M+H): 444.4.

Step 4. 1-((2S,5R)-5-((5-(2-Methoxyethyl)-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-methylpiperidin-1-yl)prop-2-en-1-one. To a solution of 5-(2-methoxyethyl)-N-((3R,6S)-6-methylpiperidin-3-yl)-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine chloroform(5 mL)) was added Hunig's base. The solution was cooled to 0 °C and acryloyl chloride was added. After 30 min, the reaction was determined to be complete by LC/MS, and $NaHCO_3$ was added. The reaction was stirred for 30min. The organic layer was separated and concentrated. The residue was purified by CombiFlash® (20 to 100 EA in heptane) to give 210 mg 1-((2S,5R)-5-((5-(2-methoxyethyl)-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-methylpiperidin-1-yl)prop-2-en-1-one. LC/MS (M+H): 498.4.

Step 5. 1-((2S,5R)-5-((5-(2-Methoxyethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-methylpiperidin-1-yl)prop-2-en-1-one. 1-((2S,5R)-5-((5-(2-

Methoxyethyl)-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-methylpiperidin-1-yl)prop-2-en-1-one (200 mg) was dissolved in 3 mL of THF. A solution of TBAF (1 M in THF, 0.804 mL, 2 eq) was added. The reaction mixture was heated to 60°C and stirred overnight. The reaction was cooled to rt and diluted with 10mL of EtOAc. The solution was washed with NH_4Cl (10%), brine and dried (Na_2SO_4). The mixture was filtered and concentrated. The residue was purified by CombiFlash® (12g gold column, 0 to 10% MeOH in DCM) to give 100 mg of 1-((2S,5R)-5-((5-(2-methoxyethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-methylpiperidin-1-yl)prop-2-en-1-one. LC/MS (M+H) = 344.3. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.21 (s, 1H), 7.18 (br s, 1H), 7.08 (s, 1H), 6.82-6.77 (m. 1H), 6.10-6.07 (m, 1H) 5.68-5.66 (m, 1H) 3.61-3.57 (m, 2H), 3.30 (s, 3H), 3.05-3.00 (m, 2H), 2.49-2.48 (m, 3H), 1.87-1.56 (m, 5H), 1.22-1.18 (m, 3H).

Example 14: 1-((3R,5S)-3-(7H-Pyrrolo[2,3-d]pyrimidin-4-ylamino)-5-methylpiperidin-1-yl)prop-2-en-1-one (chiral and rac-cis)

Step1: tert-Butyl (5-methylpyridin-3-yl)carbamate. A solution of 5-methylpyridin-3-amine (20 g, 185 mmol) and $(Boc)_2O$ (44.4 g, 203.5 mmol) in THF (360 mL) was stirred at room temperature for 5 h. TLC (PE/ EtOAc, 1:1) showed the reaction was completed. The reaction mixture was concentrated, and triturated with MTBE to give tert-butyl (5-methylpyridin-3-yl)carbamate (26.4 g, 69%) as a white solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 8.21 (d, J=2.3 Hz, 1H), 8.15 - 8.10 (m, 1H), 7.88 (br s, 1H), 6.66 (br s, 1H), 2.33 (s, 3H), 1.53 (s, 9H),

Step 2. rac-cis/trans- tert-Butyl (5-methylpiperidin-3-yl)carbamate. To a dry hydrogenation bottle, PtO_2 (3.0 g) was added under N_2 atmosphere. A solution of compound **2** (26.4 g, 127 mmol) in CH_3COOH (300 mL) was added, and the resulting mixture was heated to 50 °C under 55 psi of H_2 for 5 days. ^{1}H NMR showed most of starting material was consumed. The reaction mixture was filtered and the filter cake was washed with MeOH. The combined filtrate was evaporated under high vacuum to give rac-cis/trans- tert-butyl (5-

methylpiperidin-3-yl)carbamate (27.3 g, 100%) as a yellow oil. LC/MS (M+H) 214.2

Step 3. rac-cis/trans-Benzyl 3-((tert-butoxycarbonyl)amino)-5-methylpiperidine-1-carboxylate. To a solution of rac-cis/trans- tert-butyl (5-methylpiperidin-3-yl)carbamate (27.3 g, 127 mmol) in THF (200 mL) and H2O (100 mL) was added $NaHCO_3$ (40.53 g, 482 mmol, 3.8 eq.) at room temperature, and stirred at room temperature for 1 h. CbzCl (26 g, 152 mmol, 1.2 eq.) was added dropwise, and stirred at room temperature for 8 h. TLC (PE/EtOAc, 2:1) showed the reaction to be complete. The reaction mixture was extracted with EtOAc (200 mL x 3). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (PE/EtOAc, 8:1 ~ 4:1) to give rac-cis/trans - benzyl 3-((tert-butoxycarbonyl)amino)-5-methylpiperidine-1-carboxylate (20 g, 45 %, containing some benzyl alcohol) as a white solid. LC/MS (M+H) 348.2.

Step 4. rac-cis/trans-Benzyl 3-amino-5-methylpiperidine-1-carboxylate. To a solution of rac-cis/trans - benzyl 3-((tert-butoxycarbonyl)amino)-5-methylpiperidine-1-carboxylate (20 g, 57.4 mmol) in DCM (40 mL) was added HCl (g)/dioxane (50 mL, 4M) dropwise at room temperature, and stirred at room temperature for 6 hrs. LCMS showed the reaction to be complete. The reaction mixture was concentrated, and filtered, and then triturated with MTBE to give rac-cis/trans-benzyl 3-amino-5-methylpiperidine-1-carboxylate (5.8 g, 43%, 0.817 mol HCl) as a gray solid. ^{1}H NMR (400MHz, MeOD) δ 7.43 - 7.27 (m, 5H), 5.14 (s, 2H), 4.50 - 4.39 (m, 1H), 4.12 (d, J=10.3 Hz, 1H), 4.04 - 3.90 (m, 1H), 3.74 - 3.43 (m, 1H), 3.23 - 3.10 (m, 1H), 2.82 - 2.59 (m, 1H), 2.40 (s, 1H), 2.26 - 2.05 (m, 1H), 1.92 (d, J=11.3 Hz, 1H), 1.78 - 1.58 (m, 1H), 1.30 (s, 1H), 1.25 - 1.05 (m, 2H), 1.01 - 0.93 (m, 3H). LCMS (M+H) = 248.9.

Step 5. rac-cis-(3R,5S)-Benzyl 3-((2-chloro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-methylpiperidine-1-carboxylate and rac-trans-(3R,5R)-benzyl 3-((2-chloro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-methylpiperidine-1-carboxylate. To a mixture of rac-cis/trans - benzyl 3-((tert-butoxycarbonyl)amino)-5-methylpiperidine-1-carboxylate (prepared similarly

as described in WO201102904)) (4 g, 14.046 mmol) and 2,4-dichloro-7H-pyrrolo[2,3-d]pyrimidine (2.9 g, 15.451 mmol, 1.1 eq.) in n-BuOH (70 mL) at room temperature was added DIPEA (7.248 g, 56.184 mmol, 4.0 eq.). The reaction mixture was heated to 140 °C for 30 h. After LCMS showed the reaction to be complete, the reaction mixture was concentrated to dryness in vacuo. The residue was dissolved in EtOAc (150 mL), and diluted with water (150 mL) and the the organic layer was separated. The aqueous layer was extracted with EtOAc (150 mL×2), and the combined organic layers were washed with brine, dried with sodium sulfate. The solvent was removed under reduced pressure. The residue was purified by column chromatography (PE/EtOAc, 6:1 to 2:1) to give rac-cis-(3R,5S)-benzyl 3-((2-chloro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-methylpiperidine-1-carboxylate (rac-cis, spot 2 on the TLC plate -high polarity, 1.934 g, 34 %) and rac-trans-(3R,5R)-benzyl 3-((2-chloro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-methylpiperidine-1-carboxylate (rac-trans, spot 1 on the TLC plate-low polarity, 559 mg, 10 %) as a yellow solid.Pk2: rac-cis-(3R,5S)-benzyl 3-((2-chloro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-methylpiperidine-1-carboxylate (rac-cis): ^{1}H NMR (400MHz, DMSO-d_6) δ 11.70 (br s, 1H), 7.70 (d, J=7.5 Hz, 1H), 7.45 - 7.24 (m, 5H), 7.09 (br s, 1H), 6.58 (br s, 1H), 5.21 - 5.01 (m, 2H), 4.33 (br s, 1H), 4.07 - 3.96 (m, 2H), 3.17 (d, J=5.3 Hz, 1H), 2.61 - 2.53 (m, 1H), 2.33 (br s, 1H), 2.06 - 1.94 (m, 1H), 1.67 (br s, 1H), 1.29 - 1.13 (m, 1H), 0.91 (d, J=6.5 Hz, 3H).

Pk1: rac-trans-(3R,5R)-benzyl 3-((2-chloro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-methylpiperidine-1-carboxylate (rac-trans): ^{1}H NMR (400MHz, DMSO-d_6) δ 11.69 (br s, 1H), 7.63 - 6.59 (m, 8H), 5.05 (d, J=16.8 Hz, 1H), 4.87 (br s, 1H), 4.35 - 3.95 (m, 2H), 3.86 - 3.51 (m, 2H), 3.11 - 2.64 (m, 1H), 2.19 (br s, 1H), 1.90 - 1.72 (m, 2H), 1.56 (br s, 1H), 0.91 (d, J=6.5 Hz, 3H),

Step 6. rac-cis-N-((3R,5S)-5-Methylpiperidin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine

To a dry Parr hydrogenation bottle, dry Pd/C (500 mg) was added under N_2 atmosphere. Then, a solution of rac-cis-(3R,5S)-benzyl 3-((2-chloro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-methylpiperidine-1-carboxylate (rac-cis,

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

1.934 g, 4.835 mmol) in CH_3OH/THF (60 mL/20 mL) was added. The resulting mixture was heated to 40 °C under 50 psi of H_2 for 3 days. After LCMS showed the reaction to be complete and Cl atom was removed, the reaction mixture was filtered, and the filter cake was washed with MeOH. The combined filtrate was evaporated to give rac-cis-N-((3R,5S)-5-methylpiperidin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine (rac-cis, 1.4 g, 100 %) as a pink solid. LC/MS (M+H) = 231.2.

Step 7. rac-cis-1-((3R,5S)-3-((7H-Pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-methylpiperidin-1-yl)prop-2-en-1-one. To a solution of rac-cis-N-((3R,5S)-5-methylpiperidin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine (400 mg, 1.494 mmol) in THF (20 mL) was added saturated aq.$NaHCO_3$ (15 mL) at 0 °C was added acryloyl chloride (149 mg, 1.643 mmol, 1.1 eq.) slowly. The reaction was stirred at 0 °C for 2 hours. After TLC (EtOAc/ MeOH, 10:1) showed the reaction to be complete, the reaction mixture was diluted with water (80 mL), and extracted with EtOAc (80 mL×2). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (EtOAc/ MeOH, 10:1) to give rac-cis-1-((3R,5S)-3-((7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-methylpiperidin-1-yl)prop-2-en-1-one (300 mg, 71 %) as a white solid. ^1H NMR (400MHz, DMSO-d_6) δ 11.52 (br s, 1H), 8.10 (d, J=14.3 Hz, 1H), 7.39 - 7.22 (m, 1H), 7.07 (br s, 1H), 6.94 - 6.78 (m, 1H), 6.56 (br s, 1H), 6.12 (dd, J=8.9, 16.2 Hz, 1H), 5.69 (t, J=10.4 Hz, 1H), 4.71 (d, J=10.0 Hz, 1H), 4.47 - 4.29 (m, 1H), 4.03 (d, J=11.0 Hz, 2H), 2.73 (t, J=11.5 Hz, 1H), 2.58 (t, J=12.3 Hz, 1H), 2.40 - 2.30 (m, 1H), 2.19 (t, J=11.5 Hz, 1H), 2.05 (d, J=11.8 Hz, 1H), 1.36 - 1.17 (m, 1H), 0.97 - 0.89 (m, 3H). LCMS (M+H) 285.9.

Step 8. 1-((3R,5S)-3-((7H-Pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-methylpiperidin-1-yl)prop-2-en-1-one and 1-((3S,5R)-3-((7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-methylpiperidin-1-yl)prop-2-en-1-one. rac-cis-1-((3R,5S)-3-((7H-Pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-methylpiperidin-1-yl)prop-2-en-1-one was separated by chiral SFC (AD, 250 mm x 30 mm, 20 μm, 35% MeOH/NH4OH, 80 ml/min) to give 1-((3R,5S)-3-((7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-methylpiperidin-1-yl)prop-2-en-1-one (pk1) and 1-

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

Peak 1: ^{1}H NMR (400MHz, DMSO-d_6) δ 11.53 (br s, 1H), 8.10 (d, J=14.3 Hz, 1H), 7.42 - 7.23 (m, 1H), 7.08 (br s, 1H), 6.86 (td, J=11.4, 16.4 Hz, 1H), 6.57 (br s, 1H), 6.18 - 6.06 (m, 1H), 5.70 (t, J=10.2 Hz, 1H), 4.71 (d, J=9.8 Hz, 1H), 4.48 - 4.30 (m, 1H), 4.03 (d, J=11.8 Hz, 1H), 2.79 - 2.54 (m, 1H), 2.42 - 2.14 (m, 1H), 2.06 (d, J=12.5 Hz, 1H), 1.63 (br s, 1H), 1.39 - 1.17 (m, 1H), 0.99 - 0.87 (m, 3H). LCMS (M+H) = 285.9. Peak 2: ^{1}H NMR (400MHz, DMSO-d_6) δ 11.53 (br s, 1H), 8.10 (d, J=14.6 Hz, 1H), 7.38 - 7.23 (m, 1H), 7.08 (br s, 1H), 6.94 - 6.79 (m, 1H), 6.56 (br s, 1H), 6.12 (dd, J=7.8, 16.8 Hz, 1H), 5.75 - 5.64 (m, 1H), 4.71 (d, J=11.8 Hz, 1H), 4.49 - 4.30 (m, 1H), 4.03 (d, J=11.5 Hz, 1H), 2.81 - 2.54 (m, 1H), 2.42 - 2.15 (m, 1H), 2.06 (d, J=12.3 Hz, 1H), 1.62 (br s, 1H), 1.38 - 1.18 (m, 1H), 0.99 - 0.88 (m, 3H). LCMS (M+H) 285.9.

Example 15: 1-((3R,5S)-3-((7H-Pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-fluoropiperidin-1-yl)prop-2-en-1-one.

Step 1. (2S,4R)-Methyl 1-benzyl-4-hydroxypyrrolidine-2-carboxylate. To a stirred solution of (2S,4R)-methyl 4-hydroxypyrrolidine-2-carboxylate (35 g, 193 mmol, 1 eq.) in DCM (300 mL) was added Et_3N (78 g, 772 mmol, 4 eq.) and BnBr (39.5 g, 231 mmol, 1.2 eq.) in turns at 0 °C. The reaction mixture was stirred at room temperature for 12 hours. After TLC (DCM/MeOH, 10:1) showed the reaction complete, the reaction mixture was diluted with saturated sodium carbonate (200 ml). The organic layer was washed with brine (200 mL), dried over Na_2SO_4 and concentrated to dryness, the crude product was purified by chromatography (MeOH/ EtOAc, 0% to 10%) to give (2S,4R)-methyl 1-benzyl-4-hydroxypyrrolidine-2-carboxylate (30 g, 66%) as a yellow oil. ^{1}H NMR (400MHz, $CDCl_3$) δ ppm 2.16 - 2.39 (m, 1 H) 2.42 - 2.65 (m, 2 H) 3.18 - 3.37 (m, 2 H) 3.60 (d, *J*=13.05 Hz, 1 H) 3.71 (s, 3 H) 4.03 (d, *J*=13.05 Hz, 1 H) 4.97 - 5.23 (m, 1 H) 7.22 - 7.39 (m, 5 H).

Step 2. (2S,4S)-Methyl 1-benzyl-4-fluoropyrrolidine-2-carboxylate. To a stirred solution of (2S,4R)-methyl 1-benzyl-4-hydroxypyrrolidine-2-carboxylate

(6 g, 25.37 mmol, 1 eq.) in anhydrous DCM (100 mL) was added DAST (10.2 g, 63.4 mmol, 2.5 eq.) at -78 °C under N_2. The reaction mixture was stirred at -78 °C for 0.5 hours and then warm to room temperature for 2 hours. After TLC (petroleum ether/ethyl acetate, 1:1) showed starting material to be consumed, the reaction mixture was quenched with saturated sodium carbonate (200 ml). The organic layer was separated out and the aqueous layer was extracted with CH_2Cl_2 again. The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4 and concentrated to dryness, the crude product was purified by sp1 (EtOAc/petroleum ether, 10% to 80%) to give (2S,4S)-methyl 1-benzyl-4-fluoropyrrolidine-2-carboxylate (2 g, 34%) as a yellow oil. ^{1}H NMR (400MHz, $CDCl_3$) δ 2.20 - 2.37 (m, 1 H) 2.43 - 2.67 (m, 2 H) 3.22 - 3.35 (m, 2 H) 3.60 (d, J=13.30 Hz, 1 H) 3.67 - 3.75 (m, 3 H) 4.03 (d, J=13.05 Hz, 1 H) 4.99 - 5.22 (m, 1 H) 7.22 - 7.38 (m, 5 H).

Step 3. ((2S,4S)-1-Benzyl-4-fluoropyrrolidin-2-yl)methanol. To a stirred solution of LiAlH4 (1.28 g, 33.7 mmol, 1 eq.) in anhydrous THF (50 mL) was added dropwise a solution of (2S,4S)-methyl 1-benzyl-4-fluoropyrrolidine-2-carboxylate (8 g, 33.7 mmol, 1 eq.) in anhydrous THF (50 mL) at 0 °C. The reaction mixture was stirred at room temperature for 10 hours. After TLC (petroleum ether/ethyl acetate, 4:1) showed starting material to be consumed, the reaction mixture was cooled to 0 °C and sequentially quenched with water (1.3 ml), 15 % NaOH solution (1.3 ml) and water (3.9 ml). $MgSO_4$ (5 g) was added and the mixture was warmed to room temperature and stirred for 0.5 hours. The mixture was filtered and concentrated in vacuum to give the crude product, which was purified by sp1 (EtOAc/petroleum ether, 40% to 100%) to give (2S,4S)-1-benzyl-4-fluoropyrrolidin-2-yl)methanol (6 g, 70%) as a yellow oil. ^{1}H NMR (400MHz, $CDCl_3$) δ 2.09 - 2.51 (m, 3 H) 2.62 (d, *J*=9.03 Hz, 1 H) 2.80 (t, *J*=6.53 Hz, 1 H) 3.13 - 3.35 (m, 2 H) 3.49 (t, *J*=9.79 Hz, 1 H) 3.77 (dd, *J*=11.04, 3.01 Hz, 1 H) 4.05 (d, *J*=13.05 Hz, 1 H) 4.94 - 5.16 (m, 1 H) 7.22 - 7.39 (m, 5 H).

Step 4. (3R,5S)-3-Azido-1-benzyl-5-fluoropiperidine and (2S,4S)-2-(azidomethyl)-1-benzyl-4-fluoropyrrolidine. To a stirred solution of (2S,4S)-1-benzyl-4-fluoropyrrolidin-2-yl)methanol (4 g, 19 mmol, 1 eq.) in anhydrous

DCM (200 mL) was added n-Bu_4NN_3 (5.96 g, 21 mmol, 1.1 eq.) and XtalFluor® (4.8 g, 21 mmol, 1.1 eq.) at -78 °C under N_2 protection. The reaction mixture was stirred at -78 °C for 6 hours. After TLC (petroleum ether/ethyl acetate, 4:1) showed starting material to be consumed, the reaction mixture was quenched with 15% NaOH solution (30 ml), and concentrated to dryness. The residue was purified by chromatography (EtOAc/petroleum ether, 0% to 20%) to give a mixture of (3R,5S)-3-azido-1-benzyl-5-fluoropiperidine and (2S,4S)-2-(azidomethyl)-1-benzyl-4-fluoropyrrolidine (2.2 g, 50%) as a yellow oil. The mixture was separated via SFC (ChiralPak AD, 300 x 50 mm, 10 μm, 15% MeOH/NH_4OH, 180 mL/min) to give (3R,5S)-3-azido-1-benzyl-5-fluoropiperidine (1.2 g) and (2S,4S)-2-(azidomethyl)-1-benzyl-4-fluoropyrrolidine (1 g) as yellow oil. (3R,5S)-3-azido-1-benzyl-5-fluoropiperidine: ^{1}H NMR (400MHz, $CDCl_3$) δ 1.48 - 1.67 (m, 1 H) 2.04 - 2.22 (m, 2 H) 2.34 (br s, 4 H) 2.58 - 2.90 (m, 2 H) 2.97 - 3.10 (m, 1 H) 3.50 - 3.65 (m, 2 H) 4.55 - 4.82 (m, 1 H) 7.19 - 7.41 (m, 5 H).

Step 5. (3R,5S)-1-Benzyl-5-fluoropiperidin-3-amine. To a solution of (3R,5S)-3-azido-1-benzyl-5-fluoropiperidine (1.4 g, 5.9 mmol, 1 eq.) in THF (50 mL) was added PPh_3 (2.35 g, 90 mmol, 1.5 eq.) in portions at room temperature. The reaction mixture was stirred at rt for 3 hours. Then water (0.7 ml) was added dropwise to the mixture and heated to 60 °C for 10 hours. After TLC (petroleum ether/ethyl acetate, 4:1) showed starting material to be consumed, the reaction mixture was concentrated to dryness, and purified by sp1 (MeOH/CH_2Cl_2 0% to 10%) to give (3R,5S)-1-benzyl-5-fluoropiperidin-3-amine (1.1 g, 80%) as a colorless oil. LC/MS (M+H) = 209.2. ^{1}H NMR (400MHz, $CDCl_3$) δ 1.37 - 1.53 (m, 1 H) 1.99 (t, J=9.41 Hz, 1 H) 2.12 - 2.36 (m, 2 H) 2.70 (d, J=10.29 Hz, 1 H) 2.82 - 3.01 (m, 2 H) 3.53 - 3.62 (m, 2 H) 4.55 - 4.77 (m, 1 H) 7.22 - 7.37 (m, 5 H).

Step 6. N-((3R,5S)-1-Benzyl-5-fluoropiperidin-3-yl)-2-chloro-7H-pyrrolo[2,3-d]pyrimidin-4-amine. A mixture of (3R,5S)-1-benzyl-5-fluoropiperidin-3-amine (300 mg, 1.44 mmol), DIPEA (929 mg, 7.2 mmol) and 2,4-dichloro-7H-pyrrolo[2,3-d]pyrimidine (297 mg, 1.59 mmol) in n-BuOH (10 mL) was heated to 130-140 °C overnight. After LC-MS showed the reaction to be complete,

the reaction mixture was cooled to room temperature and evaporated to dryness in vacuo at 45 °C. The residue was diluted with EtOAc (30 mL) and washed with water (20 mL). The aqueous layer was extracted with EtOAc (30 mL). The combined organic layers were washed with water and brine, dried over Na_2SO_4 and concentrated to give crude product, which was purified via chromatography (EtOAc/petroleum ether, 10% to 80%) to give N-((3R,5S)-1-benzyl-5-fluoropiperidin-3-yl)-2-chloro-7H-pyrrolo[2,3-d]pyrimidin-4-amine (300 mg, 65 %) as a yellow solid. LC/MS (M+H) = 359.2.

Step 7. N-((3R,5S)-5-Fluoropiperidin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine. To a dry Parr hydrogenation bottle, 10% dry Pd/C (50 mg) was added under Ar atmosphere. A solution of N-((3R,5S)-1-benzyl-5-fluoropiperidin-3-yl)-2-chloro-7H-pyrrolo[2,3-d]pyrimidin-4-amine (300 mg, 0.84 mmol) in MeOH (20 mL) was added and the resulting mixture was hydrogenated under 50 psi of H_2 at 35 °C for 72 hours. The reaction mixture was filtered through a pad of Celite®, and the filter cake was washed with MeOH three times. The combined filtrate was concentrated to give N-((3R,5S)-5-fluoropiperidin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine (200 mg, 100%) as a white solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 0.74 - 1.28 (m, 1 H) 1.94 - 2.11 (m, 1 H) 2.31 - 2.46 (m, 1 H) 2.96 (dd, J=12.17, 8.41 Hz, 1 H) 3.43 - 3.56 (m, 2 H) 4.12 (br s, 1 H) 4.57 (br s, 1 H) 4.86 - 5.12 (m, 1 H) 6.62 (d, J=2.01 Hz, 1 H) 7.12 (br s, 1 H) 7.53 (d, J=7.53 Hz, 1 H) 8.06 - 8.19 (m, 1 H) 11.61 (br s, 1 H).

Step 8. 1-((3R,5S)-3-((7H-Pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-fluoropiperidin-1-yl)prop-2-en-1-one.

To a solution of N-((3R,5S)-5-fluoropiperidin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine (100 mg, 0.424 mmol) in THF (3 mL) and aq. $NaHCO_3$ solution (3 mL) at 0 °C was added acryloyl chloride (42 mg, 0.468 mmol) dropwise at 0 °C carefully. The resulting mixture was stirred at 0 °C for 2 hours. After TLC (DCM/MeOH, 10:1) showed starting material to be consumed, the reaction mixture was diluted with water (20 mL) and extracted with EtOAc (30 mL×2); the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated to give crude product, which was further purified by column chromatography on silica gel (MeOH/DCM, 0% to 8%) to give 1-((3R,5S)-3-

((7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-fluoropiperidin-1-yl)prop-2-en-1-one (60 mg, 50 %) as a white solid. The solid was further purified by RP-HPLC to give pure product (25.7 mg). HPLC: Column: DIKMA Diamonsil(2) C18 200x20mm*5μm; Mobile phase: 0% MeCN (0.225%FA) in water (0.225%FA) to 10% MeCN(0.225%FA) in water (0.225%FA). ^{1}H NMR (400MHz, DMSO-d_6) δ 1.75 - 2.13 (m, 1 H) 1.82 - 2.12 (m, 1 H) 2.36 - 2.48 (m, 1 H) 3.25 (br s, 1 H) 4.27 (br s, 3 H) 4.61 - 4.88 (m, 1 H) 5.67 (d, J=9.03 Hz, 1 H) 6.10 (dd, J=16.81, 2.26 Hz, 1 H) 6.52 (d, J=2.51 Hz, 1 H) 6.64 - 6.82 (m, 1 H) 6.90 (d, J=7.03 Hz, 1 H) 7.08 (br s, 1 H) 8.15 (s, 1 H) 11.35 (br s, 1 H).

Example 16:1-((1R,2R,5R)-2-((7H-Pyrrolo[2,3-d]pyrimidin-4-yl)amino)-8-azabicyclo[3.2.1]octan-8-yl)prop-2-en-1-one .

Step 1. Rac-N-(8-Methyl-8-azabicyclo[3.2.1]octan-2-yl)-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine. A solution of the 4-chloro-7-tosyl-7H-pyrrolo[2,3-d]pyrimidine, 8-methyl-8-azabicyclo[3.2.1]octan-2-amine (Pharmablock), and DIEA in 1-butanol (30 mL) was heated to 80 °C overnight. LCMS showed the pyrrolopyrimidine was consumed, and ionization consistent with the desired product. The reaction was concentrated in vacuo, and the crude material was partitioned between ethyl acetate (10 mL) and water (20 mL). The mixture was filtered and the solid was washed with ether to give 6g of rac-N-(8-methyl-8-azabicyclo[3.2.1]octan-2-yl)-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine. LC/MS (M+H) = 412.1.

Step 2. N-((1R,2R,5S)-8-Azabicyclo[3.2.1]octan-2-yl)-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine. To a solution of rac-N-(8-methyl-8-azabicyclo[3.2.1]octan-2-yl)-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine (4.0 g, 9.72 mmol) in DCE (50 mL) at 0 oC was added $NaHCO_3$ (10 eq, 97.2 mmol, 8.25 g mg) in DCE (50 mL) followed by 1-chloroethyl chloroformate (10 eq, 10.6 mL, 97.2 mmol). After 10min, the reaction was allowed to warm to room temperature. The resulting mixture was heated to 50°C for 4 hrs. After cooling to room temperature, the reaction mixture was poured into Na_2CO_3 (2N) and the organic layers were separated. The aqueous layer was

extracted with DCM. The combined organic layer was evaporated to dryness. The residue was dissolved in EtOH (120 mL) and refluxed for 4h. All volatiles were removed in vacuo. The residue was treated with DCM and Na_2CO_3 (aq). The organic layer was separated and the aqueous layer was extracted with DCM. The combined organic extracts were dried (Na_2SO_4) and solvent was removed to give 4.0 g of crude product. The crude product was purified by CombiFlash® (40g gold column, 0 to 10% 2M NH3 in MeOH in DCM) to give 2 g of racemic N-((1R,2R,5S)-8-azabicyclo[3.2.1]oc-tan-2-yl)-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine. LC/MS (M+H) = 398.1 (M+H). ^{1}H NMR (400MHz, $CDCl_3$) δ 8.42 (s, 1H), 8.08-8.02 (m, 2H), 7.46-7.48 (m, 1H), 7.33-7.27 (m, 2H), 6.57-6.52 (m, 1H), 5.03-4.91 (m, 1H), 4.33-4.26 (m, 1H), 3.76 (bs, 1 H), 3.60 (bs, 1 H), 2.37 (s, 3H), 2.03-1.26 (m, 9H).

racemic N-((1R,2R,5S)-8-azabicyclo[3.2.1]octan-2-yl)-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine (1g) was purified by chiral SFC to provide 400 mg of two peaks:

enantiomer 1 (pk1): N-((1R,2R,5S)-8-azabicyclo[3.2.1]octan-2-yl)-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine and enantiomer 2 (pk 2): N-((1S,2S,5R)-8-azabicyclo[3.2.1]octan-2-yl)-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine. Column: Chiral Tech AS-H 250 mm x 21.2 mm 5um Isocratic Conditions: Mobile Phase A: 80% CO2; Mobile Phase B: 20%; Methanol+0.2%NH4OH; Detection 210 nM; Flow: 80.0 mL/min; Backpressure: 120 Bar.

Step 3. 1-((1R,2R,5R)-2-((7-Tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-8-azabicyclo[3.2.1]octan-8-yl)prop-2-en-1-one. To a solution N-((1R,2R,5S)-8-azabicyclo[3.2.1]octan-2-yl)-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine (pk1) in chloroform (10 mL) was added DIPEA . The solution was cooled to 0 °C and acryloyl chloride (in 1mL of $CHCl_3$) was added over 5min. The reaction was stirred for 30 minutes. Na_2CO_3 (10%; 5 mL) was added. The reaction was stirred at 0 °C for 0.5 hr and the organic phase was separated and the solvent was evaporated. The residue (300mg) was purified by CombiFlash®(12 g gold column, 20 to 100% EA in Hept) to give 208 mg of 1-((1R,2R,5R)-2-((7-Tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-8-azabicyclo[3.2.1]octan-8-yl)prop-2-en-1-one . LC/MS (M+H): 452.2. ^{1}H NMR

(400MHz, $CDCl_3$) δ 8.44 (s, 1H), 8.08-8.02 (m, 2H), 7.50-7.45 (m, 1H), 7.31-7.25 (m, 2H), 6.92-6.83 (m, 1H), 6.50-6.41 (m, 2H), 5.80-5.71 m, 1H), 5.01-4.97 (m, 1H), 4.78-4.73 (m, 1H), 4.69-4.60 (br s, 1H), 4.26-4.16 (m, 1H), 2.40 (s, 3H), 2.01-1.53 (m, 8H).

Step 4. 1-((1R,2R,5R)-2-((7H-Pyrrolo[2,3-d]pyrimidin-4-yl)amino)-8-azabicyclo[3.2.1]octan-8-yl)prop-2-en-1-one. 1-((1R,2R,5R)-2-((7-Tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-8-azabicyclo[3.2.1]octan-8-yl)prop-2-en-1-one (200 mg) was dissolved in 5 mL of THF. TBAF (1M in THF, 1.9 mL) was added. The reaction was heated to 60 °C for 48 hrs. The solvent was removed in vacuo and the residue was treated with EtOAc and NH_4Cl (10%) (5 mL each). The layers were separated and the organic layer collected, washed with NH_4Cl (10%) and satd. $NaHCO_3$ and brine. The organic fraction was collected, dried (Na_2SO_4) and the solvent removed to give 200 mg of crude product, which was purified by RP-HPLC to provide 90 mg of product. The product was further purified by CombiFlash® (12 g gold column, 0 to 10% MeOH in DCM) give 55 mg of 1-((1R,2R,5R)-2-((7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-8-azabicyclo[3.2.1]octan-8-yl)prop-2-en-1-one. LC/MS (M+H) 298.3. ^1H NMR (400MHz, $CDCl_3$) δ 11.58-11.47 (m, 1H) 8.44-8.34 (m, 1H), 7.20-7.15 (m, 1H), 7.04-7.00 (m, 2H), 6.61-6.42 (m, 2H), 5.84-5.76 (m, 1H) 5.11-5.04 (m, 1H) 4.84-4.82 (m, 1H), 4.48-4.30 (m, 1H), 2.17-1.69 (m, 8H).

Example 17: 1-((3R,5S)-3-(7H-Pyrrolo[2,3-d]pyrimidin-4-ylamino)-5-hydroxypiperidin-1-yl)prop-2-en-1-one.

Step 1. (3S,5S)-5-((tert-Butyldimethylsilyl)oxy)piperidin-3-ol. (3S,5S)-1-benzyl-5-((tert-butyldimethylsilyl) oxy)piperidin-3-ol (3.6 g, 11.196 mmol) was taken up in EtOH (30 ml) and the ethanol solution was degassed with argon for 15 mins after which 10% Pd/C (400 mg) was added and the resultant mixture was hydrogenated using a hydrogen bladder for 16 h. After TLC (5% MeOH in DCM) showed starting material to be consumed, the reaction mixture was filtered through a Celite® bed, and the filtrate was concentrated to obtain 3g crude (3S,5S)-5-((tert-butyldimethylsilyl)oxy)piperidin-3-ol as light

yellow oil. Crude (3S,5S)-5-((tert-butyldimethylsilyl)oxy)piperidin-3-ol was directly used for the next step.

Step 2. (3S,5S)-tert-Butyl 3-((tert-butyldimethylsilyl)oxy)-5-hydroxypiperidine-1-carboxylate. To a stirred solution of (3S,5S)-5-((tert-butyldimethylsilyl)oxy)piperidin-3-ol (2.59 g, 11.192 mmol) in DCM (19 ml) at 0 °C was added TEA (3.12 ml, 22.385 mmol) and Boc_2O (3.086 ml, 13.431 mmol in a DCM (4 ml) solution). The reaction mixture was allowed to warm to room temperature over 45 min. After TLC (70% EtOAc in hexane) indicated starting material to be consumed, the reaction mixture was quenched with water (20 ml) and extracted with DCM (2 x 50 ml). The organic layers were combined and dried over Na_2SO_4 and concentrated to provide the crude product, which was purified by CombiFlash® (EtOAc/hexane, 100% hexane to 35% EtOAc in hexane) to afford 3.2 g (86%) (3S,5S)-tert-butyl 3-((tert-butyldimethylsilyl)oxy)-5-hydroxypiperidine-1-carboxylate as a light brown oil. ^1H NMR (400MHz, $CDCl_3$) δ 0.03 - 0.10 (m, 6 H) 0.87 (s, 9 H) 1.45 (s, 9 H) 1.68 (br s, 1 H) 1.78 - 1.88 (m, 1 H) 3.08 (br s, 1 H) 3.39 (br s, 2 H) 3.57 (dd, *J*=13.69, 3.42 Hz, 1 H) 3.87 - 4.11 (m, 2 H).

Step 3. (3S,5S)-tert-Butyl 3-((tert-butyldimethylsilyl)oxy)-5-((methylsulfonyl)oxy)piperidine-1-carboxylate. To a stirred solution of (3S,5S)-tert-butyl 3-((tert-butyldimethylsilyl)oxy)-5-hydroxypiperidine-1-carboxylate (3.5 g, 10.557 mmol) in DCM (25 ml) at 0 oC was added TEA (4.414 ml, 31.671 mmol) followed by mesyl chloride (1.06 ml, 13.724 mmol). The reaction mixture was allowed to stir for 4 h. After TLC (30% EtOAc in hexane) indicated clean conversion, the reaction mixture was quenched with water and extracted with DCM (2 x 75 ml). The combined organic fractions were dried over Na_2SO_4 and concentrated to provide 4.5g crude (3S,5S)-tert-butyl 3-((tert-butyldimethylsilyl)oxy)-5-((methylsulfonyl)oxy)piperidine-1-carboxylate as light yellow oil, which was used for the next step directly. ^1H NMR (400MHz, $CDCl_3$) δ 0.08 (d, *J*=1.47 Hz, 6 H) 0.88 (s, 9 H) 1.33 - 1.49 (m, 9 H) 1.85 (br s, 1 H) 2.09 (br s, 1 H) 2.90 - 3.08 (m, 4 H) 3.40 (br s, 1 H) 3.59 - 3.86 (m, 2 H) 3.95 (br s, 1 H) 4.94 (br s, 1 H).

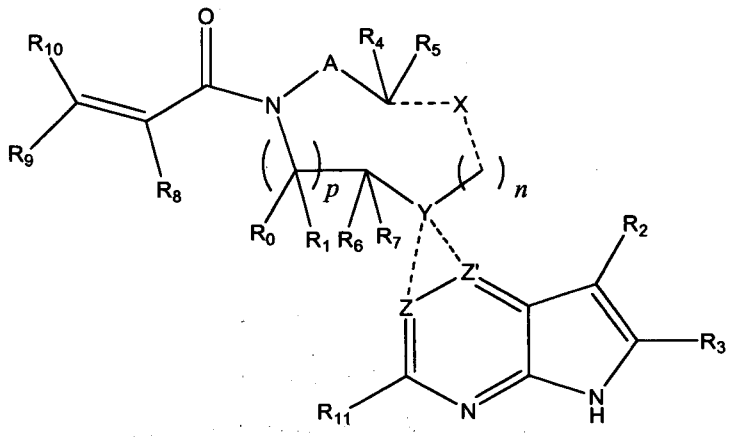
Step 4. (3R,5S)-tert-Butyl 3-azido-5-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate. To a stirred solution of (3S,5S)-tert-butyl 3-((tert-butyldimethylsilyl)oxy)-5-((methylsulfonyl)oxy)piperidine-1-carboxylate (4.32 g, 10.546 mmol) in DMF (35 ml) was added NaN_3 (2.057 g, 31.639 mmol). The reaction mixture was heated to 100 °C for 16 h. The reaction mixture was concentrated to remove DMF and the residue was taken up into EtOAc (200 ml) and washed with water (3 x 50 ml). The organic fractions were dried over Na_2SO_4 and concentrated to provide crude material, which after CombiFlash® (EtOAc/hexane, 100% hexane to 20 % EtOAc in hexane) afforded 1.9 g (51%) (3R,5S)-tert-butyl 3-azido-5-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate as a light yellow oil. ^{1}H NMR (400MHz, $CDCl_3$) δ 0.04 - 0.10 (m, 6 H) 0.88 (s, 9 H) 1.40 - 1.46 (m, 9 H) 1.48-1.45 (m, 1 H) 2.26 (d, *J*=12.23 Hz, 1 H) 2.36 - 2.60 (m, 2 H) 3.24 - 3.40 (m, 1 H) 3.49 - 3.65 (m, 1 H) 3.88 - 4.36 (m, 2 H).

Step 5. (3R,5S)-tert-Butyl 3-amino-5-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate. To a stirred solution of (3R,5S)-tert-butyl 3-azido-5-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate (1.9 g, 5.329 mmol) in THF (100 ml) was added H_2O (0.671 ml, 37.303 mmol) and PPh_3 (2.097 g, 7.993 mmol). The reaction mixture was refluxed for 16 h. The volatiles were removed under reduced pressure, and the crude product was purified by column chromatography using 100-200 silica and MeOH/DCM as eluent (100% DCM to 5% MeOH in DCM) to afford 1.52 g (86%) of (3R,5S)-tert-butyl 3-amino-5-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate as a light yellow oil. ^{1}H NMR (400MHz, $CDCl_3$) δ 0.07 (d, *J*=0.98 Hz, 6 H) 0.88 (s, 9 H) 1.20 - 1.31 (m, 1 H) 1.44 (s, 9 H) 2.07 (s, 1 H) 2.43 - 2.55 (m, 1 H) 2.60 - 2.71 (m, 1 H) 2.81 (m, *J*=9.30, 9.30 Hz, 1 H) 3.53 - 3.69 (m, 1 H) 3.78 - 3.97 (m, 2 H).

Step 6. (3S,5R)-tert-Butyl 3-((tert-butyldimethylsilyl)oxy)-5-((7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidine-1-carboxylate. To a stirred solution of (3R,5S)-tert-butyl 3-amino-5-((tert-butyldimethylsilyl)oxy)piperidine-1-carboxylate (1.52 g, 4.598 mmol) in n-butanol (10 ml) was added 4-chloro-7-tosyl-7H-pyrrolo[2,3-d]pyrimidine (1.698 g, 5.518 mmol) and DIPEA (1.642 ml, 9.197 mmol). The resulting mixture was refluxed for 36 h, and then the vola-

CLAIMS:

1. 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;

mino, 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;

ocyclic)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;

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 al-

alkyl; 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 O or —$(CR_eR_f)_s$—, 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, whereby when *n* is 0, and X is O, said O is bonded to H, and said dotted bond between X and —$(CH_2)_n$— is absent, and when X is —$(CR_eR_f)_s$—, and X is bonded directly to Y; and (b) if X is absent, said dotted bonds are absent and *n* is 0, whereby when Y is N, either (i) said N atom is substituted by H, or (ii) said N atom may 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.

11. The compound of claim 1 selected from the group consisting of:

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