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(54) **Janus kináz inhibitor N-cianometilamidok**

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(54) **N-CYANOMETHYLAMIDES AS INHIBITORS OF JANUS KINASE**

N-CYANOMETHYLAMIDE ALS JANUS KINASE HEMMER

N-CYANOMETHYL AMIDES EN TANT QU'INHIBITEURS DE KINASE JANUS

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(56) References cited:
WO-A1-2008/109943 **WO-A1-2009/029998**
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EP 3 030 561 B1

Description

FIELD OF THE INVENTION

[0001] The present invention relates to compounds of general formula (1) that are inhibitors of Janus Kinase (JAK), a family of tyrosine kinases that are involved in inflammatory conditions, autoimmune diseases, proliferative diseases, allergy, transplant rejection, diseases involving impairment of cartilage turnover, congenital cartilage malformations, and/or diseases associated with hypersecretion of IL6 or interferons. In particular, the compound of the invention inhibits JAK1 and/or JAK2 and/or JAK3 sub families. The present invention also provides methods for the production of the compounds of the invention, pharmaceutical compositions comprising the compounds of the invention, their tautomeric forms, and their pharmaceutically acceptable salts.

BACKGROUND OF THE INVENTION

[0002] Protein kinases (PKs) regulate diverse biological processes including cell growth, survival, differentiation, organ formation, morphogenesis, neovascularization, tissue repair, and regeneration. Protein kinases also play specialized roles in a host of human diseases like transplant rejection, rheumatoid arthritis, psoriasis, amyotrophic lateral sclerosis and multiple sclerosis as well as in solid and hematologic malignancies such as leukemias and lymphomas. Cytokines influence cell differentiation, proliferation and activation, and can modulate both pro-inflammatory and anti-inflammatory responses to allow the host to react appropriately to pathogens. Cytokine-stimulated immune and inflammatory responses contribute to pathogenesis of diseases: pathologies such as severe combined immunodeficiency (SCID) arise from suppression of the immune system, while a hyperactive or inappropriate immune/inflammatory response contributes to the pathology of autoimmune diseases (e.g., asthma, systemic lupus erythematosus, thyroiditis, myocarditis), and illnesses such as scleroderma and osteoarthritis (Ortmann, R. A., T. Cheng, et al. (2000) Arthritis Res 2(1): 16-32) Signaling of a wide range of cytokines involves the Janus kinase family (JAKs) of protein tyrosine kinases and Signal Transducers and Activators of Transcription (STATs). Janus kinase (JAK) is a family of intracellular non-receptor tyrosine kinases, ranging from 120-140 kDa, that transduce cytokine-mediated signals via the JAK-STAT pathway. The JAK family plays a role in the cytokine-dependent regulation of proliferation and function of cells involved in immune response. Currently, there are four known mammalian JAK family members: JAK 1, JAK 2, JAK 3 and TYK 2. JAK 1, JAK 2 and TYK 2 are ubiquitously expressed whereas JAK 3 is expressed in the myeloid and lymphoid lineages.

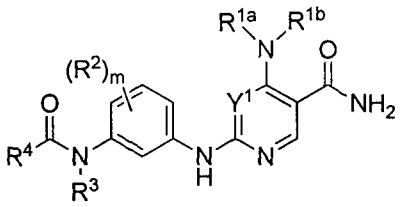
[0003] Vandeghinste et al. (WO 2005/124342) discovered JAK1 as a target whose inhibition might have therapeutic relevance for several diseases including OA. Knockout of the JAK1 gene in mice demonstrated that JAK1 plays essential and non-redundant roles during development.

[0004] JAK2 is a cytoplasmic protein-tyrosine kinase that catalyzes the transfer of the gamma-phosphate group of adenosine triphosphate to the hydroxyl groups of specific tyrosine residues in signal transduction molecules. JAK2 mediates signaling downstream of cytokine receptors after ligand- induced autophosphorylation of both receptor and enzyme. The main downstream effectors of JAK2 are a family of transcription factors known as signal transducers and activators of transcription (STAT) proteins. Studies have disclosed an association between an activating JAK2 mutation (JAK2V617F) and myeloproliferative disorders. The myeloproliferative disorders, a subgroup of myeloid malignancies, are clonal stem cell diseases characterized by an expansion of morphologically mature granulocyte, erythroid, megakaryocyte, or monocyte lineage cells. Myeloproliferative disorders (MPD) include polycythemia vera (PV), essential thrombocythemia (ET), myeloid metaplasia with myelofibrosis (MMM), chronic myelogenous leukemia (CML), chronic myelomonocytic leukemia (CMML), hypereosinophilic syndrome (HES), juvenile myelomonocytic leukemia (JMML) and systemic mast cell disease (SMCD). It has been suggested that abnormalties in signal transduction mechanisms, including constitutive activation of protein tyrosine kinases, initiate MPD. Jak2-/- mouse embryos are anemic and die around day 12.5 postcoitum due to the absence of definitive erythropoiesis.

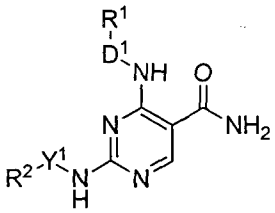
[0005] JAK3 associates with the common gamma chain of the extracellular receptors for the following interleukins: IL-2, IL-4, IL-7, IL-9 and IL- 15. A JAK3 deficiency is associated with an immune compromised (SCID) phenotype in both rodents and humans. The SCID phenotype of JAK3 (-/-) mammals and the lymphoid cell specific expression of JAK3 are two favorable attributes of a target for an immune suppressant. Data suggests that inhibitors of JAK3 could impede T-cell activation and prevent rejection of grafts following transplant surgery, or to provide therapeutic benefit to patients suffering autoimmune disorders. An important feature of JAK3 is that it specifically associates with the common cytokine receptor gamma chain which is a shared component of the receptors for IL-2, IL-4, IL-7, IL-9, and IL-15. Unlike the other JAK family members that are more widely expressed in many mammalian tissues, JAK3 expression seems to be mainly limited to the endoplasmic membranes of hematopoietic cells. JAK3 is validated by mouse and human genetics as an immune-suppression target (O' Shea J. et al. (2004)). JAK3 inhibitors were successfully taken into clinical development, initially for organ transplant rejection but later also in other immuno-inflammatory indications such as rheumatoid arthritis (RA), psoriasis and Crohn's disease.

[0006] Blocking signal transduction at the level of the JAK kinases holds promise for developing treatments for human cancers and arthritis. Inhibition of the JAK kinases is also envisioned to have therapeutic benefits in patients suffering from skin immune disorders such as psoriasis, and skin sensitization. In view of numerous conditions that are contemplated to benefit by treatment involving modulation of JAK pathways it is immediately apparent that new compounds that modulate JAK pathways and method of using these compounds should provide substantial therapeutic benefit to a wide variety of patients.

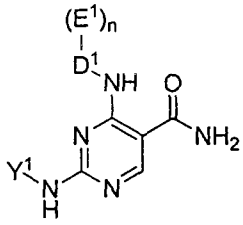
[0007] Patent applications from Portola (WO 2010/129802, WO 2009/145856, WO 2009/136995 etc.) discloses pyrimidine class of compounds as Spleen Tyrosine Kinases (SYK) or JAK inhibitors.



WO 2011/129802

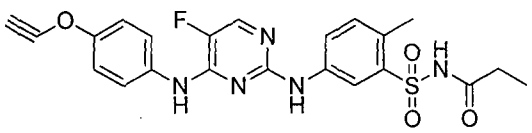


WO 2009/145856

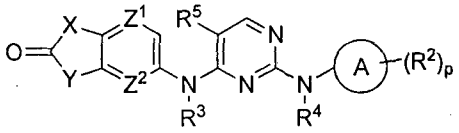


WO 2009/136995

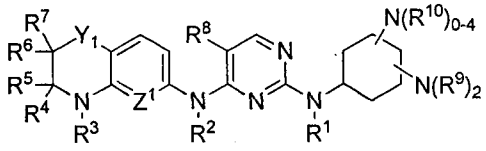
[0008] Rigel has filed a number of patent applications (WO 2011/017178, WO 2010/085684, WO 2010/078369, WO 2010/075558 and WO 2010/039518 etc.) claiming pyrimidine class of compounds as useful modulators of JAK pathways or as inhibitors of JAK kinases particularly JAK-2, JAK-3 or both.



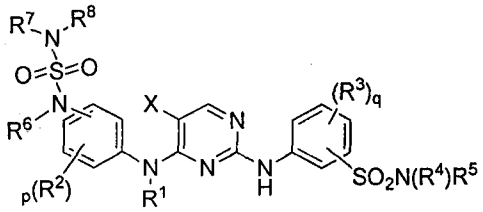
WO 2011/017178



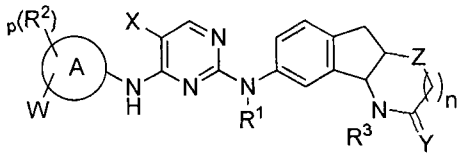
WO 2010/085684



WO 2010/078369

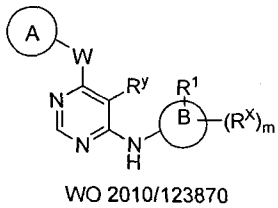


WO 2010/075558

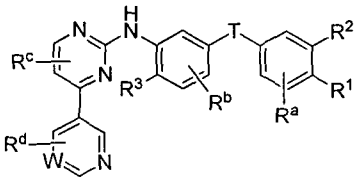


W0 2010/039518

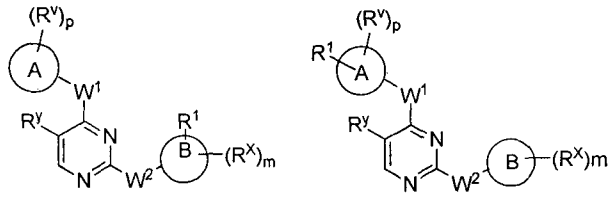
[0009] Avila Therapeutics reported pyrimidine class of compounds as protein kinase inhibitors (WO 2010123870, WO 2009/158571, WO 2009/051822 and WO 2008/151183).



WO 2010/123870
WO 2009/051822

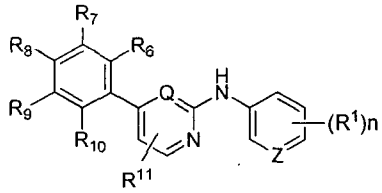


WO:2008151183

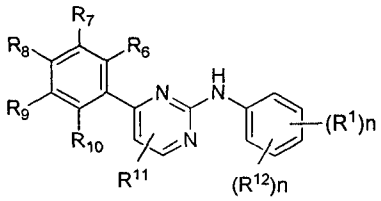


WO2009158571

[0010] Cytopia Research Pvt. Ltd reported phenyl amino pyrimidine class of compounds as protein kinase inhibitors including JAK (WO 2008109943, WO 2009029998).

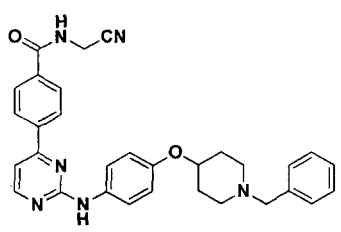


WO2008109943

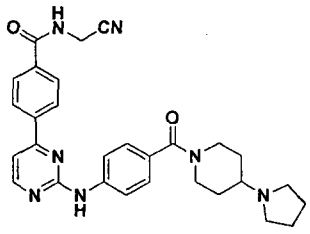


WO2009029998

[0011] Cytopia reported following two compounds in their patent application WO 2008109943. The reported *in vitro* JAK 2 and JAK-3 inhibition for compounds 2 is less than 1 μM and less than 20 μM respectively.



Compound 1

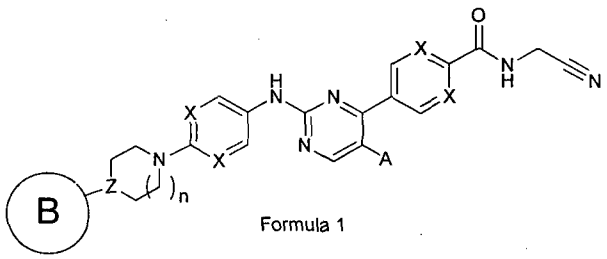


Compound 2

[0012] However, none of these compounds have reached the market and-keeping in mind the huge unmet potential for such molecules, there is a need to develop compounds which modulate the JAK enzymes in a therapeutically effective way. We herein below disclose such novel molecules.

SUMMARY OF THE INVENTION

[0013] The present invention describes a group of novel compounds as JAK inhibitors useful for the treatment of autoimmune diseases, proliferative diseases, allergy, transplant rejection, diseases involving impairment of cartilage turnover, congenital cartilage malformations, and/or diseases associated with hypersecretion of IL6 or interferons. The novel compounds are defined by the general formula (1) below:

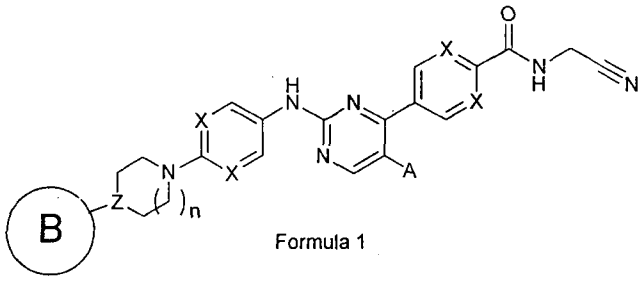


Formula 1

[0014] The compounds of the present invention are useful in the treatment of the human or animal body, by regulating Janus kinase (JAK). The compounds of this invention are therefore suitable for the treatment of autoimmune other related diseases.

EMBODIMENTS OF THE PRESENT INVENTION

[0015] The main objective of the present invention thus is to provide novel compounds of general formula **(1),** novel intermediates involved in their synthesis, their pharmaceutically acceptable salts, and pharmaceutical compositions containing them or their mixtures as therapeutic agents.



Formula 1

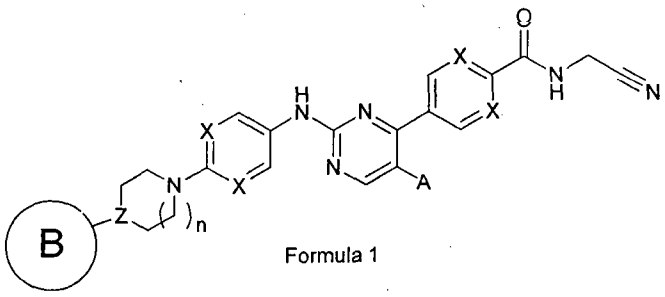
[0016] In an embodiment is provided processes for the preparation of novel compounds of general formula **(1),** novel intermediates involved in their synthesis, their pharmaceutically acceptable salts, and pharmaceutical compositions containing them.

[0017] In another embodiment is provided pharmaceutical compositions containing compounds of general formula **(1),** their pharmaceutically acceptable salts, comprising pharmaceutically acceptable carriers, solvents, diluents, excipients and other media normally employed in their manufacture.

[0018] In a further embodiment is provided the novel compounds of the present invention for use in the treatment of inflammatory conditions, autoimmune diseases, proliferative diseases, allergy and transplant rejection, diseases involving impairment of cartilage turnover, congenital cartilage malformations, and/or diseases associated with hypersecretion of IL6 or interferons wherein the JAK kinase has pathological function.

DETAILED DESCRIPTION OF THE INVENTION

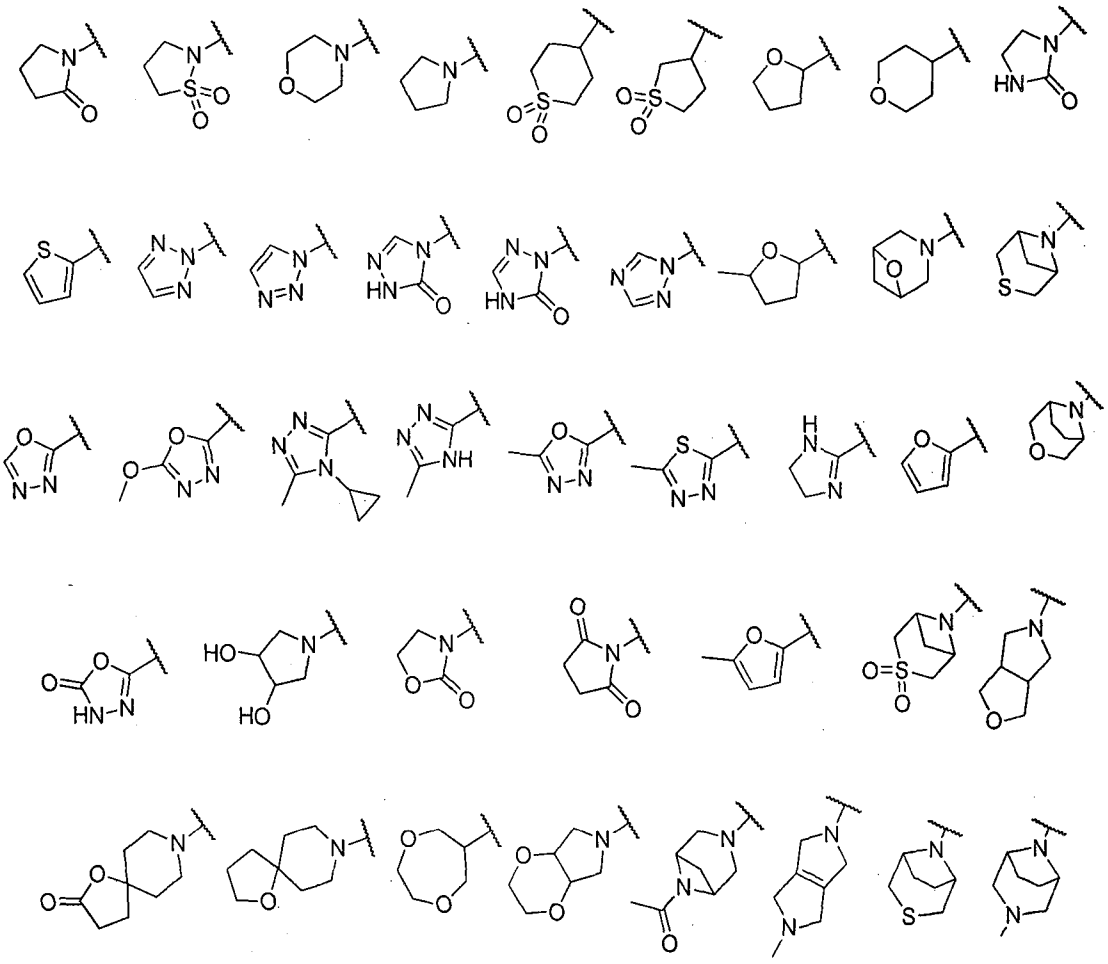
[0019] The novel compounds of the present invention are defined by the general formula **(I)** below:



Formula 1

Wherein

X at each occurrence is independently selected from N or CH;
Z at each occurrence is independently selected from N or CH;
'n' is selected from 0, 1.
A is independently selected from hydrogen, halogen, C_{1-4} alkyl, CF_3, CN, $CON(R_1)_2$, OC_{1-4}alkyl
Ring B is selected from following ring systems



the ring B may, wherever applicable, optionally be substituted with one or more substituents independently selected from H, OH, CN, NH_2, halogen, oxo, OCF_3, CF_3, C_1-C_6 alkyl, OC_1-C_6 alkyl, $(CH_2)_{1-6}OC_1$-C_6 alkyl, O-$(CH_2)_{0-4}OC_1$-C_6 alkyl, $C(O)NHC_1$-C_6 alkyl, $NHC(O)C_1$-C_6 alkyl, $S(O)_{0.2}C_1$-C_6 alkyl, $(CH_2)_{1-6}N(R_1)_2$, $(CH_2)_{1-6}NHC(=O)OR_1$, $(CH_2)_{1-6}NHC(=O)R_1$, $C(=O)OR_1$, $C(=O)R_1$, $(CH_2)_{1-4}C(=O)$ NHR_1, $(CH_2)_{0-4}O(CH_2)_{0-4}Ar_1$, $(CH_2)_{0-4}NH(CH_2)_{0-4}Ar_1$, $(CH_2)_{0-4}$ Ar_1, $(CH_2)_{0-4}C(O)(CH_2)_{0-4}Ar_1$, $(CH_2)_{0-4}$ $C(=O)$ $O(CH_2)_{0-4}Ar_1$, $(CH_2)_{0-4}C(=O)NR_1(CH_2)_{0-4}Ar_1$; The term Ar_1 at each occurrence is independently selected from unsubstituted or substituted aryl or heterocyclic ring substituted with one, two, three or four substituents independently selected from the group comprising of OH, CN, NH_2, halogen, OCF_3, CF_3, C_1-C_6 alkyl, OC_1-C_6alkyl, $(CH_2)_{1-6}OC_1$-C_6 alkyl, O-$(CH_2)_{0-4}0C_1$-C_6 alkyl, $C(O)NHC_1$-C_6 alkyl, $NHC(O)C_1$-C_6 alkyl, $S(O)_{0-2}C_1$-C_6 alkyl, $(CH_2)_{1-6}N(R_1)_2$, $(CH_2)_{1-6}NHC(=O)OR_1$, $(CH_2)_{1-6}NHC(=O)R_1$, $C(=O)OR_1$ or-$C(=O)R_1$, $CH_2(CH_2)_{0-4}C(=O)$ NHR_1;
R_1 at each occurrence is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_3-C_7 cycloalkyl groups;
Suitable substituents wherever applicable if not specifically defined elsewhere, includes, but are not limited to the following radicals, alone or in combination with other radicals: hydroxyl, oxo, halo, thio, nitro, amino, alkyl, alkoxy, haloalkyl or haloalkoxy groups;
In a further embodiment the groups, radicals described above may be selected from:

- the "alkyl" group used either alone or in combination with other radicals, denotes a linear or branched radical containing one to six carbons, selected from methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *t*-butyl, amyl, *t*-amyl, *n*-pentyl, *n*-hexyl, and the like;

- The term "halo" or "halogen" used herein, either alone or in combination with other radicals, such as "haloalkyl", "perhaloalkyl" refers to a fluoro, chloro, bromo or iodo group. The term "haloalkyl" denotes an alkyl radical, as defined above, substituted with one or more halogens; such as fluoromethyl, difluoromethyl, trifluoromethyl, fluoroethyl, difluoroethyl, trifluoroethyl, mono or polyhalo substituted methyl, ethyl, propyl, butyl, pentyl or hexyl groups. The term "haloalkoxy" denotes a haloalkyl, as defined above, directly attached to an oxygen atom, such as fluoromethoxy, chloromethoxy, fluoroethoxy chloroethoxy groups, and the like.
- The term "aryl" refers to aromatic mono- and poly-carbocyclic ring systems, wherein the individual carbocyclic rings in the poly ring systems are fused or attached to each other through a single bond. Suitable aryl groups include phenyl, naphthyl, and biphenyl.
- The term "substituted," as used herein, means that any one or more hydrogen on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound.

[0020] Compounds of formula (I) may contain one or more asymmetric centers and can thus occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. The present invention is meant to comprehend all such isomeric forms of the compounds of formula (I), either as single species or mixtures thereof.

[0021] Some of the compounds described herein contain olefinic double bonds, and unless specified otherwise, are meant to include both E and Z geometric isomers.

[0022] Some of the compounds described herein may exist with different points of attachment of hydrogen, referred to as tautomers. Such an example may be a ketone and its enol form known as keto-enol tautomers. The individual tautomers as well as mixture thereof are encompassed with compounds of formula (I).

List of Abbreviation

[0023]

DMF: Dimethyl formamide
DCM: Dichloromethane
EDAC.HCl : N-(3-Dimethyl aminopropyl)-N'-ethyl carbodiimide hydrochloride,
HOBT: 1-Hydroxy benzotriazole
TFA: Trifluoro acetic acid
DCC: Dicyclohexylcarbodiimide
DIPEA: Disopropyl ethyl amine
EtOAc: Ethyl acetate
h: Hour(s)
min: Minute(s)
t_{Ret}: Retention time
HCl : Hydrochloric acid
RT: Room temperature [25-30 °C]
BINAP : (±)-2,2'-Bis(diphenylphosphino)-1,1'binapthalene
DPPF : [1,1'-Bis(diphenylphosphino)ferrocene]dichloride palladium complex with DCM
$Pd_2(dba)_3$: Tris(dibenzylideneacetopne)dipalladium
$(PPh_3)_2PdCl_2$: Bis(triphenylphosphine)palladium(II) dichloride

Instrument details

[0024] Mass spectrum was recorded on LC-MS 2010-A Shimadzu.

[0025] UPLC purity was determined by using Waters Sequipy instrument.

UPLC Column: BEH C18 (2.1X100mm)1.7μ
Mobile phase: 0.05 % TFA in water: ACN gradient.
Flow rate: 1.0 ml/min.
Wave length: UV at 220 nm.

[0026] HPLC purity was determined by using Agilent-1100 instrument.
HPLC column J'Sphere ODS 150*4.6 mm,
Flow rate 1.0 ml/min @ 220 min
NMR spectrum: Bruker Avanc 400 mHz

Particularly useful compounds of the present invention are selected from

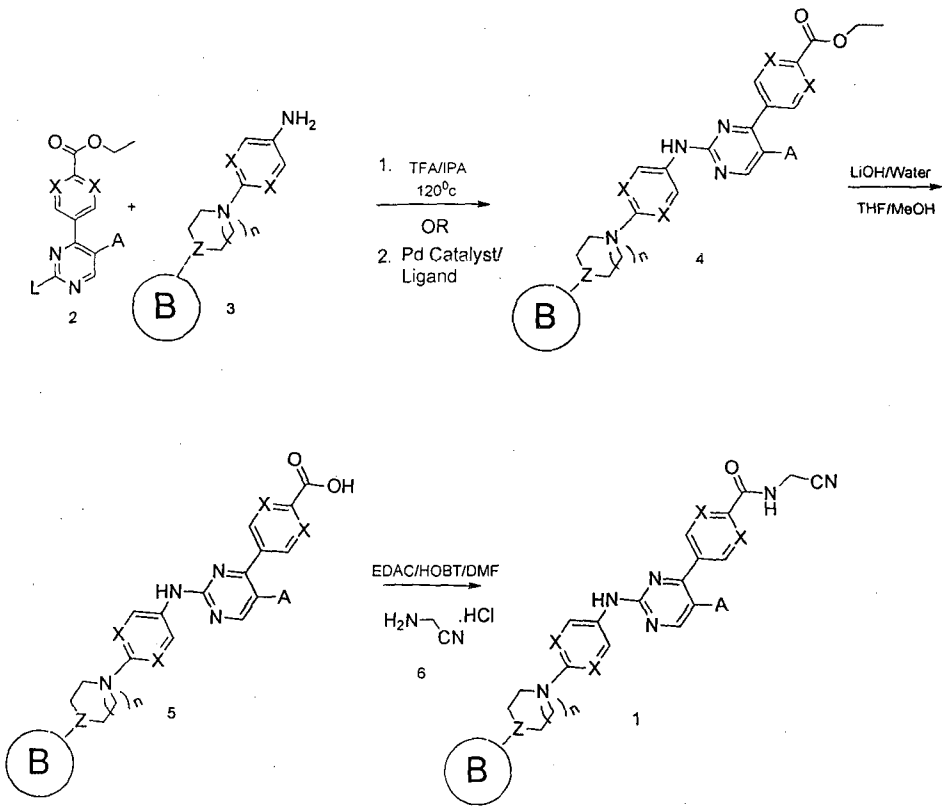
N-(Cyanomethyl)-4-(2-((4-(4-(2-oxopyrrolidin-1-yl)piperidin-1-yl)phenyl)amino) pyrimidin-4-yl)benzamide;
N-(Cyanomethyl)-4-(2-((4-(4-(1,1-dioxidoisothiazolidin-2-yl) piperidin-1-yl) phenyl)amino) pyrimidin-4-yl)benzamide;
N-(Cyanomethyl)-4-(2-((4-(4-morpholinopiperidin-1-yl)phenyl) amino)pyrimidin-4-yl)benzamide;
4-(2-((4-(4-(1H-1,2,4-Triazol-1-yl)piperidin-1-yl)phenyl) amino) pyrimidin-4-yl)-N-(cyanomethyl)benzamide;
4-(2-((4-(4-(1H-Pyrazol-1-yl)piperidin-1-yl)phenyl) amino) pyrimidin-4-yl)-N-(cyanomethyl)benzamide;
4-(2-((4-([1,3'-Bipyrrolidin]-1'-yl)phenyl)amino)pyrimidin-4-yl)-N-(cyanomethyl) benzamide;
N-(cyanomethyl)-4-(2-((4-(4-(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)piperazin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
N-(Cyanomethyl)-4-(2-((4-(4-(furan-2-yl)piperidin-1-yl)phenyl) amino)pyrimidin-4-yl)benzamide;
N-(Cyanomethyl)-4-(2-((4-(4-(1,1-dioxidotetrahydrothiophen-3-yl)piperazin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
N-(Cyanomethyl)-4-(2-((4-(4-(2,5-dioxopyrrolidin-1-yl)piperidin-1-yl)phenyl) amino)pyrimidin-4-yl)benzamide;
N-(Cyanomethyl)-4-(2-((4-(4-(thiophen-2-yl)piperidin-1-yl)phenyl) amino) pyrimidin-4-yl)benzamide;
N-(Cyanomethyl)-4-(2-((4-(4-(2-oxooxazolidin-3-yl)piperidin-1-yl)phenyl) amino)pyrimidin-4-yl)benzamide;
N-(Cyanomethyl)-4-(2-((4-(4-(tetrahydrofuran-2-yl)piperidin-1-yl)phenyl) amino)pyrimidin-4-yl)benzamide;
N-(Cyanomethyl)-4-(2-((4-(4-(5-methylfuran-2-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
N-(Cyanomethyl)-4-(2-((4-(4-(tetrahydro-2H-pyran-4-yl)piperazin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
N-(Cyanomethyl)-4-(2-((4-(4-(5-methyltetrahydrofuran-2-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
4-(2-((4-(4-(6-Oxa-3-azabicyclo[3.1.1]heptan-3-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)-N-(cyanomethyl)benzamide;
N-(Cyanomethyl)-4-(2-((4-(4-(2-oxoimidazolidin-1-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
4-(2-((4-(4-(1,3,4-Oxadiazol-2-yl)piperidin-1-yl)phenyl) amino) pyrimidin-4-yl)-N-(cyanomethyl)benzamide;
4-(2-((4-(4-(2H-1,2,3-Triazol-2-yl)piperidin-1-yl)phenyl)amino) pyrimidin-4-yl)-N-(cyano methyl) benzamide;
4-(2-((4-(4-(1H-1,2,3-Triazol-1-yl)piperidin-1-yl)phenyl)amino) pyrimidin-4-yl)-N-(cyano methyl)benzamide;
N-(Cyanomethyl)-4-(2-((4-(4-(5-oxo-1H-1,2,4-triazol-4(5H)-yl) piperidin-1-yl) phenyl) amino) pyrimidin-4-yl)benzamide;
N-(Cyanomethyl)-4-(2-((4-(4-(5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
4-(2-((4-(4-(1-Oxa-8-azaspiro[4.5]decan-8-yl)piperidin-1-yl) phenyl) amino) pyrimidin-4-yl)-N-(cyanomethyl)benzamide;
N-(Cyanomethyl)-4-(2-((4-(4-(5-methyl-1,3,4-oxadiazol-2-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
N-(Cyanomethyl)-4-(2-((4-(4-(5-methyl-1,3,4-thiadiazol-2-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
N-(Cyanomethyl)-4-(2-((4-(4-(tetrahydro-2H-[1,4]dioxino[2,3-c]pyrrol-6(3H)-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
N-(Cyanomethyl)-4-(2-((4-(4-(2-oxo-1-oxa-8-azaspiro[4.5]decan-8-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
N-(Cyanomethyl)-4-(2-((4-(4-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
N-(Cyanomethyl)-4-(2-((4-(4-(4-cyclopropyl-5-methyl-4H-1,2,4-triazol-3-yl) piperidin-1-yl) phenyl) amino)pyrimidin-4-yl)benzamide;
N-(Cyanomethyl)-4-(2-((4-(4-(5-methoxy-1,3,4-oxadiazol-2-yl)piperidin-1-yl)phenyl) amino)pyrimidin-4-yl)benzamide;
4-(2-((4-(4-(1,4-Dioxepan-6-yl)piperazin-1-yl)phenyl)amino) pyrimidin-4-yl)-N-(cyanomethyl) benzamide;
N-(Cyanomethyl)-4-(2-((4-(4-(4,5-dihydro-1H-imidazol-2-yl)piperazin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
N-(Cyanomethyl)-4-(2-((4-(4-(4,5-dihydro-1H-imidazol-2-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
N-(Cyanomethyl)-4-(2-((4-(3-(tetrahydro-2H-[1,4]dioxino[2,3-c]pyrrol-6(3H)-yl)pyrrolidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
N-(Cyanomethyl)-4-(2-((4-(4-(5-methyl-1,3,4-oxadiazol-2-yl)piperazin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
N-(Cyanomethyl)-4-(2-((4-(4-(3,4-dihydroxypyrrolidin-1-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
4-(2-((4-(4-(8-Oxa-3-azabicyclo[3.2.1]octan-3-yl)piperidin-1-yl)phenyl) amino) pyrimidin-4-yl)-N-(cyanomethyl)benzamide;
4-(2-((4-(4-(6-Acetyl-3,6-diazabicyclo[3.1.1]heptan-3-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)-N-(cyanome-

thyl)benzamide;
N-(Cyanomethyl)-4-(5-methyl-2-((4-(4-morpholinopiperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
N-(Cyanomethyl)-4-(5-methyl-2-((4-(4-(2-oxopyrrolidin-1-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
4-(2-((4-(4-(1-Oxa-8-azaspiro[4.5]decan-8-yl)piperidin-1-yl)phenyl)amino)-5-methylpyrimidin-4-yl)-N-(cyanomethyl)benzamide;
N-(Cyanomethyl)-4-(5-methyl-2-((4-(4-(5-methyl-1,3,4-oxadiazol-2-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
N-(Cyanomethyl)-4-(5-fluoro-2-((4-(4-morpholinopiperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
4-(5-Chloro-2-((4-(4-morpholinopiperidin-1-yl)phenyl)amino) pyrimidin-4-yl)-N-(cyanomethyl)benzamide;
N-(Cyanomethyl)-4-(5-fluoro-2-((4-(4-(2-oxopyrrolidin-1-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
4-(5-Chloro-2-((4-(4-(2-oxopyrrolidin-1-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)-N-(cyanomethyl)benzamide;
4-(2-((4-(4-(6-Oxa-3-azabicyclo[3.1.1]heptan-3-yl)piperidin-1-yl)phenyl)amino)-5-methylpyrimidin-4-yl)-N-(cyanomethyl)benzamide;
4-(2-((4-(4-(6-Oxa-3-azabicyclo[3.1.1]heptan-3-yl)piperidin-1-yl)phenyl)amino)-5-fluoropyrimidin-4-yl)-N-(cyanomethyl)benzamide;
-(2-((4-(4-(6-Oxa-3-azabicyclo[3.1.1]heptan-3-yl)piperidin-1-yl)phenyl)amino)-5-chloropyrimidin-4-yl)-N-(cyanomethyl)benzamide;
N-(Cyanomethyl)-4-(5-methyl-2-((4-(4-(tetrahydro-2H-[1,4]dioxino[2,3-c]pyrrol-6(3H)-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
N-(Cyanomethyl)-4-(5-fluoro-2-((4-(4-(tetrahydro-2H-[1,4]dioxino[2,3-c]pyrrol-6(3H)-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
4-(5-Chloro-2-((4-(4-(tetrahydro-2H-[1,4]dioxino[2,3-c]pyrrol-6(3H)-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)-N-(cyanomethyl)benzamide;
N-(Cyanomethyl)-4-(5-fluoro-2-((4-(4-(5-methyl-1,3,4-oxadiazol-2-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
4-(5-Chloro-2-((4-(4-(5-methyl-1,3,4-oxadiazol-2-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)-N-(cyanomethyl)benzamide;
N-(Cyanomethyl)-4-(5-methyl-2-((4-(4-(5-methyl-1,3,4-oxadiazol-2-yl)piperazin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
N-(Cyanomethyl)-4-(5-fluoro-2-((4-(4-(5-methyl-1,3,4-oxadiazol-2-yl)piperazin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
4-(5-Chloro-2-((4-(4-(5-methyl-1,3,4-oxadiazol-2-yl)piperazin-1-yl)phenyl)amino)pyrimidin-4-yl)-N-(cyanomethyl)benzamide;
4-(2-((4-(4-(3-Thia-6-azabicyclo[3.1.1]heptan-6-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)-N-(cyanomethyl)benzamide;
4-(2-((4-(4-(3-Thia-6-azabicyclo[3.1.1]heptan-6-yl)piperidin-1-yl)phenyl)amino)-5-methylpyrimidin-4-yl)-N-(cyanomethyl)benzamide;
4-(2-((4-(4-(3-Thia-6-azabicyclo[3.1.]heptan-6-yl)piperidin-1-yl)phenyl)amino)-5-fluoropyrimidin-4-yl)-N-(cyanomethyl)benzamide;
4-(2-((4-(4-(3-Thia-6-azabicyclo[3.1.1]heptan-6-yl)piperidin-1-yl)phenyl)amino)-5-chloropyrimidin-4-yl)-N-(cyanomethyl)benzamide;

[0027] The compounds of the present invention may be prepared using the methods described below, together with conventional techniques known to those skilled in the art of organic synthesis, or variations thereon as appreciated by those skilled in the art. Referred methods include, but are not limited to those described below, where all symbols are as defined earlier.

General Procedure 1:

[0028]



[0029] The ester derivative of formula **[4]** can be synthesized by reacting compound of formula **[2],** where 'L' is a suitable leaving group selected from Cl, Br, I, or $SOCH_3$ and the like, and suitable amine derivatives of formula **[3]** in the presence of an acid such as trifluoro acetic acid, *P*-toluene sulfonic acid or bases such as potassium carbonate, diisopropyl ethyl amine, tri ethyl amine & the like in solvents such as isopropyl alcohol, dimethyl sulfoxide, dimethyl formamide or dioxane & the like at temperature 25-150°C. Alternative for acid sensitive group attached to amine derivative **[3],** ester derivative can be prepared by coupling of compound of formula **[2]** with amine derivative **[3]** using catalyst like DPPF, $Pd_2(dba)_3$, $(PPh_3)_2PdCl_2$ and like in presence of ligand BINAP and like in solvent DMF, DMA, Dioxane and like at temperature 80-150°C.

[0030] Hydrolysis of ester derivative **[4]** with bases such as sodium hydroxide, lithium hydroxide in solvent(s) such as water, methanol, ethanol, tetrahydrofuran or combination thereof at temperature 25-100°C afford acid derivative of formula **[5].** Acetonitrile derivative of formula **[6]** may be synthesized by reacting amino acetonitrile **[6]** with acid derivative of formula **[5]** using suitable carboxyl groups activating agents such as N-(3-dimethyl aminopropyl)-N'-ethyl carbodiimide hydrochloride (EDAC.HCl), dicyclohexyl carbodiimide and the like in the presence of an additive 1-hydroxy benzotriazole (HOBT) and base like triethyl amine or diisopropylethyl amine (DIEA) & the like in solvent(s) like dimethyl formamide or dichloromethane & the like at temperature 0-25°C.

[0031] The compound of formula **[2]** can be synthesized as per the general procedures known in the art for e.g. as mentioned in WO2008109943 along with suitable variations as are well known to a skilled person. The amine derivative **[3],** can be synthesized by variety of methods known to those skilled in the art such as following procedures set forth in references such as Fieser and Fieser's Reagents for Organic Synthesis; Wiley & Sons: New York, Volumes 1-21; R. C. LaRock, Comprehensive Organic Transformations, 2.nd edition Wiley- VCH, New York 1999; Comprehensive Organic Synthesis, B. Trost and I. Fleming (Eds.) vol. 1-9 Pergamon, Oxford, 1991; Comprehensive Heterocyclic Chemistry, A. R. Katritzky and C. W. Rees (Eds) Pergamon, Oxford 1984, vol. 1-9; Comprehensive Heterocyclic Chemistry II, A. R. Katritzky and C. W. Rees (Eds) Pergamon, Oxford 1996, vol. 1-1 1 ; and Organic Reactions, Wiley & Sons: New York, 1991, Volumes 1-40, to name some of the known literature processes.

[0032] The pharmaceutically acceptable salts forming a part of this invention may be prepared by treating the compound of formula **(1)** with suitable acids in suitable solvents by processes known in the art.

[0033] The Ester building block [2] were synthesised by the process described below.

Ester	Chemical Name
Ester 1	Ethyl 4-(2-chloropyrimidin-4-yl)benzoate

(continued)

Ester	Chemical Name
Ester 2	Ethyl 4-(2-chloro-5-methylpyrimidin-4-yl)benzoate
Ester 3	Ethyl 4-(2-chloro-5-fluoropyrimidin-4-yl)benzoate
Ester 4	Ethyl 4-(2-chloro-5-chloropyrimidin-4-yl)benzoate

Synthesis of Ester building block

Ester 1 : Preparation of Ethyl 4-(2-chloropyrimidin-4-yl)benzoate.

[0034] To a solution of 2,4-dichloropyrimidine [70 g, 470 mmol] in DMF [600 mL] was added $(PPh_3)_2PdCl_2$ [9.9 g, 14 mmol] and mixture was heated to 90°C for 1 h. To this, (4-(ethoxycarbonyl)phenyl)boronic acid [91 g, 470 mmol] was added and mixture was heated to 90°C for additional 0.5 h. A solution of potassium bicarbonate [282 g, 2.8 mol] in 200 mL of water was added to reaction mixture and stirred for 0.5 h at 90°C. After completion of reaction, mixture was quanched in ice cooled water [500 mL]. The off white solid obtained was filtered, washed with water and dried under vacuum to get title compound. [45 g, 37%].

Ester 2: Preparation of Ethyl 4-(2-chloro-5-methylpyrimidin-4-yl)benzoate.

[0035] Prepared similar to the procedure described in **Ester 1** but using 2,4-dichloro-5-methylpyrimidine as starting material.

Ester 3: Preparation of Ethyl 4-(2-chloro-5-fluoropyrimidin-4-yl)benzoate.

[0036] Prepared similar to the procedure described in **Ester 1** but using 2,4-dichloro-5-fluoropyrimidine as starting material.

Ester 4: Preparation of Ethyl 4-(2-chloro-5-chloropyrimidin-4-yl)benzoate.

[0037] Prepared similar to the procedure described in **Ester 1** but using 2,4,5-trichloropyrimidine as starting material.

[0038] The Amine building blocks **[3]** were synthesized by the process described below:

Amine	Chemical Name
Amine 1	1-(1-(4-Aminophenyl)piperidin-4-yl)pyrrolidin-2-one
Amine 2	2-(1-(4-Aminophenyl)piperidin-4-yl)isothiazolidine 1,1-dioxide
Amine 3	4-(4-Morpholinopiperidin-1-yl)aniline
Amine 4	4-(4-(1H-1,2,4-Triazol-1-yl)piperidin-1-yl)aniline
Amine 5	4-(4-(1H-Pyrazol-1-yl)piperidin-1-yl)aniline
Amine 6	4-([1,3'-Bipyrrolidin]-1'-yl)aniline
Amine 7	4-(4-(4-Aminophenyl)piperazin-1-yl)tetrahydro-2H-thiopyran 1,1-dioxide
Amine 8	4-(4-(Furan-2-yl)piperidin-1-yl)aniline
Amine 9	3-(4-(4-Aminophenyl)piperazin-1-yl)tetrahydrothiophene 1,1-dioxide
Amine 10	1-(1-(4-Aminophenyl)piperidin-4-yl)pyrrolidine-2,5-dione
Amine 11	4-(4-(Thiophen-2-yl)piperidin-1-yl)aniline
Amine 12	3-(1-(4-Aminophenyl)piperidin-4-yl)oxazolidin-2-one
Amine 13	4-(4-(Tetrahydrofuran-2-yl)piperidin-1-yl)aniline
Amine 14	4-(4-(5-Methylfuran-2-yl)piperidin-1-yl)aniline
Amine 15	4-(4-(Tetrahydro-2H-pyran-4-yl)piperazin-1-yl)aniline

(continued)

Amine	Chemical Name
Amine 16	4-(4-(5-Methyltetrahydrofuran-2-yl)piperidin-1-yl)aniline
Amine 17	4-(4-(6-Oxa-3-azabicyclo[3.1.1]heptan-3-yl)piperidin-1-yl)aniline
Amine 18	1-(1-(4-Aminophenyl)piperidin-4-yl)imidazolidin-2-one
Amine 19	4-(4-(1,3,4-Oxadiazol-2-yl)piperidin-1-yl)aniline
Amine 20	4-(4-(2H-1,2,3-Triazol-2-yl)piperidin-1-yl)aniline
Amine 21	4-(4-(1H-1,2,3-Triazol-1-yl)piperidin-1-yl)aniline
Amine 22	4-(1-(4-Aminophenyl)piperidin-4-yl)-1H-1,2,4-triazol-5(4H)-one
Amine 23	1-(1-(4-Aminophenyl)piperidin-4-yl)-1H-1,2,4-triazol-5(4H)-one
Amine 24	4-(4-(1-Oxa-8-azaspiro[4.5]decan-8-yl)piperidin-1-yl)aniline
Amine 25	4-(4-(5-Methyl-1,3,4-oxadiazol-2-yl)piperidin-1-yl)aniline
Amine 26	4-(4-(5-methyl-1,3,4-thiadiazol-2-yl)piperidin-1-yl)aniline
Amine 27	4-(4-(Tetrahydro-2H-[1,4]dioxino[2,3-c]pyrrol-6(3H)-yl)piperidin-1-yl)aniline
Amine 28	8-(1-(4-Aminophenyl)piperidin-4-yl)-1-oxa-8-azaspiro[4.5]decan-2-one
Amine 29	5-(1-(4-Aminophenyl)piperidin-4-yl)-1,3,4-oxadiazol-2(3H)-one
Amine 30	4-(4-(4-Cyclopropyl-5-methyl-4H-1,2,4-triazol-3-yl)piperidin-1-yl)aniline
Amine 31	4-(4-(5-Methoxy-1,3,4-oxadiazol-2-yl)piperidin-1-yl)aniline
Amine 32	4-(4-(1,4-Dioxepan-6-yl)piperazin-1-yl)aniline
Amine 33	4-(4-(4,5-Dihydro-1H-imidazol-2-yl)piperazin-1-yl)aniline
Aminr 34	4-(4-(4,5-Dihydro-1H-imidazol-2-yl)piperidin-1-yl)aniline
Amine 35	4-(3-(Tetrahydro-2H-[1,4]dioxino[2,3-c]pyrrol-6(3H)-yl)pyrrolidin-1-yl)aniline
Amine 36	4-(4-(5-Methyl-1,3,4-oxadiazol-2-yl)piperazin-1 -yl)aniline
Amine 37	1-(1-(4-Aminophenyl)piperidin-4-yl)pyrrolidine-3,4-diol
Amine 38	4-(4-(3-Oxa-8-azabicyclo[3.2.1]octan-8-yl)pipendin-1-yl)aniline
Amine 39	1-(3-(1-(4-Aminophenyl)piperidin-4-yl)-3,6-diazabicyclo [3.1.1]heptan-6-yl)ethanone

Synthesis of Amine building block

Amine 1 : 1-(1-(4-Aminophenyl)piperidin-4-yl)pyrrolidin-2-one.

Step 1 : Preparation of 1-(1-(4-nitrophenyl)piperidin-4-yl)pyrrolidin-2-one

[0039] 1-(piperidin-4-yl)pyrrolidin-2-one (1.8 g, 10.7 mmol) [OPRD **2007,** 11, 482-486] was dissolved in DMF (10.0 mL) at rt. To this K_2CO_3 (2.96 g, 21.40 mmol) was added at rt followed by 1-fluoro-4-nitrobenzene (1.5 mL, 10.7 mmol). The reaction mixture was stirred at 80-90°C for 4 h. After completion of reaction mixture was quenched in water. Yellow sold obtained was filtered washed with water dried under vacuum to get desired compound (2.5 g, 81%) as yellow solid.

Step 2 : Preparation of 1-(1-(4-aminophenyl)piperidin-4-yl)pyrrolidin-2-one

[0040] In a 500 mL hydrogenation bottle was added -(1-(4-nitrophenyl)piperidin-4-yl)pyrrolidin-2-one [2.5 g, 8.6 mmol] in ethanol (50 mL). To this 10% Pd/C (0.372 g, 3.50 mmol) was added and bottle was placed on parr hydrogenation apparatus at 50 psi for 8 h. After completion of reaction, mixture was filtered through hyflow bed, washed with methanol and organic volatile was distilled under vacuum to give title amine 1 (1.7 g, 76 %) as brown solid.

Amine 2: 2-(1-(4-Aminophenyl)piperidin-4-yl)isothiazolidine 1,1-dioxide.

[0041] Prepared similar to the procedure described in Amine 1 but using 2-(piperidin-4-yl)isothiazolidine 1,1-dioxide [Ref.: JMC, 53(9), 3517-3531, 2010].

Amine 3 : 4-(4-Morpholinopiperidin-1-yl)aniline.

[0042] Prepared similar to the procedure described in Amine 1 but using 4-(piperidin-4-yl)morpholine [Ref.: BMCL 22(9), 3157-3162, 2012].

Amine 4: 4-(4-(1H-1,2,4-Triazol-1-yl)piperidin-1-yl)aniline

[0043] Prepared similar to the procedure described in Amine 1 but using 4-(1H-1,2,4-triazol-1-yl)piperidine [Ref.: WO2008060621].

Amine 5: 4-(4-(1H-Pyrazol-1-yl)piperidin-1-yl)aniline

[0044] Prepared similar to the procedure described in Amine 1 but using 4-(1H-pyrazol-1-yl)piperidine [Ref.: WO2013010453].

Amine 6: 4-([1,3'-Bipyrrolidin]-1'-yl)aniline

[0045] Prepared similar to the procedure described in Amine 1 but using 1,3'-bipyrrolidine [Ref.: WO2004039780].

Amine 7: 4-(4-(4-Aminophenyl)piperazin-1-yl)tetrahydro-2H-thiopyran 1,1-dioxide

[0046] Prepared similar to the procedure described in Amine 1 but using 4-(piperazin-1-yl)tetrahydro-2H-thiopyran 1,1-dioxide [Ref.: WO20070072847].

Amine 8: 4-(4-(Furan-2-yl)piperidin-1-yl)aniline

[0047] Prepared similar to the procedure described in Amine 1 but using 4-(furan-2-yl)piperidine [Ref.: WO 9737979].

Amine 9 : 3-(4-(4-Aminophenyl)piperazin-1-yl)tetrahydrothiophene 1,1-dioxide.

[0048] Prepared similar to the procedure described in Amine 1 but using 3-(piperazin-1-yl)tetrahydrothiophene 1,1-dioxide [Ref.: US20080045517].

Amine 10 : 1-(1-(4-Aminophenyl)piperidin-4-yl)pyrrolidine-2,5-dione.

[0049] Prepared similar to the procedure described in Amine 1 but using 1-(piperidin-4-yl)pyrrolidine-2,5-dione.

Amine 11 : 4-(4-(Thiophen-2-yl)piperidin-1-yl)aniline.

[0050] Prepared similar to the procedure described in Amine 1 but using 4-(thiophen-2-yl)piperidine [Ref.: WO 9737979].

Amine 12 : 3-(1-(4-Aminophenyl)piperidin-4-yl)oxazolidin-2-one.

[0051] Prepared similar to the procedure described in Amine 1 but using 3-(piperidin-4yl) oxazolidin-2-one [Ref.: Journal of Medicinal Chemsitry, 2008, 51, 144, 4150-69].

Amine 13 : 4-(4-(Tetrahydrofuran-2-yl)piperidin-1-yl)aniline.

[0052] Prepared similar to the procedure described in Amine 1 but using 4-(tetrahydrofuran-2-yl)piperidine [Ref.: WO 9737979].

Amine 14 : 4-(4-(5-Methylfuran-2-yl)piperidin-1-yl)aniline.

[0053] Prepared similar to the procedure described in Amine 1 but using 4-(5-methylfuran-2-yl)piperidine [Ref.: WO 9737979].

Amine 15 : 4-(4-(Tetrahydro-2H-pyran-4-yl)piperazin-1-yl)aniline.

[0054] Prepared similar to the procedure described in Amine 1 but using 1-(tetrahydro-2H-pyran-4-yl)piperazine.

Amine 16 : 4-(4-(5-Methyltetrahydrofuran-2-yl)piperidin-1-yl)aniline.

[0055] Prepared similar to the procedure described in Amine 1 but using 4-(5-methyltetrahydrofuran-2-yl)piperidine [Ref.: WO 9737979].

Amine 17 : 4-(4-(6-Oxa-3-azabicyclo[3.1.1]heptan-3-yl)piperidin-1-yl)aniline.

[0056] Prepared similar to the procedure described in Amine 1 but using 3-(piperidin-4-yl)-6-oxa-3-azabicyclo[3.1.1]heptane [Ref.: Synthesis 2011, 16, 2619-2624].

Amine 18 : 1-(1-(4-Aminophenyl)piperidin-4-yl)imidazolidin-2-one.

[0057] Prepared similar to the procedure described in Amine 1 but using 1-(piperidin-4-yl)imidazolidin-2-one.

Amine 19 : 4-(4-(1,3,4-Oxadiazol-2-yl)piperidin-1-yl)aniline.

[0058] Prepared similar to the procedure described in Amine 1 but using 2-(piperidin-4-yl)-1,3,4-oxadiazole [Ref.: Journal of Med. Chem. 51, 15, 4430-4448, 2008].

Amine 20 : 4-(4-(2H-1,2,3-Triazol-2-yl)piperidin-1-yl)aniline.

[0059] Prepared similar to the procedure described in Amine 1 but using 4-(2H-1,2,3-triazol-2-yl)piperidine [Ref.: Tetrahedron letter 53, 6842-52, 2012].

Amine 21 : 4-(4-(1H-1,2,3-Triazol-1-yl)piperidin-1-yl)aniline.

[0060] Prepared similar to the procedure described in Amine 1 but using 4-(1H-1,2,3-triazol-1-yl)piperidine [Ref.: Tetrahedron letter 53, 6842-52, 2012].

Amine 22 : 4-(1-(4-Aminophenyl)piperidin-4-yl)-1H-1,2,4-triazol-5(4H)-one.

[0061] Prepared similar to the procedure described in Amine 1 but using 4-(piperidin-4-yl)-1H-1,2,4-triazol-5(4H)-one [Ref.: WO 2009039257].

Amine 23 : 1-(1-(4-Aminophenyl)piperidin-4-yl)-1H-1,2,4-triazol-5(4H)-one.

[0062] Prepared similar to the procedure described in Amine 1 but using 8-(piperidin-4-yl)-1-oxa-8-azaspiro[4.5]decane [Ref.: BMCL 12, 1759, 2002].

Amine 24 : 4-(4-(1-Oxa-8-azaspiro[4.5]decan-8-yl)piperidin-1-yl)aniline.

[0063] Prepared similar to the procedure described in Amine 1 but using 8-(piperidin-4-yl)-1-oxa-8-azaspiro[4.5]decane [Ref.: BMCL 12, 1759, 2002].

Amine 25 : 4-(4-(5-Methyl-1,3,4-oxadiazol-2-yl)piperidin-1-yl)aniline.

[0064] Prepared similar to the procedure described in Amine 1 but using 2-methyl-5-(piperidin-4-yl)-1,3,4-oxadiazole [Ref.: Journal of Medicinal Chemistry 51, 15, 4430-4448, 2008].

Amine 26 : 4-(4-(5-methyl-1,3,4-thiadiazol-2-yl)piperidin-1-yl)aniline.

[0065] Prepared similar to the procedure described in Amine 1 but using 2-methyl-5-(piperidin-4-yl)-1,3,4-thiadiazole [Ref.: Org. Lett. 2006, 8, 1625-28].

Amine 27 : 4-(4-(Tetrahydro-2H-[1,4]dioxino[2,3-c]pyrrol-6(3H)-yl)piperidin-1-yl)aniline.

[0066] Prepared similar to the procedure described in Amine 1 but using 6-(piperidin-4-yl)hexahydro-2H-[1,4]dioxino[2,3-c]pyrrole [Ref.: Synthesis 1995, 795-800].

Amine 28 : 8-(1-(4-Aminophenyl)piperidin-4-yl)-1-oxa-8-azaspiro[4.5]decan-2-one.

[0067] Prepared similar to the procedure described in Amine 1 but using 8-(piperidin-4-yl)-1-oxa-8-azaspiro[4.5]decan-2-one [Ref.: WO 0187838, BMCL 12, 1759, 2002].

Amine 29 : 5-(1-(4-Aminophenyl)piperidin-4-yl)-1,3,4-oxadiazol-2(3H)-one.

[0068] Prepared similar to the procedure described in Amine 1 but using 5-(piperidin-4-yl)-1,3,4-oxadiazol-2(3H)-one [Ref.: WO 2013093940].

Amine 30 : 4-(4-(4-Cyclopropyl-5-methyl-4H-1,2,4-triazol-3-yl)piperidin-1-yl) aniline.

[0069] Prepared similar to the procedure described in Amine 1 but using 4-(4-cyclopropyl-5-methyl-4H-1,2,4-triazol-3-yl)piperidine [Ref.: BMCL 21,5684-87, 2011].

Amine 31 : 4-(4-(5-Methoxy-1,3,4-oxadiazol-2-yl)piperidin-1-yl)aniline.

[0070] Prepared similar to the procedure described in Amine 1 but using 2-methoxy-5-(piperidin-4-yl)-1,3,4-oxadiazole [Ref.: US 20020111358].

Amine 32 : 4-(4-(1,4-Dioxepan-6-yl)piperazin-1-yl)aniline.

[0071] Prepared similar to the procedure described in Amine 1 but using 1-(1,4-dioxepan-6-yl)piperazine [Ref.: WO 20101139717].

Amine 33 : 4-(4-(4,5-Dihydro-1H-imidazol-2-yl)piperazin-1-yl)aniline.

[0072] Prepared similar to the procedure described in Amine 1 but using 1-(4,5-dihydro-1H-imidazol-2-yl)piperazine [Ref.: WO 2002036562].

Amine 34 : 4-(4-(4,5-Dihydro-1H-imidazol-2-yl)piperidin-1-yl)aniline.

[0073] Prepared similar to the procedure described in Amine 1 but using 4-(4,5-dihydro-1H-imidazol-2-yl)piperidine [Ref.: BMCL 21, 2244-51, 2011].

Amine 35 : 4-(3-(Tetrahydro-2H-[1,4]dioxino[2,3-c]pyrrol-6(3H)-yl)pyrrolidin-1-yl)aniline.

[0074] Prepared similar to the procedure described in Amine 1 but using 6-(pyrrolidin-3-yl)hexahydro-2H-[1,4]dioxino[2,3-c]pyrrole [Ref.: Synthesis 795-800, 1995].

Amine 36 : 4-(4-(5-Methyl-1,3,4-oxadiazol-2-yl)piperazin-1-yl)aniline.

[0075] Prepared similar to the procedure described in Amine 1 but using 2-methyl-5-(piperazin-1-yl)-1,3,4-oxadiazole.

Amine 37 : 1-(1-(4-Aminophenyl)piperidin-4-yl)pyrrolidine-3,4-diol.

[0076] Prepared similar to the procedure described in Amine 1 but using 1-(piperidin-4-yl)pyrrolidine-3,4-diol.

Amine 38 : 4-(4-(3-Oxa-8-azabicyclo[3.2.1]octan-8-yl)piperidin-1-yl)aniline.

[0077] Prepared similar to the procedure described in Amine 1 but using 8-(piperidin-4-yl)-3-oxa-8-azabicyclo[3.2.1]octane [Ref.: WO2005108402].

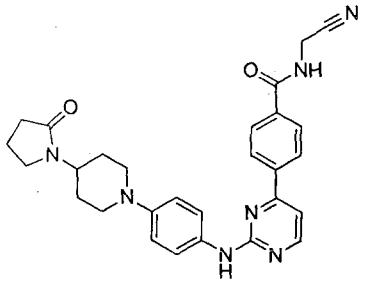
Amine 39 : 1-(3-(1-(4-Aminophenyl)piperidin-4-yl)-3,6-diazabicyclo [3.1.1] heptan-6-yl) ethanone.

[0078] Prepared similar to the procedure described in Amine 1 but using 1-(3-(piperidin-4-yl)-3,6-diazabicyclo[3.1.1]heptan-6-yl)ethanone [Ref.: WO2011120854].

[0079] The invention is further exemplified by the following examples below, which provides some of the several preferred embodiments of the present invention. These examples are provided merely as representative embodiments and should not be construed to limit the scope of the invention in any way.

Example 1 : Preparation of N-(cyanomethyl)-4-(2-((4-(4-(2-oxopyrrolidin-1-yl) piperidin-1-yl)phenyl)amino) pyrimidin-4-yl)benzamide.

[0080]



Step 1 : Preperation of ethyl 4-(2-((4-(4-(2-oxopyrrolidin-1-yl)piperidin-1-yl) phenyl) amino) pyrimidin-4-yl)benzoate.

[0081] To a solution of ethyl 4-(2-chloropyrimidin-4-yl)benzoate (7.09 g, 27.0 mmol), in isopropyl alcohol [100 mL] was added 1-(1-(4-aminophenyl)piperidin-4-yl)pyrrolidin-2-one (7.0 g, 27.0 mmol). To this, trifluoro acetic acid (4.62 g, 40.0 mmol) was added and mixture was heated at 120 °C in sealed tube for 16 h. After completion of reaction, mixture was quenched in water, basified with ammonia solution and extracted with ethyl acetate. Organic layer was washed with water, dried over sodium sulfate and removed under reduced pressure to give crude off white solid compound. Purification of crude product was done by the way of column chromatography (SiO_2, hexane to 30 % EtOAc in hexane) to get solid compound (10.7 g, 82%). The title compound was characterized by spectral analysis. ESI-MS: 486.2 $(M+H)^+$.

Step 2: Preparation of 4-(2-((4-(4-(2-oxopyrrolidin-1-yl)piperidin-1-yl)phenyl) amino)pyrimidin-4-yl)benzoic acid.

Ethyl 4-(2-((4-(4-(2-oxopyrrolidin-1-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzoate

[0082] (25.0 g, 51.5 mmol) was dissolved in 3:1 methanol/THF(100 mL). To this lithium hydroxide (9.86 g, 412 mmol) in water (25 mL) was added and mixture was refluxed for 2 h., cooled, concentrated and acidified with dil HCl. The dark precipitate was filtered, washed with water and dried under vacuum to give title compound (20.0 g, 85 %). The title compound was characterized by spectral analysis ESI-MS: 458.2 $(M+H)^+$.

Step 3 : N-(cyanomethyl)-4-(2-((4-(4-(2-oxopyrrolidin-1-yl)piperidin-1-yl)phenyl) amino) pyrimidin-4-yl)benzamide

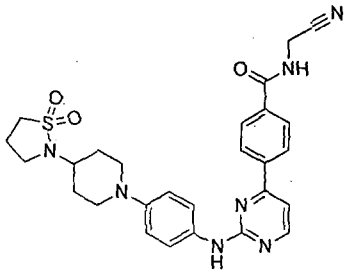
[0083] To a solution of 4-(2-((4-(4-(2-oxopyrrolidin-1-yl)piperidin-1-yl)phenyl)amino) pyrimidin-4-yl)benzoic acid [20.0 g, 43.7 mmol] in 200 mL DMF, was added HOBt [8.03g, 52.5 mmol]. To this reaction mixture, was added EDAC.HCl [10.06 g, 52.5 mmol], 2-aminoacetonitrile hydrochloride [8.09 g, 87 mmol] and triethyl amine [26.5 g, 262 mmol] under N_2 at 0-5 °C. The resulting reaction mixture was stirred at 25 °C for 16 h. Mixture was diluted with water. The aqueous layer was extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated *in vacuo* to afford semi solid compound. Purification of crude product was done by the way of column chromatography (SiO_2, $CHCl_3$ to 4 % MeOH in $CHCl_3$) to get yellow solid compound (600 mg, 46%). ^1H NMR (400 MHz, d_6-DMSO) : 9.47 (s, 1H), 9.33 (1H, *t, J*= 5.8 Hz,), 8.53 (1H, d, *J* = 5.2 Hz), 8.26 (2H, d , *J* = 8.4 Hz), 8.02 (2H, *d, J* = 8.4 Hz), 7.64

(2H, d, *J* = 8.8 Hz), 7.39 (1H, d , *J* = 5.2 Hz), 6.94 (2H, d, *J* = 9.2 Hz), 4.35 (2H, d, *J* = 5.6 Hz), 3.88 (1H, m), 3.68 - 3.66 (2H, m), 3.44 (2H, m), 2.71 - 2.66 (2H, m), 2.25 - 2.13 (2H, m), 1.93 - 1.89 (2H, m), 1.80 - 1.76 (2H, m), 1.63 - 1.61 (2H, m). ESI-MS: $(M)^+$: 496.05. UPLC t_{ret}: 2.57 min.

[0084] Several compounds of the present invention were prepared following the processes described above along with suitable modifications, alterations etc. as are within the scope of a skilled person.

Example 2 : Preparation of N-(cyanomethyl)-4-(2-((4-(4-(1,1-dioxido isothiazolidin-2-yl) piperidin-1-yl) phenyl)amino)pyrimidin-4-yl)benzamide.

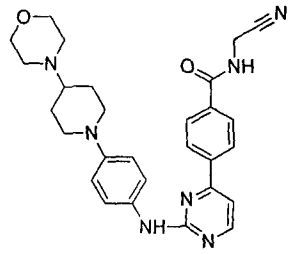
[0085]



[0086] Prepared similar to the procedure described in Example 1 but using **Ester 1** and **Amine 2** as starting materials. The title compound was obtained as yellow solid. ^{1}H NMR (400 MHz, d_6-DMSO) : 9.47 (1H, s), 9.33 (1H, t, *J*= 5.2 Hz), 8.53 (1H, d, *J* = 5.2 Hz), 8.26 (2H, *d, J* = 8.4 Hz), 8.01 (2H, d, *J* = 8.4 Hz), 7.64 (2H, d, *J* = 9.2 Hz), 7.40 (1H, d, *J* = 5.2 Hz), 6.93 (2H, d, *J* = 8.8 Hz), 4.35 (2H, d, *J* = 5.6 Hz), 3.64 (2H, d, *J* = 13.2 Hz), 3.42-3.17 (4H, m), 2.67-2.66 (3H, m), 2.30-2.10 (2H, m), 1.85-1.70 (4H, m). ESI-MS: 531.90 $(M+H)^+$. UPLC t_{ret}: 2.73 min.

Example 3 : Preparation of N-(cyanomethyl)-4-(2-((4-(4-morpholinopiperidin-1-yl)phenyl) amino)pyrimidin-4-yl)benzamide.

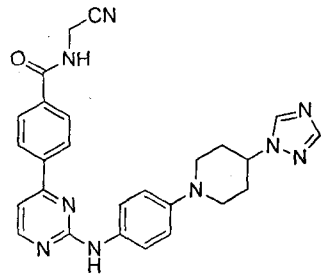
[0087]



[0088] Prepared similar to the procedure described in Example 1 but using **Ester 1** and **Amine 3** as starting material. The title compound was obtained as yellow solid. ^{1}H NMR (400 MHz, d_6-DMSO) : 9.47 (1H, s), 9.33 (1H, t, *J*= 5.2 Hz), 8.53 (1H, *d, J* = 5.2 Hz), 8.26 (2H, d, *J* = 8.4 Hz), 8.02 (2H, d, *J* = 8.4 Hz), 7.63 (2H, d, *J* = 8.8 Hz), 7.44 (1H, d, *J* = 5.2 Hz), 6.92 (2H, d, *J* = 9.2 Hz), 4.35 (2H, d, *J* = 5.6 Hz), 3.65-3.56 (6H, m), 2.73-2.52 (2H, m), 2.50-2.47 (4H, m), 2.23 (1H, *t, J*= 3.6 Hz), 1.87-1.85 (2H, m), 1.52-1.45 (2H, m). ESI-MS: = 514.20 $(M+NH_4)^+$. UPLC t_{ret} : 2.37 min.

Example 4 : Preparation of 4-(2-((4-(4-(1H-1,2,4-triazol-1-yl)piperidin-1-yl) phenyl)amino) pyrimidin-4-yl)-N-(cyanomethyl)benzamide.

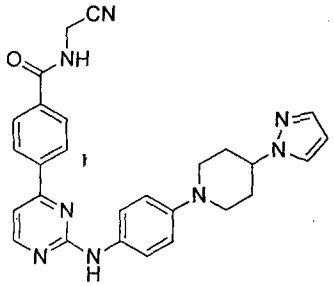
[0089]



[0090] Prepared similar to the procedure described in Example 1 but using **Ester 1** and **Amine 4** as starting materials. The title compound was obtained as yellow solid. ^{1}H NMR (400 MHz, d_6-DMSO): 9.51 (1H, s), 9.35 (1H, t, *J* = 5.2 Hz), 8.61 (1H, s), 8.55 (1H, d, *J* = 5.2 Hz), 8.28 (2H, d, *J* = 8.4 Hz), 8.02 (2H, d, *J* = 8.4 Hz), 7.91 (1H, S), 7.65 (2H, d, *J*= 8.8 Hz), 7.41 (1H, d, *J* = 5.2 Hz), 7.0 (2H, d, *J*= 8.8 Hz), 4.4 (1H, m), 4.3 (1H, d, *J*= 5.6 Hz), 3.74-3.71 (2H, m), 2.9-2.8 (2H, m), 2.3 -2.1 (4H, m). ESI-MS : 480.20 $(M+H)^+$. UPLC t_{ret}: 2.56 min

Example 5 : Preparation of 4-(2-((4-(4-(1H-pyrazol-1-yl)piperidin-1-yl)phenyl) amino) pyrimidin-4-yl)-N-(cyanomethyl)benzamide.

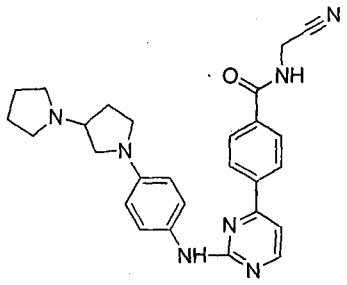
[0091]



[0092] Prepared similar to the procedure described in Example 1 but using **Ester 1** and **Amine 5** as starting materials. The title compound was obtained as light yellow solid. ^{1}H NMR (400 MHz, d_6-DMSO) : 9.50 (1H, s), 9.34 (1H, t, *J*= 5.2 Hz), 8.54 (1H, d, *J* = 5.2 Hz), 8.27 (2H, d, *J* = 8.4 Hz), 8.02 (2H, d, *J* = 8.4 Hz), 7.81 (1H, d, *J* = 2.0 Hz), 7.66 (2H, d, *J*= 8.8 Hz), 7.45 (1H, d, *J*= 4 Hz), 7.40 (1H, d, *J* = 5.2 Hz), 6.98 (2H, d, *J* = 8.8 Hz), 6.24 (1H, t, *J* = 2 Hz), 4.36-4.33 (3H, m), 3.71-3.74 (2H, m), 2.85-2.78 (2H, m), 2.04 -2.10 (4H, m). ESI-MS : 479.35 $(M+H)^+$. UPLC t_{ret} : 2.83 min.

Example 6 : Preparation of 4-(2-((4-([1,3'-Bipyrrolidin]-1'-yl)phenyl) amino)pyrimidin-4-yl)-N-(cyanomethyl) benzamide.

[0093]

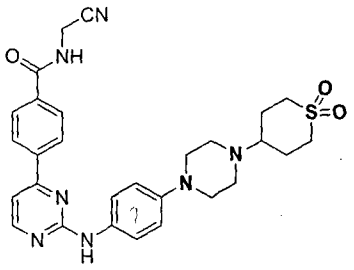


[0094] Prepared similar to the procedure described in Example 1 but using **Ester 1** and **Amine 6** as starting materials. The title compound was obtained as dark yellow solid. ^{1}H NMR (400 MHz, d_6-DMSO): 9.32 (2H, t, *J*= 5.2 Hz), 9.30 (1H, s), 8.49 (1H, d, *J* = 5.2 Hz), 8.25 (2H, d, *J* = 8.8 Hz), 8.01 (2H, d, *J* = 8.8 Hz), 7.56 (2H, d, *J*= 8.8 Hz), 7.35 (1H, d, *J* = 5.2 Hz), 6.53 (2H, d, *J* = 9.2 Hz), 4.35 (2H, d, *J* = 5.2 Hz), 3.41-3.43 (1H, m), 3.32-3.26 (2H, m), 3.09-3.05 (1H, m), 2.85-2.81 (1H, m), 2.70-2.69 (4H, m), 2.16-2.14 (1H, m), 1.92-1.85 (1H, m), 1.75-1.70 (4H, m). ESI-MS : 468.12$(M+H)^+$.

UPLC t_{ret}: 2.56 min.

Example 7 : Preparation of N-(cyanomethyl)-4-(2-((4-(4-(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)piperazin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide.

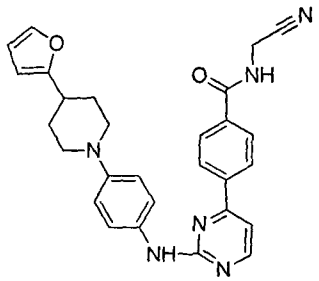
[0095]



[0096] Prepared similar to the procedure described in Example 1 but using **Ester 1** and **Amine 7** as starting material. The title compound was obtained as light yellow solid. ^{1}H NMR (400 MHz, d_6-DMSO): 9.48 (1H, s), 9.33 (1H, t, *J*= 5.6 Hz), 8.53 (1H, d, *J*= 4.8 Hz), 8.26 (2H, d, *J* = 8.4 Hz), 8.02 (2H, d, *J*= 8.4 Hz), 7.64 (2H, d, *J*= 8.8 Hz), 7.40 (1H, d, *J*= 5.2 Hz), 6.92 (2H, d, *J* = 8.8 Hz), 4.35 (2H, d, *J*= 5.6 Hz), 3.08 (8H, m), 2.67-2.66 (4H, m), 2.04 (4H, m). ESI-MS : 545.95$(M+H)^+$. UPLC t_{ret} : 2.51 min.

Example 8 : Preparation of N-(cyanomethyl)-4-(2-((4-(4-(furan-2-yl)piperidin-1-yl)phenyl) amino)pyrimidin-4-yl)benzamide.

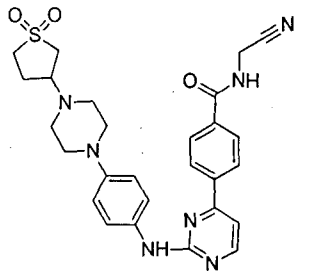
[0097]



[0098] Prepared similar to the procedure described in Example 1 but using **Ester 1** and **Amine 8** as starting material. The title compound was obtained as light yellow solid. ^{1}H NMR (400 MHz, d_6-DMSO): 9.43 (1H, s), 9.33 (1H, *t, J*= 5.6 Hz), 8.53 (1H, d, *J* = 5.2 Hz), 8.02 (2H, d, *J* = 8.4 Hz), 7.65 (2H, d, *J*= 9.2 Hz), 7.53 (1H, t, *J*= 1.6 Hz), 7.39 (1H, d, *J*= 5.2 Hz), 6.95 (2H, d, *J*= 9.2 Hz), 6.38-6.36 (1H, m), 6.13 (1H, d, *J* = 3.2 Hz), 4.35 (2H, d, *J* = 5.6 Hz), 3.65-3.62 (2H, m), 2.78-2.74 (3H, m), 2.10-1.97 (2H, m), 1.82-1.62 (2H, m). ESI-MS : 479.3 $(M+H)^+$. UPLC t_{ret} : 3.24 min.

Example 9 : Preparation of N-(cyanomethyl)-4-(2-((4-(4-(1,1-dioxidotetrahydro thiophen-3-yl)piperazin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide.

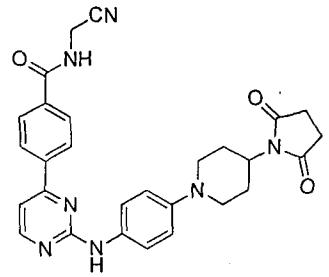
[0099]



[0100] Prepared similar to the procedure described in Example 1 but using **Ester 1** and **Amine 9** as starting material. The title compound was obtained as light yellow solid. ^{1}H NMR (400 MHz, d_6-DMSO): 9.48 (1H, s), 9.33 (1H, t, *J* = 5.6 Hz), 8.53 (1H, d, *J*= 5.2 Hz), 8.26 (2H, d, *J*= 8.8 Hz), 8.02 (2H, d, *J* = 8.8 Hz), 7.65 (2H, d, *J*= 8.8 Hz), 7.39 (1H, *d, J* = 5.2 Hz), 6.92 (2H, *d, J* = 9.2 Hz), 4.32 (2H, *d, J* = 5.6 Hz), 3.40-3.35 (1H, m), 3.28-3.25 (2H, m), 3.12-3.07 (5H, m), 3.04-2.97 (1H, m), 2.68-2.58 (4H, m), 2.36-2.32 (1H, m), 2.02-1.97 (1H, m). ESI-MS : 532.08 $(M+H)^+$. UPLC t_{ret} : 2.52 min.

Example 10 : Preparation of N-(cyanomethyl)-4-(2-((4-(4-(2,5-dioxopyrrolidin-1-yl)piperidin-1-yl)phenyl) amino)pyrimidin-4-yl)benzamide.

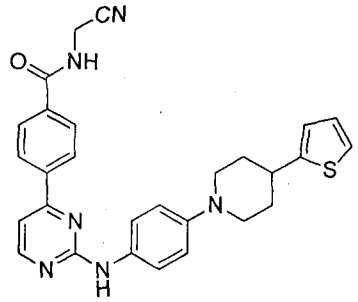
[0101]



[0102] Prepared similar to the procedure described in Example 1 but using **Ester 1** and **Amine 10** as starting material. The title compound was obtained as yellow solid. ^{1}H NMR (400 MHz, d_6-DMSO) : 9.49 (1H, s), 9.34 (1H, *t, J*= 5.6 Hz), 8.53 (1H, d, *J*= 5.2 Hz), 8.26 (2H, *d, J*= 8.8 Hz), 8.02 (2H, d, *J*= 8.8 Hz), 7.63 (2H, d, *J* = 5.2 Hz), 7.40 (1H, d, *J* = 5.2 Hz), 6.93 (2H, d, *J* = 9.2 Hz), 4.35 (2H, d, *J* = 5.6 Hz), 3.99 (1H, m), 3.68 (2H, m), 2.63-2.69 (2H, m), 2.52 (4H, s), 2.32-2.43 (2H, m), 1.56-1.59 (2H, m). ESI-MS : 510.35 $(M+H)^+$.

Example 11 : Preparation of N-(cyanomethyl)-4-(2-((4-(4-(thiophen-2-yl) piperidin-1-yl)phenyl) amino) pyrimidin-4-yl)benzamide.

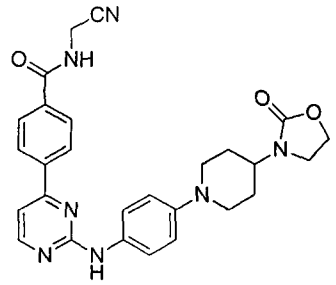
[0103]



[0104] Prepared similar to the procedure described in Example 1 but using **Ester 1** and **Amine 11** as starting material. The title compound was obtained as brown solid. ^{1}H NMR (400 MHz, d_6-DMSO) : 9.49 (1H, s), 9.34 (1H, t, *J*= 5.6 Hz), 8.54 (1H, d, *J* = 5.2 Hz), 8.27 (2H, d, *J* = 8.4Hz), 8.02 (2H, d, *J* = 8.4 Hz), 7.65 (2H, d, *J* = 9.2 Hz), 7.40 (1H, d, *J* = 5.2 Hz), 7.35 (1H, d, *J* = 5.2 Hz), 6.98-6.93 (4H, m), 4.36 (2H, d, *J*= 5.2 Hz), 3.70 (2H, d, *J* = 12.4 Hz), 3.11-2.97 (1H, m),), 2.77-2.72 (2H, m), 2.07-2.03 (2H, d, *J* = 12.8 Hz), 1.77-1.73 (2H, m). ESI-MS : 495.25 $(M+H)^+$. UPLC t_{ret} : 3.39 min.

Example 12 : Preparation of N-(cyanomethyl)-4-(2-((4-(4-(2-oxooxazolidin-3-yl)piperidin-1-yl)phenyl) amino)pyrimidin-4-yl)benzamide.

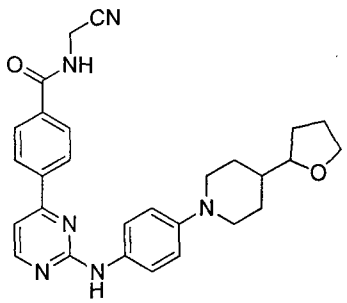
[0105]



[0106] Prepared similar to the procedure described in Example 1 but using **Ester 1** and **Amine 12** as starting material. The title compound was obtained as light yellow solid. ^{1}H NMR (400 MHz, d_6-DMSO) : 10.04 (1H, s), 9.41 (1H, t, *J* = 5.2 Hz), 8.64 (1H, d, *J* = 5.2 Hz), 8.28 (2H, d, *J* = 8.8 Hz), 8.03 (2H, *d, J* = 8.4 Hz), 7.65 (2H, d, J = 9.2 Hz), 7.40 (1H, d, *J*= 5.2 Hz), 6.96 (2H, d, *J*= 9.2 Hz), 4.35 (2H, d, *J*= 5.2 Hz), 4.26 (2H, t, *J*= 6.8 Hz), 3.71-3.63 (3H, m), 3.53 (2H, t, *J* = 6.8 Hz), 2.73-2.67 (2H, m), 1.80-1.74 (4H, m). ESI-MS : 498.30 $(M+H)^+$. UPLC t_{ret} : 2.58 min.

Example 13 : Preparation of N-(cyanomethyl)-4-(2-((4-(4-(tetrahydrofuran-2-yl) piperidin-1-yl)phenyl) amino)pyrimidin-4-yl)benzamide.

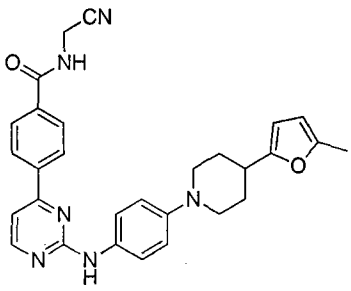
[0107]



[0108] Prepared similar to the procedure described in Example 1 but using **Ester 1** and **Amine 13** as starting material. The title compound was obtained as light yellow solid. ^{1}H NMR (400 MHz, d_6-DMSO) : 9.46 (1H, s), 9.35 (1H, t, *J* = 5.6 Hz), 8.53 (1H, d, *J* = 5.2 Hz), 8.26 (2H, d, *J* = 8.4 Hz), 8.02 (2H, d, *J* = 8.4 Hz), 7.63 (2H, d, *J* = 9.2 Hz), 7.40 (1H, *d, J* = 5.2 Hz), 6.92 (2H, d , *J*= 8.8 Hz), 4.35 (2H, *d, J* = 7.2 Hz), 3.75-3.63 (1H, m), 3.61-3.51 (3H, m), 3.49-3.32 (1H, m), 2.50-2.49 (2H, m), 1.92-1.89 (2H, m), 1.88-1.86 (2H, m), 1.84-1.78 (1H, m), 1.64-1.61 (1H, m), 1.52-1.48 (3H, m). ESI-MS : 483.20 $(M+H)^+$. UPLC t_{ret} : 2.88 min.

Example 14 : Preparation of N-(cyanomethyl)-4-(2-((4-(4-(5-methylfuran-2-yl) piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide.

[0109]

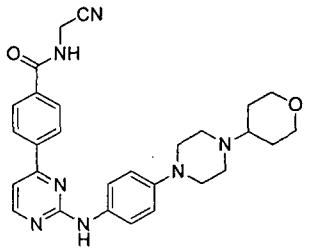


[0110] Prepared similar to the procedure described in Example 1 but using **Ester 1** and **Amine 14** as starting material. The title compound was obtained as light yellow solid. ^{1}H NMR (400 MHz, d_6-DMSO) : 9.48 (1H, s), 9.34 (1H, t, *J*= 4.8

Hz), 8.54 (1H, d, *J* = 5.2 Hz), 8.27 (2H, d, *J* = 8.4 Hz), 8.03 (2H, d, *J* = 8.4 Hz), 7.64 (2H, d, *J* = 8.8 Hz), 7.40 (1H, d, *J* = 5.2 Hz), 6.95 (2H, d, *J*= 9.2 Hz), 5.96 (2H, t, *J* = 2.8 Hz), 4.36 (2H, d, *J* = 5.6 Hz), 2.67-2.60 (2H, m), 2.76-2.67 (3H, m), 2.33 (3H, s), 2.01-1.98 (2H, m), 1.72-1.65 (2H, m). ESI-MS : 493.20 $(M+H)^+$. UPLC t_{ret} : 3.42 min.

Example 15 : Preparation of N-(cyanomethyl)-4-(2-((4-(4-(tetrahydro-2H-pyran-4-yl)piperazin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide.

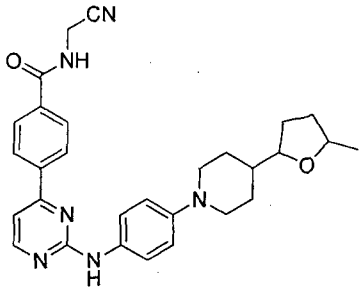
[0111]



[0112] Prepared similar to the procedure described in Example 1 but using **Ester 1** and **Amine 15** as starting material. The title compound was obtained as light yellow solid. ^{1}H NMR (400 MHz, d_6-DMSO): 9.46 (s, 1H), 9.33 (1H, t, *J*= 5.6 Hz), 8.52 (1H, d , *J* = 4.8 Hz), 8.25 (2H, d , *J* = 8.4 Hz), 8.01 (2H, d, *J*= 8.4 Hz), 7.63 (2H, d, *J*= 8.8 Hz), 7.39 (1H, d , *J*= 5.2 Hz), 6.92 (2H, d, *J* = 9.2 Hz), 4.34 (2H, d, *J* = 5.6 Hz), 3.88-3.91 (2H, m), 3.29 (2H, m), 3.07 (4H, m), 2.63 (4H, m) 2.49 (1H, m), 1.73 (2H, m), 1.41 (2H, m). ESI-MS : 498.25 $(M+H)^+$. UPLC t_{ret} : 2.52 min.

Example 16 : Preparation of N-(cyanomethyl)-4-(2-((4-(4-(5-methyltetrahydrofuran-2-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide.

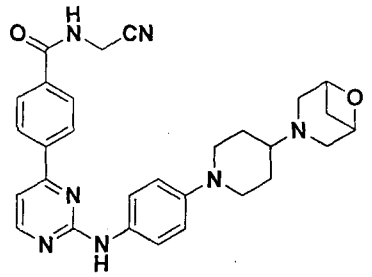
[0113]



[0114] Prepared similar to the procedure described in Example 1 but using **Ester 1** and **Amine 16** as starting material. The title compound was obtained as light yellow solid. ^{1}H NMR (400 MHz, d_6-DMSO): 9.44 (1H, s), 9.32 (1H, bs), 8.51 (1H, d, *J* = 4.8 Hz), 8.24 (2H, d, *J* = 8 Hz), 7.9 (2H, d, *J*= 8.4 Hz), 7.61 (2H, d, *J* = 8.8 Hz), 7.38 (1H, d, *J* = 6 Hz), 6.90 (2H, d, *J* = 8.4 Hz), 4.34 (2H, d, *J* = 5.2 Hz), 3.91-3.82 (1H, m), 3.61-3.58 (2H, m), 3.53-3.51 (1H, m), 1.95-1.75 (4H, m), 1.7-1.62 (2H, m), 1.58-1.27 (4H, m), 1.31-1.11 (3H, m). ESI-MS : 497.20 $(M+H)^+$. UPLC t_{ret} : 3.10 min.

Example 17 : Preparation of 4-(2-((4-(4-(6-oxa-3-azabicyclo[3.1.1]heptan-3-yl) piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)-N-(cyanomethyl)benzamide.

[0115]



Step I : Preparation of ethyl 4-(2-((4-(4-(6-oxa-3-azabicyclo[3.1.1]heptan-3-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzoate.

[0116] Placed ethyl 4-(2-chloropyrimidin-4-yl)benzoate [4.37 g, 16.64 mmol] in rb flask followed by DMA [60 mL]. To this, 4-(4-(6-oxa-3-azabicyclo[3.1.1]heptan-3-yl)piperidin-1-yl)aniline (**Amine 17**) [3.5 g, 12.80 mmol], cesium carbonate [6.26 g, 19.20 mmol], BINAP [1.19 g, 1.92 mmol] and bis triphenyl phosphie Pd (II)dichloride [1.34 g, 1.92 mmol] was added at 25°C under N_2 atm. The mixture was heated to 90°C for 16 h. After completion of reaction mixture was quanched in water, compound was extracted with ethyl acetate (50 mL X 4). Combined the organic layers and washed with water and brine soln. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford desired product as light yellow solid. Title compound was characterised by spectral analysis. ESI-MS : 500.30 $(M+H)^+$.

Step II : Preparation of 4-(2-((4-(4-(6-oxa-3-azabicyclo[3.1.1]heptan-3-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzoic acid.

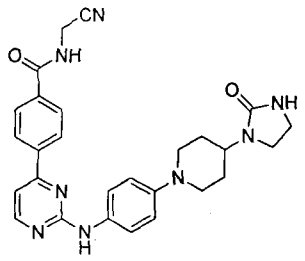
[0117] 4-(2-(4-(4-(6-oxa-3-azabicyclo[3.1.1]heptan-3-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzoic acid was prepared by following method as describe in Example 1 Step II using ethyl 4-(2-((4-(4-(6-oxa-3-azabicyclo[3.1.1]heptan-3-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzoate.

Step III. Preparation of 4-(2-((4-(4-(6-oxa-3-azabicyclo[3.1.1]heptan-3-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)-N-(cyanomethyl)benzamide.

[0118] 4-(2-((4-(4-(6-oxa-3-azabicyclo[3.1.]heptan-3-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)-N-(cyanomethyl)benzamide was synthesised by following method as described in Example 1 step II using 4-(2-((4-(4-(6-oxa-3-azabicyclo[3.1.1]heptan-3-yl)piperidin-1-yl)phenyl) amino) pyrimidin-4-yl)benzoic acid. The title compound was obtained as green solid. ^{1}H NMR (400 MHz, d_6-DMSO) : 9.47 (s, 1H), 9.33 (1H, t, *J* = 5.2 Hz), 8.53 (1H, d, *J* = 5.2 Hz), 8.26 (2H, *d, J*= 8.8 Hz), 8.32 (2H, d, *J*= 8.8 Hz), 7.63 (2H, d, *J*= 9.2 Hz), 7.39 (1H, d, *J*= 5.2 Hz), 6.93 (2H, d, *J*= 9.2 Hz), 4.44-4.43 (2H, m), 4.35 (2H, d, *J* = 5.2 Hz), 3.62-3.59 (2H, m), 3.05-3.03 (2H, m), 2.83-2.81 (1H, m), 2.74-2.69 (3H, m), 2.66 (2H, m), 2.32 (1H, m), 1.96-1.93 (2H, m), 1.59-1.56 (2H, m). ESI-MS : 510.15 $(M+H)^+$. UPLC t_{ret} : 2.35 min.

Example 18 : Preparation of N-(cyanomethyl)-4-(2-((4-(4-(2-oxoimidazolidin-1-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide.

[0119]

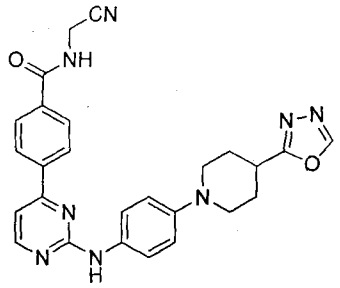


[0120] Prepared similar to the procedure described in Example 17 but using **Ester 1** and **Amine 18** as starting material. The title compound was obtained as light yellow solid. ^{1}H NMR (400 MHz, d_6-DMSO): 9.47 (1H, s), 9.43 (1H, bs), 8.53 (1H, d, *J* = 4.8 Hz), 8.26 (2H, d, *J* = 8.0 Hz), 8.02 (2H, d, *J* = 8.0 Hz) 7.64 (2H, d, *J* = 8.8 Hz), 7.40 (1H, d, J = 4.8 Hz), 6.94 (2H, d, *J*= 8.4 Hz) 6.26 (1H, s), 4.36 (2H, d, *J* = 4.8 Hz), 3.58-3.68 (3H, m), 3.21-3.23 (2H, m), 2.64-2.70 (2H, m),

1.70-1.78 (2H, m), 1.61-1.64 (2H, m). ESI-MS : 497.40 $(M+H)^+$. UPLC t_{ret} : 2.48 min.

Example 19 : Preparation of 4-(2-((4-(4-(1,3,4-oxadiazol-2-yl)piperidin-1-yl)phenyl) amino) pyrimidin-4-yl)-N-(cyanomethyl)benzamide.

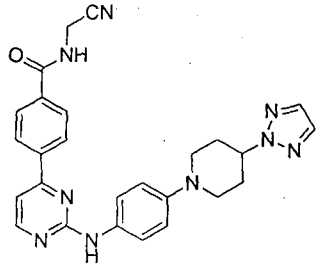
[0121]



[0122] Prepared similar to the procedure described in Example 1 but using **Ester 1** and **Amine 19** as starting material. The title compound was obtained as light yellow solid. ^{1}H NMR (400 MHz, d_6-DMSO) : 9.47 (1H, s), 9.34 (1H, t, *J* = 5.2 Hz), 9.16 (1H, s), 8.53 (1H, d, *J* = 5.2 Hz), 8.26 (2H, d, *J*= 8.4 Hz), 8.02 (2H, d, *J* = 8.4 Hz), 7.44 (2H, d, *J* = 8.8 Hz), 7.40 (1H, d, *J* = 5.2 Hz), 6.98 (2H, d, *J*= 5.2 Hz), 4.35 (2H, d, *J*= 5.2 Hz), 3.63-3.60 (2H, s), 3.14-3.19 (1H, m), 2.83-2.80 (2H, m), 2.13-2.19 (2H, m), 1.88-1.85 (2H, m). ESI-MS : 481.05 $(M+H)^+$. UPLC t_{ret} : 2.52 min.

Example 20 : Preparation of 4-(2-((4-(4-(2H-1,2,3-triazol-2-yl)piperidin-1-yl) phenyl)amino) pyrimidin-4-yl)-N-(cyanomethyl)benzamide.

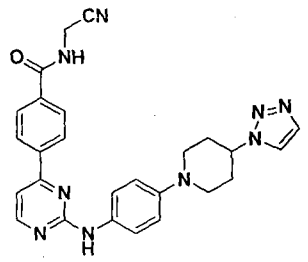
[0123]



[0124] Prepared similar to the procedure described in Example 17 but using **Ester 1** and **Amine 20** as starting material. The title compound was obtained as light yellow solid. ^{1}H NMR (400 MHz, d_6-DMSO): 9.50 (1H, s), 9.34 (1H, *t, J*= 5.6 Hz), 8.55 (1H, d, *J* = 5.2 Hz), 8.28 (2H, d, *J* = 8.4 Hz), 8.03 (2H, d, *J* = 8.8 Hz), 7.80 (2H, s), 7.67 (2H, d, *J* = 9.2 Hz), 7.41 (1H, d, *J* = 5.2 Hz), 7.00 (2H, d, *J* = 9.2 Hz), 4.70 (1H, m), 4.36 (2H, d, *J* = 5.2 Hz), 3.71-3.68 (2H, m), 2.94-2.88 (2H, m), 2.11-2.18 (4H, m). ESI-MS : 479.85 $(M+H)^+$. UPLC t_{ret} : 2.85 min.

Example 21 : Preparaion of 4-(2-((4-(4-(1H-1,2,3-triazol-1-yl)piperidin-1-yl)phenyl)amino) pyrimidin-4-yl)-N-(cyanomethyl)benzamide.

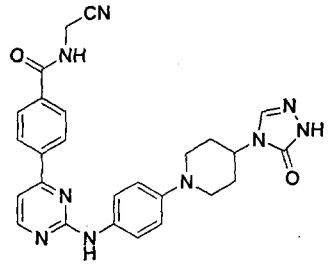
[0125]



[0126] Prepared similar to the procedure described in Example 1 but using **Ester 1** and **Amine 21** as starting material. The title compound was obtained as light yellow solid. ^{1}H NMR (400 MHz, d_6-DMSO) : 9.5 (1H, s), 9.34 (1H, t, *J*= 5.2 Hz), 8.55 (1H, *d, J*= 5.2 Hz), 8.28 (2H, d, *J* = 8.4 Hz), 8.27 (1H, s), 8.03 (2H, d, *J*= 8.8 Hz), 7.80 (1H, s), 7.67 (2H, d, *J* = 9.2 Hz), 7.41 (1H, *d, J* = 5.2 Hz), 7.00 (2H, d, *J* = 9.2 Hz), 4.70-4.67 (1H, m), 4.36 (2H, d, *J*= 5.2 Hz), 3.75-3.72 (2H, m), 2.88-2.94 (2H, m), 2.11-2.18 (4H, m). ESI-MS : 479.85 $(M+H)^+$. UPLC t_{ret} : 2.85 min.

Example 22 : Preparation of N-(cyanomethyl)-4-(2-((4-(4-(5-oxo-1H-1,2,4-triazol-4(5H)-yl) piperidin-1-yl) phenyl)amino)pyrimidin-4-yl)benzamide.

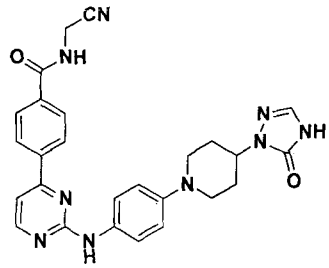
[0127]



[0128] Prepared similar to the procedure described in Example 1 but using **Ester 1** and **Amine 22** as starting material. The title compound was obtained as yellow solid. ^{1}H NMR (400 MHz, d_6-DMSO) : 13.28 (1H, s) 9.48 (1H, s), 9.33 (1H, t, *J* = 5.2 Hz), 8.54 (1H, *d, J* = 5.2 Hz), 8.27-8.22 (3H, m) 8.00 (2H, d, *J* = 8.8 Hz), 7.64 (2H, d, *J* = 8.8 Hz), 7.40 (1H, d, *J* = 5.2 Hz), 6.96 (2H, d, *J* = 8.8 Hz), 4.74-4.73 (1H, m), 4.35 (2H, d, *J*= 8.8 Hz), 3.42-3.31 (2H,m), 3.00-2.95 (2H, m), 2.10-2.08 (2H, m), 1.80-1.77 (2H, m). ESI-MS : 518.18 $(M+Na)^+$. UPLC t_{ret} : 2.49 min

Example 23 : Preparation of N-(cyanomethyl)-4-(2-((4-(4-(5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide.

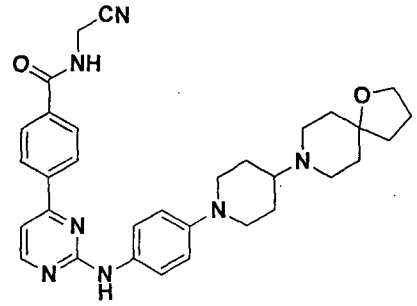
[0129]



[0130] Prepared similar to the procedure described in Example 1 but using **Ester 1** and **Amine 23** as starting material. The title compound was obtained as light yellow solid. ^{1}H NMR (400 MHz, d_6-DMSO) : 11.65 (1H, s) 9.50 (1H, s), 9.34 (1H, t, *J* = 5.2 Hz), 8.54 (1H, d, *J* = 5.2 Hz), 8.27-8.22 (3H, m) 8.00 (2H, d, *J* = 8.8 Hz), 7.64 (2H, d, *J* = 8.8 Hz), 7.4 (1H, d, *J*= 5.2 Hz), 6.96 (2H, d, *J* = 8.8 Hz), 4.74-4.73 (1H, m), 4.35 (2H, d, *J* = 8.8 Hz), 3.42-3.31 (2H, m), 3.00-2.95 (2H, m), 2.10-2.08 (2H, m), 1.80-1.77 (2H, m). ESI-MS : 518.18 $(M+Na)^+$. UPLC t_{ret} : 2.49 min.

Example 24 : Preparation of 4-(2-((4-(4-(1-oxa-8-azaspiro[4.5]decan-8-yl)piperidin-1-yl) phenyl) amino)pyrimidin-4-yl)-N-(cyanomethyl)benzamide.

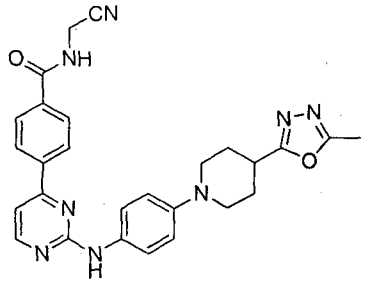
[0131]



[0132] Prepared similar to the procedure described in Example 1 but using **Ester 1** and **Amine 24** as starting material. The title compound was obtained as light yellow solid. ^{1}H NMR (400 MHz, d_6-DMSO) : 9.44 (1H, s), 9.32 (1H, t, *J* = 5.2 Hz), 8.51 (1H, d, *J* = 5.2 Hz), 8.25 (2H, d, *J* = 8.4 Hz), 7.99 (2H, d, *J* = 8.4 Hz), 7.62 (2H, d, *J* = 8.8 Hz), 7.39 (1H, *d, J* = 5.2 Hz), 6.91 (2H, d, *J* = 8.8 Hz), 4.33 (2H, t, *J* = 5.2 Hz), 3.68-3.65 (4H, m) 2.57-2.48 (6H, m), 1.81-1.79 (4H, m), 1.61-1.59 (3H, m), 1.51-1.49 (6H, m). ESI-MS : 552.20 $(M+H)^+$. UPLC t_{ret} : 2.63 min.

Example 25 : Preparation of N-(cyanomethyl)-4-(2-((4-(4-(5-methyl-1,3,4-oxadiazol-2-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide.

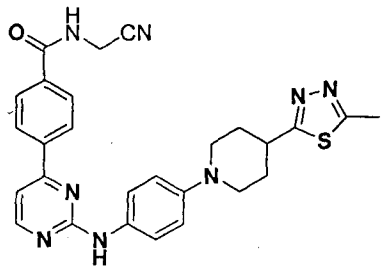
[0133]



[0134] Prepared similar to the procedure described in Example 17 but using **Ester 1** and **Amine 25** as starting material. The title compound was obtained as light yellow solid. ^{1}H NMR (400 MHz, d_6-DMSO) : 9.48 (s, 1H); 9.33 (1H, t, *J* = 5.2 Hz), 8.53 (1H, d, *J* = 5.2 Hz), 8.26 (2H, d, *J* = 8.0 Hz), 8.00 (2H, d, *J* = 8.4 Hz), 7.65 (2H, d, *J* = 8.8 Hz), 7.40 (1H, d, *J*= 5.2 Hz), 6.95 (2H, d, *J* = 8.8 Hz), 4.35 (2H, d, *J* = 5.6 Hz), 3.63-3.59 (2H, m), 3.09-3.07 (2H, m), 2.85-2.80 (2H, m), 2.49 (2H, s), 2.09-2.06 (2H, m), 1.85-1.82 (2H, m). ESI-MS : 495.25 $(M+H)^+$. UPLC t_{ret} : 2.65 min.

Example 26 : Preparation of N-(cyanomethyl)-4-(2-((4-(4-(5-methyl-1,3,4-thiadiazol-2-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide.

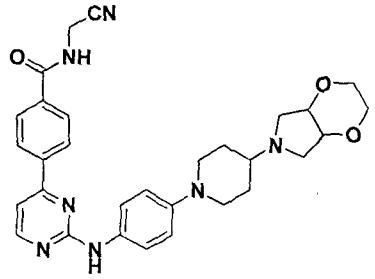
[0135]



[0136] Prepared similar to the procedure described in Example 17 but using **Ester 1** and **Amine 26** as starting material. The title compound was obtained as light yellow solid. ^{1}H NMR (400 MHz, d_6-DMSO) : 9.49 (1H, s), 9.42 (1H, t, *J*= 5.2 Hz), 8.52 (1H, d, *J* = 5.2 Hz), 8.25 (2H, d, *J* = 8.4 Hz), 8.01 (2H, d, *J*= 8.4 Hz), 7.64 (2H, d, *J*= 8.4 Hz), 7.39 (1H, d, *J* = 5.2 Hz), 6.95 (2H, d, *J*= 9.2 Hz), 4.34 (2H, *d, J*= 5.2 Hz), 3.65 (1H, d, *J* = 12.4 Hz), 3.29-3.26 (1H, m), 2.79 (2H, t, J = 10 hz), 2.69 (3H, s), 2.14-2.11 (2H, m), 1.85-1.82 (2H, m). ESI-MS : 511.50 $(M+H)^+$. UPLC t_{ret} : 2.71 min.

Example 27 : Preparation of N-(cyanomethyl)-4-(2-((4-(4-(tetrahydro-2H-[1,4]dioxino[2,3-c]pyrrol-6(3H)-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide.

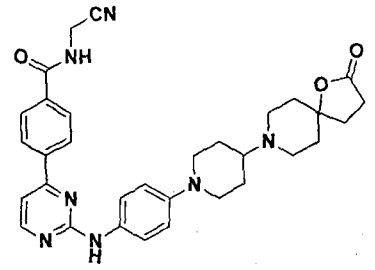
[0137]



[0138] Prepared similar to the procedure described in Example 1 but using **Ester 1** and **Amine 27** as starting material. The title compound was obtained as light yellow solid. ^{1}H NMR (400 MHz, d_6-DMSO) : 9.46 (1H, s), 9.33 (1H, t, *J* = 5.6 Hz), 8.52 (1H, d, *J* = 5.2 Hz), 8.25 (2H, d, *J*= 8.4 Hz), 8.01 (2H, d, *J*= 8.8 Hz), 7.61 (2H, d, *J* = 9.2 Hz), 7.39 (1H, d, *J*= 5.2 Hz), 6.90 (2H, d, *J* = 9.2 Hz), 4.34 (2H, d, *J* = 5.6 Hz), 3.91-3.97 (2H, m), 3.68-2.65 (2H, m), 3.45-2.57 (4H, m), 2.87-2.84 (2H, m), 2.66-2.64 (2H, m), 2.63-2.53 (3H, m), 1.90-1.88 (2H, m), 1.55-1.53 (2H, m). ESI-MS : 540.35 $(M+H)^+$. UPLC t_{ret} : 2.46 min.

Example 28: Preparation of N-(cyanomethyl)-4-(2-((4-(4-(2-oxo-1-oxa-8-azaspiro[4.5]decan-8-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide.

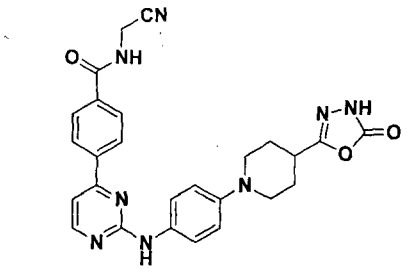
[0139]



[0140] Prepared similar to the procedure described in Example 1 but using **Ester 1** and **Amine 28** as starting material. The title compound was obtained as light yellow solid. ^{1}H NMR (400 MHz, d_6-DMSO): 9.46 (1H, s), 9.33 (1H, t, *J* = 5.2 Hz), 8.52 (1H, *d, J* = 5.2 Hz), 8.26 (2H, d, *J* = 8.4 Hz), 8.00 (2H, d, *J* = 8.4 Hz), 7.61 (2H, d, *J*= 9.2), 7.38 (1H, d, *J* = 5.2 Hz), 6.80 (2H, d, *J*= 9.2 Hz), 4.34 (2H, d, *J* = 5.6 Hz), 3.70-3.66 (2H, m), 2.50-2.49 (7H, m), 2.33-2.32 (2H, m), 1.99-1.95 (2H, m), 1.85-1.77 (4H, m), 1.62-1.52 (2H, m),1.51-1.47 (2H, m). ESI-MS : 566.22 $(M+H)^+$. UPLC t_{ret} : 2.50 min.

Example 29 : Preparation of N-(cyanomethyl)-4-(2-((4-(4-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide.

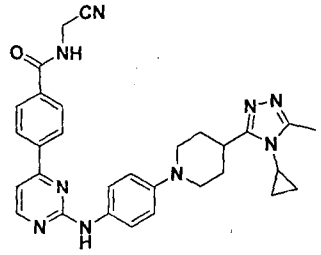
[0141]



[0142] Prepared similar to the procedure described in Example 17 but using **Ester 1** and **Amine 29** as starting material. The title compound was obtained as light yellow solid. ^{1}H NMR (400 MHz, d_6-DMSO): 12.10 (1H, s), 9.48 (1H, s), 9.33 (1H, t, *J* = 5.6 Hz), 8.53 (1H, d, *J*= 5.2 Hz), 8.26 (2H, d, *J*= 8.0 Hz), 8.02 (2H, d, *J*= 8.8 Hz), 7.64 (2H, d, *J* = 9.2 Hz), 7.40 (1H, d, *J* = 5.2 Hz), 6.95 (2H, d, *J* = 9.2 Hz), 4.35 (2H, *d, J*= 5.2 Hz), 3.60-3.57 (2H, m), 2.80-2.74 (3H, m), 2.00-1.98 (2H, m), 1.74-1.71 (2H, m). ESI-MS : 497.10 $(M+H)^+$. UPLC t_{ret} : 2.67 min.

Example 30 : Preparation of N-(cyanomethyl)-4-(2-((4-(4-(4-cyclopropyl-5-meth yl-4H-1,2,4-triazol-3-yl) piperidin-1-yl)phenyl)amino)pyrimidin-4-yl) benzamide.

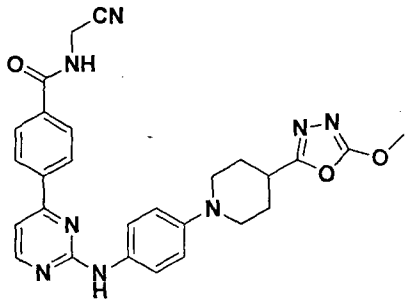
[0143]



[0144] Prepared similar to the procedure described in Example 1 but using **Ester 1** and **Amine 30** as starting material. The title compound was obtained as light yellow solid. ^{1}H NMR (400 MHz, d_6-DMSO) : 9.48 (1H,s), 9.33 (1H, *t, J*= 5.2 Hz), 8.53 (1H, *d, J* = 5.2 Hz), 8.26 (2H, d, *J* = 8.4 Hz); 8.02 (2H, d, *J* = 8.8 Hz), 7.65 (2H, d, *J* = 9.2 Hz), 7.40 (1H, d, *J* = 5.2 Hz), 6.97 (2H, d, *J*= 9.2 Hz) 4.35 (2H, d, *J* = 5.6 Hz), 3.72-3.69 (2H, m), 3.17-3.13 (1H, m); 3.00-3.02 (1H, m), 2.77-2.66 (2H, m), 2.33 (3H, s), 2.04-2.01 (2H, m), 1.86-1.84 (2H, m), 1.10-1.09 (2H, m), 1.0-0.98 (2H, m). ESI-MS : 543.30 $(M+H)^+$. UPLC t_{ret} : 2.59 min.

Example 31 : Preparation of N-(cyanomethyl)-4-(2-((4-(4-(5-methoxy-1,3,4-oxadiazol-2-yl)piperidin-1-yl)phenyl) amino)pyrimidin-4-yl)benzamide.

[0145]

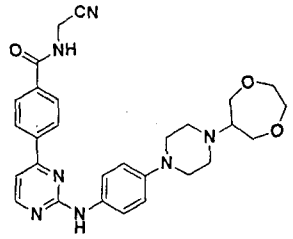


[0146] Prepared similar to the procedure described in Example 1 but using **Ester 1** and **Amine 31** as starting material. The title compound was obtained as light yellow solid. ^{1}H NMR (400 MHz, d_6-DMSO) : 9.48 (1H, s), 9.33 (1H, t, *J* = 5.6 Hz), 8.53 (1H, d, *J* = 5.2 Hz), 8.26 (2H, d, *J* = 8.4 Hz), 8.02 (2H, d, *J* = 8.8 Hz), 7.64 (2H, d, *J* = 8.8 Hz), 7.40 (1H, d, *J* = 5.2 Hz), 6.94 (2H, d, *J* = 9.2 Hz), 4.35 (2H, d, *J* = 5.2 Hz), 3.62-3.58 (2H, m), 3.28 (3H, s), 2.83-2.66 (3H, m) 2.01-1.98

(2H, m) 1.74-1.72 (2H, m). ESI-MS : 511.25 $(M+H)^+$. UPLC t_{ret} : 2.83 min.

Example 32 : Preparation of 4-(2-((4-(4-(1,4-dioxepan-6-yl)piperazin-1-yl) phenyl)amino) pyrimidin-4-yl)-N-(cyanomethyl) benzamide.

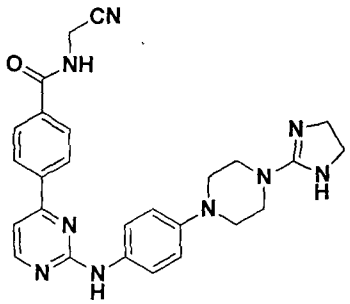
[0147]



[0148] Prepared similar to the procedure described in Example 1 but using **Ester 1** and **Amine 32** as starting material. The title compound was obtained as light yellow solid. ^{1}H NMR (400 MHz, d_6-DMSO) : 9.47 (1H, s), 9.32 (1H, t, *J*= 5.2 Hz), 8.52 (1H, d, *J* = 5.2 Hz), 8.25 (2H, d, *J* = 8.4 Hz), 8.00 (2H, d, *J* = 8 Hz), 7.62 (2H, d, *J* = 8.8 Hz), 7.38 (1H, d, *J* = 5.2 Hz), 6.90 (2H, d, *J* = 9.2 Hz), 4.34 (2H, d, *J* = 5.2 Hz), 3.82-3.80 (4H, m), 3.56-3.60 (4H, m), 3.02-3.09 (4H, m), 2.71-2.73 (4H, m. ESI-MS : 514.15 $(M+H)^+$. UPLC t_{ret} : 2.66 min.

Example 33 : Preparation of N-(cyanomethyl)-4-(2-((4-(4-(4,5-dihydro-1H-imidazol-2-yl)piperazin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide.

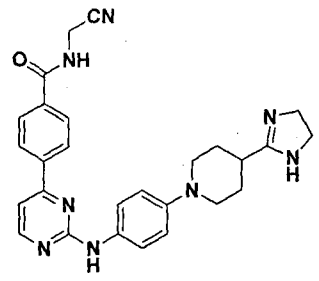
[0149]



[0150] Prepared similar to the procedure described in Example 1 but using **Ester 1** and **Amine 33** as starting material. The title compound was obtained as light yellow solid. ^{1}H NMR (400 MHz, d_6-DMSO) : 9.52 (1H, s), 9.37 (1H, t, *J* = 4 Hz), 8.54-8.53 (3H, m), 8.26 (2H, d, *J* = 8.4 Hz), 8.02 (2H, *d, J* = 8.4 Hz), 7.68 (2H, d, *J* = 8.8 Hz), 7.41 (1H, d, *J* = 5.2 Hz), 7.09-7.07 (2H, m), 4.34 (2H, d, *J* = 5.6 Hz), 3.66 (4H, s), 3.59-3.57 (4H, m), 3.19-3.15 (4H, m). ESI-MS : 482.05 $(M+H)^+$. UPLC t_{ret}: 2.60 min.

Example 34 : Preparation of N-(cyanomethyl)-4-(2-((4-(4-(4,5-dihydro-1H-imidazol-2-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide.

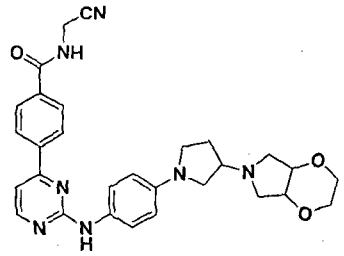
[0151]



[0152] Prepared similar to the procedure described in Example 1 but using **Ester 1** and **Amine 34** as starting material. The title compound was obtained as light yellow solid. ^{1}H NMR (400 MHz, d_6-DMSO) : 9.48 (1H, s), 9.33 (1H, t, *J* = 5.2 Hz), 8.53 (1H, d, *J* = 5.2 Hz), 8.26 (2H, d, *J* = 8.0 Hz), 8.00 (d, *J*= 8.4 Hz), 7.65 (2H, d, *J* = 8.8 Hz), 7.40 (1H, d, *J* = 5.2 Hz), 6.95 (2H, d, *J* = 8.8 Hz), 4.35 (2H, d, *J* = 5.6 Hz), 4.35 (2H, m), 3.63-3.59 (2H, m), 3.09-3.07 (2H, m), 2.85-2.80 (2H, m), 2.49 (3H, s), 2.09-2.06 (2H, m), 1.85-1.82 (2H, m). ESI-MS : 495.25 $(M+H)^+$. UPLC t_{ret} : 2.28 min.

Example 35 : Preparation of N-(cyanomethyl)-4-(2-((4-(3-(tetrahydro-2H-[1,4]dioxino[2,3-c]pyrrol-6(3H)-yl)pyrrolidin-1-yl)phenyl)amino)pyrimidin-4-yl) benzamide.

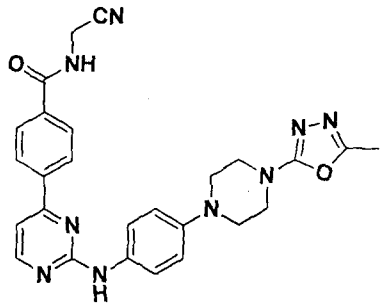
[0153]



[0154] Prepared similar to the procedure described in Example 1 but using **Ester 1** and **Amine 35** as starting material. The title compound was obtained as light yellow solid. ^{1}H NMR (400 MHz, d_6-DMSO) : 9.33-9.29 (2H, m), 8.48 (1H, d, *J* = 4.8 Hz), 8.25 (1H, d, *J* = 8.4 Hz), 8.05 (2H, d, *J* = 8.8 Hz), 7.55 (2H, d, *J* = 8.8 Hz), 7.34 (1H, d, *J* = 5.2 Hz), 6.51 (2H, d, *J* = 8.8 Hz), 4.34 (2H, d, *J* = 5.2 Hz), 4.01-4.03 (2H, m), 3.71-3.72 (2H, m), 3.62-3.57 (1H, m), 3.45-3.47 (1H, m), 3.22-3.19 (2H, m), 3.01-3.08 (2H, m), 2.94-2.90 (2H, m), 2.86-2.89 (2H, m), 2.09-2.10 (2H, m), 1.82-1.90 (1H, m). ESI-MS : 526.35 $(M+H)^+$. UPLC t_{ret} : 2.60 min.

Example 36 : Preparation of N-(cyanomethyl)-4-(2-((4-(4-(5-methyl-1,3,4-oxadiazol-2-yl)piperazin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide.

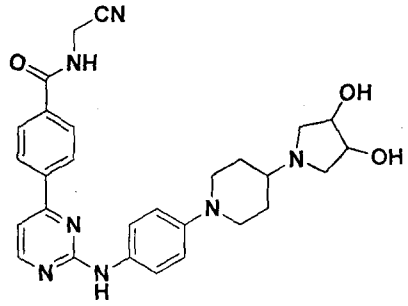
[0155]



[0156] Prepared similar to the procedure described in Example 1 but using **Ester 1** and **Amine 36** as starting material. The title compound was obtained as light yellow solid. ^{1}H NMR (400 MHz, d_6-DMSO) : 9.50 (1H, s), 9.32 (1H, t, *J* = 5.2 Hz), 8.53 (1H, d, *J* = 5.2 Hz), 8.25 (2H, d, *J* = 8.4 Hz), 8.01 (2H, d, *J* = 8.4 Hz), 7.67 (2H, d, *J* = 8.4 Hz), 7.40 (1H, d, *J* = 5.2 Hz), 6.95 (2H, d, *J* = 9.2 Hz), 4.34 (2H, d, *J* = 5.2 Hz), 3.52-3.50 (4H, m), 3.19-1.16 (4H, m), 2.32 (3H, s). ESI-MS : 496.25 $(M+H)^+$. UPLC t_{ret} : 2.93 min.

Example 37 : Preparation of N-(cyanomethyl)-4-(2-((4-(4-(3,4-dihydroxy pyrrolidin-1-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide.

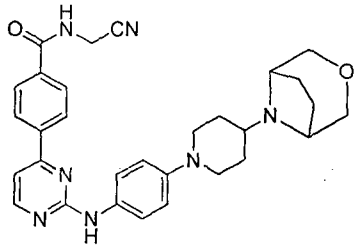
[0157]



[0158] Prepared similar to the procedure described in Example 1 but using **Ester 1** and Amine **37** as starting material. The title compound was obtained as light yellow solid. ^{1}H NMR (400 MHz, d_6-DMSO): 9.54 (1H, s), 9.40 (1H, t, *J* = 5.2 Hz), 8.54 (1H, d, *J* = 5.2 Hz), 8.26 (2H, d, *J*= 8.4 Hz), 8.04 (2H, d, *J* = 8.4 Hz), 7.69 (2H, d, *J* = 8 Hz), 7.42 (1H, d, *J* = 5.2 Hz), 7.09-7.07 (2H, m), 4.34 (2H, d, *J* = 5.2 Hz), 4.22-4.01 (2H, m), 3.73-3.65 (6H, m), 2.8-2.69 (2H, m), 2.13-2.11 (2H, m), 1.63 (1H, m), 1.9-1.68 (2H, m), 1.28-1.22 (2H, m). ESI-MS : 514.15 $(M+H)^+$. UPLC t_{ret} : 2.34 min.

Example 38 : Preparation of 4-(2-((4-(4-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)piperidin-1-yl)phenyl) amino) pyrimidin-4-yl)-N-(cyanomethyl)benzamide.

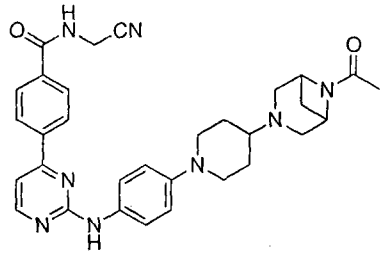
[0159]



[0160] Prepared similar to the procedure described in Example 17 but using **Ester 1** and **Amine 38** as starting material. The title compound was obtained as light yellow solid. ^{1}H NMR (400 MHz, d_6-DMSO) : 9.48 (1H, s), 9.36 (1H, t, *J*= 5.2 Hz), 8.53 (1H, d, *J* = 5.2 Hz), 8.27 (2H, d, *J*= 8.4 Hz), 8.03 (2H, d, *J* = 8.4 Hz), 7.66 (2H, d, *J* = 8.8 Hz), 7.41 (1H, d, *J*= 4.8 Hz), 6.98 (2H, d, *J* = 9.2 Hz), 4.35 (2H, d, *J*= 5.2 Hz), 4.20 (2H, m), 3.89 (1H, m), 3.80 (2H, m), 3.71 (2H, m), 2.66 (1H, m) 2.03-1.96 (4H, m), 2.01 (3H, m), 1.68 (2H, m). ESI-MS : 524.25$(M+H)^+$. UPLC t_{ret} : 2.48 min.

Example 39 : Prepartion of 4-(2-((4-(4-(6-acetyl-3,6-diazabicyclo[3.1.1]heptan-3-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)-N-(cyanomethyl)benzamide.

[0161]

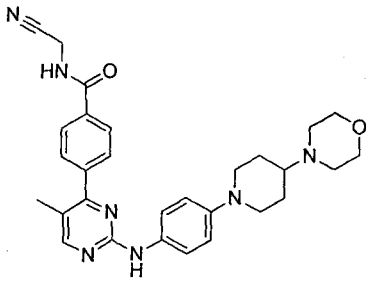


[0162] Prepared similar to the procedure described in Example 17 but using **Ester 1** and **Amine 39** as starting material. The title compound was obtained as light yellow solid. ^{1}H NMR (400 MHz, d_6-DMSO) : 9.44 (s, 1H), 9.32 (t, 1H, *J* = 5.2 Hz), 8.52 (d, 1H, *J*= 5.2 Hz), 8.25 (d, 2H, *J* = 8.4 Hz), 8.01 (d, 2H, *J* = 8.4 Hz), 7.61 (d, 2H, *J* = 9.2 Hz), 7.38 (d, 1H, *J* = 5.2 Hz), 6.90 (d, 2H, *J* = 9.2 Hz), 4.34 (d, 2H, *J* = 5.6 Hz), 3.73-3.76 (m, 1H), 3.61-3.62 (m, 2H), 3.40-3.49 (m, 4H), 3.34-3.38 (m, 1H), 2.69-2.78 (m, 3H), 2.31-2.34 (m, 1H), 2.00 (s, 3H), 1.70-1.80 (m, 2H), 1.22-1.38 (m, 3H). ESI-

MS :551.25 $(M+H)^+$. UPLC t_{ret} : 2.38 min.

Example 40 : Preparation of N-(cyanomethyl)-4-(5-methyl-2-((4-(4-morpholinopiperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide.

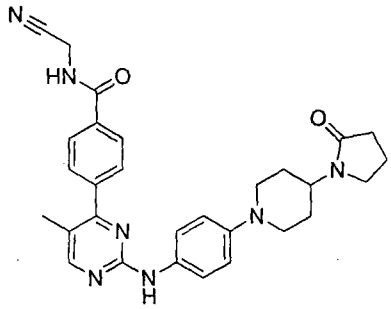
[0163]



[0164] Prepared similar to the procedure described in Example 1 but using **Ester 2** and **Amine 3** as starting material. The title compound was obtained as light yellow solid. ^{1}H NMR (400 MHz, d_6-DMSO) : 9.30 (t, 2H, *J* = 5.2 Hz), 8.36 (s, 1H), 7.98 (d, 2H, *J* = 8.4 Hz), 7.77 (d, 2H, *J* = 8.0 Hz), 7.57 (d, 2H, *J* = 8.8 Hz), 6.85 (d, *2H, J*= 8.8 Hz), 4.34 (d, 2H, *J* = 5.6 Hz), 3.57-3.60 (m, 6H), 2.54-2.59 (m, 2H), 2.19 (s, 3H), 1.82-1.85 (m, 2H), 1.47-1.49 (m, 2H)., ESI-MS : 512.25 $(M+H)^+$. UPLC t_{ret} : 2.50 min.

Example 41 : Preparation of N-(cyanomethyl)-4-(5-methyl-2-((4-(4-(2-oxopyrrolidin-1-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide.

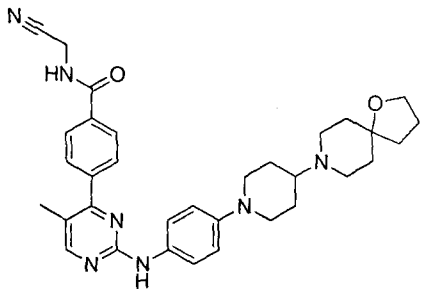
[0165]



[0166] Prepared similar to the procedure described in Example 1 but using Ester 2 and **Amine 1** as starting material. The title compound was obtained as light yellow solid. ^{1}H NMR (400 MHz, d_6-DMSO): 9.32 (bs, 2H), 8.38 (bs, 1H), 7.99 (d, 2H, *J*= 7.6 Hz), 7.77 (d, 2H, *J* = 8.0 Hz), 7.59 (d, 2H, *J* = 7.6 Hz), 6.88 (d, 2H, *J*= 8.8 Hz), 4.34 (d, 2H, *J* = 4.8 Hz), 3.85 (m, 1H), 3.61-3.63 (m, 2H), 2.61-2.65 (m, 2H), 2.22-2.24 (m, 3H), 2.19 (s, 3H), 1.88-1.92 (m, 3H), 1.72-1.81 (m, 2H), 1.61-1.67 (m, 2H). ESI-MS : 510.20 $(M+H)^+$. UPLC t_{ret} : 2.71 min.

Example 42 : Preparation of 4-(2-((4-(4-(1-oxa-8-azaspiro[4.5]decan-8-yl) piperidin-1-yl)phenyl)amino)-5-methylpyrimidin-4-yl)-N-(cyanomethyl)benzamide.

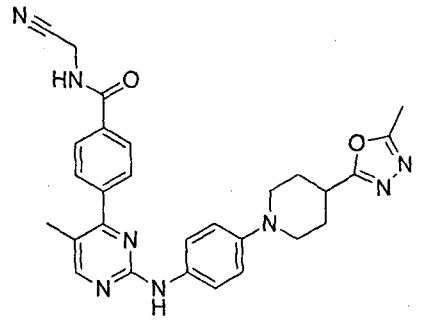
[0167]



[0168] Prepared similar to the procedure described in Example 1 but using **Ester 2** and **Amine 24** as starting material. The title compound was obtained as light yellow solid. ^{1}H NMR (400 MHz, d_6-DMSO) : 9.43 (1H, s), 9.30 (1H, t, *J* = 5.6 Hz), 8.37 (1H, s), 8.00 (2H, d, *J* = 8.4 Hz), 7.77 (2H, d, *J* = 8.4 Hz), 7.60 (2H, d, *J* = 9.2 Hz), 6.89 (2H, d, *J* = 9.2 Hz), 4.35 (2H, d, *J* = 5.6 Hz), 3.77-3.70 (4H, m), 3.42-3.40 (2H, m), 3.06-3.03 (2H, m), 2.66-2.59 (2H, m), 2.18 (3H, s), 2.11-2.08 (2H, m), 1.91-1.85 (2H, m), 1.80-1.69 (6H, m). ESI-MS : 566.22 $(M+H)^+$. UPLC t_{ret} : 2.80 min.

Example 43 : Preparation of N-(cyanomethyl)-4-(5-methyl-2-((4-(4-(5-methyl-1,3,4-oxadiazol-2-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide.

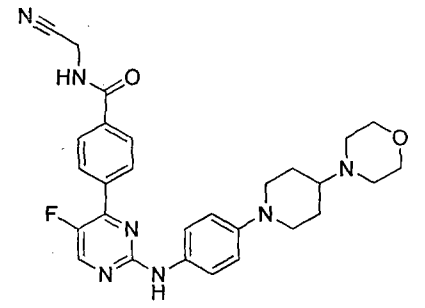
[0169]



[0170] Prepared similar to the procedure described in Example 17 but using **Ester 2** and **Amine 25** as starting material. The title compound was obtained as light yellow solid. ^{1}H NMR (400 MHz, d_b-DMSO) : 9.30-9.32 (m, 2H), 8.37 (s, 1H), 7.99 (d, 2H, *J* = 8.4 Hz), 7.77 (d, 2H, *J* = 8.4 Hz), 7.60 (d, 2H, *J* = 8.8 Hz), 6.89 (d, 2H, *J* = 9.2 Hz), 4.34 (d, 2H, *J* = 5.2 Hz), 3.55-3.58 (m, 2H), 3.06 (m, 1H), 2.75-2.82 (m, 2H), 2.46 (s, 3H), 2.19 (s, 3H), 2.03-2.07 (m, 2H), 1.80-1.83 (m, 2H). ESI-MS: 509.10 $(M+H)^+$. UPLC t_{ret} : 2.86 min.

Example 44 : Preparation of N-(cyanomethyl)-4-(5-fluoro-2-((4-(4-morpholinopiperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide.

[0171]

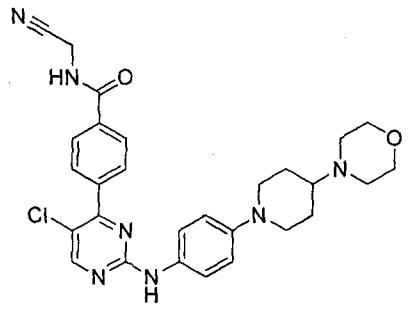


[0172] Prepared similar to the procedure described in Example 1 but using **Ester 3** and **Amine 3** as starting material. The title compound was obtained as light yellow solid. ^{1}H NMR (400 MHz, d_6-DMSO) : 9.30 (t, 2H, *J* = 5.2 Hz), 8.36 (s,

1H), 7.98 (d, 2H, *J* = 8.4 Hz), 7.77 (d, 2H, *J*= 8.0 Hz), 7.57 (d, 2H, *J* = 8.8 Hz), 6.85 (d, 2H, *J* = 8.8 Hz), 4.34 (d, 2H, *J* = 5.6 Hz), 3.57-3.60 (m, 6H), 2.54-2.59 (m, 2H), 2.19 (s, 3H), 1.82-1.85 (m, 2H), 1.47-1.49 (m, 2H). ESI-MS : 512.25 $(M+H)^+$. UPLC t_{ret}: 2.50 min.

Example 45 : Preparation of 4-(5-chloro-2-((4-(4-morpholinopiperidin-1-yl)phenyl)amino) pyrimidin-4-yl)-N-(cyanomethyl)benzamide.

[0173]

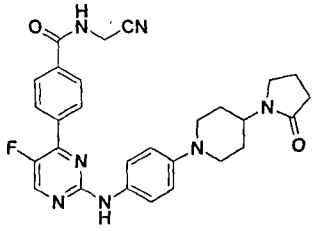


[0174] Prepared similar to the procedure described in Example 1 but using **Ester 4** and **Amine 3** as starting material. The title compound was obtained as light yellow solid. ^{1}H NMR (400 MHz, d_6-DMSO) : 9.70 (s, 1H), 9.33 (t, 1H, *J* = 5.6 Hz), 8.57 (s, 1H), 8.00 (d, 2H, *J* = 8.4 Hz), 7.90 (d, 2H, *J* = 8.4 Hz), 7.53 (d, 2H, *J* = 8.8 Hz), 6.88 (d, 2H, *J* = 9.2 Hz), 4.35 (d, 2H, *J* = 5.6 Hz), 3.53-3.63 (m, 6H), 2.56-2.62 (m, 2H), 2.49-2.50 (m, 4H), 2.10-2.23 (m, 1H), 1.83-1.86 (m, 2H), 1.47-1.49 (m, 2H). ESI-MS : 532.20 $(M+H)^+$. UPLC t_{ret} : 2.75 min.

[0175] The following compounds can be synthesized following the same procedure as described above and are considered to be encompassed within the scope of the present invention.

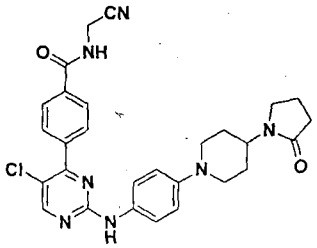
N-(Cyanomethyl)-4-(5-fluoro-2-((4-(4-(2-oxopyrrolidin-1-yl)piperidin-1-yl) phenyl)amino)pyrimidin-4-yl)benzamide.

[0176]



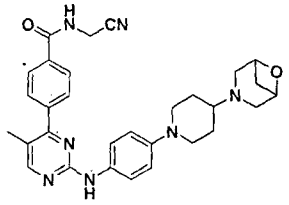
4-(5-Chloro-2-((4-(4-(2-oxopyrrolidin-1-yl)piperidin-1-yl)phenyl)amino) pyrimidin-4-yl)-N-(cyanomethyl)benzamide.

[0177]



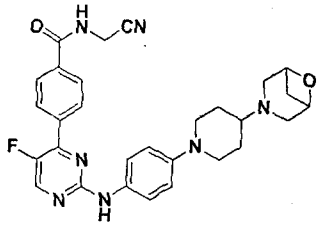
4-(2-((4-(4-(6-Oxa-3-azabicyclo[3.1.1]heptan-3-yl)piperidin-1-yl)phenyl)amino)-5-methylpyrimidin-4-yl)-N-(cyanomethyl)benzamide.

[0178]



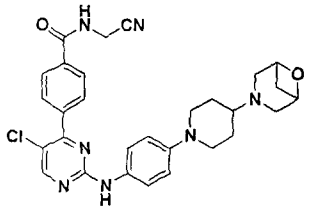
4-(2-((4-(4-(6-Oxa-3-azabicyclo[3.1.1]heptan-3-yl)piperidin-1-yl)phenyl)amino)-5-fluoropyrimidin-4-yl)-N-(cyanomethyl)benzamide.

[0179]



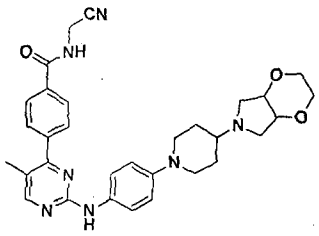
4-(2-((4-(4-(6-Oxa-3-azabicyclo[3.1.1]heptan-3-yl)piperidin-1-yl)phenyl)amino)-5-chloropyrimidin-4-yl)-N-(cyanomethyl)benzamide.

[0180]



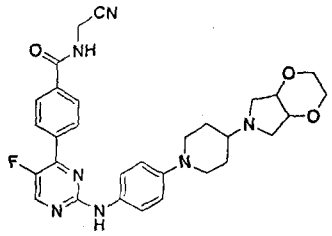
N-(Cyanomethyl)-4-(5-methyl-2-((4-(4-(tetrahydro-2H-[1,4]dioxino[2,3-c]pyrrol-6(3H)-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide.

[0181]



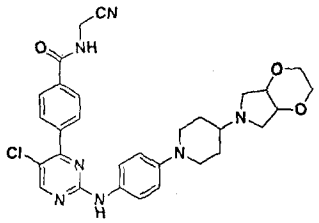
N-(Cyanomethyl)-4-(5-fluoro-2-((4-(4-(tetrahydro-2H-[1,4] dioxino[2,3-c]pyrrol-6(3H)-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide.

[0182]



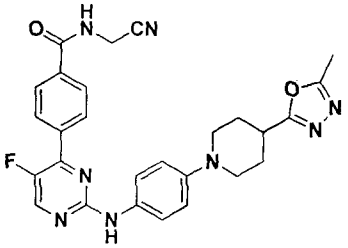
4-(5-Chloro-2-((4-(4-(tetrahydro-2H-[1,4]dioxino[2,3-c]pyrrol-6(3H)-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)-N-(cyanomethyl)benzamide.

[0183]



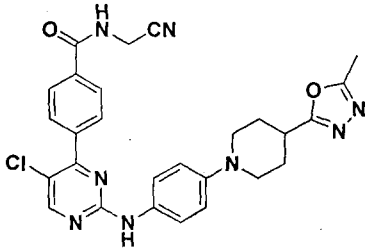
N-(Cyanomethyl)-4-(5-fluoro-2-((4-(4-(5-methyl-1,3,4-oxadiazol-2-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide.

[0184]



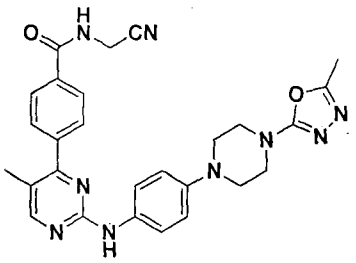
4-(5-Chloro-2-((4-(4-(5-methyl-1,3,4-oxadiazol-2-yl)piperidin-1-yl)phenyl) amino)pyrimidin-4-yl)-N-(cyanomethyl)benzamide.

[0185]



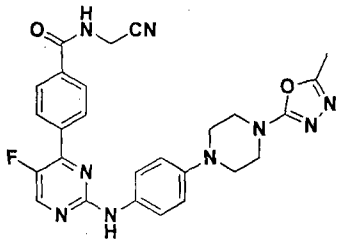
N-(Cyanomethyl)-4-(5-methyl-2-((4-(4-(5-methyl-1,3,4-oxadiazol-2-yl)piperazin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide.

[0186]



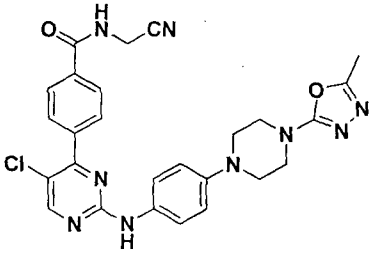
N-(Cyanomethyl)-4-(5-fluoro-2-((4-(4-(5-methyl-1,3,4-oxadiazol-2-yl)piperazin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide

[0187]



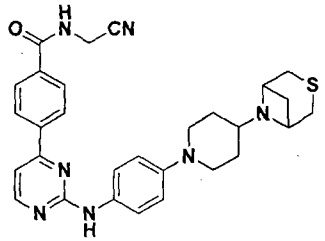
4-(5-Chloro-2-((4-(4-(5-methyl-1,3,4-oxadiazol-2-yl)piperazin-1-yl)phenyl) amino)pyrimidin-4-yl)-N-(cyanomethyl)benzamide.

[0188]



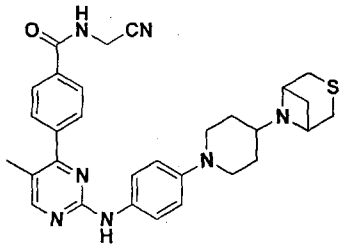
4-(2-((4-(4-(3-Thia-6-azabicyclo[3.1.1]heptan-6-yl)piperidin-1-yl)phenyl) amino)pyrimidin-4-yl)-N-(cyanomethyl)benzamide.

[0189]



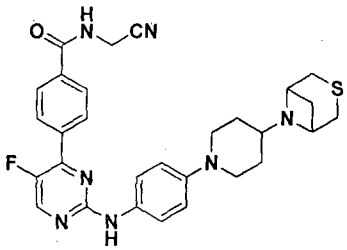
4-(2-((4-(4-(3-Thia-6-azabicyclo[3.1.1]heptan-6-yl)piperidin-1-yl)phenyl)amino)-5-methylpyrimidin-4-yl)-N-(cyanomethyl)benzamide

[0190]



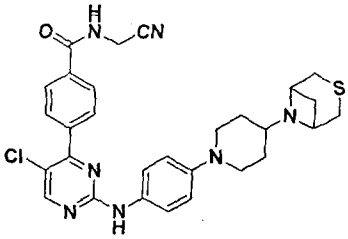
4-(2-((4-(4-(3-Thia-6-azabicyclo[3.1.1]heptan-6-yl)piperidin-1-yl)phenyl)amino)-5-fluoropyrimidin-4-yl)-N-(cyanomethyl)benzamide

[0191]



4-(2-((4-(4-(3-Thia-6-azabicyclo[3.1.1]heptan-6-yl)piperidin-1-yl)phenyl)amino)-5-chloropyrimidin-4-yl)-N-(cyanomethyl)benzamide.

[0192]



[0193] It will be appreciated that in any of the above mentioned reactions any reactive group in the substrate molecule may be protected, according to conventional chemical practice. Suitable protecting groups in any of the above mentioned reactions are those used conventionally in the art. The methods of formation and removal of such protecting groups are those conventional methods appropriate to the molecule being protected. T. W. Greene and P. G. M. Wuts "Protective groups in Organic Synthesis", John Wiley & Sons, Inc, 1999, 3rd Ed., 201-245 along with references therein gives such conventional methods.

[0194] The novel compounds of the present invention can be formulated into suitable pharmaceutically acceptable compositions by combining with suitable excipients by techniques and processes and concentrations as are well known.

[0195] The compounds of formula (1) or pharmaceutical compositions containing them are useful as renin inhibitors suitable for humans and other warm blooded animals, and may be administered either by oral, topical or parenteral administration.

[0196] The pharmaceutical composition is provided by employing conventional techniques. Preferably the composition is in unit dosage form containing an effective amount of the active component, that is, the compounds of formula (1) according to this invention.

[0197] The quantity of active component, that is, the compounds of formula (1) according to this invention, in the pharmaceutical composition and unit dosage form thereof may be varied or adjusted widely depending upon the particular application method, the potency of the particular compound and the desired concentration.

[0198] The compounds of the present invention may be used alone or in combination with one or more other therapeutic agents which a skilled medical practitioner can easily identify. Such other therapeutic agent may be selected depending on the type of disease being treated, the severity, other medications being taken by the patients etc. Thus for example, for treatment of rheumatoid arthritis, one or more DMARDs may be used in combination with the compounds of the

present invention.

Biological activity:

In vitro study

Evaluation of JAK inhibition.

[0199] NCEs were screened using *in vitro* JAK (1, 2 and 3) kinase assay on ADP Glo platform (Promega). Fixed amount of recombinant purified human JAK (25 ng of JAK1 and 10 ng of JAK2 and JAK3 per reaction, from Life Technologies Ltd) were incubated with increasing concentration of NCEs in 1xkinase reaction buffer (40 mM Tris-Cl, pH7.5, 20 mM $MgCl_2$, 0.1mg/ml BSA and 50 μM DTT). Enzymatic reaction was initiated by adding a substrate cocktail containing 50μM of ATP (final concentration) and 5μg for JAK1 and 2.5μg for JAK2 and JAK3 of $polyGln_4Tyr_1$ (Signal Chem) in total 25μl of reaction in 96 well plate. The reaction was incubated at room temperature for 1 hr.

[0200] After 1 hr of incubation equal volume (25)μl per reaction) of ADP Glo was added and incubated at room temperature for 40 min.

[0201] This was followed by addition of kinase detection reagent (50μl per reaction) and incubation at room temperature for 30 min. Finally, plate was read for luminescence at an integration time of 500 millisecond per well.

[0202] Data were plotted taking Enzyme with no inhibitor set as the 100% kinase activity. IC_{50} values were calculated using Graph Pad Prism software.

Example No	JAK-1 IC_{50} (nM)	JAK-2 IC_{50} (nM)	JAK-3 IC_{50} (nM)
1	12.1	5.6	72
2	5.1	4	51
3	11.7	6.6	62.3
4	21	17	66
6	16	19	155
7	14	12	62
9	14	8	40
12	25	18	78
15	16	11	88
17	13	8	69
18	9	11	50
19	10	7	40
24	5	5	23
25	12	8	48
27	10	5	49
28	11	6	55
29	15	21	56
31	20	17	74
33	20	11	54
34	13	20	124
35	15	21	138
36	9.2	6.7	46.9
38	1.5	4.3	ND
39	8.8	5	50.7

(continued)

Example No	JAK-1 IC_{50} (nM)	JAK-2 IC_{50} (nM)	JAK-3 IC_{50} (nM)
40	1.3	2.8	32
41	0.6	2.5	10.7
42	2.5	4.3	59
43	1.2	2.6	52.3
44	6.7	4.9	16.6
*ND: Not determined			

[0203] From the *in vitro* data it is clear that the synthesized compounds have nano molar potency against JAK-1, JAK-2 and JAK-3. Also synthesized compound showed selectivity to JAK-1 & JAK-2. Thus these compounds can be used as potential agent to treat human cancers, arthritis and skin immune disorders such as psoriasis.

In vivo study

Peptidogylcan Polysaccharide Polymers (PGPS) Arthritis.

[0204] Female Sprague dawley rats were primed with an intra-articular injection of 20μl of PGPS at 0.5 mg/ml of rhamnose in the right ankle. At 2 weeks the ankle diameters were measured with plethysmometer and rats assigned to groups of similar distribution of initial joint diameters. Rats then received their first dose of compound followed 1 h later by an i.v. injection of 0.5 ml of PGPS (0.5 mg/ml of rhamnose) in the tail vein. Compounds were dosed at 10 mg/kg and ankle diameters measured for 3 days [i.e. day 15,16, 17]. Values are given for day 16.

Example No.	% Reduction in PAW inflammation at dose 10 mg/Kg
1	51
3	56
4	52
17	57
24	41
25	63
29	43

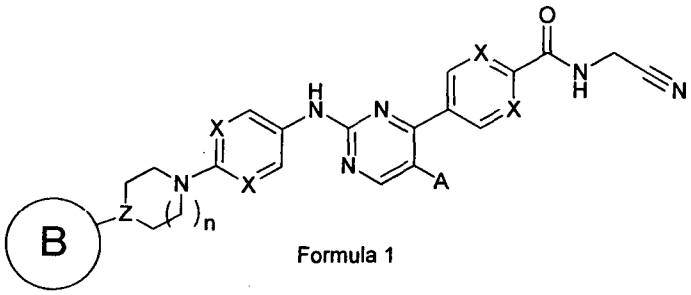
Induction and Assessment of Arthritis (Collagen-Induced Arthritis).

[0205] Male DBA1j (8 to 12-weeks old) mice were injected native bovine type II collagen (Chondrex, Redmond, WA) was mixed with complete Freund's adjuvant and injected s.c. on days 0 and 21 at the base of the tail of (200 μg of type II collagen in 100 μl of emulsion). Animals were observed for clinical score and assigned to different groups of similar score. Mice were then dosed and determined for clinical scores for 3 weeks. The degree of arthritis was determined based on a clinical score of 0-4 per paw and summed for all four paws. Few of the synthesised compounds showed activity at 10 mg/kg BID dose.

[0206] The compounds of the present invention are suitable as JAK inhibitors and are useful for the treatment inflammatory conditions, autoimmune diseases, proliferative diseases, allergy, and transplant rejection, diseases involving impairment of cartilage turnover, congenital cartilage malformations, and/or diseases associated with hypersecretion of IL6 or interferons.

Claims

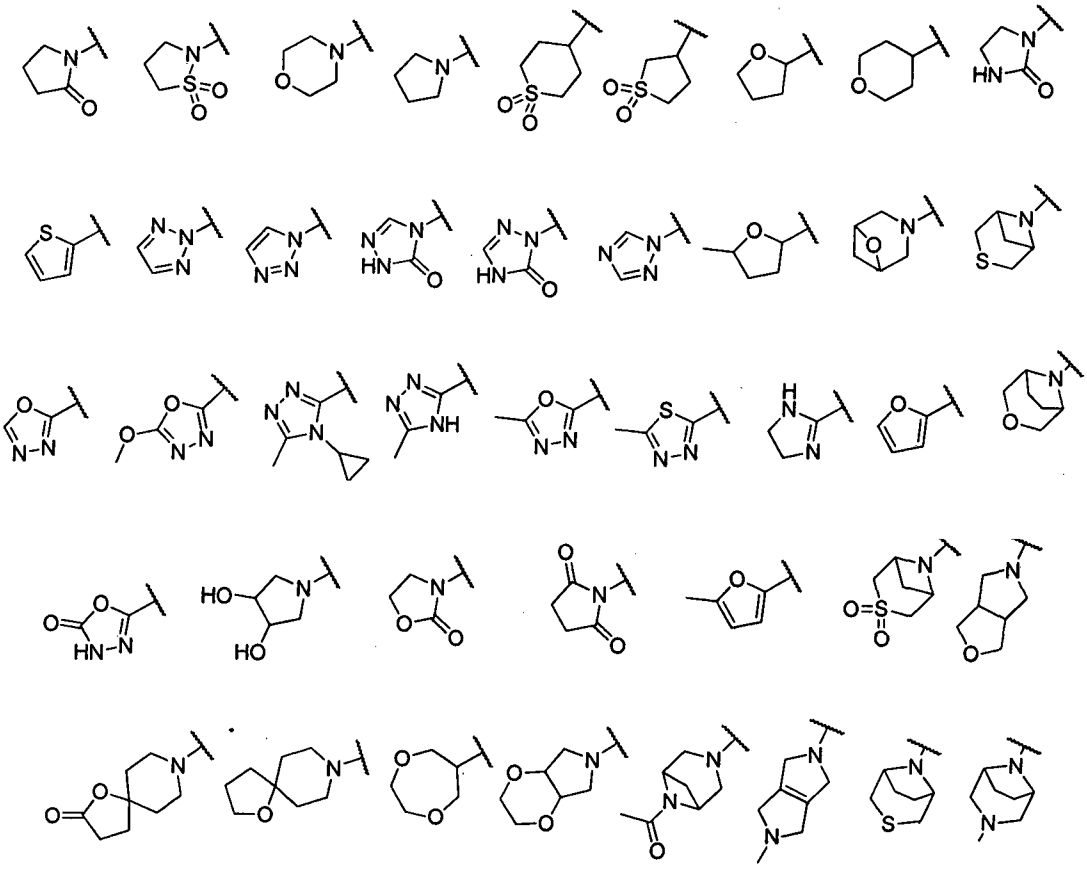
1. Compound having the structure of general formula (I)



Formula 1

or pharmaceutically acceptable salts thereof
Wherein

X at each occurrence is independently selected from N or CH;
Z at each occurrence is independently selected from N or CH;
n is selected from 0,1.
A is independently selected from hydrogen, halogen, C_{1-4} alkyl, CF_3, CN, $CON(R_1)_2$, OC_{1-4}alkyl
Ring B is selected from following ring systems, each of which can be substituted



2. The compounds according to claim 1 wherein substituents on the ring B wherever applicable is independently selected from H, OH, CN, NH_2, halogen, oxo, OCF_3, CF_3, C_1-C_6 alkyl, OC_1-C_6 alkyl, $(CH_2)_{1-6}OC_1$-C_6 alkyl, O-$(CH_2)_{0-4}OC_1$-C_6 alkyl, $C(O)NHC_1$-C_6 alkyl, $NHC(O)C_1$-C_6 alkyl, $S(O)_{0-2}C_1$-C_6 alkyl, $(CH_2)_{1-6}N(R_1)_2$, $(CH_2)_{1-6}NHC(=O)OR_1$, $(CH_2)_{1-6}NHC(=O)R_1$, $C(=O)OR_1$, $C(=O)R_1$, $(CH_2)_{1-4}C(=O)$ NHR_1, $(CH_2)_{0-4}O(CH_2)_{0-4}Ar_1$, $(CH_2)_{0-4}NH(CH_2)_{0-4}Ar_1$, $(CH_2)_{0-4}$ Ar_1, $(CH_2)_{0-4}C(O)(CH_2)_{0-4}Ar_1$, $(CH_2)_{0-4}$ $C(=O)$ $O(CH_2)_{0-4}Ar_1$, $(CH_2)_{0-4}C(=O)NR_1(CH_2)_{0-4}Ar_1$.

3. The compound according to claim 1 and 2 wherein R_1 at each occurrence is independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_3-C_7 cycloalkyl groups.

4. The compound according to claim 2 wherein Ar_1 at each iteration is independently selected from unsubstituted or substituted aryl or heterocyclic ring substituted with one, two, three or four substituents.

5. The compounds according to claim 4 wherein substituents on Ar_1 are independently selected from the group comprising of OH, CN, NH_2, halogen, OCF_3, CF_3, C_1-C_6 alkyl, OC_1-C_6alkyl, $(CH_2)_{1\text{-}6}OC_1$-C_6 alkyl, O-$(CH_2)_{0\text{-}4}OC_1$-C_6 alkyl, $C(O)NHC_1$-C_6 alkyl, $NHC(O)C_1$-C_6 alkyl, $S(O)_{0\text{-}2}C_1$-C_6 alkyl, $(CH_2)_{1\text{-}6}N(R_1)_2$, $(CH_2)_{1\text{-}6}NHC(=O)OR_1$, $(CH_2)_{1\text{-}6}NHC(=O)R_1$, $C(=O)OR_1$ or $-C(=O)R_1$, $CH_2(CH_2)_{0\text{-}4}C(=O)NHR_1$.

6. The compound as claimed in claim 1 selected from the group consisting of:

N-(Cyanomethyl)-4-(2-((4-(4-(2-oxopyrrolidin-1-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
N-(Cyanomethyl)-4-(2-((4-(4-(1,1-dioxidoisothiazolidin-2-yl)piperidin-1-yl)phenyl)amino) pyrimidin-4-yl)benzamide;
N-(Cyanomethyl)-4-(2-((4-(4-morpholinopiperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
4-(2-((4-(4-(1H-1,2,4-Triazol-1-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)-N-(cyanomethyl)benzamide;
4-(2-((4-(4-(1H-Pyrazol-1-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)-N-(cyanomethyl)benzamide;
4-(2-((4-([1,3'-Bipyrrolidin]-1'-yl)phenyl)amino)pyrimidin-4-yl)-N-(cyanomethyl) benzamide;
N-(cyanomethyl)-4-(2-((4-(4-(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)piperazin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
N-(Cyanomethyl)-4-(2-((4-(4-(furan-2-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
N-(Cyanomethyl)-4-(2-((4-(4-(1,1-dioxidotetrahydrothiophen-3-yl)piperazin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
N-(Cyanomethyl)-4-(2-((4-(4-(2,5-dioxopyrrolidin-1-yl)piperidin-1-yl)phenyl) amino)pyrimidin-4-yl)benzamide;
N-(Cyanomethyl)-4-(2-((4-(4-(thiophen-2-yl)piperidin-1-yl)phenyl)amino) pyrimidin-4-yl)benzamide;
N-(Cyanomethyl)-4-(2-((4-(4-(2-oxooxazolidin-3-yl)piperidin-1-yl)phenyl) amino)pyrimidin-4-yl)benzamide;
N-(Cyanomethyl)-4-(2-((4-(4-(tetrahydrofuran-2-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
N-(Cyanomethyl)-4-(2-((4-(4-(5-methylfuran-2-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
N-(Cyanomethyl)-4-(2-((4-(4-(tetrahydro-2H-pyran-4-yl)piperazin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
N-(Cyanomethyl)-4-(2-((4-(4-(5-methyltetrahydrofuran-2-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
4-(2-((4-(4-(6-Oxa-3-azabicyclo[3.1.1]heptan-3-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)-N-(cyanomethyl)benzamide;
N-(Cyanomethyl)-4-(2-((4-(4-(2-oxoimidazolidin-1-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
4-(2-((4-(4-(1,3,4-Oxadiazol-2-yl)piperidin-1-yl)phenyl)amino) pyrimidin-4-yl)-N-(cyanomethyl)benzamide;
4-(2-((4-(4-(2H-1,2,3-Triazol-2-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)-N-(cyano methyl) benzamide;
4-(2-((4-(4-(1H-1,2,3-Triazol-1-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)-N-(cyano methyl)benzamide;
N-(Cyanomethyl)-4-(2-((4-(4-(5-oxo-1H-1,2,4-triazol-4(SH)-yl)piperidin-1-yl)phenyl) amino)pyrimidin-4-yl)benzamide;
N-(Cyanomethyl)-4-(2-((4-(4-(5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
4-(2-((4-(4-(1-Oxa-8-azaspiro[4.5]decan-8-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)-N-(cyanomethyl)benzamide;
N-(Cyanomethyl)-4-(2-((4-(4-(5-methyl-1,3,4-oxadiazol-2-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
N-(Cyanomethyl)-4-(2-((4-(4-(5-methyl-1,3,4-thiadiazol-2-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
N-(Cyanomethyl)-4-(2-((4-(4-(tetrahydro-2H-[1,4]dioxino[2,3-c]pyrrol-6(3H)-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
N-(Cyanomethyl)-4-(2-((4-(4-(2-oxo-1-oxa-8-azaspiro[4.5]decan-8-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
N-(Cyanomethyl)-4-(2-((4-(4-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
N-(Cyanomethyl)-4-(2-((4-(4-(4-cyclopropyl-5-methyl-4H-1,2,4-triazol-3-yl)piperidin-1-yl) phenyl) amino)pyrimidin-4-yl)benzamide;
N-(Cyanomethyl)-4-(2-((4-(4-(5-methoxy-1,3,4-oxadiazol-2-yl)piperidin-1-yl)phenyl) amino)pyrimidin-4-yl)benzamide;
4-(2-((4-(4-(1,4-Dioxepan-6-yl)piperazin-1-yl)phenyl)amino)pyrimidin-4-yl)-N-(cyanomethyl) benzamide;

N-(Cyanomethyl)-4-(2-((4-(4-(4,5-dihydro-1H-imidazol-2-yl)piperazin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
N-(Cyanomethyl)-4-(2-((4-(4-(4,5-dihydro-1H-imidazol-2-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
N-(Cyanomethyl)-4-(2-((4-(3-(tetrahydro-2H-[1,4]dioxino[2,3-c]pyrrol-6(3H)-yl)pyrrolidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
N-(Cyanomethyl)-4-(2-((4-(4-(5-methyl-1,3,4-oxadiazol-2-yl)piperazin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
N-(Cyanomethyl)-4-(2-((4-(4-(3,4-dihydroxypyrrolidin-1-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
4-(2-((4-(4-(8-Oxa-3-azabicyclo[3.2.1]octan-3-yl)piperidin-1-yl)phenyl)amino) pyrimidin-4-yl)-N-(cyanomethyl)benzamide;
4-(2-((4-(4-(6-Acetyl-3,6-diazabicyclo[3.1.1]heptan-3-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)-N-(cyanomethyl)benzamide;
N-(Cyanomethyl)-4-(5-methyl-2-((4-(4-morpholinopiperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
N-(Cyanomethyl)-4-(5-methyl-2-((4-(4-(2-oxopyrrolidin-1-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
4-(2-((4-(4-(1-Oxa-8-azaspiro[4.5]decan-8-yl)piperidin-1-yl)phenyl)amino)-5-methylpyrimidin-4-yl)-N-(cyanomethyl)benzamide;
N-(Cyanomethyl)-4-(5-methyl-2-((4-(4-(5-methyl-1,3,4-oxadiazol-2-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
N-(Cyanomethyl)-4-(5-fluoro-2-((4-(4-morpholinopiperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
4-(5-Chloro-2-((4-(4-morpholinopiperidin-1-yl)phenyl)amino)pyrimidin-4-yl)-N-(cyanomethyl)benzamide;
N-(Cyanomethyl)-4-(5-fluoro-2-((4-(4-(2-oxopyrrolidin-1-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
4-(5-Chloro-2-((4-(4-(2-oxopyrrolidin-1-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)-N-(cyanomethyl)benzamide;
4-(2-((4-(4-(6-Oxa-3-azabicyclo[3.1.1]heptan-3-yl)piperidin-1-yl)phenyl)amino)-5-methylpyrimidin-4-yl)-N-(cyanomethyl)benzamide;
4-(2-((4-(4-(6-Oxa-3-azabicyclo[3.1.1]heptan-3-yl)piperidin-1-yl)phenyl)amino)-5-fluoropyrimidin-4-yl)-N-(cyanomethyl)benzamide;
-(2-((4-(4-(6-Oxa-3-azabicyclo[3.1.1]heptan-3-yl)piperidin-1-yl)phenyl)amino)-5-chloropyrimidin-4-yl)-N-(cyanomethyl)benzamide;
N-(Cyanomethyl)-4-(5-methyl-2-((4-(4-(tetrahydro-2H-[1,4]dioxino[2,3-c]pyrrol-6(3H)-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
N-(Cyanomethyl)-4-(5-fluoro-2-((4-(4-(tetrahydro-2H-[1,4]dioxino[2,3-c]pyrrol-6(3H)-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
4-(5-Chloro-2-((4-(4-(tetrahydro-2H-[1,4]dioxino[2,3-c]pyrrol-6(3H)-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)-N-(cyanomethyl)benzamide;
N-(Cyanomethyl)-4-(5-fluoro-2-((4-(4-(5-methyl-1,3,4-oxadiazol-2-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
4-(5-Chloro-2-((4-(4-(5-methyl-1,3,4-oxadiazol-2-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)-N-(cyanomethyl)benzamide;
N-(Cyanomethyl)-4-(5-methyl-2-((4-(4-(5-methyl-1,3,4-oxadiazol-2-yl)piperazin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
N-(Cyanomethyl)-4-(5-fluoro-2-((4-(4-(5-methyl-1,3,4-oxadiazol-2-yl)piperazin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
4-(5-Chloro-2-((4-(4-(5-methyl-1,3,4-oxadiazol-2-yl)piperazin-1-yl)phenyl)amino)pyrimidin-4-yl)-N-(cyanomethyl)benzamide;
4-(2-((4-(4-(3-Thia-6-azabicyclo[3.1.1]heptan-6-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)-N-(cyanomethyl)benzamide;
4-(2-((4-(4-(3-Thia-6-azabicyclo[3.1.1]heptan-6-yl)piperidin-1-yl)phenyl)amino)-5-methylpyrimidin-4-yl)-N-(cyanomethyl)benzamide;
4-(2-((4-(4-(3-Thia-6-azabicyclo[3.1.1]heptan-6-yl)piperidin-1-yl)phenyl)amino)-5-fluoropyrimidin-4-yl)-N-(cyanomethyl)benzamide;
4-(2-((4-(4-(3-Thia-6-azabicyclo[3.1.1]heptan-6-yl)piperidin-1-yl)phenyl)amino)-5-chloropyrimidin-4-yl)-N-(cyanomethyl)benzamide;

7. The compound as claimed in any preceding claim selected from the group consisting of:

N-(Cyanomethyl)-4-(2-((4-(4-(2-oxopyrrolidin-1-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
N-(Cyanomethyl)-4-(2-((4-(4-(1,1-dioxidoisothiazolidin-2-yl)piperidin-1-yl) phenyl)amino) pyrimidin-4-yl)benzamide;
N-(Cyanomethyl)-4-(2-((4-(4-morpholinopiperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
4-(2-((4-(4-(1H-1,2,4-Triazol-1-yl)piperidin-1-yl)phenyl)amino) pyrimidin-4-yl)-N-(cyanomethyl)benzamide;
4-(2-(4-((4-(1H-Pyrazol-1-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)-N-(cyanomethyl)benzamide;
4-(2-((4-([1,3'-Bipyrrolidin]-1'-yl)phenyl)amino)pyrimidin-4-yl)-N-(cyanomethyl) benzamide;
N-(cyanomethyl)-4-(2-((4-(4-(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)piperazin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
N-(Cyanomethyl)-4-(2-((4-(4-(furan-2-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
N-(Cyanomethyl)-4-(2-((4-(4-(1,1-dioxidotetrahydrothiophen-3-yl)piperazin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
N-(Cyanomethyl)-4-(2-((4-(4-(2,5-dioxopyrrolidin-1-yl)piperidin-1-yl)phenyl) amino)pyrimidin-4-yl)benzamide;
N-(Cyanomethyl)-4-(2-((4-(4-(thiophen-2-yl)piperidin-1-yl)phenyl)amino) pyrimidin-4-yl)benzamide;
N-(Cyanomethyl)-4-(2-((4-(4-(2-oxooxazolidin-3-yl)piperidin-1-yl)phenyl) amino)pyrimidin-4-yl)benzamide;
N-(Cyanomethyl)-4-(2-((4-(4-(tetrahydrofuran-2-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
N-(Cyanomethyl)-4-(2-((4-(4-(5-methylfuran-2-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
N-(Cyanomethyl)-4-(2-((4-(4-(tetrahydro-2H-pyran-4-yl)piperazin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
N-(Cyanomethyl)-4-(2-((4-(4-(5-methyltetrahydrofuran-2-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
4-(2-((4-(4-(6-Oxa-3-azabicyclo[3.1.1]heptan-3-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)-N-(cyanomethyl)benzamide;
N-(Cyanomethyl)-4-(2-((4-(4-(2-oxoimidazolidin-1-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
4-(2-((4-(4-(1,3,4-Oxadiazol-2-yl)piperidin-1-yl)phenyl)amino) pyrimidin-4-yl)-N-(cyanomethyl)benzamide;
4-(2-((4-(4-(2H-1,2,3-Triazol-2-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)-N-(cyano methyl) benzamide;
4-(2-((4-(4-(1H-1,2,3-Triazol-1-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)-N-(cyano methyl)benzamide;
N-(Cyanomethyl)-4-(2-((4-(4-(5-oxo-1H-1,2,4-triazol-4(SH)-yl)piperidin-1-yl)phenyl) amino) pyrimidin-4-yl)benzamide;
N-(Cyanomethyl)-4-(2-((4-(4-(5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
4-(2-((4-(4-(1-Oxa-8-azaspiro[4.5]decan-8-yl)piperidin-1-yl)phenyl) amino)pyrimidin-4-yl)-N-(cyanomethyl)benzamide;
N-(Cyanomethyl)-4-(2-((4-(4-(5-methyl-1,3,4-oxadiazol-2-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
N-(Cyanomethyl)-4-(2-((4-(4-(5-methyl-1,3,4-thiadiazol-2-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
N-(Cyanomethyl)-4-(2-((4-(4-(tetrahydro-2H-[1,4]dioxino[2,3-c]pyrrol-6(3H)-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
N-(Cyanomethyl)-4-(2-((4-(4-(2-oxo-1-oxa-8-azaspiro[4.5]decan-8-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
N-(Cyanomethyl)-4-(2-((4-(4-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
N-(Cyanomethyl)-4-(2-((4-(4-(4-cyclopropyl-5-methyl-4H-1,2,4-triazol-3-yl)piperidin-1-yl) phenyl) amino)pyrimidin-4-yl)benzamide;
N-(Cyanomethyl)-4-(2-((4-(4-(5-methoxy-1,3,4-oxadiazol-2-yl)piperidin-1-yl)phenyl) amino)pyrimidin-4-yl)benzamide;
4-(2-((4-(4-(1,4-Dioxepan-6-yl)piperazin-1-yl)phenyl)amino)pyrimidin-4-yl)-N-(cyanomethyl) benzamide;
N-(Cyanomethyl)-4-(2-((4-(4-(4,5-dihydro-1H-imidazol-2-yl)piperazin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
N-(Cyanomethyl)-4-(2-((4-(4-(4,5-dihydro-1H-imidazol-2-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
N-(Cyanomethyl)-4-(2-((4-(3-(tetrahydro-2H-[1,4]dioxino[2,3-c]pyrrol-6(3H)-yl)pyrrolidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
N-(Cyanomethyl)-4-(2-((4-(4-(5-methyl-1,3,4-oxadiazol-2-yl)piperazin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;

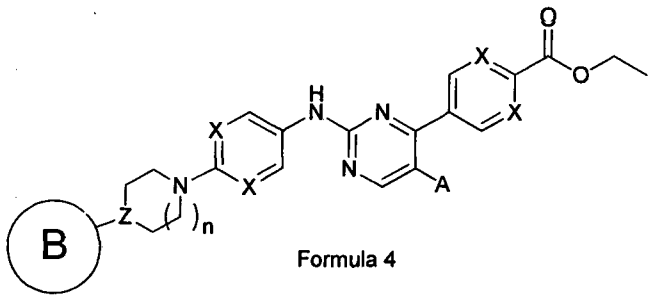
N-(Cyanomethyl)-4-(2-((4-(4-(3,4-dihydroxypyrrolidin-1-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
4-(2-((4-(4-(8-Oxa-3-azabicyclo[3.2.1]octan-3-yl)piperidin-1-yl)phenyl)amino) pyrimidin-4-yl)-N-(cyanomethyl)benzamide;
4-(2-((4-(4-(6-Acetyl-3,6-diazabicyclo[3.1.1]heptan-3-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)-N-(cyanomethyl)benzamide;
N-(Cyanomethyl)-4-(5-methyl-2-((4-(4-morpholinopiperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
N-(Cyanomethyl)-4-(5-methyl-2-((4-(4-(2-oxopyrrolidin-1-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
4-(2-((4-(4-(1-Oxa-8-azaspiro[4.5]decan-8-yl)piperidin-1-yl)phenyl)amino)-5-methylpyrimidin-4-yl)-N-(cyanomethyl)benzamide;
N-(Cyanomethyl)-4-(5-methyl-2-((4-(4-(5-methyl-1,3,4-oxadiazol-2-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
N-(Cyanomethyl)-4-(5-fluoro-2-((4-(4-morpholinopiperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;
4-(5-Chloro-2-((4-(4-morpholinopiperidin-1-yl)phenyl)amino)pyrimidin-4-yl)-N-(cyanomethyl)benzamide;

8. A pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula (I) as claimed in any of the preceding claims and optionally one or more pharmaceutically acceptable carriers, diluents or excipients.

9. The compounds as claimed in any preceding claims for use in the treatment of inflammatory conditions, autoimmune diseases, proliferative diseases, allergy and transplant rejection, diseases involving impairment of cartilage turnover, congenital cartilage malformations, and/or diseases associated with hypersecretion of IL6 or interferons wherein the JAK kinase has a pathophysiological function.

10. The pharmaceutical composition comprising compounds of formula 1 according to claim 1 along with suitable excipients suitable for the treatment of inflammatory conditions, autoimmune diseases, proliferative diseases, allergy and transplant rejection, diseases involving impairment of cartilage turnover, congenital cartilage malformations, and/or diseases associated with hypersecretion of IL6 or interferons.

11. An intermediate of formula 4

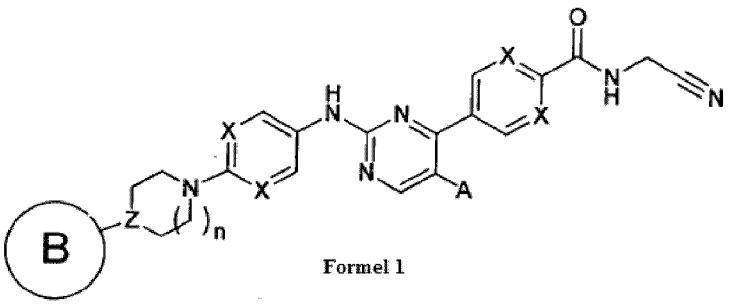


Formula 4

wherein B, Z, X, n and A are defined as in claim 1.

Patentansprüche

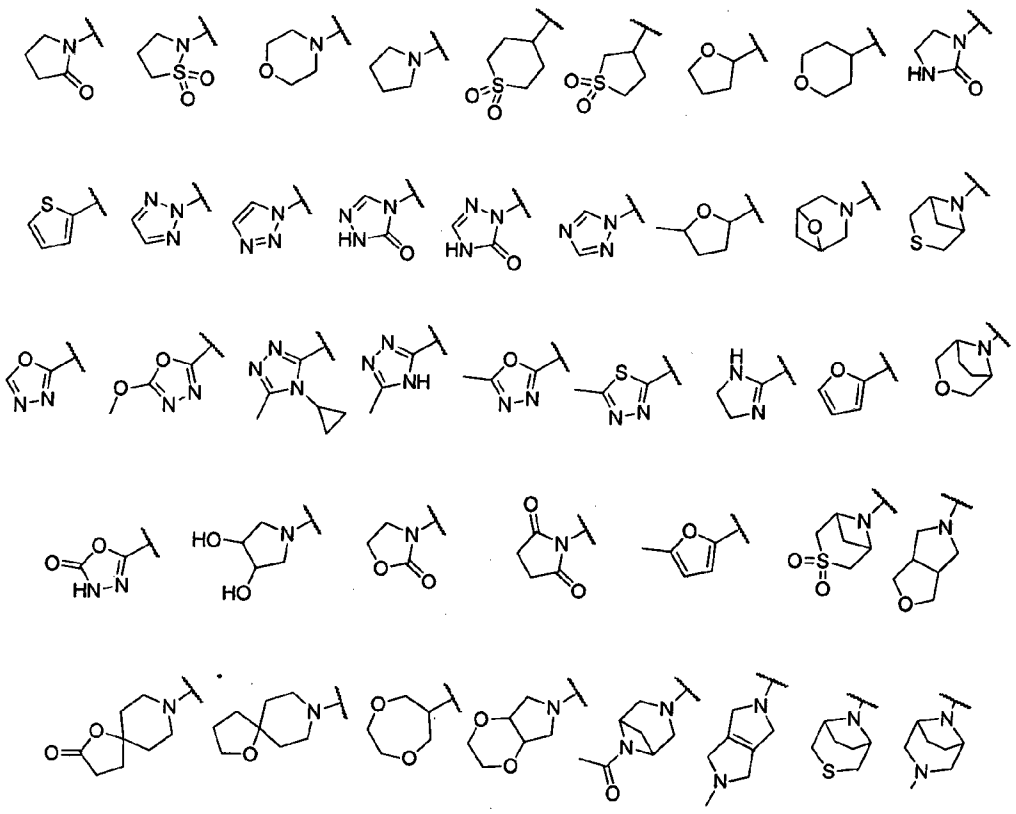
1. Verbindung, die die Struktur der allgemeinen Formel (I) aufweist:



Formel 1

oder pharmazeutisch verträgliche Salze davon,
wobei

X bei jedem Auftreten unabhängig aus N oder CH ausgewählt ist;
Z bei jedem Auftreten unabhängig aus N oder CH ausgewählt ist;
n aus 0, 1 ausgewählt ist;
A unabhängig aus Wasserstoff, Halogen, C_{1-4}-Alkyl, CF_3, CN, $CON(R_1)_2$, OC_{1-4}-Alkyl ausgewählt ist;
Ring B aus den folgenden Ringssystemen ausgewählt ist, von denen jedes substituiert sein kann:



2. Verbindungen nach Anspruch 1, wobei Substituenten am Ring B, soweit zutreffend, unabhängig aus Folgenden ausgewählt sind: H, OH, CN, NH_2, Halogen, Oxo, OCF_3, CF_3, C_1-C_6-Alkyl, OC_1-C_6-Alkyl, $(CH_2)_{1-6}OC_1$-C_6-Alkyl, O-$(CH_2)_{0-4O}C_1$-C_6-Alkyl, $C(O)NHC_1$-C_6-Alkyl, $NHC(O)C_1$-C_6-Alkyl, $S(O)_{0-2}C_1$-C_6-Alkyl, $(CH_2)_{1-6}N(R_1)_2$, $(CH2)_{1-6}NHC(=O)OR_1$, $(CH_2)_{1-6}NHC(=O)R_1$, $C(=O)OR_1$, $C(=O)R_1$, $(CH_2)_{1-4}C(=O)NHR_1$, $(CH_2)_{0-4}O(CH_2)_{0-4}Ar_1$, $(CH_2)_{0-4}NH(CH_2)_{0-4}Ar_1$, $(CH_2)_{0-4}Ar_1$, $(CH_2)_0$-$4C(O)(CH_2)_{0-4}Ar_1$, $(CH_2)_{0-4}C(=O)O(CH_2)_{0-4}Ar_1$, $(CH_2)_{0-4}C(=O)NR_1(CH_2)_{0-4}Ar_1$.

3. Verbindung nach Anspruch 1 und 2, wobei R_1 bei jedem Auftreten unabhängig aus Wasserstoff, C_1-C_4-Alkyl-, C_1-C_4-Halogenalkyl-, C_3-C_7-Cycloalkylgruppen ausgewählt ist.

4. Verbindung nach Anspruch 2, wobei Ar_1 bei jeder Wiederholung unabhängig aus unsubstituiertem oder substituiertem Aryl oder heterocyclischem Ring, der mit einem, zwei, drei oder vier Substituenten substituiert ist, ausgewählt ist.

5. Verbindungen nach Anspruch 4, wobei die Substituenten am Ar_1 unabhängig aus der Gruppe ausgewählt sind, die Folgende umfasst: OH, CN, NH_2, Halogen, OCF_3, CF_3, C_1-C_6-Alkyl, OC_1-C_6-Alkyl, $(CH_2)_{1-6}OC_1$-C_6-Alkyl, O-$(CH_2)_{0-4}OC_1$-C_6-Alkyl, $C(O)NHC_1$-C_6-Alkyl, $NHC(O)C_1$-C_6-Alkyl, $S(O)_{0-2}C_1$-C_6-Alkyl, $(CH_2)_{1-6}N(R_1)_2$, $(CH_2)_{1-6}NHC(=O)OR_1$, $(CH_2)_{1-6}NHC(=O)R_1$, $C(=O)OR_1$ oder $-C(=O)R_1$, $CH_2(CH_2)_{0-4}C(=O)NHR_1$.

6. Verbindung nach Anspruch 1, die aus der Gruppe ausgewählt ist, die aus Folgenden besteht:

N-(Cyanomethyl)-4-(2-((4-(4-(2-oxopyrrolidin-1-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamid;
N-(Cyanomethyl)-4-(2-((4-(4-(1,1-dioxidoisothiazolidin-2-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamid;
N-(Cyanomethyl)-4-(2-((4-(4-morpholinopiperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamid;
4-(2-((4-(4-(1H-1,2,4-Triazol-1-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)-N-(cyanomethyl)benzamid;
4-(2-((4-(4-(1H-Pyrazol-1-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)-N-(cyanomethyl)benzamid;
4-(2-((4-([1,3'-Bipyrrolidin]-1'-yl)phenyl)amino)pyrimidin-4-yl)-N-(cyanomethyl)benzamid;
N-(Cyanomethyl)-4-(2-((4-(4-(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)piperazin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamid;
N-(Cyanomethyl)-4-(2-((4-(4-(furan-2-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamid;
N-(Cyanomethyl)-4-(2-((4-(4-(1,1-dioxidotetrahydrothiophen-3-yl)piperazin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamid;
N-(Cyanomethyl)-4-(2-((4-(4-(2,5-dioxopyrrolidin-1-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamid;
N-(Cyanomethyl)-4-(2-((4-(4-(thiophen-2-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamid;
N-(Cyanomethyl)-4-(2-((4-(4-(2-oxooxazolidin-3-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamid;
N-(Cyanomethyl)-4-(2-((4-(4-(tetrahydrofuran-2-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamid;
N-(Cyanomethyl)-4-(2-((4-(4-(5-methylfuran-2-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamid;
N-(Cyanomethyl)-4-(2-((4-(4-(tetrahydro-2H-pyran-4-yl)piperazin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamid;
N-(Cyanomethyl)-4-(2-((4-(4-(5-methyltetrahydrofuran-2-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamid;
4-(2-((4-(4-(6-Oxa-3-azabicyclo[3.1.1]heptan-3-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)-N-(cyanomethyl)benzamid;
N-(Cyanomethyl)-4-(2-((4-(4-(2-oxoimidazolidin-1-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamid;
4-(2-((4-(4-(1,3,4-Oxadiazol-2-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)-N-(cyanomethyl)benzamid;
4-(2-((4-(4-(2H-1,2,3-Triazol-2-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)-N-(cyanomethyl)benzamid;
4-(2-((4-(4-(1H-1,2,3-Triazo1-1-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)-N-(cyanomethyl)benzamid;
N-(Cyanomethyl)-4-(2-((4-(4-(5-oxo-1H-1,2,4-triazo1-4(5H)-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamid;
N-(Cyanomethyl)-4-(2-((4-(4-(5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamid;
4-(2-((4-(4-(1-Oxa-8-azaspiro[4.5]decan-8-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)-N-(cyanomethyl)benzamid;
N-(Cyanomethyl)-4-(2-((4-(4-(5-methyl-1,3,4-oxadiazol-2-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamid;
N-(Cyanomethyl)-4-(2-((4-(4-(5-methyl-1,3,4-thiadiazol-2-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamid;
N-(Cyanomethyl)-4-(2-((4-(4-(tetrahydro-2H-[1,4]dioxino[2,3-c]pyrrol-6(3H)-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamid;
N-(Cyanomethyl)-4-(2-((4-(4-(2-oxo-1-oxa-8-azaspiro[4.5]decan-8-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamid;
N-(Cyanomethyl)-4-(2-((4-(4-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamid;
N-(Cyanomethyl)-4-(2-((4-(4-(4-cyclopropyl-5-methyl-4H-1,2,4-triazol-3-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamid;
N-(Cyanomethyl)-4-(2-((4-(4-(5-methoxy-1,3,4-oxadiazol-2-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamid;
4-(2-((4-(4-(1,4-Dioxepan-6-yl)piperazin-1-yl)phenyl)amino)pyrimidin-4-yl)-N-(cyanomethyl)benzamid;

N-(Cyanomethyl)-4-(2-((4-(4-(4,5-dihydro-1H-imidazol-2-yl)piperazin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamid;
N-(Cyanomethyl)-4-(2-((4-(4-(4,5-dihydro-1H-imidazol-2-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamid;
N-(Cyanomethyl)-4-(2-((4-(3-(tetrahydro-2H-[1,4]dioxino[2,3-c]pyrrol-6(3H)-yl)pyrrolidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamid;
N-(Cyanomethyl)-4-(2-((4-(4-(5-methyl-1,3,4-oxadiazol-2-yl)piperazin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamid;
N-(Cyanomethyl)-4-(2-((4-(4-(3,4-dihydroxypyrrolidin-1-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamid;
4-(2-((4-(4-(8-Oxa-3-azabicyclo[3.2.1]octan-3-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)-N-(cyanomethyl)benzamid;
4-(2-((4-(4-(6-Acetyl-3,6-diazabicyclo[3.1.1]heptan-3-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)-N-(cyanomethyl)benzamid;
N-(Cyanomethyl)-4-(5-methyl-2-((4-(4-morpholinopiperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamid;
N-(Cyanomethyl)-4-(5-methyl-2-((4-(4-(2-oxopyrrolidin-1-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamid;
4-(2-((4-(4-(1-Oxa-8-azaspiro[4.5]decan-8-yl)piperidin-1-yl)phenyl)amino)-5-methylpyrimidin-4-yl)-N-(cyanomethyl)benzamid;
N-(Cyanomethyl)-4-(5-methyl-2-((4-(4-(5-methyl-1,3,4-oxadiazol-2-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamid;
N-(Cyanomethyl)-4-(5-fluor-2-((4-(4-morpholinopiperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamid;
4-(5-Chlor-2-((4-(4-morpholinopiperidin-1-yl)phenyl)amino)pyrimidin-4-yl)-N-(cyanomethyl)benzamid;
N-(Cyanomethyl)-4-(5-fluor-2-((4-(4-(2-oxopyrrolidin-1-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamid;
4-(5-Chlor-2-((4-(4-(2-oxopyrrolidin-1-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)-N-(cyanomethyl)benzamid;
4-(2-((4-(4-(6-Oxa-3-azabicyclo[3.1.1]heptan-3-yl)piperidin-1-yl)phenyl)amino)-5-methylpyrimidin-4-yl)-N-(cyanomethyl)benzamid;
4-(2-((4-(4-(6-Oxa-3-azabicyclo[3.1.1]heptan-3-yl)piperidin-1-yl)phenyl)amino)-5-fluorpyrimidin-4-yl)-N-(cyanomethyl)benzamid;
-(2-((4-(4-(6-Oxa-3-azabicyclo[3.1.1]heptan-3-yl)piperidin-1-yl)phenyl)amino)-5-chlorpyrimidin-4-yl)-N-(cyanomethyl)benzamid;
N-(Cyanomethyl)-4-(5-methyl-2-((4-(4-(tetrahydro-2H-[1,4]dioxino[2,3-c]pyrrol-6(3H)-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamid;
N-(Cyanomethyl)-4-(5-fluor-2-((4-(4-(tetrahydro-2H-[1,4]dioxino[2,3-c]pyrrol-6(3H)-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamid;
4-(5-Chlor-2-((4-(4-(tetrahydro-2H-[1,4]dioxino[2,3-c]pyrrol-6(3H)-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)-N-(cyanomethyl)benzamid;
N-(Cyanomethyl)-4-(5-fluor-2-((4-(4-(5-methyl-1,3,4-oxadiazol-2-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamid;
4-(5-Chlor-2-((4-(4-(5-methyl-1,3,4-oxadiazol-2-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)-N-(cyanomethyl)benzamid;
N-(Cyanomethyl)-4-(5-methyl-2-((4-(4-(5-methyl-1,3,4-oxadiazol-2-yl)piperazin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamid;
N-(Cyanomethyl)-4-(5-fluor-2-((4-(4-(5-methyl-1,3,4-oxadiazol-2-yl)piperazin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamid;
4-(5-Chlor-2-((4-(4-(5-methyl-1,3,4-oxadiazol-2-yl)piperazin-1-yl)phenyl)amino)pyrimidin-4-yl)-N-(cyanomethyl)benzamid;
4-(2-((4-(4-(3-Thia-6-azabicyclo[3.1.1]heptan-6-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)-N-(cyanomethyl)benzamid;
4-(2-((4-(4-(3-Thia-6-azabicyclo[3.1.1]heptan-6-yl)piperidin-1-yl)phenyl)amino)-5-methylpyrimidin-4-yl)-N-(cyanomethyl)benzamid;
4-(2-((4-(4-(3-Thia-6-azabicyclo[3.1.1]heptan-6-yl)piperidin-1-yl)phenyl)amino)-5-fluorpyrimidin-4-yl)-N-(cyanomethyl)benzamid;
4-(2-((4-(4-(3-Thia-6-azabicyclo[3.1.1]heptan-6-yl)piperidin-1-yl)phenyl)amino)-5-chlorpyrimidin-4-yl)-N-(cyanomethyl)benzamid;

7. Verbindung nach einem vorstehenden Anspruch, die aus der Gruppe ausgewählt ist, die aus Folgenden besteht:

N-(Cyanomethyl)-4-(2-((4-(4-(2-oxopyrrolidin-1-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamid;
N-(Cyanomethyl)-4-(2-((4-(4-(1,1-dioxidoisothiazolidin-2-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamid;
N-(Cyanomethyl)-4-(2-((4-(4-morpholinopiperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamid;
4-(2-((4-(4-(1H-1,2,4-Triazol-1-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)-N-(cyanomethyl)benzamid;
4-(2-((4-(4-(1H-Pyrazol-1-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)-N-(cyanomethyl)benzamid;
4-(2-((4-([1,3'-Bipyrrolidin]-1'-yl)phenyl)amino)pyrimidin-4-yl)-N-(cyanomethyl)benzamid;
N-(Cyanomethyl)-4-(2-((4-(4-(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)piperazin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamid;
N-(Cyanomethyl)-4-(2-((4-(4-(furan-2-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamid;
N-(Cyanomethyl)-4-(2-((4-(4-(1,1-dioxidotetrahydrothiophen-3-yl)piperazin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamid;
N-(Cyanomethyl)-4-(2-((4-(4-(2,5-dioxopyrrolidin-1-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamid;
N-(Cyanomethyl)-4-(2-((4-(4-(thiophen-2-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamid;
N-(Cyanomethyl)-4-(2-((4-(4-(2-oxooxazolidin-3-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamid;
N-(Cyanomethyl)-4-(2-((4-(4-(tetrahydrofuran-2-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamid;
N-(Cyanomethyl)-4-(2-((4-(4-(5-methylfuran-2-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamid;
N-(Cyanomethyl)-4-(2-((4-(4-(tetrahydro-2H-pyran-4-yl)piperazin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamid;
N-(Cyanomethyl)-4-(2-((4-(4-(5-methyltetrahydrofuran-2-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamid;
4-(2-((4-(4-(6-Oxa-3-azabicyclo[3.1.1]heptan-3-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)-N-(cyanomethyl)benzamid;
N-(Cyanomethyl)-4-(2-((4-(4-(2-oxoimidazolidin-1-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamid;
4-(2-((4-(4-(1,3,4-Oxadiazol-2-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)-N-(cyanomethyl)benzamid;
4-(2-((4-(4-(2H-1,2,3-Triazol-2-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)-N-(cyanomethyl)benzamid;
4-(2-((4-(4-(1H-1,2,3-Triazol-1-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)-N-(cyanomethyl)benzamid;
N-(Cyanomethyl)-4-(2-((4-(4-(5-oxo-1H-1,2,4-triazol-4(5H)-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamid;
N-(Cyanomethyl)-4-(2-((4-(4-(5-oxo-4,5-dihydro-1H-1,2,4-triazo1-1-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamid;
4-(2-((4-(4-(1-Oxa-8-azaspiro[4.5]decan-8-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)-N-(cyanomethyl)benzamid;
N-(Cyanomethyl)-4-(2-((4-(4-(5-methyl-1,3,4-oxadiazol-2-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamid;
N-(Cyanomethyl)-4-(2-((4-(4-(5-methyl-1,3,4-thiadiazol-2-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamid;
N-(Cyanomethyl)-4-(2-((4-(4-(tetrahydro-2H-[1,4]dioxino[2,3-c]pyrrol-6(3H)-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamid;
N-(Cyanomethyl)-4-(2-((4-(4-(2-oxo-1-oxa-8-azaspiro[4.5]decan-8-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamid;
N-(Cyanomethyl)-4-(2-((4-(4-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamid;
N-(Cyanomethyl)-4-(2-((4-(4-(4-cyclopropyl-5-methyl-4H-1,2,4-triazol-3-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamid;
N-(Cyanomethyl)-4-(2-((4-(4-(5-methoxy-1,3,4-oxadiazol-2-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamid;
4-(2-((4-(4-(1,4-Dioxepan-6-yl)piperazin-1-yl)phenyl)amino)pyrimidin-4-yl)-N-(cyanomethyl)benzamid;
N-(Cyanomethyl)-4-(2-((4-(4-(4,5-dihydro-1H-imidazol-2-yl)piperazin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamid;
N-(Cyanomethyl)-4-(2-((4-(4-(4,5-dihydro-1H-imidazol-2-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamid;
N-(Cyanomethyl)-4-(2-((4-(3-(tetrahydro-2H-[1,4] dioxino[2,3-c]pyrrol-6(3H)-yl)pyrrolidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamid;
N-(Cyanomethyl)-4-(2-((4-(4-(5-methyl-1,3,4-oxadiazol-2-yl)piperazin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamid;
N-(Cyanomethyl)-4-(2-((4-(4-(3,4-dihydroxypyrrolidin-1-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benza-

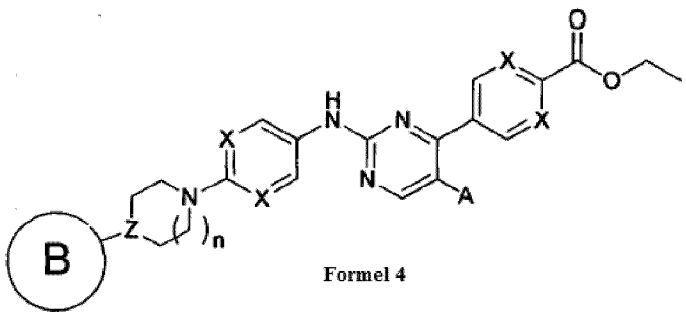
mid;
4-(2-((4-(4-(8-Oxa-3-azabicyclo[3.2.1]octan-3-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)-N-(cyanomethyl)benzamid;
4-(2-((4-(4-(6-Acetyl-3,6-diazabicyclo[3.1.1]heptan-3-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)-N-(cyanomethyl)benzamid;
N-(Cyanomethyl)-4-(5-methyl-2-((4-(4-morpholinopiperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamid;
N-(Cyanomethyl)-4-(5-methyl-2-((4-(4-(2-oxopyrrolidin-1-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamid;
4-(2-((4-(4-(1-Oxa-8-azaspiro[4.5]decan-8-yl)piperidin-1-yl)phenyl)amino)-5-methylpyrimidin-4-yl)-N-(cyanomethyl)benzamid;
N-(Cyanomethyl)-4-(5-methyl-2-((4-(4-(5-methyl-1,3,4-oxadiazol-2-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamid;
N-(Cyanomethyl)-4-(5-fluor-2-((4-(4-morpholinopiperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamid;
4-(5-Chlor-2-((4-(4-morpholinopiperidin-1-yl)phenyl)amino)pyrimidin-4-yl)-N-(cyanomethyl)benzamid;

8. Pharmazeutische Zusammensetzung, die eine therapeutisch wirksame Menge einer Verbindung der Formel (I) nach einem der vorstehenden Ansprüche und optional einen/ein oder mehrere pharmazeutisch verträgliche Träger, Verdünnungsmittel oder Hilfsstoffe umfasst.

9. Verbindungen nach einem vorstehenden Anspruch für die Verwendung bei der Behandlung von Entzündungszuständen, Autoimmunerkrankungen, proliferativen Erkrankungen, Allergie und Transplantatabstoßung, Erkrankungen, die mit einer Beeinträchtigung des Knorpelumsatzes einhergehen, angeborenen Knorpelfehlbildungen und/oder Erkrankungen, die mit Hypersekretion von IL6 oder Interferonen verbunden sind, wobei die JAK-Kinase eine pathophysiologische Funktion hat.

10. Pharmazeutische Zusammensetzung, die Verbindungen der Formel 1 nach Anspruch 1 zusammen mit geeigneten Hilfsstoffen umfasst, die für die Behandlung von Folgendem geeignet sind: Entzündungszuständen, Autoimmunerkrankungen, proliferativen Erkrankungen, Allergie und Transplantatabstoßung, Erkrankungen, die mit einer Beeinträchtigung des Knorpelumsatzes einhergehen, angeborenen Knorpelfehlbildungen und/oder Erkrankungen, die mit Hypersekretion von IL6 oder Interferonen verbunden sind.

11. Zwischenprodukt der Formel 4:



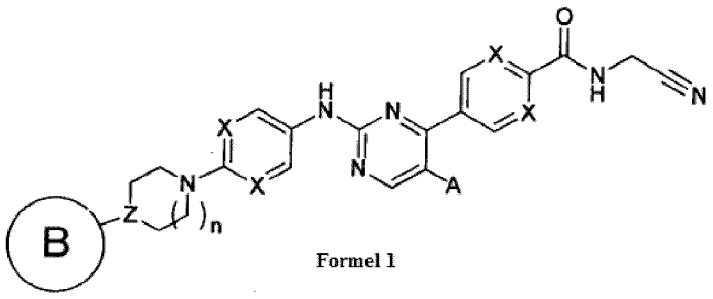
Formel 4

,

wobei B, Z, X, n und A wie in Anspruch 1 definiert sind.

Revendications

1. Composé ayant la structure de la formule générale (1)



Formel 1

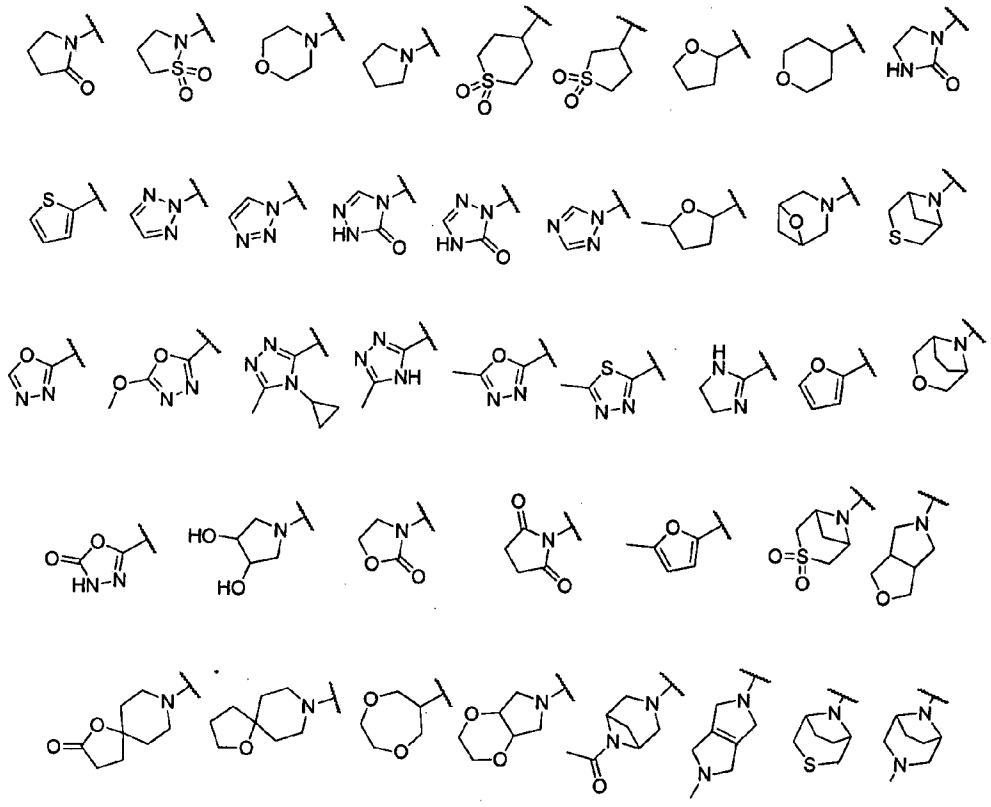
,

[Formule 1]

ou les sels pharmaceutiquement acceptables de celui-ci

Dans lequel

X est, à chaque occurrence, sélectionné indépendamment parmi N ou CH ;
Z est, à chaque occurrence, sélectionné indépendamment parmi N ou CH ;
n est sélectionné dans 0,1.
A est sélectionné indépendamment parmi : hydrogène, halogène, alkyle C_{1-4}, CF_3, CN, $CON(R_1)_2$, OC_{1-4}alkyle
L'anneau B est sélectionné parmi les systèmes d'anneaux suivants, chacun pouvant être substitué



[Schémas]

2. Les composés, selon la revendication 1, dans lesquels les substituants de l'anneau B sont, à chaque fois que c'est applicable, sélectionnés indépendamment parmi H, OH, CN, NH_2, halogène, oxo, OCF_3, CF_3, C_1-C_6 alkyle, OC_1-C_6 alkyle, $(CH_2)_{1-6}OC_1$-C_6 alkyle, O-$(CH_2)0$-$_4OC_1$-C_6 alkyle, $C(O)NHC_1$-C_6 alkyle, NHC(O) C_1-C_6 alkyle, $S(O)_{0-2}C_1$-C_6 alkyle, $(CH_2)_{1-6}N(R_1)_2$, $(CH_2)_{1-6}NHC(=O)OR_1$, $(CH_2)_{1-6}NHC(=O)R_1$, $C(=O)OR_1$, $C(=O)R_1$, $(CH_2)_{1-4}C(=O)NHR_1$, $(CH_2)_{0-4}O(CH_2)_{0-4}Ar_1$, $(CH_2)_{0-4}NH(CH_2)_{0-4}Ar_1$, $(CH_2)_{0-4}Ar_1$, $(CH_2)_{0-4}C(O)(CH_2)_{0-4}Ar_1$, $(CH_2)_{0-4}$ C(O) $O(CH_2)_{0-4}Ar_1$, $(CH2)_{0-4}$ $C(=O)NR_1(CH2)_{0-4}Ar_1$.

3. Le composé, selon les revendications 1 et 2, dans lequel R_1 est, à chaque occurrence, sélectionné indépendamment parmi les groupes hydrogène, C_1-C_4 alkyle, C_1-C_4, haloalkyle, C_3-C_7 cycloalkyle.

4. Le composé, selon la revendication 2, dans lequel Ar_1 est, à chaque itération, sélectionné indépendamment dans un aryle non substitué ou substitué ou un anneau hétérocyclique substitué par un, deux, trois ou quatre substituants.

5. Les composés, selon la revendication 4, dans lesquels les substituants sur Ar_1 sont indépendamment sélectionnés dans le groupe comprenant OH, CN, NH_2, halogène, OCF_3, CF_3, C_1-C_6 alkyle, OC_1-C_6 alkyle, $(CH_2)_{1\text{-}6}OC_1$-C_6 alkyle, O-$(CH_2)_{0\text{-}4}OC_1$-C_6 alkyle, $C(O)NHC_1$-C_6 alkyle, $NHC(O)C_1$-C_6 alkyle, $S(O)_{0\text{-}2}C_1$-C_6 alkyle, $(CH_2)_{1\text{-}6}N(R_1)_2$, $(CH_2)_{1\text{-}6}NHC(=O)OR_1$, $(CH_2)_{1\text{-}6}NHC(=O)R_1$,$C(=O)OR_1$ ou -$C(=O)R_1$, $CH_2(CH_2)_{0\text{-}4}C(=O)NHR_1$.

6. Le composé, selon la revendication 1, sélectionné parmi le groupe composé de :

N-(Cyanométhyle)-4-(2-((4-(4-(2-oxopyrrolidine-1-yl)pipéridine-1-yl)phényle)amino) pyrimidine-4-yl)benzamide;
N-(Cyanométhyle)-4-(2-((4-(4-(1,1-dioxidoisothiazolidine-2-yl)pipéridine-1-yl)phényle)amino)pyrimidine-4-yl)benzamide;
N-(Cyanométhyle)-4-(2-((4-(4-morpholinopipéridine-l-yl)phényle)amino)pyrimidine-4-yl)benzamide;
4-(2-((4-(4-(1H-1,2,4-Triazole-1-yl)pipéridine-1-yl)phényle)amino)pyrimidine-4-yl)-N-(cyanométhyle)benzamide;
4-(2-((4-(4-(1H-Pyrazole-1-yl)pipéridine-1-yl)phényle)amino)pyrimidine-4-yl)-N-(cyanométhyle)benzamide;
4-(2-((4-([1,3'-Bipyrrolidine]-1'-yl)phényle)amino)pyrimidine-4-yl)-N-(cyanométhyle)benzamide;
N-(cyanométhyle)-4-(2-((4-(4-(1,1-dioxidotétrahydro-2H-thiopyran-4-yl)pipérazine-1-yl)phényle)amino)pyrimidine-4-yl)benzamide;
N-(Cyanométhyle)-4-(2-((4-(4-(furane-2-yl)pipéridine-1-yl)phényle)amino)pyrimidine-4-yl)benzamide;
N-(Cyanométhyle)-4-(2-((4-(4-(1,1-dioxidotétrahydrothiophène-3-yl)pipérazine-1-yl)phényle)amino)pyrimidine-4-yl)benzamide;
N-(Cyanométhyle)-4-(2-((4-(4-(2,5-dioxopyrrolidine-1-yl)pipéridine-1-yl)phényle) amino)pyrimidine-4-yl)benzamide;
N-(Cyanométhyle)-4-(2-((4-(4-(thiophène-2-yl)pipéridine-1-yl)phényle) amino) pyrimidine-4-yl)benzamide;
N-(Cyanométhyle)-4-(2-((4-(4-(2-oxooxazolidinr-3-yl)pipéridine-1-yl)phényle) amino)pyrimidine-4-yl)benzamide;
N-(Cyanométhyle)-4-(2-((4-(4-(tétrahydrofurane-2-yl)pipéridine-1-yl)phényle) amino)pyrimidine-4-yl)benzamide;
N-(Cyanométhyle)-4-(2-((4-(4-(5-méthylfurane-2-yl)pipéridine-1-yl)phényle)amino)pyrimidine-4-yl)benzamide;
N-(Cyanométhyle)-4-(2-((4-(4-(tétrahydro-2H-pyrane-4-yl)pipérazine-1-yl)phényle)amino)pyrimidine-4-yl)benzamide;
N-(Cyanométhyle)-4-(2-((4-(4-(5-méthyltetrahydrofurane-2-yl)pipéridine-1-yl)phényle)amino)pyrimidine-4-yl)benzamide;
4-(2-((4-(4-(6-Oxa-3-azabicyclo[3.1.1]heptane-3-yl)pipéridine-1-yl)phényle)amino)pyrimidine-4-yl)-N-(cyanométhyle)benzamide;
N-(Cyanométhyle)-4-(2-((4-(4-(2-oxoimidazolidine-1-yl)pipéridine-1-yl)phényle)amino)pyrimidine-4-yl)benzamide;
4-(2-((4-(4-(1,3,4-Oxadiazole-2-yl)pipéridine-1-yl)phényle)amino)pyrimidine-4-yl)-N-(cyanométhyle)benzamide;
4-(2-((4-(4-(2H-1,2,3-Triazole-2-yl)pipéridine-1-yl)phényle)amino)pyrimidine-4-yl)-N-(cyano méthyle) benzamide;
4-(2-((4-(4-(1H-1,2,3-Triazole-1-yl)pipéridine-1-yl)phényle)amino) pyrimidine-4-yl)-N-(cyano méthyle)benzamide;
N-(Cyanométhyle)-4-(2-((4-(4-(5-oxo-1H-1,2,4-triazole-4(5H)-yl)pipéridine-1 -yl) phényle) amino) pyrimidine-4-yl)benzamide;
N-(Cyanométhyle)-4-(2-((4-(4-(5-oxo-4,5-dihydro-1H-1,2,4-triazole-1-yl)pipéridine-1-yl)phényle)amino)pyrimidine-4-yl)benzamide;
4-(2-((4-(4-(1-Oxa-8-azaspiro[4.5]décane-8-yl)pipéridine-1-yl)phényle) amino)pyrimidine-4-yl)-N-(cyanométhyle)benzamide;
N-(Cyanométhyle)-4-(2-((4-(4-(5-méthyle-1,3,4-oxadiazole-2-yl)pipéridine-1-yl)phényle)amino)pyrimidine-4-yl)benzamide;
N-(Cyanométhyle)-4-(2-((4-(4-(5-méthyle-1,3,4-thiadiazole-2-yl)pipéridine-1-yl)phényle)amino)pyrimidine-4-

yl)benzamide;
N-(Cyanométhyle)-4-(2-((4-(4-(tétrahydro-2H-[1,4]dioxine[2,3-c]pyrrole-6(3H)-yl)pipéridine-1-yl)phényle)amino)pyrimidine-4-yl)benzamide,
N-(Cyanométhyle)-4-(2-((4-(4-(2-oxo-1-oxa-8-azaspiro[4.5]décane-8-yl)pipéridine-1-yl)phényle)amino)pyrimidine-4-yl)benzamide;
N-(Cyanométhyle)-4-(2-((4-(4-(5-oxo-4,5-dihydro-1,3,4-oxadiazole-2-yl)piperidine-1-yl)phényle)amino)pyrimidine-4-yl)benzamide;
N-(Cyanométhyle)-4-(2-((4-(4-(4-cyclopropyle-5-méthyle-4H-1,2,4-triazole-3-yl) pipéridine-1-yl)phényle)amino)pyrimidine-4-yl)benzamide;
N-(Cyanométhyle)-4-(2-((4-(4-(5-méthoxy-1,3,4-oxadiazole-2-yl)pipéridine-1-yl)phényle) amino)pyrimidine-4-yl)benzamide;
4-(2-((4-(4-(1,4-Dioxépane-6-yl)pipérazine-1-yl)phényle)amino)pyrimidine-4-yl)-N-(cyanométhyle) benzamide;
N-(Cyanométhyle)-4-(2-((4-(4-(4,5-dihydro-1H-imidazole-2-yl)pipérazine-1-yl)phényle)amino)pyrimidine-4-yl)benzamide;
N-(Cyanométhyle)-4-(2-((4-(4-(4,5-dihydro-1H-imidazole-2-yl)pipéridine-1-yl)phényle)amino)pyrimidine-4-yl)benzamide;
N-(Cyanométhyle)-4-(2-((4-(3-(tétrahydro-2H-[1,4] dioxine[2,3-c]pyrrole-6(3H)-yl)pyrrolidine-1-yl)phényle)amino)pyrimidine-4-yl)benzamide;
N-(Cyanométhyle)-4-(2-((4-(4-(5-méthyle-1,3,4-oxadiazole-2-yl)pipérazine-1-yl)phényle)amino)pyrimidine-4-yl)benzamide;
N-(Cyanométhyle)-4-(2-((4-(4-(3,4-dihydroxypyrrolidine-1-yl)pipéridine-1-yl)phényle)amino)pyrimidine-4-yl)benzamide;
4-(2-((4-(4-(8-Oxa-3-azabicyclo[3.2.1]octane-3-yl)pipéridine-1-yl)phényle) amino) pyrimidine-4-yl)-N-(cyanométhyle)benzamide;
4-(2-((4-(4-(6-Acétyle-3,6-diazabicyclo[3.1.1]heptane-3-yl)pipéridine-1-yl)phényle)amino)pyrimidine-4-yl)-N-(cyanométhyle)benzamide;
N-(Cyanométhyle)-4-(5-méthyle-2-((4-(4-morpholinopipéridine-1-yl)phényle)amino)pyrimidine-4-yl)benzamide;
N-(Cyanométhyle)-4-(5-méthyle-2-((4-(4-(2-oxopyrrolidine-1-yl)pipéridine-1-yl)phényle)amino)pyrimidine-4-yl)benzamide;
4-(2-((4-(4-(1-Oxa-8-azaspiro[4.5]décane-8-yl)pipéridine-1-yl)phényle)amino)-5-méthylepyrimidine-4-yl)-N-(cyanométhyle)benzamide;
N-(Cyanométhyle)-4-(5-méthyle-2-((4-(4-(5-méthyle-1,3,4-oxadiazole-2-yl)pipéridine-1-yl)phényle)amino)pyrimidine-4-yl)benzamide;
N-(Cyanométhyle)-4-(5-fluoro-2-((4-(4-morpholinopipéridine-1-yl)phényle)amino)pyrimidine-4-yl)benzamide;
4-(5-Chloro-2-((4-(4-morpholinopipéridine-1-yl)phényle)amino)pyrimidine-4-yl)-N-(cyanométhyle)benzamide;
N-(Cyanométhyle)-4-(5-fluoro-2-((4-(4-(2-oxopyrrolidine-1-yl)pipéridine-1-yl)phényle)amino)pyrimidine-4-yl)benzamide;
4-(5-Chloro-2-((4-(4-(2-oxopyrrolidine-1-yl)pipéridine-1-yl)phényle)amino)pyrimidine-4-yl)-N-(cyanométhyle)benzamide;
4-(2-((4-(4-(6-Oxa-3-azabicyclo[3.1.1]heptane-3-yl)pipéridine-1-yl)phényle)amino)-5-méthylepyrimidine-4-yl)-N-(cyanométhyle)benzamide;
4-(2-((4-(4-(6-Oxa-3-azabicyclo[3.1.1heptane-3-yl)pipéridine-1-yl)phényle)amino)-5-fluoropyrimidine-4-yl)-N-(cyanométhyle)benzamide;
-(2-((4-(4-(6-Oxa-3-azabicyclo[3.1.1]heptane-3-yl)pipéridine-1-yl)phényle)amino)-5-chloropyrimidine-4-yl)-N-(cyanométhyle)benzamide;
N-(Cyanométhyle)-4-(5-méthyle-2-((4-(4-(tétrahydro-2H-[1,4]dioxine[2,3-c]pyrrole-6(3H)-yl)pipéridine-1-yl)phényle)amino)pyrimidine-4-yl)benzamide;
N-(Cyanométhyle)-4-(5-fluoro-2-((4-(4-(tétrahydro-2H-[1,4]dioxine[2,3-c]pyrrole-6(3H)-yl)pipéridine-1-yl)phényle)amino)pyrimidine-4-yl)benzamide;
4-(5-Chloro-2-((4-(4-(tétrahydro-2H-[1,4]dioxine[2,3-c]pyrrole-6(3H)-yl)pipéridine-1-yl)phényle)amino)pyrimidine-4-yl)-N-(cyanométhyle)benzamide;
N-(Cyanométhyle)-4-(5-fluoro-2-((4-(4-(5-méthyle-1,3,4-oxadiazole-2-yl)pipéridine-1-yl)phényle)amino)pyrimidine-4-yl)benzamide;
4-(5-Chloro-2-((4-(4-(5-méthyle-1,3,4-oxadiazole-2-yl)pipéridine-1yl)phényle)amino)pyrimidine-4-yl)-N-(cyanométhyle)benzamide;
N-(Cyanométhyle)-4-(5-méthyle-2-((4-(4-(5-méthyle-1,3,4-oxadiazole-2-yl)pipérazine-1-yl)phényle)amino)pyrimidine-4-yl)benzamide;

N-(Cyanométhyle)-4-(5-fluoro-2-((4-(4-(5-méthyle-1,3,4-oxadiazole-2-yl)pipérazine-1-yl)phényle)amino)pyrimidine-4-yl)benzamide;
4-(5-Chloro-2-((4-(4-(5-méthyle-1,3,4-oxadiazole-2-yl)pipérazine-1-yl)phényle)amino)pyrimidine-4-yl)-N-(cyanométhyle)benzamide;
4-(2-((4-(4-(3-Thia-6-azabicyclo[3.1.1]heptane-6-yl)pipéridine-1-yl)phényle)amino)pyrimidine-4-yl)-N-(cyanométhyle)benzamide;
4-(2-((4-(4-(3-Tia-6-azabicyclo[3.1.1]heptane-6-yl)pipéridine-1-yl)phényle)amino)-5-méthylepyrimidine-4-yl)-N-(cyanométhyle)benzamide;
4-(2-((4-(4-(3-Thia-6-azabicyclo[3.1.1]heptane-6-yl)pipéridine-1-yl)phényle)amino)-5-fluoropyrimidine-4-yl)-N-(cyanométhyle)benzamide;
4-(2-((4-(4-(3-Thia-6-azabicyclo[3.1.1]heptane-6-yl)pipéridine-1-yl)phényle)amino)-5-chloropyrimidine-4-yl)-N-(cyanométhyle)benzamide;

7. Le composé selon l'une quelconque des revendications précédentes, sélectionné dans le groupe composé de :

N-(Cyanométhyle)-4-(2-((4-(4-(2-oxopyrrolidine-1-yl)pipéridine-1-yl)phényle)amino) pyrimidine-4-yl)benzamide;
N-(Cyanométhyle)-4-(2-((4-(4-(1,1-dioxidoisothiazolidine-2-yl) pipéridine-1-yl) phényle)amino)pyrimidine-4-yl)benzamide;
N-(Cyanométhyle)-4-(2-((4-(4-morpholinopipéridine-1-yl)phényle)amino)pyrimidine-4-yl)benzamide;
4-(2-((4-(4-(1H-1,2,4-Triazole-1-yl)pipéridine-1-yl)phényle)amino)pyrimidine-4-yl)-N-(cyanométhyle)benzamide;
4-(2-((4-(4-(1H-Pyrazole-1-yl)pipéridine-1-yl)phényle)amino) pyrimidine-4-yl)-N-(cyanométhyle)benzamide;
4-(2-((4-([1,3'-Bipyrrolidine]-1'-yl)phényle)amino)pyrimidine-4-yl)-N-(cyanométhyle) benzamide;
N-(cyanométhyle)-4-(2-((4-(4-(1,1-dioxidotétrahydro-2H-thiopyrane-4-yl)pipérazine-1-yl)phényle)amino)pyrimidine-4-yl)benzamide;
N-(Cyanométhyle)-4-(2-((4-(4-(furane-2-yl)pipéridine-1-yl)phényle)amino)pyrimidine-4-yl)benzamide;
N-(Cyanométhyle)-4-(2-((4-(4-(1,1-dioxido-tétrahydrothiophène-3-yl)pipérazine-1-yl)phényle)amino)pyrimidine-4-yl)benzamide;
N-(Cyanométhyle)-4-(2-((4-(4-(2,5-dioxopyrrolidine-1-yl)pipéridine-1-yl)phényle) amino)pyrimidine-4-yl)benzamide;
N-(Cyanométhyle)-4-(2-((4-(4-(thiophène-2-yl)pipéridine-1-yl)phényle)amino)pyrimidine-4-yl)benzamide;
N-(Cyanométhyle)-4-(2-((4-(4-(2-oxo-oxazolidine-3-yl)pipéridine-1-yl)phényle) amino)pyrimidine-4-yl)benzamide;
N-(Cyanométhyle)-4-(2-((4-(4-(tétrahydrofurane-2-yl)pipéridine-1-yl)phényle)amino)pyrimidine-4-yl)benzamide;
N-(Cyanométhyle)-4-(2-((4-(4-(5-méthyle-furane-2-yl)pipéridine-1-yl)phényle)amino)pyrimidine-4-yl)benzamide;
N-(Cyanométhyle)-4-(2-((4-(4-(tétrahydro-2H-pyrane-4-yl)pipérazine-1-yl)phényle)amino)pyrimidine-4-yl)benzamide;
N-(Cyanométhyle)-4-(2-((4-(4-(5-méthyle-tétrahydrofurane-2-yl)pipéridine-1-yl)phényle)amino)pyrimidine-4-yl)benzamide;
4-(2-((4-(4-(6-Oxa-3-azabicyclo[3.1.1]heptane-3-yl)pipéridine-1-yl)phényle)amino)pyrimidine-4-yl)-N-(cyanométhyle)benzamide;
N-(Cyanométhyle)-4-(2-((4-(4-(2-oxoimidazolidine-1-yl)pipéridine-1-yl)phényle)amino)pyrimidine-4-yl)benzamide;
4-(2-((4-(4-(1,3,4-Oxadiazole-2-yl)pipéridine-1-yl)phényle)amino)pyrimidine-4-yl)-N-(cyanométhyle)benzamide;
4-(2-((4-(4-(2H-1,2,3-Triazole-2-yl)pipéridine-1-yl)phényle)amino) pyrimidine-4-yl)-N-(cyano méthyle) benzamide;
4-(2-((4-(4-(1H-1,2,3-Triazole-1-yl)pipéridine-1-yl)phényle)amino)pyrimidine-4-yl)-N-(cyano méthyle)benzamide;
N-(Cyanométhyle)-4-(2-((4-(4-(5-oxo-1H-1,2,4-triazole-4(5H)-yl)pipéridine-1-yl) phényle) amino) pyrimidine-4-yl)benzamide;
N-(Cyanométhyle)-4-(2-((4-(4-(5-oxo-4,5-dehydro-1H-1,2,4-triazole-llyl)pipéridine-1-yl)phényle)amino)pyrimidine-4-yl)benzamide;
4-(2-((4-(4-(1-Oxa-8-azaspiro[4.5]décane-8-yl)pipéridine-1-yl)phényle) amino)pyrimidine-4-yl)-N-(cyanométhyle)benzamide;

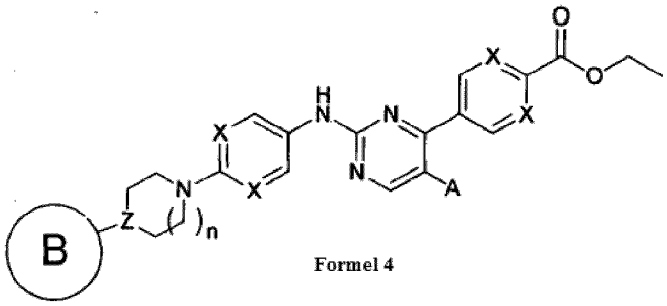
N-(Cyanométhyle)-4-(2-((4-(4-(5-méthyle-1,3,4-oxadiazole-2-yl)pipéridine-1-yl)phényle)amino)pyrimidine-4-yl)benzamide;
N-(Cyanométhyle)-4-(2-((4-(4-(5-méthyle-1,3,4-thiadiazole-2-yl)pipéridine-1-yl)phényle)amino)pyrimidine-4-yl)benzamide;
N-(Cyanométhyle)-4-(2-((4-(4-(tétrahydro-2H-[1,4]]dioxine[2,3-c]pyrrole-6(3H)-yl)pipéridine-1-yl)phényle)amino)pyrimidine-4-yl)benzamide;
N-(Cyanométhyle)-4-(2-((4-(4-(2-oxo-1-oxa-8-azaspiro[4.5]décane-8-yl)pipéridine-1-yl)phényle)amino)pyrimidine-4-yl)benzamide;
N-(Cyanométhyle)-4-(2-((4-(4-(5-oxo-4,5-dihydro-1,3,4-oxadiazole-2-yl)pipéridine-1-yl)phényle)amino)pyrimidine-4-yl)benzamide;
N-(Cyanométhyle)-4-(2-((4-(4-(4-cyclopropyl-5-méthyle-4H-1,2,4-triazole-3-yl) pipéridine-1-yl)phényle)amino)pyrimidine-4-yl)benzamide;
N-(Cyanométhyle)-4-(2-((4-(4-(5-méthoxy-1,3,4-oxadiazole-2-yl)pipéridine-1-yl)phényle) amino)pyrimidine-4-yl)benzamide;
4-(2-((4-(4-(1,4-Dioxépane-6-yl)pipérazine-1-yl)phényle)amino) pyrimidine-4-yl)-N-(cyanométhyle) benzamide;
N-(Cyanométhyle)-4-(2-((4-(4-(4,5-dihydro-1H-imidazole-2-yl)pipérazine-1-yl)phényle)amino)pyrimidine-4-yl)benzamide;
N-(Cyanométhyle)-4-(2-((4-(4-(4,5-dihydro-1H-imidazole-2-yl)pipéridine-1-yl)phényle)amino)pyrimidine-4-yl)benzamide;
N-(Cyanométhyle)-4-(2-((4-(3-(tétrahydro-2H-[1,4]dioxine[2,3-c]pyrrole-6(3H)-yl)pyrrolidine-1-yl)phényle)amino)pyrimidine-4-yl)benzamide;
N-(Cyanométhyle)-4-(2-((4-(4-(5-méthyle-1,3,4-oxadiazole-2-yl)pipérazine-1-yl)phényle)amino)pyrimidine-4-yl)benzamide;
N-(Cyanométhyle)-4-(2-((4-(4-(3,4-dihydroxypyrrolidine-1-yl)pipéridine-1-yl)phényle)amino)pyrimidine-4-yl)benzamide;
4-(2-((4-(4-(8-Oxa-3-azabicyclo[3.2.1]octane-3-yl)pipéridine-1-yl)phényle)amino) pyrimidine-4-yl)-N-(cyanométhyle)benzamide;
4-(2-((4-(4-(6-Acétyle-3,6-diazabicyclo[3.1.1]heptane-3-yl)pipéridine-1-yl)phényle)amino)pyrimidine-4-yl)-N-(cyanométhyle)benzamide;
N-(Cyanométhyle)-4-(5-méthyle-2-((4-(4-morpholinopipéridine-1-yl)phényle)amino)pyrimidine-4-yl)benzamide;
N-(Cyanométhyle)-4-(5-méthyle-2-((4-(4-(2-oxopyrrolidine-1-yl)pipéridine-1-yl)phényle)amino)pyrimidine-4-yl)benzamide;
4-(2-((4-(4-(1-Oxa-8-azaspiro[4.5]décane-8-yl)pipéridine-1-yl)phényle)amino)-5-méthylepyrimidine-4-yl)-N-(cyanométhyle)benzamide;
N-(Cyanométhyle)-4-(5-méthyle-2-((4-(4-(5-méthyle-1,3,4-oxadiazole-2-yl)pipéridine-1-yl)phényle)amino)pyrimidine-4-yl)benzamide;
N-(Cyanométhyle)-4-(5-fluoro-2-((4-(4-morpholinopipéridine-1-yl)phényle)amino)pyrimidine-4-yl)benzamide;
4-(5-Chloro-2-((4-(4-morpholinopipéridine-1-yl)phényle)amino)pyrimidine-4-yl)-N-(cyanométhyle)benzamide;

8. Une composition pharmaceutique comprenant une quantité thérapeutiquement efficace d'un composé de Formule (1) selon l'une quelconque des revendications précédentes, et éventuellement, un ou plusieurs véhicules, diluants ou excipients pharmaceutiquement acceptables.

9. Les composés, selon l'une quelconque des revendications précédentes, destinés à traiter les maladies inflammatoires, auto-immunes ou prolifératives, les allergies et rejets de greffe, les maladies impliquant une déficience du renouvellement cartilagineux, les malformations congénitales du cartilage, et/ou les maladies liées à l'hypersécrétion d'IL6 ou d'interférons impliquant une fonction physiopathologique de la kinase JAK.

10. La composition pharmaceutique comprenant des composés de formule 1 2 selon la revendication 1 2 avec des excipients adéquats permettant le traitement des maladies inflammatoires, auto-immunes, ou prolifératives, des allergies et rejets de greffe, des maladies impliquant une déficience du renouvellement cartilagineux, des malformations congénitales du cartilage, et/ou des maladies liées à l'hypersécrétion d'IL6 ou d'interférons impliquant une fonction physiopathologique de la kinase JAK.

11. Un intermédiaire de la formule 4



Formel 4

,

[Formule 4]

dans lequel B, Z, X, n et A sont définis tel que dans la revendication 1.

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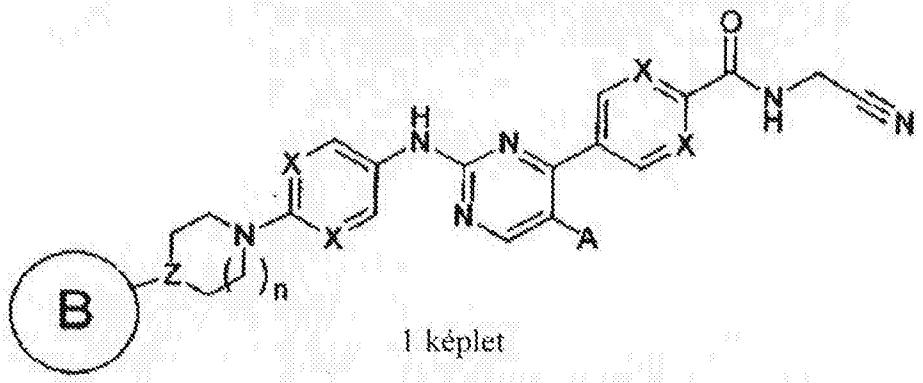
Janus kináz inhibitor N-cianometilamidok

Szabadalmi igénypontok

1. (I):



1 képlet

szerkezetű vegyület vagy gyógyászatilag elfogadható sója, ahol

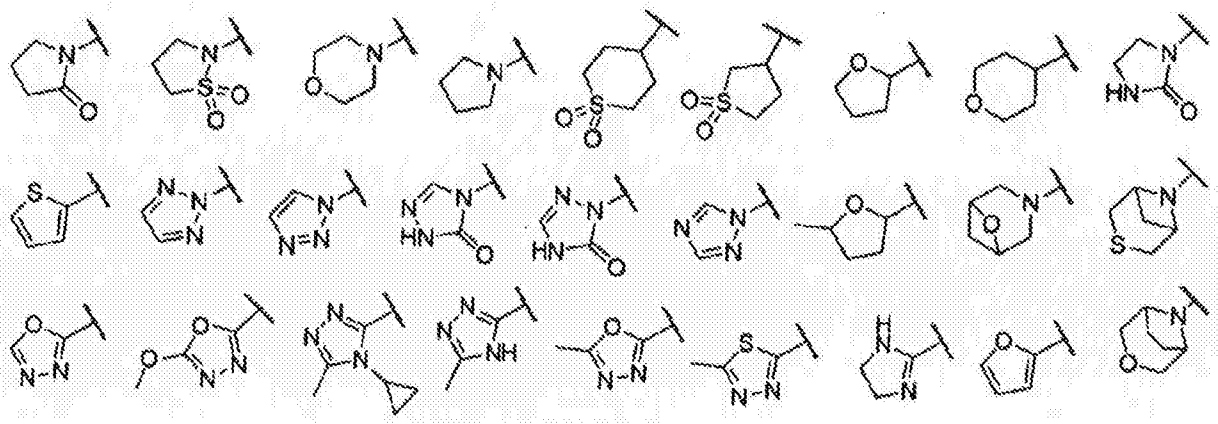
X valamennyi jelenléte esetén egymástól függetlenül N vagy CH közül választott;

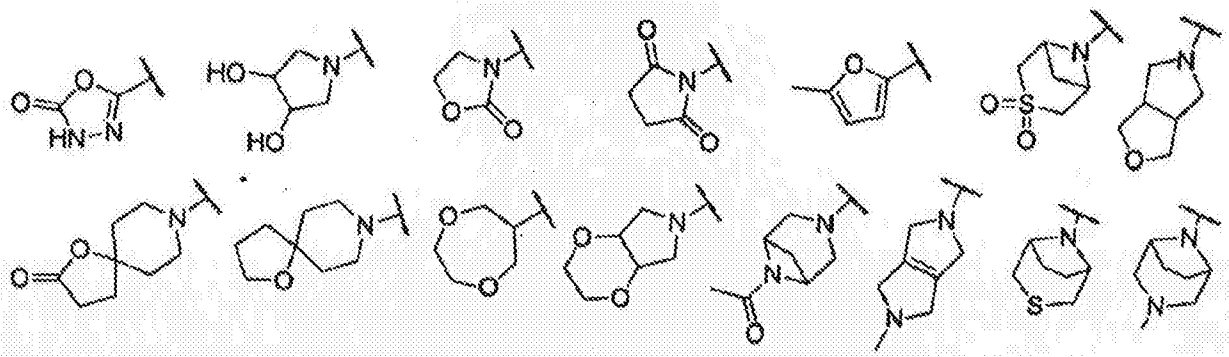
Z valamennyi jelenléte esetén egymástól függetlenül N vagy CH közül választott;

n 0 és 1 közül választott,

A egymástól függetlenül hidrogénatom, halogénatom, (1-4 szénatomos)- alkil, CF_3, CN, $CON(R_1)_2$, O(1-4 szénatomos)-alkilcsoport közül választott;

a B gyűrű az alábbi:





gyűrűrendszerek közül választott, melyek mindegyike szubsztituált lehet.

2. Az 1. igénypont szerinti vegyületek, ahol a B gyűrű szubsztituensei, amennyiben jelen vannak, egymástól függetlenül H, OH, CN, NH_2, halogénatom, oxo, OCF_3, CF_3, (1-6 szénatomos)-alkil, O(1-6 szénatomos)-alkil, $(CH_2)_{1-6}O$(1-6 szénatomos)-alkil, O-$(CH_2)_{0-4}O$(1-6 szénatomos)-alkil, C(O)NH(1-6 szénatomos)-alkil, NHC(O)(1-6 szénatomos)-alkil, $S(O)_{0-2}$(1-6 szénatomos)-alkil, $(CH_2)_{1-6}N(R_1)_2$, $(CH_2)_{1-6}NHC(=O)OR_1$, $(CH_2)_{1-6}NHC(=O)R_1$, $C(=O)OR_1$, $C(=O)R_1$, $(CH_2)_{1-4}C(=O)$ NHR_1, $(CH_2)_{0-4}O(CH_2)_{0-4}Ar_1$, $(CH_2)_{0-4}NH(CH_2)_{0-4}Ar_1$, $(CH_2)_{0-4}Ar_1$, $(CH_2)_{0-4}C(O)$-$(CH_2)_{0-4}Ar_1$, $(CH_2)_{0-4}C(=O)$ $O(CH_2)_{0-4}Ar_1$, $(CH_2)_{0-4}C(=O)NR_1(CH_2)_{0-4}Ar_1$ csoportok közül választottak.

3. Az 1. vagy 2. igénypont szerinti vegyület, ahol R_1 valamennyi jelenléte esetén egymástól függetlenül hidrogénatom, (1-4 szénatomos)-alkil, (1-4 szénatomos)-halogénalkil, (3-7 szénatomos)-cikloalkilcsoportok közül választott.

4. A 2. igénypont szerinti vegyület, ahol valamennyi Ar_1 jelentése egymástól függetlenül szubsztituálatlan vagy szubsztituált aril vagy egy, két, három vagy négy szubsztituenst tartalmazó heterociklusos gyűrű közül választott.

5. A 4. igénypont szerinti vegyületek, ahol az Ar_1 csoporton álló szubsztituensek egymástól függetlenül OH, CN, NH_2, halogénatom, OCF_3, CF_3, (1-6 szénatomos)-alkil, O(1-6 szénatomos)-alkil, $(CH_2)_{1-6}O$(1-6 szénatomos)-alkil, O-$(CH_2)_{0-4}O$(1-6 szénatomos)-alkil, C(O)NHC(1-6 szénatomos)-alkil, NHC(O)(1-6 szénatomos)-alkil, $S(O)_{0-2}$(1-6 szénatomos)-alkil, $(CH_2)_{1-6}N(R_1)_2$, $(CH_2)_{1-6}NHC(=O)OR_1$, $(CH_2)_{1-6}NHC(=O)R_1$, $C(=O)OR_1$ vagy -$C(=O)R_1$, $CH_2(CH_2)_{0-4}C(=O)NHR_1$ csoportok közül választottak.

6. Az alábbiak közül választott 1. igénypont szerinti vegyület:

N-(cianometil)-4-(2-((4-(4-(2-oxopirrolidin-1-il)piperidin-1-il)fenil)amino)-pirimidin-4-il)benzamid;

N-(cianometil)-4-(2-((4-(4-(1,1-dioxidoizotiazolidin-2-il)piperidin-1-il)fenil)amino)pirimidin-4-il)benzamid;

N-(cianometil)-4-(2-((4-(4-morfolinopiperidin-1-il)fenil)amino)pirimidin-4-il)benzamid;

4-(2-((4-(4-(1H-1,2,4-triazol-1-il)piperidin-1-il)fenil)amino)pirimidin-4-il)-N-(cianometil)benzamid;

4-(2-((4-(4-(1H-pirazol-1-il)piperidin-1-il)fenil)amino)pirimidin-4-il)-N-(cianometil)benzamid;

4-(2-((4-([1,3'-bipirrolidin]-1'-il)fenil)amino)pirimidin-4-il)-N-(cianometil)-benzamid;

N-(cianometil)-4-(2-((4-(4-(1,1-dioxidotetrahidro-2H-tiopiran-4-il)piperazin-1-il)fenil)amino)pirimidin-4-il)benzamid;

N-(cianometil)-4-(2-((4-(4-(furan-2-il)piperidin-1-il)fenil)amino)pirimidin-4-il)benzamid;

N-(cianometil)-4-(2-((4-(4-(1,1-dioxidotetrahidrotiofen-3-il)piperazin-1-il)fenil)amino)pirimidin-4-il)benzamid;

N-(cianometil)-4-(2-((4-(4-(2,5-dioxopirrolidin-1-il)piperidin-1-il)fenil)- amino)pirimidin-4-il)benzamid;

N-(cianometil)-4-(2-((4-(4-(tiofen-2-il)piperidin-1-il)fenil)amino) pirimidin-4-il)benzamid;

N-(cianometil)-4-(2-((4-(4-(2-oxooxazolidin-3-il)piperidin-1-il)fenil)-amino)pirimidin-4-il)benzamid;

N-(cianometil)-4-(2-((4-(4-(tetrahidrofuran-2-il)piperidin-1-il)fenil)amino)-pirimidin-4-il)benzamid;

N-(cianometil)-4-(2-((4-(4-(5-metilfuran-2-il)piperidin-1-il)fenil)amino)pirimidin-4-il)benzamid;

N-(cianometil)-4-(2-((4-(4-(tetrahidro-2H-piran-4-il)piperazin-1-il)fenil)amino)-pirimidin-4-il)benzamid;

N-(cianometil)-4-(2-((4-(4-(5-metiltetrahidrofuran-2-il)piperidin-1-il)fenil)amino)-pirimidin-4-il)benzamid;

4-(2-((4-(4-(6-oxa-3-azabiciklo[3.1.1]heptan-3-il)piperidin-1-il)fenil)amino)-pirimidin-4-il)-N-(cianometil)-benzamid;

N-(cianometil)-4-(2-((4-(4-(2-oxoimidazolidin-1-il)piperidin-1-il)fenil)amino)-pirimidin-4-il)benzamid;

4-(2-((4-(4-(1,3,4-oxadiazol-2-il)piperidin-1-il)fenil)amino) pirimidin-4-il)-N-(cianometil)benzamid;

4-(2-((4-(4-(2H-1,2,3-triazol-2-il)piperidin-1-il)fenil)amino)pirimidin-4-il)-N-(cianometil)benzamid;

4-(2-((4-(4-(1H-1,2,3-triazol-1-il)piperidin-1-il)fenil)amino)pirimidin-4-il)-N-(ciano metil)benzamid;

N-(cianometil)-4-(2-((4-(4-(5-oxo-1H-1,2,4-triazol-4(SH)-il)piperidin-1-il)fenil)-amino)pirimidin-4-il)benzamid;

N-(cianometil)-4-(2-((4-(4-(5-oxo-4,5-dihidro-1H-1,2,4-triazol-1-il)piperidin-1-il)fenil)amino)pirimidin-4-il)benzamid;

4-(2-((4-(4-(1-oxa-8-azaspiro[4.5]dekan-8-il)piperidin-1-il)fenil)amino)pirimidin-4-il)-N-(cianometil)benzamid;

N-(cianometil)-4-(2-((4-(4-(5-metil-1,3,4-oxadiazol-2-il)piperidin-1-il)fenil)-amino)pirimidin-4-il)benzamid;

N-(cianometil)-4-(2-((4-(4-(5-metil-1,3,4-tiadiazol-2-il)piperidin-1-il)fenil)-amino)pirimidin-4-il)benzamid;

N-(cianometil)-4-(2-((4-(4-(tetrahidro-2H-[1,4]dioxino[2,3-c]pirrol-6(3H)-il)piperidin-1-il)fenil)amino)pirimidin-4-il)benzamid;

N-(cianometil)-4-(2-((4-(4-(2-oxo-1-oxa-8-azaspiro[4.5]dekan-8-il)piperidin-1-il)fenil)amino)pirimidin-4-il)benzamid;

N-(cianometil)-4-(2-((4-(4-(5-oxo-4,5-dihidro-1,3,4-oxadiazol-2-il)piperidin-1-il)fenil)amino)pirimidin-4-il)benzamid;

N-(cianometil)-4-(2-((4-(4-(4-ciklopropil-5-metil-4H-1,2,4-triazol-3-il)piperidin-1-il)fenil)amino)pirimidin-4-il)benzamid;

N-(cianometil)-4-(2-((4-(4-(5-metoxi-1,3,4-oxadiazol-2-il)piperidin-1-il)fenil)-amino)pirimidin-4-il)benzamid;

4-(2-((4-(4-(1,4-dioxepan-6-il)piperazin-1-il)fenil)amino)pirimidin-4-il)-N-(cianometil)benzamid;

N-(cianometil)-4-(2-((4-(4-(4,5-dihidro-1H-imidazol-2-il)piperazin-1-il)fenil)-amino)pirimidin-4-il)benzamid;

N-(cianometil)-4-(2-((4-(4-(4,5-dihidro-1H-imidazol-2-il)piperidin-1-il)fenil)-amino)pirimidin-4-il)benzamid;

N-(cianometil)-4-(2-((4-(3-(tetrahidro-2H-[1,4]dioxino[2,3-c]pirrol-6(3H)-il)pirrolidin-1-il)fenil)amino)pirimidin-4-il)benzamid;

N-(cianometil)-4-(2-((4-(4-(5-metil-1,3,4-oxadiazol-2-il)piperazin-1-il)fenil)-amino)pirimidin-4-il)benzamid;

N-(cianometil)-4-(2-((4-(4-(3,4-dihidroxipirrolidin-1-il)piperidin-1-il)fenil)amino)-pirimidin-4-il)benzamid;

4-(2-((4-(4-(8-oxa-3-azabiciklo[3.2.1]oktan-3-il)piperidin-1-il)fenil)amino)- pirimidin-4-il)-N-(cianometil)benzamid;

4-(2-((4-(4-(6-acetil-3,6-diazabiciklo[3.1.1]heptan-3-il)piperidin-1-il)fenil)-amino)pirimidin-4-il)-N-(cianometil)benzamid;

N-(cianometil)-4-(5-metil-2-((4-(4-morfolinopiperidin-1-il)fenil)amino)pirimidin-4-il)benzamid;

N-(cianometil)-4-(5-metil-2-((4-(4-(2-oxopirrolidin-1-il)piperidin-1-il)fenil)-amino)pirimidin-4-il)benzamid;

4-(2-((4-(4-(1-oxa-8-azaspiro[4.5]dekan-8-il)piperidin-1-il)fenil)amino)-5-metilpirimidin-4-il)-N-(cianometil)benzamid;

N-(cianometil)-4-(5-metil-2-((4-(4-(5-metil-1,3,4-oxadiazol-2-il)piperidin-1-il)fenil)amino)pirimidin-4-il)benzamid;

N-(cianometil)-4-(5-fluor-2-((4-(4-morfolinopiperidin-1-il)fenil)amino)pirimidin-4-il)benzamid;

4-(5-klór-2-((4-(4-morfolinopiperidin-1-il)fenil)amino)pirimidin-4-il)-N-(cianometil)benzamid;

N-(cianometil)-4-(5-fluor-2-((4-(4-(2-oxopirrolidin-1-il)piperidin-1-il)fenil)-amino)pirimidin-4-il)benzamid;

4-(5-klór-2-((4-(4-(2-oxopirrolidin-1-il)piperidin-1-il)fenil)amino)pirimidin-4-il)-N-(cianometil)benzamid;

4-(2-((4-(4-(6-oxa-3-azabiciklo[3.1.1]heptan-3-il)piperidin-1-il)fenil)amino)-5-metilpirimidin-4-il)-N-(cianometil)benzamid;

4-(2-((4-(4-(6-oxa-3-azabiciklo[3.1.1]heptan-3-il)piperidin-1-il)fenil)amino)-5-fluorpirimidin-4-il)-N-(cianometil)benzamid;

4-(2-((4-(4-(6-oxa-3-azabiciklo[3.1.1]heptan-3-il)piperidin-1-il)fenil)amino)-5-klórpirimidin-4-il)-N-(cianometil)benzamid;

N-(cianometil)-4-(5-metil-2-((4-(4-(tetrahidro-2H-[1,4]dioxino[2,3-c]pirrol-6(3H)-il)piperidin-1-il)fenil)amino)pirimidin-4-il)benzamid;

N-(cianometil)-4-(5-fluor-2-((4-(4-(tetrahidro-2H-[1,4]dioxino[2,3-c]pirrol-6(3H)-il)piperidin-1-il)fenil)amino)pirimidin-4-il)benzamid;

4-(5-klór-2-((4-(4-(tetrahidro-2H-[1,4]dioxino[2,3-c]pirrol-6(3H)-il)piperidin-1-il)fenil)amino)pirimidin-4-il)-N-(cianometil)benzamid;

N-(cianometil)-4-(5-fluor-2-((4-(4-(5-metil-1,3,4-oxadiazol-2-il)piperidin-1-il)fenil)amino)pirimidin-4-il)benzamid;
4-(5-klór-2-((4-(4-(5-metil-1,3,4-oxadiazol-2-il)piperidin-1-il)fenil)amino)-pirimidin-4-il)-N-(cianometil)benzamid;
N-(cianometil)-4-(5-metil-2-((4-(4-(5-metil-1,3,4-oxadiazol-2-il)piperazin-1-il)fenil)amino)pirimidin-4-il)benzamid;
N-(cianometil)-4-(5-fluor-2-((4-(4-(5-metil-1,3,4-oxadiazol-2-il)piperazin-1-il)fenil)amino)pirimidin-4-il)benzamid;
4-(5-klór-2-((4-(4-(5-metil-1,3,4-oxadiazol-2-il)piperazin-1-il)fenil)amino)-pirimidin-4-il)-N-(cianometil)benzamid;
4-(2-((4-(4-(3-tia-6-azabiciklo[3.1.1]heptan-6-il)piperidin-1-il)fenil)amino)-pirimidin-4-il)-N-(cianometil)benzamid;
4-(2-((4-(4-(3-tia-6-azabiciklo[3.1.1]heptan-6-il)piperidin-1-il)fenil)amino)-5-metilpirimidin-4-il)-N-(cianometil)benzamid;
4-(2-((4-(4-(3-tia-6-azabiciklo[3.1.1]heptan-6-il)piperidin-1-il)fenil)amino)-5-fluorpirimidin-4-il)-N-(cianometil)benzamid;
4-(2-((4-(4-(3-tia-6-azabiciklo[3.1.1]heptan-6-il)piperidin-1-il)fenil)amino)-5-klórpirimidin-4-il)-N-(cianometil)benzamid.

7. Az előző igénypontok bármelyike szerinti vegyületek közül választott alábbi vegyületek:
N-(cianometil)-4-(2-((4-(4-(2-oxopirrolidin-1-il)piperidin-1-il)fenil)amino)-pirimidin-4-il)benzamid;
N-(cianometil)-4-(2-((4-(4-(1,1-dioxidoizotiazolidin-2-il)piperidin-1-il)- fenil)amino) pirimidin-4-il)benzamid;
N-(cianometil)-4-(2-((4-(4-morfolinopiperidin-1-il)fenil)amino)pirimidin-4-il)benzamid;
4-(2-((4-(4-(1H-1,2,4-triazol-1-il)piperidin-1-il)fenil)amino) pirimidin-4-il)-N-(cianometil)benzamid;
4-(2-(4-((4-(1H-pirazol-1-il)piperidin-1-il)fenil)amino)pirimidin-4-il)-N-(cianometil)benzamid;
4-(2-((4-([1,3'-bipirrolidin]-1'-il)fenil)amino)pirimidin-4-il)-N-(cianometil)- benzamid;
N-(cianometil)-4-(2-((4-(4-(1,1-dioxidotetrahidro-2H-tiopiran-4-il)piperazin-1-il)fenil)amino)pirimidin-4-il)benzamid;
N-(cianometil)-4-(2-((4-(4-(furan-2-il)piperidin-1-il)fenil)amino)pirimidin-4-il)benzamid;

N-(cianometil)-4-(2-((4-(4-(1,1-dioxidotetrahidrotiofen-3-il)piperazin-1-il)fenil)amino)pirimidin-4-il)benzamid;

N-(cianometil)-4-(2-((4-(4-(2,5-dioxopirrolidin-1-il)piperidin-1-il)fenil)amino)-pirimidin-4-il)benzamid;

N-(cianometil)-4-(2-((4-(4-(tiofen-2-il)piperidin-1-il)fenil)amino) pirimidin-4-il)benzamid;

N-(cianometil)-4-(2-((4-(4-(2-oxooxazolidin-3-il)piperidin-1-il)fenil) amino)-pirimidin-4-il)benzamid;

N-(cianometil)-4-(2-((4-(4-(tetrahidrofuran-2-il)piperidin-1-il)fenil)amino)-pirimidin-4-il)benzamid;

N-(cianometil)-4-(2-((4-(4-(5-metilfuran-2-il)piperidin-1-il)fenil)amino)pirimidin-4-il)benzamid;

N-(cianometil)-4-(2-((4-(4-(tetrahidro-2H-piran-4-il)piperazin-1-il)fenil)amino)-pirimidin-4-il)benzamid;

N-(cianometil)-4-(2-((4-(4-(5-metiltetrahidrofuran-2-il)piperidin-1-il)fenil)-amino)pirimidin-4-il)benzamid;

4-(2-((4-(4-(6-oxa-3-azabiciklo[3.1.1]heptan-3-il)piperidin-1-il)fenil)amino)-pirimidin-4-il)-N-(cianometil)benzamid;

N-(cianometil)-4-(2-((4-(4-(2-oxoimidazolidin-1-il)piperidin-1-il)fenil)amino)-pirimidin-4-il)benzamid;

4-(2-((4-(4-(1,3,4-oxadiazol-2-il)piperidin-1-il)fenil)amino) pirimidin-4-il)-N-(cianometil)benzamid;

4-(2-((4-(4-(2H-1,2,3-triazol-2-il)piperidin-1-il)fenil)amino)pirimidin-4-il)-N-(cianometil)benzamid;

4-(2-((4-(4-(1H-1,2,3-triazol-1-il)piperidin-1-il)fenil)amino)pirimidin-4-il)-N-(cianometil)benzamid;

N-(cianometil)-4-(2-((4-(4-(5-oxo-1H-1,2,4-triazol-4(SH)-il)piperidin-1-il)fenil) amino) pirimidin-4-il)benzamid;

N-(cianometil)-4-(2-((4-(4-(5-oxo-4,5-dihidro-1H-1,2,4-triazol-1-il)piperidin-1-il)fenil)amino)pirimidin-4-il)benzamid;

4-(2-((4-(4-(1-oxa-8-azaspiro[4.5]dekan-8-il)piperidin-1-il)fenil)amino)-pirimidin-4-il)-N-(cianometil)benzamid;

N-(cianometil)-4-(2-((4-(4-(5-metil-1,3,4-oxadiazol-2-il)piperidin-1-il)fenil)-amino)pirimidin-4-il)benzamid;

N-(cianometil)-4-(2-((4-(4-(5-metil-1,3,4-tiadiazol-2-il)piperidin-1-il)fenil)-amino)pirimidin-4-il)benzamid;

N-(cianometil)-4-(2-((4-(4-(tetrahidro-2H-[1,4]dioxino[2,3-c]pirrol-6(3H)-il)piperidin-1-il)fenil)amino)pirimidin-4-il)benzamid;

N-(cianometil)-4-(2-((4-(4-(2-oxo-1-oxa-8-azaspiro[4.5]dekan-8-il)piperidin-1-il)fenil)amino)pirimidin-4-il)benzamid;

N-(cianometil)-4-(2-((4-(4-(5-oxo-4,5-dihidro-1,3,4-oxadiazol-2-il)piperidin-1-il)fenil)amino)pirimidin-4-il)benzamid;

N-(cianometil)-4-(2-((4-(4-(4-ciklopropil-5-metil-4H-1,2,4-triazol-3-il)piperidin-1-il)fenil)amino)pirimidin-4-il)benzamid;

N-(cianometil)-4-(2-((4-(4-(5-metoxi-1,3,4-oxadiazol-2-il)piperidin-1-il)fenil)-amino)pirimidin-4-il)benzamid;

4-(2-((4-(4-(1,4-dioxepan-6-il)piperazin-1-il)fenil)amino)pirimidin-4-il)-N-(cianometil) benzamid;

N-(cianometil)-4-(2-((4-(4-(4,5-dihidro-1H-imidazol-2-il)piperazin-1-il)fenil)-amino)pirimidin-4-il)benzamid;

N-(cianometil)-4-(2-((4-(4-(4,5-dihidro-1H-imidazol-2-il)piperidin-1-il)fenil)-amino)pirimidin-4-il)benzamid;

N-(cianometil)-4-(2-((4-(3-(tetrahidro-2H-[1,4]dioxino[2,3-c]pirrol-6(3H)-il)pirrolidin-1-il)fenil)amino)pirimidin-4-il)benzamid;

N-(cianometil)-4-(2-((4-(4-(5-metil-1,3,4-oxadiazol-2-il)piperazin-1-il)fenil)-amino)pirimidin-4-il)benzamid;

N-(cianometil)-4-(2-((4-(4-(3,4-dihidroxipirrolidin-1-il)piperidin-1-il)fenil)-amino)pirimidin-4-il)benzamid;

4-(2-((4-(4-(8-oxa-3-azabiciklo[3.2.1]octan-3-il)piperidin-1-il)fenil)amino) -pirimidin-4-il)-N-(cianometil)benzamid;

4-(2-((4-(4-(6-Acetil-3,6-diazabiciklo[3.1.1]heptan-3-il)piperidin-1-il)fenil)-amino)pirimidin-4-il)-N-(cianometil)benzamid;

N-(cianometil)-4-(5-metil-2-((4-(4-morfolinopiperidin-1-il)fenil)amino)pirimidin-4-il)benzamid;

N-(cianometil)-4-(5-metil-2-((4-(4-(2-oxopirrolidin-1-il)piperidin-1-il)fenil)-amino)pirimidin-4-il)benzamid;

4-(2-((4-(4-(1-oxa-8-azaspiro[4.5]dekan-8-il)piperidin-1-il)fenil)amino)-5-metilpirimidin-4-il)-N-(cianometil)benzamid;

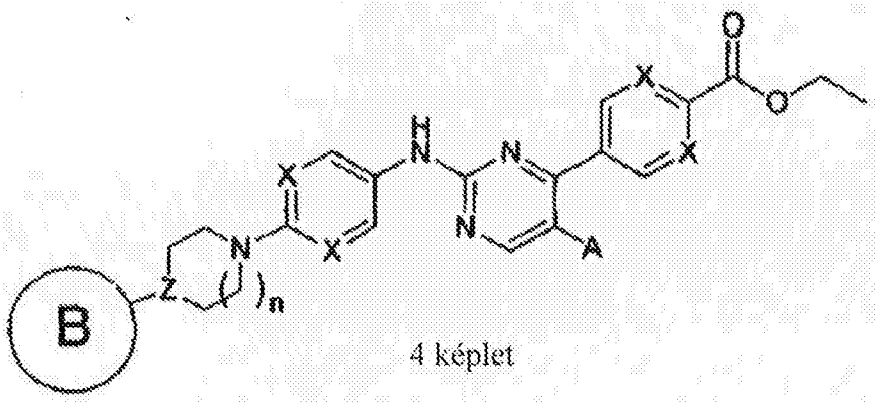
N-(cianometil)-4-(5-metil-2-((4-(4-(5-metil-1,3,4-oxadiazol-2-il)piperidin-1-il)fenil)amino)pirimidin-4-il)benzamid;
N-(cianometil)-4-(5-fluor-2-((4-(4-morfolinopiperidin-1-il)fenil)amino)pirimidin-4-il)benzamid;
4-(5-klór-2-((4-(4-morfolinopiperidin-1-il)fenil)amino)pirimidin-4-il)-N-(cianometil)benzamid.

8. Gyógyászati készítmény, mely terápiásan hatékony mennyiségű előző igénypontok bármelyike szerinti vegyületet és adott esetben egy vagy több gyógyászatilag elfogadható hordozóanyagot, hígítószert vagy kötőanyagot tartalmaz.

9. Az előző igénypontok bármelyike szerinti vegyület gyulladásos állapotok, autoimmun betegségek, proliferatív betegségek, allergia és transzplantátum kilökődés, porc mozgás romlásával, veleszületett porcelváltozásokkal összefüggő betegségek és/vagy IL6 vagy interferonok túltermelésével - ahol a JAK kináznak patofiziológiás funkciója van - összefüggő betegségek kezelésében történő alkalmazásra.

10. Gyulladásos állapotok, autoimmun betegségek, proliferatív betegségek, allergia és transzplantátum kilökődés, porc mozgás romlásával, veleszületett porcelváltozásokkal összefüggő betegségek és/vagy IL6 vagy interferonok túltermelésével összefüggő betegségek kezelésére alkalmas gyógyászati készítmény, mely az 1. igénypont szerinti vegyületeket megfelelő kötőanyagokkal együtt tartalmazza.

11. 4:



4 képlet

képletű intermedier, ahol B, Z, X, n és A az 1. igénypontban megadott.