

Therefore, a strong need exists for compounds which selectively and potently inhibit JAK3 wildtype and mutants as well as are selective over other JAK family members to provide an effective and safe clinical therapy for the diseases associated with or mediated by JAK3.

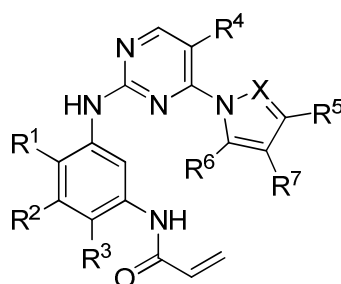
5 A need also exists for methods of administering such compounds, pharmaceutical formulations and medicaments to patients or subjects in need thereof.

SUMMARY OF THE INVENTION

10 The present invention relates to novel chemical compounds and pharmaceutically acceptable compositions thereof which display inhibition activity against certain mutated forms of EGFR.

The invention provides pyrimidine derivatives represented by Formula (I). Their use for the treatment or prevention of a number of different cancers associated with one or more
15 EGFR mutations is also disclosed.

Such compounds have general Formula (I) as well as pharmaceutically acceptable salts, diastereomers, enantiomers, racemates, hydrates or solvates thereof,



20 wherein:

X is CH or N;

R¹ is H, R⁸ or -OR⁸;

R² is hydrogen, C₁₋₆ alkyl, 6-10 membered monocyclic or bicyclic aryl, or 5-10 membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the
25 aryl or heteroaryl is optionally and independently substituted at one or more carbon atoms with R¹³; and wherein the heteroaryl having one or more nitrogen atoms is optionally and independently substituted at one or more nitrogen atoms with R⁸;

R³ is hydrogen, 4-7 membered monocyclic heterocyclyl comprising 1-2 heteroatoms selected from N, O and S, and optionally substituted with oxo, 5-6 membered heteroaryl comprising 1-3 heteroatoms selected from N, O and S, NR⁹R¹⁰, NR¹¹R¹², or
30 phenyl, wherein the heteroaryl or phenyl is optionally and independently substituted at one or more carbon atoms with R¹³; and wherein the heterocyclyl or heteroaryl having one or

more nitrogen atoms is optionally and independently substituted at one or more nitrogen atoms with R⁸;

R⁴ is hydrogen, C₁₋₄ alkyl, C₃₋₅ cycloalkyl, F, Cl, Br, CN, or CF₃;

R⁵ is hydrogen, CF₃, C₁₋₆ alkyl, C₃₋₇ cycloalkyl, 5-6 membered heteroaryl comprising 1-3 heteroatoms selected from N, O and S, or 6-10 membered monocyclic or bicyclic aryl, wherein the heteroaryl or aryl is optionally and independently substituted at one or more carbon atoms with R¹³;

R⁶ is hydrogen or C₁₋₆ alkyl;

R⁷ is hydrogen, -CH₂OH, -CH₂OR⁸, C₁₋₃ alkyl, (CH₂)_nNR⁹R¹⁰, (CH₂)_nNR¹¹R¹², C(O)NR⁹R¹⁰, or C(O)NR¹¹R¹², wherein each n is independently 1 or 2;

R⁸ is selected from C₁₋₆ alkyl or C₃₋₇ cycloalkyl;

R⁹ is selected from C₁₋₆ alkyl, C₃₋₇ cycloalkyl or 4-7 membered heterocyclyl comprising 1-2 heteroatoms selected from N, O and S, wherein the C₁₋₆ alkyl or C₃₋₇ cycloalkyl is optionally substituted with halogen or -OR⁸, and wherein the 4-7 membered heterocyclyl having one nitrogen atom is optionally and independently substituted with -R⁸, -C(O)R⁸, -C(O)OR⁸, or C(O)NHR⁸;

R¹⁰ is C₁₋₆ alkyl, C₃₋₇ cycloalkyl, or (CH₂)_nNR⁹R⁹, wherein each n is independently 1 or 2;

R¹¹ and R¹², taken together with nitrogen atom to which they are bonded form, independently for each occurrence,

i) a 3-8 membered saturated or partially saturated monocyclic group having no heteroatom other than the nitrogen atom to which R¹¹ and R¹² are bonded, wherein said 3-8 membered saturated or partially saturated monocyclic group is optionally and independently substituted at one or more carbons (e.g., at one, two, or three carbon atoms) with halogen, hydroxyl, -OR⁸, -NR⁹R¹⁰, or -NR¹¹R¹²; or

ii) a 5-8 membered saturated or partially saturated monocyclic group having 1 or 2 heteroatoms, in addition to the nitrogen atom to which R¹¹ and R¹² are bonded, wherein said heteroatoms are independently selected from nitrogen, oxygen, sulfur, sulfone or sulfoxide, wherein said 5-8 membered saturated or partially saturated monocyclic group having 1 or 2 nitrogen atoms is optionally substituted at one or more carbon or nitrogen atoms (e.g., at one, two, or three carbon or nitrogen atoms) with -R⁸, -C(O)R⁸, -C(O)OR⁸, -C(O)NHR⁸, -SO₂R⁸, -SO₂NH₂, or -SO₂NR⁸₂; and

R¹³ is selected from halogen, CN, CF₃, R⁸, -OR⁸ or C₂₋₄ alkenyl;

or a pharmaceutically acceptable salt thereof.

Also disclosed are compositions comprising these compounds, methods of making these compounds, methods of inhibiting enzyme activity, particularly one or more EGFR mutant and JAK3 kinase activity, through use of these compounds, and a method of treating disease or disease symptoms in a mammal, particularly where inhibition of the kinase activity, can affect disease outcome.

BRIEF DESCRIPTION OF THE DRAWINGS

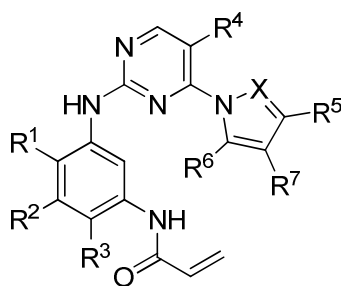
Figure 1 shows visualization of Western blots showing the results of inhibition of phosphorylation level of mutant EGFR as compared to wildtype EGFR.

DETAILED DESCRIPTION OF THE INVENTION

The present disclosure provides a group of aminopyrimidine derivatives and pharmaceutically acceptable salts thereof that are useful for inhibiting one or more protein kinases and for treating diseases and disorders that are mediated by the protein kinase, for example, cell proliferative disease and disorder such as cancer, autoimmune diseases, infection, cardiovascular disease, and neurodegenerative disease and disorder. The present disclosure also provides methods for synthesizing and administering the aminopyrimidine derivatives. The present disclosure also provides pharmaceutical formulations comprising at least one of the compounds of Formula (I) together with a pharmaceutically acceptable carrier, diluent or excipient therefor. The disclosure also provides useful intermediates generated during syntheses of the aminopyrimidine derivative compounds.

The present disclosure provides compositions and methods for modulating the activity of the epidermal growth factor receptor (EGFR) mutants and/or Janus kinase 3 (JAK3). In one aspect, there are provided compounds which act as inhibitors of EGFR mutants or JAK3.

In a first embodiment, provided herein is a compound of Formula (I), individual stereoisomer, or mixture of isomers.



I

wherein:

In certain embodiments of the compound of Formula (IV), R⁵ is hydrogen, methyl, isopropyl, t-butyl, cyclopropyl, 2-thiophenyl, 2-furanyl, 3-furanyl, 3-pyridyl, 4-pyridyl or phenyl.

5 In a fifth embodiment, provided herein is a compound of Formula (I), Formula (II), or Formula (III), or a pharmaceutically acceptable salt thereof, wherein R¹ is -OCH₃; and n is 1.

10 In a sixth embodiment, provided herein is a compound of Formula (IV), or a pharmaceutically acceptable salt thereof, wherein R¹ is H; and n is 1.

In certain embodiments, the compound is a compound described herein or a pharmaceutically acceptable salt thereof.

15 In another aspect a method of treating protein kinase-mediated disease in a subject in need thereof is disclosed, comprising administering to said subject a therapeutically effective amount of a compound of the invention (such as a compound of Formula (I)) or a pharmaceutically acceptable salt thereof, that is effective in treating abnormal cell growth and immune disease.

20 In another aspect, a method of inhibiting at least one mutant of EGFR selectively as compared to wild type EGFR, in biological sample or in a patient is disclosed, comprising contacting the biological sample with or administering to the patient a compound according of the invention, or a composition thereof (e.g., a pharmaceutical composition comprising 25 the compound of the invention and a pharmaceutically acceptable carrier). In certain embodiments, the at least one mutant is Del E746-A750, L858R or T790M. In certain embodiments, the at least one mutant is at least one double mutant selected from Del E746-A750/T790M or L858R/T790M.

30 In another aspect, a method of inhibiting Janus kinase 3 (JAK3) selectively as compared to other kinases, in biological sample or in a patient is disclosed, comprising contacting the biological sample with or administering to the patient a compound of the invention, or a composition thereof, that is effective in treating abnormal cell growth including leukemia and lymphoma (B-cell & T-cell) and immune diseases including arthritis, 35 rheumatoid arthritis and autoimmune diseases.

In another aspect, use of a compound invention (such as a compound of Formula (I)) or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for treating protein kinase-mediated disease is disclosed. Further,

use of a compound of the invention or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for inhibiting at least one mutant of EGFR selectively as compared to wild type EGFR is disclosed.

5 In another aspect, a pharmaceutical composition for treating protein kinase-mediated disease is provided, comprising a compound of the invention (such as a compound of Formula (I)) or a pharmaceutically acceptable salt thereof as active ingredients. Further, a pharmaceutical composition for inhibiting at least one mutant of EGFR selectively as compared to wild type EGFR may be provided, comprising a compound of the invention or
10 a pharmaceutically acceptable salt thereof as active ingredients.

The term "alkyl," used alone or as part of a larger moiety such as "arylalkyl" or "cycloalkyl" refers to a straight or branched hydrocarbon radical having from 1 to 15 carbon atoms or from 1-8 carbon atoms (unless stated otherwise) and includes, for example, methyl,
15 ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, n-pentyl, iso-pentyl, n-hexyl and the like. An alkyl can be unsubstituted or substituted with one or more suitable substituents.

The term "cycloalkyl" refers to a monocyclic or polycyclic hydrocarbon ring group and includes, for example, cyclopropyl, cycloheptyl, cyclooctyl, cyclodecyl, cyclobutyl,
20 adamantyl, norpinanyl, decalanyl, norbornyl, cyclohexyl, cyclopentyl, and the like. A cycloalkyl group can be unsubstituted or substituted with one or more suitable substituents.

The term "hetero" refers to the replacement of at least one carbon atom member in a ring system with at least one heteroatom such as nitrogen, sulfur, and oxygen.

The term "heterocycloalkyl" means a non-aromatic monocyclic or polycyclic ring comprising carbon and hydrogen atoms and at least one heteroatom, preferably, 1 to 4
25 heteroatoms selected from nitrogen, sulfur, oxygen, sulfone, or sulfoxide. A heterocycloalkyl group can have one or more carbon-carbon double bonds or carbon-heteroatom double bonds in the ring group as long as the ring group is not rendered aromatic by their presence.

30 Examples of heterocycloalkyl groups include azetidiny, aziridiny, pyrrolidiny, piperidiny, piperaziny, homopiperaziny, morpholino, thiomorpholino, tetrahydrofuranyl, tetrahydrothiofuranyl, tetrahydropyranyl, pyranyl, and the like. A heterocycloalkyl group can be unsubstituted or substituted with one or more suitable substituents.

As used herein, the term "halogen" includes fluoro, chloro, bromo, and iodo.

35 As used herein, the term "alkoxy" refers to the alkyl groups above bound through oxygen, examples of which include methoxy, ethoxy, iso-propoxy, tert-butoxy, and the like. In addition, alkoxy also refers to polyethers such as $-O-(CH_2)_2-O-CH_3$, and the like. An alkoxy can be unsubstituted or substituted with one or more suitable substituents.

As used herein, the term "aryl" refers to unsubstituted or substituted aromatic monocyclic or polycyclic groups and includes, for example, phenyl and naphthyl. The term "aryl" also includes a phenyl ring fused to a non-aromatic carbocyclic or heterocyclic ring. The term "aryl" may be interchangeably used with "aryl ring," aromatic group," and "aromatic ring. " Heteroaryl groups have 4 to 14 atoms, 1 to 9 of which are independently selected from the group consisting of oxygen, sulfur and nitrogen. Heteroaryl groups have 1-3 heteroatoms in a 5-8 membered aromatic group. An aryl or heteroaryl can be a mono- or bicyclic aromatic group. Typical aryl and heteroaryl groups include, for example, phenyl, quinolinyl, indazolyl, indolyl, dihydrobenzodioxynyl, 3-chlorophenyl, 2,6-dibromophenyl, pyridyl, pyrimidinyl, 3-methylpyridyl, benzothienyl, 2,4,6-tribromophenyl, 4-ethylbenzothienyl, furanyl, 3,4-diethylfuranyl, naphthyl, 4,7-dichloronaphthyl, pyrrole, pyrazole, imidazole, thiazole, and the like. An aryl or heteroaryl can be unsubstituted or substituted with one or more suitable substituents.

As used herein, the term "haloalkyl" refers to any alkyl radical having one or more hydrogen atoms replaced by a halogen atom. Examples of haloalkyl include -CF₃, -CHF₂, -CH₂F, and the like.

As used herein, the term "hydroxyl" or "hydroxy" refers to -OH.

As used herein, the term "amino" refers to -NH₂.

As used herein, the term "hydroxyalkyl" refers to any hydroxyl derivative of alkyl radical. The term "hydroxyalkyl" includes any alkyl radical having one or more hydrogen atoms replaced by a hydroxy group.

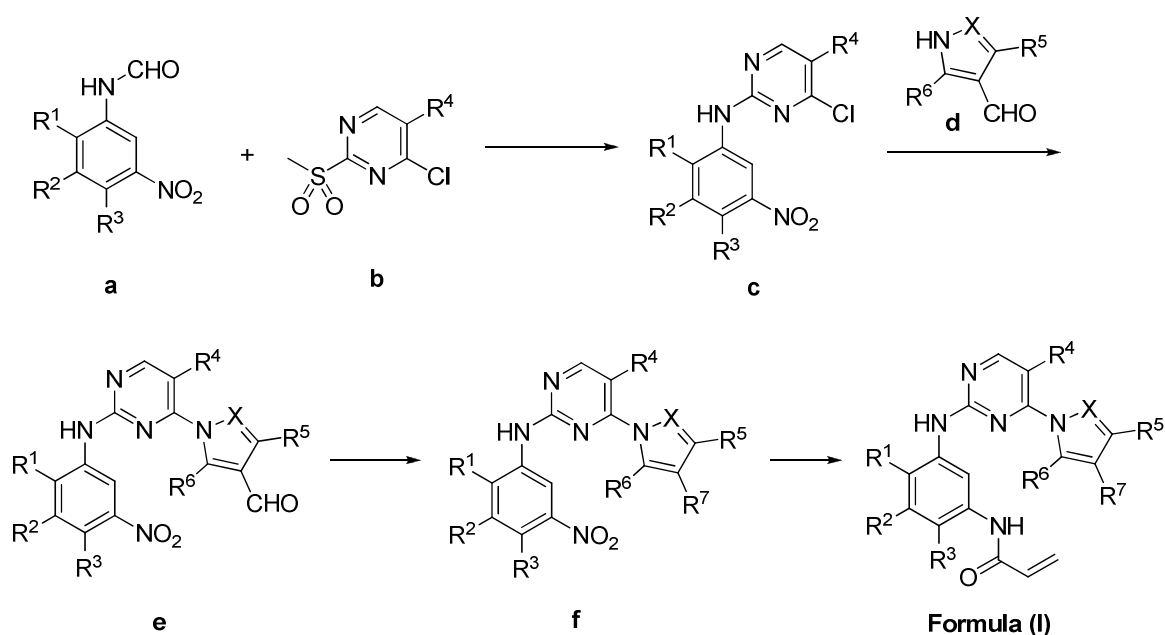
A "substituent" as used herein, refers to a molecular moiety that is covalently bonded to an atom within a molecule of interest. For example, a ring substituent may be a moiety such as a halogen, alkyl group, haloalkyl group or other group that is covalently bonded to an atom (preferably a carbon or nitrogen atom) that is a ring member. Substituents of aromatic groups are generally covalently bonded to a ring carbon atom. The term "substitution" refers to replacing a hydrogen atom in a molecular structure with a substituent, such that the valence on the designated atom is not exceeded, and such that a chemically stable compound (i.e., a compound that can be isolated, characterized, and tested for biological activity) results from the substitution.

As described above, certain groups can be unsubstituted or substituted with one or more suitable substituents other than hydrogen at one or more available positions, typically 1, 2, 3, 4 or 5 positions, by one or more suitable groups (which may be the same or different). Certain groups, when substituted, are substituted with 1, 2, 3 or 4 independently selected substituents. Suitable substituents include halogen, alkyl, haloalkyl, aryl, hydroxy, alkoxy, hydroxyalkyl, amino, and the like.

In certain aspects, the disclosure also provides (i) a method of preparing a compound of formula (c) by reacting a compound of formula (a) with a compound of formula (b) in the presence of the first base in the first organic solvent (see Scheme 1); (ii)

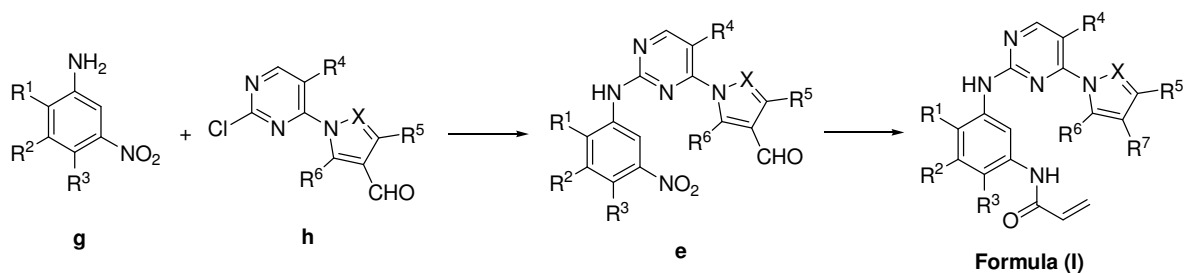
a method of preparing a compound of formula (e) by reacting the compound of formula (c) with heteroaryl intermediates (d) in the presence of the second base, in the second organic solvent (see Scheme 1); (iii) a method of preparing a compound of formula (f) by reductive amination of the compound of formula (e) and an amine derivatives by using a reducing agent in the third solvent (see Scheme 1); (iv) a method of preparing a compound of Formula (I) by reduction of the compound of formula (f) by using a reducing agent in the fourth solvent and followed by amide formation in the presence of acryloyl chloride, the third base in the fifth solvent (see Scheme 1). The disclosure also provides a method of preparing a compound of Formula (I) according to Scheme 1.

Scheme 1



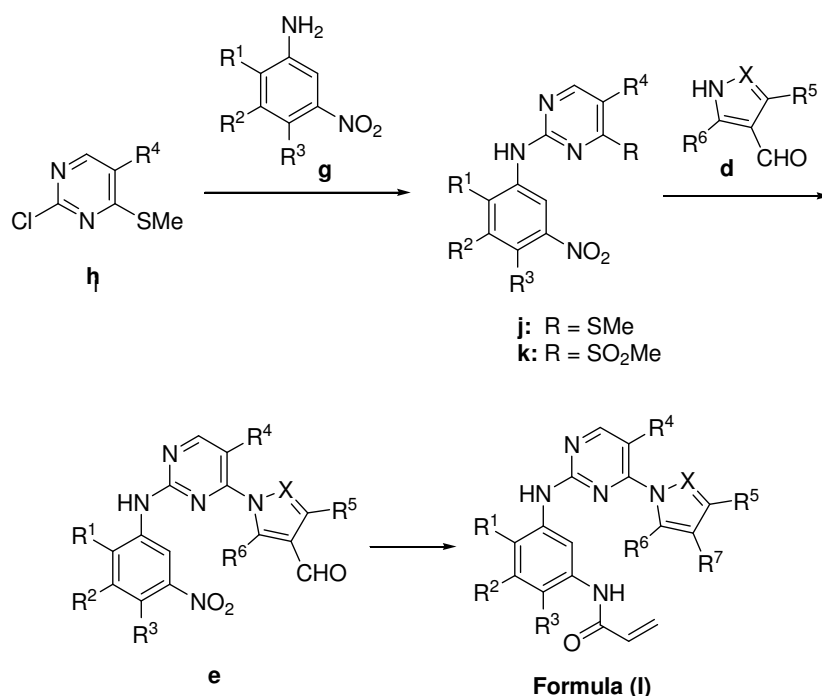
In certain aspects, the disclosure also provides a method of preparing a compound of formula (e) by reaction of the compound of formula (h) with aniline intermediates (g) in the presence of the fourth base in the first solvent, a ligand, a palladium catalyst in the first organic solvent (see Scheme 2). The disclosure also provides a method of preparing a compound of Formula (I) according to Scheme 2.

Scheme 2



In certain aspects, the disclosure also provides (i) a method of preparing a compound of formula (j) from the compound of formula (i) with aniline intermediates (g) with the procedure as described in WO2013/109882 A1; (ii) a method of preparing a compound of formula (j) from the compound of formula (j) by oxidation with mCPBA or Oxone[®] as described in WO2013/109882 A1; (iii) a method of preparing the compound of formula (e) from a compound of formula (k) by reaction with the compound of formula (d) in the presence of the second base in the second organic solvent (see Scheme 3). The disclosure also provides a method of preparing a compound of Formula (I) according to Scheme 3.

10 Scheme 3



With reference to Schemes 1-3, while appropriate reaction solvents can be selected by one of ordinary skill in the art, the first organic solvent is generally selected from relatively polar, aprotic solvents such as acetone, tetrahydrofuran, N,N- dimethylformamide, N,N-dimethylacetamide, dichloromethane, dichloroethane, or acetonitrile; the second organic solvent is generally selected from aprotic solvents such as toluene, dioxane, tetrahydrofuran, N,N-dimethylformamide, N,N-dimethylacetamide or N- methylmorpholine; the third organic solvent is generally selected from relatively polar, solvents such as tetrahydrofuran, methanol, ethanol, dichloromethane, dichloroethane, N,N-dimethylacetamide or N,N-dimethylformamide; the fourth solvent is generally selected from relatively polar, protic solvents such as methanol, ethanol, tert-butanol or

N-(5-(4-(3-((dimethylamino)methyl)-4-(furan-3-yl)-1H-pyrrol-1-yl)-5-fluoropyrimidin-2-ylamino)-4-methoxy-2-morpholinophenyl)acrylamide,
 N-(5-(4-(3-cyclopropyl-4-((dimethylamino)methyl)-1H-pyrazol-1-yl)-5-methylpyrimidin-2-ylamino)-4-methoxy-2-(methyl(oxetan-3-yl)amino)phenyl)acrylamide,
 5 N-(2-(4-acetylpiperazin-1-yl)-5-(4-(4-(azetidin-1-ylmethyl)-3-phenyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxyphenyl)acrylamide,
 N-(2-(4-acetylpiperazin-1-yl)-5-(4-(4-((dimethylamino)methyl)-3-phenyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxyphenyl)acrylamide,
 N-(5-(4-(4-((dimethylamino)methyl)-3-(pyridin-4-yl)-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-morpholinophenyl)acrylamide,
 10 N-(2-(4-acetylpiperazin-1-yl)-5-(4-(3-cyclopropyl-4-((ethyl(methyl)amino)methyl)-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxyphenyl)acrylamide,
 N-(2-(4-acetylpiperazin-1-yl)-5-(4-(4-(azetidin-1-ylmethyl)-3-cyclopropyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxyphenyl)acrylamide,
 15 N-(2-(azetidin-1-yl)-5-(4-(4-(azetidin-1-ylmethyl)-3-cyclopropyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxyphenyl)acrylamide,
 N-(5-(4-(3-cyclopropyl-4-((ethyl(methyl)amino)methyl)-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-morpholinophenyl)acrylamide,
 N-(2-(azetidin-1-yl)-5-(4-(3-(azetidin-1-ylmethyl)-4-methyl-1H-pyrrol-1-yl)-5-fluoropyrimidin-2-ylamino)-4-methoxyphenyl)acrylamide,
 20 N-(5-(4-(3-(azetidin-1-ylmethyl)-4-methyl-1H-pyrrol-1-yl)-5-fluoropyrimidin-2-ylamino)-2-(dimethylamino)-4-methoxyphenyl)acrylamide,
 N-(2-(dimethylamino)-5-(4-(3-((dimethylamino)methyl)-4-methyl-1H-pyrrol-1-yl)-5-fluoropyrimidin-2-ylamino)-4-methoxyphenyl)acrylamide,
 25 N-(2-((2-(dimethylamino)ethyl)(methyl)amino)-5-(4-(3-((dimethylamino)methyl)-4-(trifluoromethyl)-1H-pyrrol-1-yl)-5-fluoropyrimidin-2-ylamino)-4-methoxyphenyl)acrylamide,
 N-(5-(4-(4-((ethyl(methyl)amino)methyl)-3-methyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-morpholinophenyl)acrylamide,
 30 or a pharmaceutically acceptable salt thereof.

As used herein, the term “cancer” refers to an abnormal growth of cells which tend to proliferate in an uncontrolled way and, in some cases, to metastasize. The types of cancer include, but is not limited to, solid tumors, such as those of the bladder, bowel, brain, breast,
 35 endometrium, heart, kidney, lung, lymphatic tissue (lymphoma), ovary, pancreas or other endocrine organ (thyroid), prostate, skin (melanoma) or hematological tumors (such as the leukemias).

As used herein, the term “EGFR mutation” refers to mutation of T790M (resistant or oncogenic), L858R (activating), del E746-A750 (activating) or a combination thereof.

40 In certain embodiments, at one activating

mutation and at one point mutation may be selectively inhibited. In some embodiments, an at least one activating mutation is a deletion mutation, del E746-A750. In some embodiments, an at least one activating mutation is a point mutation L858R. In some embodiments, the at least one resistant mutation is a point mutation, T790M. In some embodiments, the at least one mutation of EGFR is L858R and/or T790M.

As used herein, the term “mutant selective inhibition”, as used in comparison to inhibition of wildtype (WT) EGFR, refers to the state that the techniques disclosed herein inhibit at least one mutation of EGFR (i.e. at least one deletion mutation, at least one activating mutation, at least one resistant mutation, or a combination of at least one deletion mutation and at least one point mutation) in at least one assay described herein (e.g., biochemical or cellular).

As used herein, the term “selectively inhibits”, as used in comparison to inhibition of other kinases, refers to that techniques disclosed herein poorly inhibit at least one of kinase panel.

As used herein, the term “EGFR wildtype selectivity” refers to that a selective inhibitor of at least one mutation of EGFR, as defined and described above and herein, inhibits EGFR at the upper limit of detection of at least one assay as described herein (e.g. cellular as described in detail in Table 1 and Table 2). In some embodiments, the term “EGFR wildtype selectivity” means that the techniques disclosed herein inhibit WT EGFR with an IC₅₀ of at least 200-1000nM or > 1000nM.

As used herein, the term “inhibitor” refers to a compound which inhibits one or more kinase described herein. For example, the term “EGFR mutant inhibitor” refers to a compound which inhibits the EGFR mutant receptor or reduces the signaling effect.

As used herein, the term “pharmaceutically acceptable” refers a material, such as a carrier or diluent, which does not abrogate the biological activity or properties of the compounds described herein. Such materials are administered to an individual without causing undesirable biological effects or interacting in a deleterious manner with any of the components of the composition in which it is contained.

As used herein, the term “pharmaceutically acceptable salt” refers to a formulation of a compound that does not cause significant irritation to an organism to which it is administered and does not abrogate the biological activity and properties of the compounds described herein.

As used herein, the term “pharmaceutical combination” means a product that results from the mixing or combining of more than one active ingredient.

As used herein, the term “pharmaceutical composition” refers to a mixture of a compound described herein with other chemical components, such as carriers, stabilizers, diluents, dispersing agents, suspending agents, thickening agents, and/or excipients.

As used herein, the term “prodrug” refers to an agent that is converted into the parent drug *in vivo*. Prodrugs are often useful because, in some situations, they may be easier to administer than the parent drug. Prodrugs are bio-available by oral administration whereas the parent is not. Prodrugs improve solubility in pharmaceutical compositions over the parent drug. A non-limiting example of a prodrug of the compounds described

herein is a compound described herein administered as an ester which is then metabolically hydrolyzed to a carboxylic acid, the active entity, once inside the cell. A further example of a prodrug is a short peptide bonded to an acid group where the peptide is metabolized to reveal the active moiety.

5 As used herein, the term “protein kinase-mediated disease” or a “disorder or disease or condition mediated by inappropriate protein kinase activity” refers to any disease state mediated or modulated by protein kinases described herein. Such disease states include, but are not limited to non-small cell lung cancer (NSCLC).

10 As used herein, the term “EGFR mutant-mediated disease” or a “disorder or disease or condition mediated by inappropriate EGFR activity” refers to any disease state mediated or modulated by EGFR mutant kinase mechanisms. Such disease states include, but are not limited to NSCLC, metastatic brain cancer and other solid cancers.

15 As used herein, the term “JAK3-mediated disease” or a “disorder or disease or condition mediated by inappropriate JAK3 activity” refers to any disease state mediated or modulated by JAK3 kinase mechanisms. Such disease states include, but are not limited to rheumatoid arthritis, psoriasis and organ transplant rejection and some solid cancers.

20 As used herein, the term “treat,” “treating” or “treatment” refers to methods of alleviating, abating or ameliorating a disease or condition symptoms, preventing additional symptoms, ameliorating or preventing the underlying metabolic causes of symptoms, inhibiting the disease or condition, arresting the development of the disease or condition, relieving the disease or condition, causing regression of the disease or condition, relieving a condition caused by the disease or condition, or stopping the symptoms of the disease or condition either prophylactically and/or therapeutically.

25 As used herein, the term “solvate” refers to a complex of variable stoichiometry formed by a solute (in this disclosure, a compound of Formula (I) or a pharmaceutically acceptable salt thereof) and a solvent. Such solvents for the purpose of the disclosure may not interfere with the biological activity of the solute. Non-limiting examples of suitable solvents include water, acetone, methanol, ethanol and acetic acid. Preferably the solvent used is a pharmaceutically acceptable solvent. Non-limiting examples of suitable
30 pharmaceutically acceptable solvents include water, ethanol and acetic acid.

35 As used herein, the term “subject” or “patient” encompasses mammals and non-mammals. Examples of mammals include, but are not limited to, humans, chimpanzees, apes monkeys, cattle, horses, sheep, goats, swine; rabbits, dogs, cats, rats, mice, guinea pigs, and the like. Examples of non-mammals include, but are not limited to, birds, fish and the like.

As used herein, the term “administration” or “administering” of the subject compound refers to providing a compound of the invention and/or prodrugs thereof to a subject in need of treatment.

40 As used herein, the term “carrier” refers to chemical compounds or agents that facilitate the incorporation of a compound described herein into cells or tissues.

As used herein, the term “co-administration” or “combined administration” or the like as used herein are meant to encompass administration of the selected therapeutic agents to a single patient, and are intended to include treatment regimens in which the agents are not necessarily administered by the same route of administration or at the same time.

As used herein, the term “acceptable” with respect to a formulation, composition or ingredient, as used herein, means having no persistent detrimental effect on the general health of the subject being treated.

As used herein, the term “diluent” refers to chemical compounds that are used to dilute a compound described herein prior to delivery. Diluents can also be used to stabilize compounds described herein.

As used herein, the term “effective amount” or “therapeutically effective amount” refer to a sufficient amount of a compound described herein being administered which will relieve to some extent one or more of the symptoms of the disease or condition being treated. The result can be reduction and/or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. For example, an “effective amount” for therapeutic uses is the amount of the composition comprising a compound as disclosed herein required to provide a clinically significant decrease in disease symptoms. An appropriate “effective” amount in any individual case may be determined using techniques, such as a dose escalation study. By way of example only, a therapeutically effective amount of a compound of the invention may be in the range of e.g., about 0.01 mg/kg/day to about 100 mg/kg/day, or from about 0.1 mg/kg/day to about 10 mg/kg/day.

Human Protein Kinase

Compounds of the present invention are screened against the kinase panel (wild type and/or mutation thereof) and inhibit the activity of at least one kinase on the kinase panel. Examples of kinases include, but are not limited to EGFR and JAK3 (JH1domain-catalytic) kinases, and mutant forms thereof. As such, the compounds and compositions of the invention may be useful for treating diseases or disorders in which such kinases contribute to the pathology and/or symptomology of a disease or disorder associated with or mediated by such kinase.

Many diseases are associated with abnormal cellular responses triggered by protein kinase mediated events. These diseases include, but are not limited to, autoimmune diseases, inflammatory diseases, bone diseases, metabolic diseases, neurological and neurodegenerative diseases, cancer, cardiovascular diseases, respiratory diseases, allergies and asthma, Alzheimer’s disease, and hormone related diseases.

Phosphorylation regulates a variety of cellular processes such as proliferation, growth, differentiation, metabolism, apoptosis, motility, transcription, translation and other signaling processes. Aberrant or excessive PTK activity has been observed in many

Furthermore, the compounds, compositions and methods of the present disclosure provide methods of regulating, and in particular inhibiting, signal transduction cascades in which EGFR mutant(s) plays a role. The method generally involves contacting a EGFR mutant-dependent receptor or a cell expressing a EGFR mutant -dependent receptor with an amount of a compound described herein, or prodrug a compound described herein, or an acceptable salt, hydrate, solvate, N-oxide and/or composition thereof, effective to regulate or inhibit the signal transduction cascade. The methods are used to regulate, and in particular inhibit, downstream processes or cellular responses elicited by activation of the particular EGFR mutant-dependent signal transduction cascade. The methods are practiced to regulate any signal transduction cascade where EGFR mutant is not known or later discovered to play a role. The methods are practiced in *in vitro* contexts or in *in vivo* contexts as a therapeutic approach towards the treatment or prevention of diseases characterized by, caused by or associated with activation of the EGFR mutant-dependent signal transduction cascade.

Janus kinase 3 (JAK3)

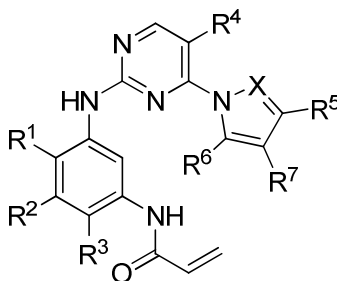
Janus kinase 3 (JAK3) is a tyrosine kinase that belongs to the Janus family of kinases. Other members of the Janus family include JAK1, JAK2 and TYK2. They are cytosolic tyrosine kinases that are specifically associated with cytokine receptors. Since cytokine receptor proteins lack enzymatic activity, they are dependent upon JAKs to initiate signaling upon binding of their ligands (e.g. cytokines). The cytokine receptors can be divided into five major subgroups based on their different domains and activation motifs. JAK3 is required for signaling of the type I receptors that use the common gamma chain (γ_c).

In contrast to the relatively ubiquitous expression of JAK1, JAK2 and Tyk2, JAK3 is predominantly expressed in hematopoietic lineage such as NK cells, T cells and B cells and intestinal epithelial cells. JAK3 functions in signal transduction and interacts with members of the STAT (signal transduction and activators of transcription) family. JAK3 is involved in signal transduction by receptors that employ the common gamma chain (γ_c) of the type I cytokine receptor family (e.g. IL-2R, IL-4R, IL-7R, IL-9R, IL-15R, and IL-21R). Mutations of JAK3 result in severe combined immunodeficiency (SCID). Mice that do not express JAK3 have T-cells and B-cells that fail to respond to many cytokines.

Since JAK3 is required for immune cell development, targeting JAK3 could be a useful strategy to generate a novel class of immunosuppressant drugs. Moreover, unlike other JAKs, JAK3 is primarily expressed in hematopoietic cells, so a highly specific JAK3 inhibitor should have precise effects on immune cells and minimal pleiotropic defects. The selectivity of a JAK3 inhibitor would also have advantages over the current widely used immunosuppressant drugs, which have abundant targets and diverse side effects. A JAK3 inhibitor could be useful for treating autoimmune diseases, especially those in which a particular cytokine receptor has a direct role on disease pathogenesis. For example,

WHAT IS CLAIMED IS:

1. A compound of Formula (I):



I

wherein:

X is CH or N;

R¹ is H, R⁸ or -OR⁸;

R² is hydrogen, C₁₋₆ alkyl, 6-10 membered monocyclic or bicyclic aryl, or 5-10 membered heteroaryl comprising 1-4 heteroatoms selected from N, O and S, wherein the heteroaryl or aryl is optionally and independently substituted at one or more carbon atoms with R¹³; and wherein the heteroaryl having one or more nitrogen atoms is optionally and independently substituted at one or more nitrogen atoms with R⁸;

R³ is hydrogen, 4-7 membered monocyclic heterocyclyl comprising 1-2 heteroatoms selected from N, O and S, and optionally substituted with oxo, 5-6 membered heteroaryl comprising 1-3 heteroatoms selected from N, O and S, NR⁹R¹⁰, NR¹¹R¹², or phenyl, wherein the heteroaryl or phenyl is optionally and independently substituted at one or more carbon atoms with R¹³; and wherein the heterocyclyl or heteroaryl having one or more nitrogen atoms is optionally and independently substituted at one or more nitrogen atoms with R⁸;

R⁴ is hydrogen, C₁₋₄ alkyl, C₃₋₅ cycloalkyl, F, Cl, Br, CN, or CF₃;

R⁵ is hydrogen, CF₃, C₁₋₆ alkyl, C₃₋₇ cycloalkyl, 5-6 membered heteroaryl comprising 1-3 heteroatoms selected from N, O and S, or 6-10 membered monocyclic or bicyclic aryl, wherein the heteroaryl or aryl is optionally and independently substituted at one or more carbon atoms with R¹³;

R⁶ is hydrogen or C₁₋₆ alkyl;

R⁷ is hydrogen, -CH₂OH, -CH₂OR⁸, C₁₋₃ alkyl, (CH₂)_nNR⁹R¹⁰, (CH₂)_nNR¹¹R¹², C(O)NR⁹R¹⁰, or C(O)NR¹¹R¹², wherein each n is independently 1 or 2;

R⁸ is selected from C₁₋₆ alkyl or C₃₋₇ cycloalkyl;

R⁹ is selected from C₁₋₆ alkyl, C₃₋₇ cycloalkyl or 4-7 membered heterocyclyl comprising 1-2 heteroatoms selected from N, O and S, wherein the C₁₋₆ alkyl or C₃₋₇ cycloalkyl is optionally substituted with halogen or -OR⁸, and wherein the 4-7 membered heterocyclyl having one nitrogen atom is optionally and independently substituted with -R⁸, -C(O)R⁸, -C(O)OR⁸, or C(O)NHR⁸;

R¹⁰ is C₁₋₆ alkyl, C₃₋₇ cycloalkyl, or (CH₂)_nNR⁹R⁹, wherein each n is independently 1 or

2;

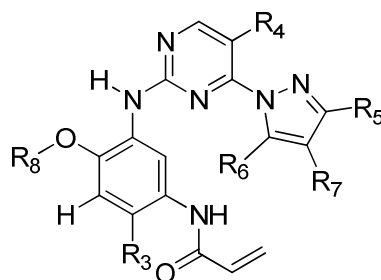
R^{11} and R^{12} , taken together with nitrogen atom to which they are bonded form, independently for each occurrence,

i) a 3-8 membered saturated or partially saturated monocyclic group having no heteroatom other than the nitrogen atom to which R^{11} and R^{12} are bonded, wherein said 3-8 membered saturated or partially saturated monocyclic group is optionally and independently substituted at one or more carbons with halogen, hydroxyl, $-OR^8$, $-NR^9R^{10}$, or $-NR^{11}R^{12}$; or

ii) a 5-8 membered saturated or partially saturated monocyclic group having 1 or 2 heteroatoms, in addition to the nitrogen atom to which R^{11} and R^{12} are bonded, wherein said heteroatoms are independently selected from nitrogen, oxygen, sulfur, sulfone or sulfoxide, wherein said 5-8 membered saturated or partially saturated monocyclic group having 1 or 2 nitrogen atoms is optionally substituted at one or more carbon or nitrogen atoms with $-R^8$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NHR^8$, $-SO_2R^8$, $-SO_2NH_2$, or $-SO_2NR^8_2$; and

R^{13} is selected from halogen, CN, CF_3 , R^8 , $-OR^8$ or C_{2-4} alkenyl, or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1 or pharmaceutically acceptable salt thereof, wherein said compound is represented by Formula (II):



II

wherein:

R^3 is hydrogen, 4-7 membered monocyclic heterocyclyl comprising 1-2 heteroatoms selected from N, O and S, and optionally substituted with oxo, 5-6 membered heteroaryl comprising 1-3 heteroatoms selected from N, O and S, NR^9R^{10} , $NR^{11}R^{12}$, or phenyl, wherein the heteroaryl or phenyl is optionally and independently substituted at one or more carbon atoms with R^{13} ; and wherein the heterocyclyl or heteroaryl having one or more nitrogen atoms is optionally and independently substituted at one or more nitrogen atoms with R^8 ;

R^4 is hydrogen, C_{1-4} alkyl, C_{3-5} cycloalkyl, F, Cl, Br, CN, or CF_3 ;

R^5 is hydrogen, CF_3 , C_{1-6} alkyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl comprising 1-3 heteroatoms selected from N, O and S, or 6-10 membered monocyclic or bicyclic aryl, wherein the heteroaryl or aryl is optionally and independently substituted at one or more carbon atoms with R^{13} ;

R^6 is hydrogen or C_{1-6} alkyl;

R^7 is hydrogen, $-CH_2OH$, $-CH_2OR^8$, C_{1-3} alkyl, $(CH_2)_nNR^9R^{10}$, $(CH_2)_nNR^{11}R^{12}$, $C(O)NR^9R^{10}$, or $C(O)NR^{11}R^{12}$, wherein each n is independently 1 or 2;

R⁸ is selected from C₁₋₆ alkyl or C₃₋₇ cycloalkyl;

R⁹ is selected from C₁₋₆ alkyl, C₃₋₇ cycloalkyl or 4-7 membered heterocyclyl comprising 1-2 heteroatoms selected from N, O and S, wherein C₁₋₆ alkyl or C₃₋₇ cycloalkyl is optionally substituted with halogen or -OR⁸, wherein the 4-7 membered heterocyclyl having one nitrogen atom is optionally and independently substituted with -R⁸, -C(O)R⁸, -C(O)OR⁸, or C(O)NHR⁸;

R¹⁰ is C₁₋₆ alkyl, C₃₋₇ cycloalkyl, or (CH₂)_nNR⁹R⁹, wherein each n is independently 1 or 2;

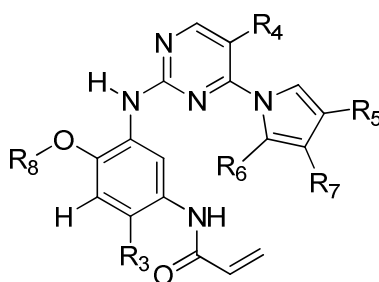
R¹¹ and R¹², taken together with nitrogen atom to which they are bonded form, independently for each occurrence,

i) a 3-8 membered saturated or partially saturated monocyclic group having no heteroatom other than the nitrogen atom to which R¹¹ and R¹² are bonded, wherein said 3-8 membered saturated or partially saturated monocyclic group is optionally and independently substituted at one or more carbons with halogen, hydroxyl, -OR⁸, -NR⁹R¹⁰, or -NR¹¹R¹²; or

ii) a 5-8 membered saturated or partially saturated monocyclic group having 1 or 2 heteroatoms, in addition to the nitrogen atom to which R¹¹ and R¹² are bonded, wherein said heteroatoms are independently selected from nitrogen, oxygen, sulfur, sulfone or sulfoxide, wherein said 5-8 membered saturated or partially saturated monocyclic group having 1 or 2 nitrogen atoms is optionally substituted at one or more carbon or nitrogen atoms with -R⁸, -C(O)R⁸, -C(O)OR⁸, -C(O)NHR⁸, -SO₂R⁸, -SO₂NH₂, or -SO₂NR⁸₂; and

R¹³ is selected from halogen, CN, CF₃, R⁸, -OR⁸ or C₂₋₄ alkenyl.

3. The compound of claim 1, or pharmaceutically acceptable salt thereof, wherein said compound is represented by Formula (III):



III

wherein:

R³ is hydrogen, 4-7 membered monocyclic heterocyclyl comprising 1-2 heteroatoms selected from N, O and S, and optionally substituted with oxo, 5-6 membered heteroaryl comprising 1-3 heteroatoms selected from N, O and S, NR⁹R¹⁰, NR¹¹R¹², or phenyl, wherein the heteroaryl or phenyl is optionally and independently substituted at one or more carbon atoms with R¹³; and wherein the heterocyclyl or heteroaryl having one or more nitrogen atoms is optionally and independently substituted at one or more nitrogen atoms with R⁸;

R⁴ is hydrogen, C₁₋₄ alkyl, C₃₋₅ cycloalkyl, F, Cl, Br, CN, or CF₃;

R⁵ is hydrogen, CF₃, C₁₋₆ alkyl, C₃₋₇ cycloalkyl, 5-6 membered heteroaryl comprising

1-3 heteroatoms selected from N, O and S, or 6-10 membered monocyclic or bicyclic aryl, wherein the heteroaryl or aryl is optionally and independently substituted at one or more carbon atoms with R¹³;

R⁶ is hydrogen or C₁₋₆ alkyl;

R⁷ is hydrogen, -CH₂OH, -CH₂OR⁸, C₁₋₃ alkyl, (CH₂)_nNR⁹R¹⁰, (CH₂)_nNR¹¹R¹², C(O)NR⁹R¹⁰, or C(O)NR¹¹R¹², wherein each n is independently 1 or 2;

R⁸ is selected from C₁₋₆ alkyl or C₃₋₇ cycloalkyl;

R⁹ is selected from C₁₋₆ alkyl, C₃₋₇ cycloalkyl or 4-7 membered heterocyclyl comprising 1-2 heteroatoms selected from N, O and S, wherein C₁₋₆ alkyl or C₃₋₇ cycloalkyl is optionally substituted with halogen or -OR⁸, wherein the 4-7 membered heterocyclyl having one nitrogen atom is optionally and independently substituted with -R⁸, -C(O)R⁸, -C(O)OR⁸, or C(O)NHR⁸;

R¹⁰ is C₁₋₆ alkyl, C₃₋₇ cycloalkyl, or (CH₂)_nNR⁹R⁹, wherein each n is independently 1 or 2;

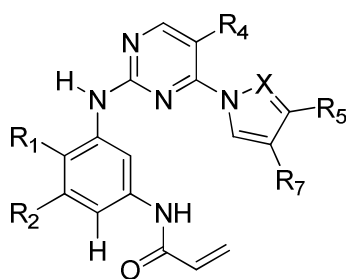
R¹¹ and R¹², taken together with nitrogen atom to which they are bonded form, independently for each occurrence,

i) a 3-8 membered saturated or partially saturated monocyclic group having no heteroatom other than the nitrogen atom to which R¹¹ and R¹² are bonded, wherein said 3-8 membered saturated or partially saturated monocyclic group is optionally and independently substituted at one or more carbons with halogen, hydroxyl, -OR⁸, -NR⁹R¹⁰, or -NR¹¹R¹²; or

ii) a 5-8 membered saturated or partially saturated monocyclic group having 1 or 2 heteroatoms, in addition to the nitrogen atom to which R¹¹ and R¹² are bonded, wherein said heteroatoms are independently selected from nitrogen, oxygen, sulfur, sulfone or sulfoxide, wherein said 5-8 membered saturated or partially saturated monocyclic group having 1 or 2 nitrogen atoms is optionally substituted at one or more carbon or nitrogen atoms with -R⁸, -C(O)R⁸, -C(O)OR⁸, -C(O)NHR⁸, -SO₂R⁸, -SO₂NH₂, or -SO₂NR⁸₂; and

R¹³ is selected from halogen, CN, CF₃, R⁸, -OR⁸ or C₂₋₄ alkenyl.

4. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein said compound is represented by Formula (IV):



IV

wherein:

X is CH or N;

R¹ is H, R⁸ or -OR⁸;

R² is hydrogen, C₁₋₆ alkyl, 6-10 membered monocyclic or bicyclic aryl, or 5-10 membered heteroaryl comprising 1-4 heteroatoms selected from N, O and S, wherein the heteroaryl or aryl is optionally and independently substituted at one or more carbon atoms with R¹³; and wherein the heteroaryl having one or more nitrogen atoms is optionally and independently substituted at one or more nitrogen atoms with R⁸;

R⁴ is hydrogen, C₁₋₄ alkyl, C₃₋₅ cycloalkyl, F, Cl, Br, CN, or CF₃;

R⁵ is hydrogen, CF₃, C₁₋₆ alkyl, C₃₋₇ cycloalkyl, 5-6 membered heteroaryl comprising 1-3 heteroatoms selected from N, O and S, or 6-10 membered monocyclic or bicyclic aryl, wherein the heteroaryl or aryl is optionally and independently substituted at one or more carbon atoms with R¹³;

R⁷ is hydrogen, -CH₂OH, -CH₂OR⁸, C₁₋₃ alkyl, (CH₂)_nNR⁹R¹⁰, (CH₂)_nNR¹¹R¹², C(O)NR⁹R¹⁰, or C(O)NR¹¹R¹², wherein each n is independently 1 or 2;

R⁸ is selected from C₁₋₆ alkyl or C₃₋₇ cycloalkyl;

R⁹ is selected from C₁₋₆ alkyl, C₃₋₇ cycloalkyl or 4-7 membered heterocyclyl comprising 1-2 heteroatoms selected from N, O and S, wherein C₁₋₆ alkyl or C₃₋₇ cycloalkyl is optionally substituted with halogen or -OR⁸, wherein the 4-7 membered heterocyclyl having one nitrogen atom is optionally and independently substituted with -R⁸, -C(O)R⁸, -C(O)OR⁸, or C(O)NHR⁸;

R¹⁰ is C₁₋₆ alkyl, C₃₋₇ cycloalkyl, or (CH₂)_nNR⁹R⁹, wherein each n is independently 1 or 2;

R¹¹ and R¹², taken together with nitrogen atom to which they are bonded form, independently for each occurrence,

i) a 3-8 membered saturated or partially saturated monocyclic group having no heteroatom other than the nitrogen atom to which R¹¹ and R¹² are bonded, wherein said 3-8 membered saturated or partially saturated monocyclic group is optionally and independently substituted at one or more carbons with halogen, hydroxyl, -OR⁸, -NR⁹R¹⁰, or -NR¹¹R¹²; or

ii) a 5-8 membered saturated or partially saturated monocyclic group having 1 or 2 heteroatoms, in addition to the nitrogen atom to which R¹¹ and R¹² are bonded, wherein said heteroatoms are independently selected from nitrogen, oxygen, sulfur, sulfone or sulfoxide, wherein said 5-8 membered saturated or partially saturated monocyclic group having 1 or 2 nitrogen atoms is optionally substituted at one or more carbon or nitrogen atoms with -R⁸, -C(O)R⁸, -C(O)OR⁸, -C(O)NHR⁸, -SO₂R⁸, -SO₂NH₂, or -SO₂NR⁸₂; and

R¹³ is selected from halogen, CN, CF₃, R⁸, -OR⁸ or C₂₋₄ alkenyl.

5. The compound of claim 1, wherein R¹ is -OCH₃; R⁴ is H, -CH₃, F, or Cl; R⁵ is hydrogen, C₁₋₆ alkyl, C₃₋₇ cycloalkyl, pyridinyl, thiophenyl, furanyl, N-methyl pyrrolidinyl, N-methyl pyrazolyl, or phenyl; R⁸ is methyl; and n is 1.

6. The compound of claim 4, wherein R¹ is H; R² is furanyl, thiophenyl, N-methyl pyrazolyl, or phenyl; R⁴ is H, -CH₃, F, or Cl; R⁵ is hydrogen, C₁₋₆ alkyl, C₃₋₇ cycloalkyl, pyridinyl, thiophenyl, furanyl, N-methyl pyrrolyl, N-methyl pyrazolyl, or phenyl; and n is 1.

7. The compound of claim 5, wherein R^2 is H; R^6 is H; R^3 is morpholino, N-methyl piperazinyl, piperidinyl, azetidiny, pyrroldinyl, 4-acetyl piperidinyl, N,N-dimethylamino, 1,4-oxazepan-4-yl, or 4-methyl-1,4,-diazepan-1-yl; and R^7 is $-(CH_2)NR^9R^{10}$ or $-(CH_2)NR^{11}R^{12}$.

8. The compound of claim 6, wherein R^7 is $-(CH_2)NR^9R^{10}$ or $-(CH_2)NR^{11}R^{12}$.

9. The compound of claim 7, wherein R^9 is methyl, ethyl, propyl, cyclopropylmethyl, or cyclobutylmethyl; and R^{10} is methyl, ethyl, propyl, cyclopropylmethyl, oxetanyl, oxethanemethyl, N-methyazetidiny, N,N-dimethylethyl, or methoxyethyl; and $NR^{11}R^{12}$ is azetidiny, 3-hydroxy azetidiny, 3-methoxy azetidiny, pyrrolidinyl, (S)-3-hydroxy pyrrolidinyl, (R)-3-hydroxy pyrrolidinyl, (3R,4S)-3,4-dihydroxypyrrolidinyl, (3S,4R)-3-hydroxy-4-methoxypyrrolidinyl, piperidinyl, morpholinyl, N-methylpiperazinyl, azamorpholinyl, N-methylazapiperazinyl, N-acetyl piperazinyl, or thiomorpholinyl.

10. The compound of claim 8, wherein R^9 is methyl, ethyl, propyl, cyclopropylmethyl, or cyclobutylmethyl; and R^{10} is methyl, ethyl, propyl, cyclopropylmethyl, oxetanyl, oxethanemethyl, N-methyazetidiny, N,N-dimethylethyl, or methoxyethyl; and $NR^{11}R^{12}$ is azetidiny, 3-hydroxy azetidiny, 3-methoxy azetidiny, pyrrolidinyl, (S)-3-hydroxy pyrrolidinyl, (R)-3-hydroxy pyrrolidinyl, (3R,4S)-3,4-dihydroxypyrrolidinyl, (3S,4R)-3-hydroxy-4-methoxypyrrolidinyl, piperidinyl, morpholinyl, N-methylpiperazinyl, azamorpholinyl, N-methylazapiperazinyl, N-acetyl piperazinyl, or thiomorpholinyl.

11. The compound of claim 5, wherein R^5 is hydrogen, methyl, isopropyl, t-butyl, cyclopropyl, 2-thiophenyl, 2-furanyl, 3-furanyl, 3-pyridyl, 4-pyridyl or phenyl.

12. The compound of claim 6, wherein R^5 is hydrogen, methyl, isopropyl, t-butyl, cyclopropyl, 2-thiophenyl, 2-furanyl, 3-furanyl, 3-pyridyl, 4-pyridyl or phenyl.

13. The compound of claim 1, selected from:

N-(3-(4-(4-(azetidin-1-ylmethyl)-3-methyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxyphenyl)acrylamide,

N-(3-(4-(4-((3-hydroxyazetidin-1-yl)methyl)-3-methyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxyphenyl)acrylamide,

N-(3-(4-(4-(azetidin-1-ylmethyl)-3-methyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)phenyl)acrylamide,

N-(3-(4-(4-((3-hydroxyazetidin-1-yl)methyl)-3-methyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)phenyl)acrylamide,

N-(3-(4-(4-((3-hydroxyazetidin-1-yl)methyl)-3-methyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-5-methylphenyl)acrylamide,

N-(5-(4-(4-((dimethylamino)methyl)-3-(4-fluorophenyl)-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-morpholinophenyl)acrylamide,

N-(5-(4-(3-tert-butyl-4-((dimethylamino)methyl)-1H-pyrazol-1-yl)-5-methylpyrimidin-2-ylamino)-4-methoxy-2-morpholinophenyl)acrylamide,
 N-(3-(4-(4-((3-hydroxyazetidin-1-yl)methyl)-3-methyl-1H-pyrazol-1-yl)-5-methylpyrimidin-2-ylamino)-4-methoxyphenyl)acrylamide,
 N-(4-methoxy-3-(4-(3-methyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)phenyl)acrylamide,
 N-(3-(4-(4-((3-hydroxyazetidin-1-yl)methyl)-3-methyl-1H-pyrazol-1-yl)-5-methylpyrimidin-2-ylamino)-5-methylphenyl)acrylamide,
 N-(3-(4-(4-((3-hydroxyazetidin-1-yl)methyl)-1H-pyrazol-1-yl)-5-methylpyrimidin-2-ylamino)-4-methoxyphenyl)acrylamide,
 N-(5-(4-(4-(azetidin-1-ylmethyl)-3-methyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-2-morpholinophenyl)acrylamide,
 N-(2-(4-acetylpiperazin-1-yl)-5-(4-(4-(azetidin-1-ylmethyl)-3-methyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)phenyl)acrylamide,
 N-(5-(4-(4-(azetidin-1-ylmethyl)-3-methyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-morpholinophenyl)acrylamide,
 N-(5-(4-(4-((3-hydroxyazetidin-1-yl)methyl)-3-methyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-morpholinophenyl)acrylamide,
 N-(5-(4-(4-(azetidin-1-ylmethyl)-3-methyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-2-((2-(dimethylamino)ethyl)(methyl)amino)-4-methoxyphenyl)acrylamide,
 N-(5-(4-(4-(azetidin-1-ylmethyl)-3-methyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-(4-methylpiperazin-1-yl)phenyl)acrylamide,
 N-(5-(4-(4-(azetidin-1-ylmethyl)-3-methyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-(piperidin-1-yl)phenyl)acrylamide,
 N-(5-(4-(4-((3-hydroxyazetidin-1-yl)methyl)-1H-pyrazol-1-yl)-5-methylpyrimidin-2-ylamino)-4-methoxy-2-morpholinophenyl)acrylamide,
 N-(5-(4-(4-(((3R,4S)-3,4-dihydroxypyrrolidin-1-yl)methyl)-1H-pyrazol-1-yl)-5-methylpyrimidin-2-ylamino)-4-methoxy-2-morpholinophenyl)acrylamide,
 N-(5-(4-(4-(((3S,4R)-3-hydroxy-4-methoxypyrrolidin-1-yl)methyl)-1H-pyrazol-1-yl)-5-methylpyrimidin-2-ylamino)-4-methoxy-2-morpholinophenyl)acrylamide,
 N-(5-(4-(4-((dimethylamino)methyl)-1H-pyrazol-1-yl)-5-methylpyrimidin-2-ylamino)-4-methoxy-2-morpholinophenyl)acrylamide,
 N-(4-methoxy-5-(5-methyl-4-(4-((methyl(1-methylazetidin-3-yl)amino)methyl)-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-2-morpholinophenyl)acrylamide,
 N-(5-(4-(4-((3-hydroxyazetidin-1-yl)methyl)-3-methyl-1H-pyrazol-1-yl)-5-methylpyrimidin-2-ylamino)-4-methoxy-2-morpholinophenyl)acrylamide,
 N-(5-(4-(4-(((3R,4S)-3,4-dihydroxypyrrolidin-1-yl)methyl)-3-methyl-1H-pyrazol-1-yl)-5-methylpyrimidin-2-ylamino)-4-methoxy-2-morpholinophenyl)acrylamide,
 N-(5-(4-(4-(((3S,4R)-3-hydroxy-4-methoxypyrrolidin-1-yl)methyl)-3-methyl-1H-pyrazol-1-yl)-5-methylpyrimidin-2-ylamino)-4-methoxy-2-morpholinophenyl)acrylamide,
 (R)-N-(5-(4-(4-((3-hydroxypyrrolidin-1-yl)methyl)-3-methyl-1H-pyrazol-1-yl)-5-

methylpyrimidin-2-ylamino)-4-methoxy-2-morpholinophenyl)acrylamide,
 (S)-N-(5-(4-(4-((3-hydroxypyrrolidin-1-yl)methyl)-3-methyl-1H-pyrazol-1-yl)-5-methylpyrimidin-2-ylamino)-4-methoxy-2-morpholinophenyl)acrylamide,
 N-(5-(4-(4-((3-hydroxyazetidin-1-yl)methyl)-3-methyl-1H-pyrazol-1-yl)-5-methylpyrimidin-2-ylamino)-4-methoxy-2-(4-methylpiperazin-1-yl)phenyl)acrylamide,
 N-(5-(4-(4-((3-hydroxyazetidin-1-yl)methyl)-3-methyl-1H-pyrazol-1-yl)-5-methylpyrimidin-2-ylamino)-4-methoxy-2-(piperidin-1-yl)phenyl)acrylamide,
 N-(2-((2-(dimethylamino)ethyl)(methyl)amino)-5-(4-(4-((3-hydroxyazetidin-1-yl)methyl)-3-methyl-1H-pyrazol-1-yl)-5-methylpyrimidin-2-ylamino)-4-methoxyphenyl)acrylamide,
 N-(5-(4-(4-(azetidin-1-yl)methyl)-1H-pyrazol-1-yl)-5-methylpyrimidin-2-ylamino)-4-methoxy-2-morpholinophenyl)acrylamide,
 N-(4-methoxy-5-(5-methyl-4-(4-(morpholinomethyl)-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-2-(4-methylpiperazin-1-yl)phenyl)acrylamide,
 N-(5-(4-(4-(azetidin-1-yl)methyl)-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-morpholinophenyl)acrylamide,
 (S)-N-(5-(4-(4-((3-(dimethylamino)pyrrolidin-1-yl)methyl)-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-morpholinophenyl)acrylamide,
 N-(5-(4-(4-(azetidin-1-yl)methyl)-1H-pyrazol-1-yl)-5-methylpyrimidin-2-ylamino)-4-methoxy-2-(4-methylpiperazin-1-yl)phenyl)acrylamide,
 N-(2-(4-acetyl-piperazin-1-yl)-5-(4-(4-(azetidin-1-yl)methyl)-1H-pyrazol-1-yl)-5-methylpyrimidin-2-ylamino)-4-methoxyphenyl)acrylamide,
 N-(5-(4-(4-(azetidin-1-yl)methyl)-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-2-(dimethylamino)-4-methoxyphenyl)acrylamide,
 (R)-N-(5-(4-(4-((3-(dimethylamino)pyrrolidin-1-yl)methyl)-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-morpholinophenyl)acrylamide,
 N-(5-(4-(4-(azetidin-1-yl)methyl)-1H-pyrazol-1-yl)-5-methylpyrimidin-2-ylamino)-4-methoxy-2-(1,4-oxazepan-4-yl)phenyl)acrylamide,
 N-(5-(4-(4-(azetidin-1-yl)methyl)-1H-pyrazol-1-yl)-5-methylpyrimidin-2-ylamino)-4-methoxy-2-(4-methyl-1,4-diazepan-1-yl)phenyl)acrylamide,
 N-(5-(4-(4-(azetidin-1-yl)methyl)-1H-pyrazol-1-yl)-5-methylpyrimidin-2-ylamino)-2-((2-(dimethylamino)ethyl)(methyl)amino)-4-methoxyphenyl)acrylamide,
 N-(2-((2-(dimethylamino)ethyl)(methyl)amino)-5-(4-(4-(((3S,4R)-3-hydroxy-4-methoxypyrrolidin-1-yl)methyl)-1H-pyrazol-1-yl)-5-methylpyrimidin-2-ylamino)-4-methoxyphenyl)acrylamide,
 N-(4-methoxy-5-(4-(4-((3-methoxyazetidin-1-yl)methyl)-3-methyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-2-morpholinophenyl)acrylamide,
 N-(5-(4-(4-(((3S,4R)-3-hydroxy-4-methoxypyrrolidin-1-yl)methyl)-3-methyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-morpholinophenyl)acrylamide,
 N-(5-(4-(4-((dimethylamino)methyl)-3-methyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-morpholinophenyl)acrylamide,

N-(5-(4-(4-((dimethylamino)methyl)-3-methyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-(4-methylpiperazin-1-yl)phenyl)acrylamide,
 N-(5-(4-(3-((3-hydroxyazetidin-1-yl)methyl)-4-methyl-1H-pyrrol-1-yl)-5-methylpyrimidin-2-ylamino)-4-methoxy-2-morpholinophenyl)acrylamide,
 N-(5-(5-chloro-4-(4-((3-hydroxyazetidin-1-yl)methyl)-3-methyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-morpholinophenyl)acrylamide,
 N-(5-(4-(4-(azetidin-1-yl)methyl)-3-methyl-1H-pyrazol-1-yl)-5-chloropyrimidin-2-ylamino)-4-methoxy-2-morpholinophenyl)acrylamide,
 N-(5-(5-chloro-4-(4-(((3S,4R)-3-hydroxy-4-methoxypyrrolidin-1-yl)methyl)-3-methyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-morpholinophenyl)acrylamide,
 N-(5-(5-chloro-4-(4-((dimethylamino)methyl)-3-methyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-morpholinophenyl)acrylamide,
 N-(5-(4-(4-(azetidin-1-yl)methyl)-3-methyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-(1H-pyrazol-1-yl)phenyl)acrylamide,
 N-(5-(5-chloro-4-(4-(((3R,4S)-3,4-dihydroxypyrrolidin-1-yl)methyl)-3-methyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-(4-methylpiperazin-1-yl)phenyl)acrylamide,
 N-(5-(4-(4-(azetidin-1-yl)methyl)-3-cyclopropyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-morpholinophenyl)acrylamide,
 N-(5-(4-(3-cyclopropyl-4-(((3S,4R)-3-hydroxy-4-methoxypyrrolidin-1-yl)methyl)-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-morpholinophenyl)acrylamide,
 N-(3-(4-(4-((3-hydroxyazetidin-1-yl)methyl)-3-methyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)acrylamide,
 N-(5-(4-(4-((3-hydroxyazetidin-1-yl)methyl)-3-methyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-(1-methyl-1H-pyrazol-4-yl)phenyl)acrylamide,
 N-(5-(4-(4-(azetidin-1-yl)methyl)-3-methyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)phenyl)acrylamide,
 N-(5-(4-(3-(azetidin-1-yl)methyl)-4-methyl-1H-pyrrol-1-yl)-5-fluoropyrimidin-2-ylamino)-4-methoxy-2-morpholinophenyl)acrylamide,
 N-(5-(5-fluoro-4-(4-(((3S,4R)-3-hydroxy-4-methoxypyrrolidin-1-yl)methyl)-3-methyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-morpholinophenyl)acrylamide,
 N-(5-(4-(4-(azetidin-1-yl)methyl)-3-methyl-1H-pyrazol-1-yl)-5-fluoropyrimidin-2-ylamino)-4-methoxy-2-morpholinophenyl)acrylamide,
 N-(5-(4-(4-(azetidin-1-yl)methyl)-1H-pyrazol-1-yl)-5-methylpyrimidin-2-ylamino)-4-isopropoxy-2-morpholinophenyl)acrylamide,
 N-(5-(4-(4-(azetidin-1-yl)methyl)-1H-pyrazol-1-yl)-5-methylpyrimidin-2-ylamino)-4-methoxy-2-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)phenyl)acrylamide,
 N-(4-(4-(4-(azetidin-1-yl)methyl)-3-methyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-5-methoxybiphenyl-2-yl)acrylamide,
 N-(5-(4-(4-(hydroxymethyl)-3-methyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-morpholinophenyl)acrylamide,
 N-(5-(4-(4-(azetidin-1-yl)methyl)-3-tert-butyl-1H-pyrazol-1-yl)-5-methylpyrimidin-2-

ylamino)-4-methoxy-2-morpholinophenyl)acrylamide,
N-(4-(4-(4-(azetidin-1-ylmethyl)-3-methyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-2',5-dimethoxybiphenyl-2-yl)acrylamide,
N-(5-(4-(4-(azetidin-1-ylmethyl)-3-methyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-2-(4,4-difluoropiperidin-1-yl)-4-methoxyphenyl)acrylamide,
N-(5-(4-(4-(azetidin-1-ylmethyl)-3,5-dimethyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-morpholinophenyl)acrylamide,
N-(2-(dimethylamino)-5-(4-(4-((dimethylamino)methyl)-3-methyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxyphenyl)acrylamide,
N-(5-(4-(4-((3-fluoroazetidin-1-yl)methyl)-3-methyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-morpholinophenyl)acrylamide,
N-(5-(4-(4-((dimethylamino)methyl)-3-phenyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-morpholinophenyl)acrylamide,
N-(5-(4-(3-cyclopropyl-4-((dimethylamino)methyl)-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-morpholinophenyl)acrylamide,
N-(5-(4-(4-((dimethylamino)methyl)-3-methyl-1H-pyrazol-1-yl)-5-methylpyrimidin-2-ylamino)-4-methoxy-2-morpholinophenyl)acrylamide,
N-(5-(4-(4-(azetidin-1-ylmethyl)-3-methyl-1H-pyrazol-1-yl)-5-methylpyrimidin-2-ylamino)-4-methoxy-2-morpholinophenyl)acrylamide,
N-(5-(5-chloro-4-(4-((dimethylamino)methyl)-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-morpholinophenyl)acrylamide,
N-(5-(4-(4-(azetidin-1-ylmethyl)-3-phenyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-morpholinophenyl)acrylamide,
N-(5-(4-(4-((dimethylamino)methyl)-3-methyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-2-(4-(2-fluoroethyl)piperazin-1-yl)-4-methoxyphenyl)acrylamide,
N-(5-(4-(4-((dimethylamino)methyl)-3-p-tolyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-morpholinophenyl)acrylamide,
N-(5-(4-(4-(azetidin-1-ylmethyl)-3-(4-fluorophenyl)-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-morpholinophenyl)acrylamide,
N-(5-(4-(4-(azetidin-1-ylmethyl)-3-p-tolyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-morpholinophenyl)acrylamide,
N-(2-(dimethylamino)-5-(4-(4-((dimethylamino)methyl)-3-phenyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxyphenyl)acrylamide,
N-(2-(azetidin-1-yl)-5-(4-(4-((dimethylamino)methyl)-3-phenyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxyphenyl)acrylamide,
N-(4-methoxy-2-(4-methylpiperazin-1-yl)-5-(4-(3-phenyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)phenyl)acrylamide,
N-(5-(4-(3-tert-butyl-4-((dimethylamino)methyl)-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-morpholinophenyl)acrylamide,
N-(2-(azetidin-1-yl)-5-(4-(4-(azetidin-1-ylmethyl)-3-phenyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxyphenyl)acrylamide,

N-(5-(4-(4-((dimethylamino)methyl)-3-(thiophen-2-yl)-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-morpholinophenyl)acrylamide,
 N-(5-(4-(4-((dimethylamino)methyl)-3-(2,5-dimethylphenyl)-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-morpholinophenyl)acrylamide,
 N-(4-methoxy-2-morpholino-5-(4-(3-phenyl-4-(pyrrolidin-1-yl)methyl)-1H-pyrazol-1-yl)pyrimidin-2-ylamino)phenyl)acrylamide,
 N-(5-(4-(4-(hydroxymethyl)-3-phenyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-morpholinophenyl)acrylamide,
 N-(5-(4-(4-((ethyl(methyl)amino)methyl)-3-phenyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-morpholinophenyl)acrylamide,
 N-(5-(4-(4-((dimethylamino)methyl)-3-isopropyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-morpholinophenyl)acrylamide,
 N-(5-(4-(4-((dimethylamino)methyl)-3-phenyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-((2-methoxyethyl)(methyl)amino)phenyl)acrylamide,
 N-(5-(4-(4-(azetidin-1-yl)methyl)-3-phenyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-((2-methoxyethyl)(methyl)amino)phenyl)acrylamide,
 N-(5-(4-(4-((dimethylamino)methyl)-3-phenyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-(methyl(oxetan-3-yl)amino)phenyl)acrylamide,
 N-(5-(4-(4-(azetidin-1-yl)methyl)-3-phenyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-(methyl(oxetan-3-yl)amino)phenyl)acrylamide,
 N-(5-(4-(4-((dimethylamino)methyl)-3-phenyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-(pyrrolidin-1-yl)phenyl)acrylamide,
 N-(5-(4-(4-(azetidin-1-yl)methyl)-3-phenyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-(pyrrolidin-1-yl)phenyl)acrylamide,
 N-(5-(4-(3-tert-butyl-4-((dimethylamino)methyl)-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-((2-methoxyethyl)(methyl)amino)phenyl)acrylamide,
 N-(5-(4-(4-(azetidin-1-yl)methyl)-3-tert-butyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-((2-methoxyethyl)(methyl)amino)phenyl)acrylamide,
 N-(5-(4-(3-tert-butyl-4-((dimethylamino)methyl)-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-(methyl(oxetan-3-yl)amino)phenyl)acrylamide,
 N-(5-(4-(4-(azetidin-1-yl)methyl)-3-tert-butyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-(methyl(oxetan-3-yl)amino)phenyl)acrylamide,
 N-(5-(4-(3-tert-butyl-4-((dimethylamino)methyl)-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-(pyrrolidin-1-yl)phenyl)acrylamide,
 N-(5-(4-(4-(azetidin-1-yl)methyl)-3-tert-butyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-(pyrrolidin-1-yl)phenyl)acrylamide,
 N-(5-(4-(3-cyclopropyl-4-((dimethylamino)methyl)-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-((2-methoxyethyl)(methyl)amino)phenyl)acrylamide,
 N-(5-(4-(4-(azetidin-1-yl)methyl)-3-cyclopropyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-((2-methoxyethyl)(methyl)amino)phenyl)acrylamide,
 N-(5-(4-(3-cyclopropyl-4-((dimethylamino)methyl)-1H-pyrazol-1-yl)pyrimidin-2-

ylamino)-4-methoxy-2-(methyl(oxetan-3-yl)amino)phenyl)acrylamide,
N-(5-(4-(4-(azetidin-1-ylmethyl)-3-cyclopropyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-(methyl(oxetan-3-yl)amino)phenyl)acrylamide,
N-(5-(4-(3-cyclopropyl-4-((dimethylamino)methyl)-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-(pyrrolidin-1-yl)phenyl)acrylamide,
N-(5-(4-(4-(azetidin-1-ylmethyl)-3-cyclopropyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-(pyrrolidin-1-yl)phenyl)acrylamide,
N-(5-(4-(4-((dimethylamino)methyl)-3-isopropyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-((2-methoxyethyl)(methyl)amino)phenyl)acrylamide,
N-(5-(4-(4-(azetidin-1-ylmethyl)-3-isopropyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-((2-methoxyethyl)(methyl)amino)phenyl)acrylamide,
N-(5-(4-(4-((dimethylamino)methyl)-3-isopropyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-(methyl(oxetan-3-yl)amino)phenyl)acrylamide,
N-(5-(4-(4-(azetidin-1-ylmethyl)-3-isopropyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-(methyl(oxetan-3-yl)amino)phenyl)acrylamide,
N-(5-(4-(4-((dimethylamino)methyl)-3-isopropyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-(pyrrolidin-1-yl)phenyl)acrylamide,
N-(5-(4-(4-(azetidin-1-ylmethyl)-3-isopropyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-(pyrrolidin-1-yl)phenyl)acrylamide,
N-(5-(4-(4-(azetidin-1-ylmethyl)-3-(thiophen-2-yl)-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-morpholinophenyl)acrylamide,
N-(5-(4-(4-(azetidin-1-ylmethyl)-3-isopropyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-morpholinophenyl)acrylamide,
N-(5-(4-(4-((dimethylamino)methyl)-3-phenyl-1H-pyrazol-1-yl)-5-methylpyrimidin-2-ylamino)-4-methoxy-2-morpholinophenyl)acrylamide,
N-(5-(4-(4-(azetidin-1-ylmethyl)-3-phenyl-1H-pyrazol-1-yl)-5-methylpyrimidin-2-ylamino)-4-methoxy-2-morpholinophenyl)acrylamide,
N-(5-(4-(3-cyclopropyl-4-((dimethylamino)methyl)-1H-pyrazol-1-yl)-5-methylpyrimidin-2-ylamino)-4-methoxy-2-morpholinophenyl)acrylamide,
N-(5-(4-(4-(azetidin-1-ylmethyl)-3-cyclopropyl-1H-pyrazol-1-yl)-5-methylpyrimidin-2-ylamino)-4-methoxy-2-morpholinophenyl)acrylamide,
N-(5-(4-(4-((dimethylamino)methyl)-3-isopropyl-1H-pyrazol-1-yl)-5-methylpyrimidin-2-ylamino)-4-methoxy-2-morpholinophenyl)acrylamide,
N-(5-(4-(4-(azetidin-1-ylmethyl)-3-isopropyl-1H-pyrazol-1-yl)-5-methylpyrimidin-2-ylamino)-4-methoxy-2-morpholinophenyl)acrylamide,
N-(5-(4-(3-tert-butyl-4-((dimethylamino)methyl)-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-2-(ethyl(2-methoxyethyl)amino)-4-methoxyphenyl)acrylamide,
N-(5-(4-(4-((dimethylamino)methyl)-3-(furan-3-yl)-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-morpholinophenyl)acrylamide,
N-(5-(4-(4-((dimethylamino)methyl)-3-(pyridin-3-yl)-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-morpholinophenyl)acrylamide,

N-(2-(4-acetylpiperazin-1-yl)-5-(4-(3-cyclopropyl-4-((dimethylamino)methyl)-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxyphenyl)acrylamide,
 N-(5-(4-(3-(azetidin-1-ylmethyl)-4-(furan-3-yl)-1H-pyrrol-1-yl)-5-fluoropyrimidin-2-ylamino)-4-methoxy-2-morpholinophenyl)acrylamide,
 N-(5-(4-(3-((dimethylamino)methyl)-4-(furan-3-yl)-1H-pyrrol-1-yl)-5-fluoropyrimidin-2-ylamino)-4-methoxy-2-morpholinophenyl)acrylamide,
 N-(5-(4-(3-cyclopropyl-4-((dimethylamino)methyl)-1H-pyrazol-1-yl)-5-methylpyrimidin-2-ylamino)-4-methoxy-2-(methyl(oxetan-3-yl)amino)phenyl)acrylamide,
 N-(2-(4-acetylpiperazin-1-yl)-5-(4-(4-(azetidin-1-ylmethyl)-3-phenyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxyphenyl)acrylamide,
 N-(2-(4-acetylpiperazin-1-yl)-5-(4-(4-((dimethylamino)methyl)-3-phenyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxyphenyl)acrylamide,
 N-(5-(4-(4-((dimethylamino)methyl)-3-(pyridin-4-yl)-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-morpholinophenyl)acrylamide,
 N-(2-(4-acetylpiperazin-1-yl)-5-(4-(3-cyclopropyl-4-((ethyl(methyl)amino)methyl)-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxyphenyl)acrylamide,
 N-(2-(4-acetylpiperazin-1-yl)-5-(4-(4-(azetidin-1-ylmethyl)-3-cyclopropyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxyphenyl)acrylamide,
 N-(2-(azetidin-1-yl)-5-(4-(4-(azetidin-1-ylmethyl)-3-cyclopropyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxyphenyl)acrylamide,
 N-(5-(4-(3-cyclopropyl-4-((ethyl(methyl)amino)methyl)-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-morpholinophenyl)acrylamide,
 N-(2-(azetidin-1-yl)-5-(4-(3-(azetidin-1-ylmethyl)-4-methyl-1H-pyrrol-1-yl)-5-fluoropyrimidin-2-ylamino)-4-methoxyphenyl)acrylamide,
 N-(5-(4-(3-(azetidin-1-ylmethyl)-4-methyl-1H-pyrrol-1-yl)-5-fluoropyrimidin-2-ylamino)-2-(dimethylamino)-4-methoxyphenyl)acrylamide,
 N-(2-(dimethylamino)-5-(4-(3-((dimethylamino)methyl)-4-methyl-1H-pyrrol-1-yl)-5-fluoropyrimidin-2-ylamino)-4-methoxyphenyl)acrylamide,
 N-(2-((2-(dimethylamino)ethyl)(methyl)amino)-5-(4-(3-((dimethylamino)methyl)-4-(trifluoromethyl)-1H-pyrrol-1-yl)-5-fluoropyrimidin-2-ylamino)-4-methoxyphenyl)acrylamide,
 N-(5-(4-(4-((ethyl(methyl)amino)methyl)-3-methyl-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-4-methoxy-2-morpholinophenyl)acrylamide,
 or a pharmaceutically acceptable salt thereof.

14. A pharmaceutical composition comprising a compound of claim 1 together with a pharmaceutically acceptable carrier, diluent or excipient.