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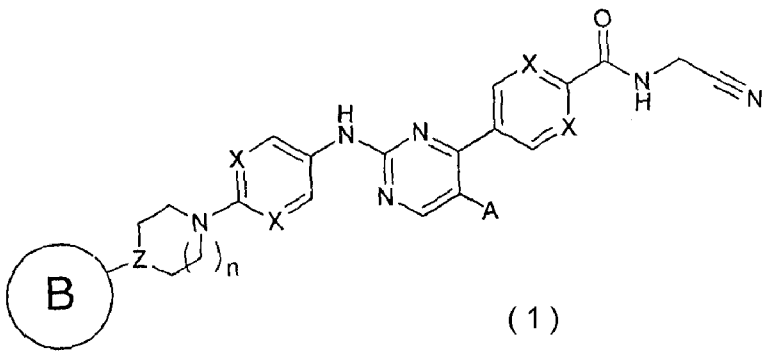
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(54) Title: N-CYANOMETHYLAMIDES AS INHIBITORS OF JANUS KINASE



(1)

(57) Abstract: 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.

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N-CYANOMETHYLAMIDES AS INHIBITORS OF JANUS KINASE

FIELD OF THE INVENTION

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

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.

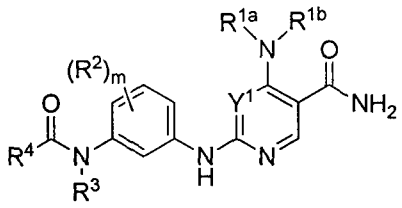
Vandeghinste et al. (WO 2005/124342) discovered JAK1 as a target whose inhibition might have therapeutic relevance for several diseases including OA. Knockout of the JAK1 gene in mice demonstrated that JAK1 plays essential and non-redundant roles during development.

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.

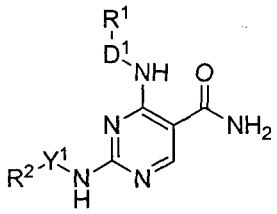
JAK3 associates with the common gamma chain of the extracellular receptors for the following interleukins: IL-2, IL-4, IL-7, IL-9 and IL- 15. A JAK3 deficiency is associated with an immune compromised (SCID) phenotype in both rodents and humans. The SCID phenotype of JAK3 (-/-) mammals and the lymphoid 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.

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.

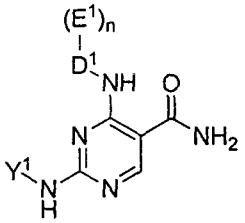
Patent applications from Portola (WO 2010/129802, WO 2009/145856, WO 2009/136995 etc.) discloses pyrimidine class of compounds as Spleen Tyrosine Kinases (SYK) or JAK inhibitors.



WO 2011/129802

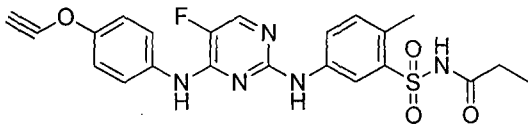


WO 2009/145856

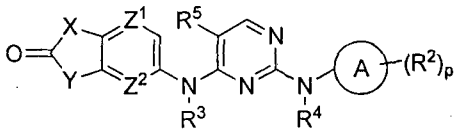


WO 2009/136995

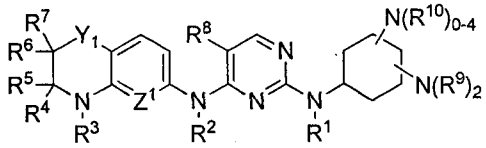
Rigel has filed a number of patent applications (WO 2011/017178, WO 2010/085684, WO 2010/078369, WO 2010/075558 and WO 2010/039518 etc.) claiming pyrimidine class of compounds as useful modulators of JAK pathways or as inhibitors of JAK kinases particularly JAK-2, JAK-3 or both.



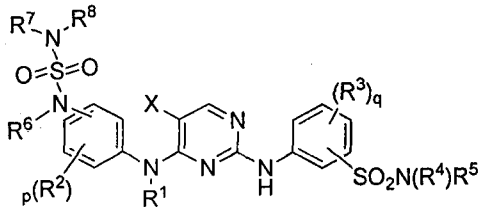
WO 2011/017178



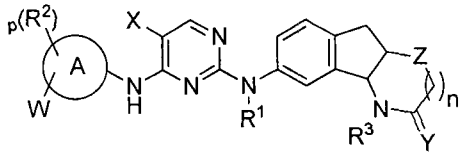
WO 2010/085684



WO 2010/078369

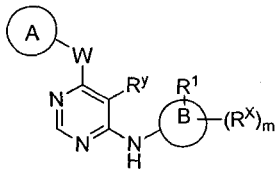


WO 2010/075558

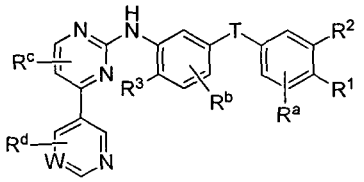


WO 2010/039518

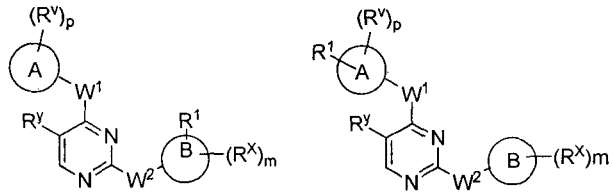
Avila Therapeutics reported pyrimidine class of compounds as protein kinase inhibitors (WO 2010123870, WO 2009/158571, WO 2009/051822 and WO 2008/151183).



WO 2010/123870
WO 2009/051822

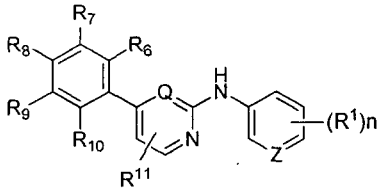


WO:2008151183

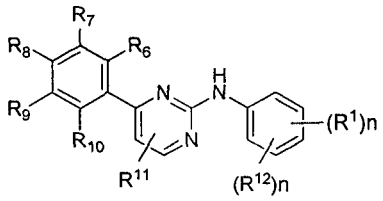


WO2009158571

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

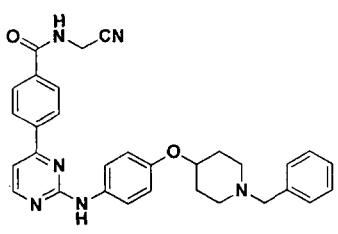


WO2008109943

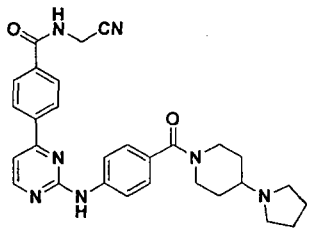


WO2009029998

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 1μM and less than 20 μM respectively.



Compound 1

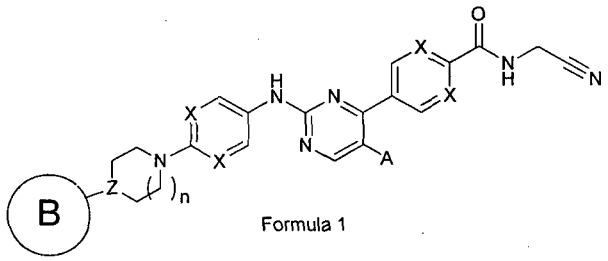


Compound 2

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

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:

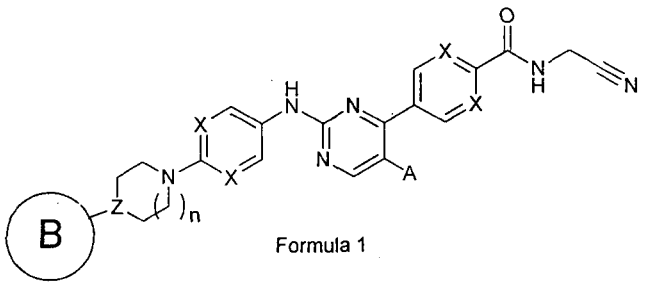


Formula 1

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

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

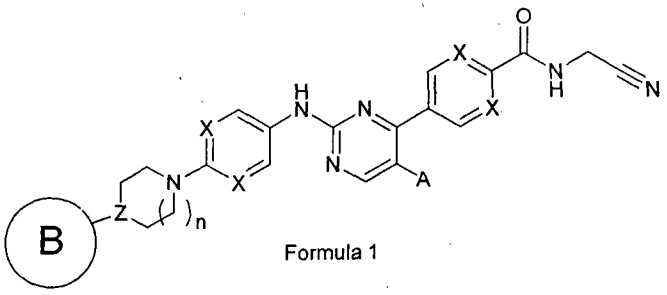
In an embodiment is provided processes for the preparation of novel compounds of general formula **(1)**, novel intermediates involved in their synthesis, their pharmaceutically acceptable salts, and pharmaceutical compositions containing them.

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.

In a further embodiment is provided the use of the novel compounds of the present invention in disease conditions developed by deregulation of JAK, by administering a therapeutically effective & non-toxic amount of the compounds of formula **(1)** or their pharmaceutically acceptable compositions to the mammals.

DETAILED DESCRIPTION OF THE INVENTION

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



Formula 1

Wherein

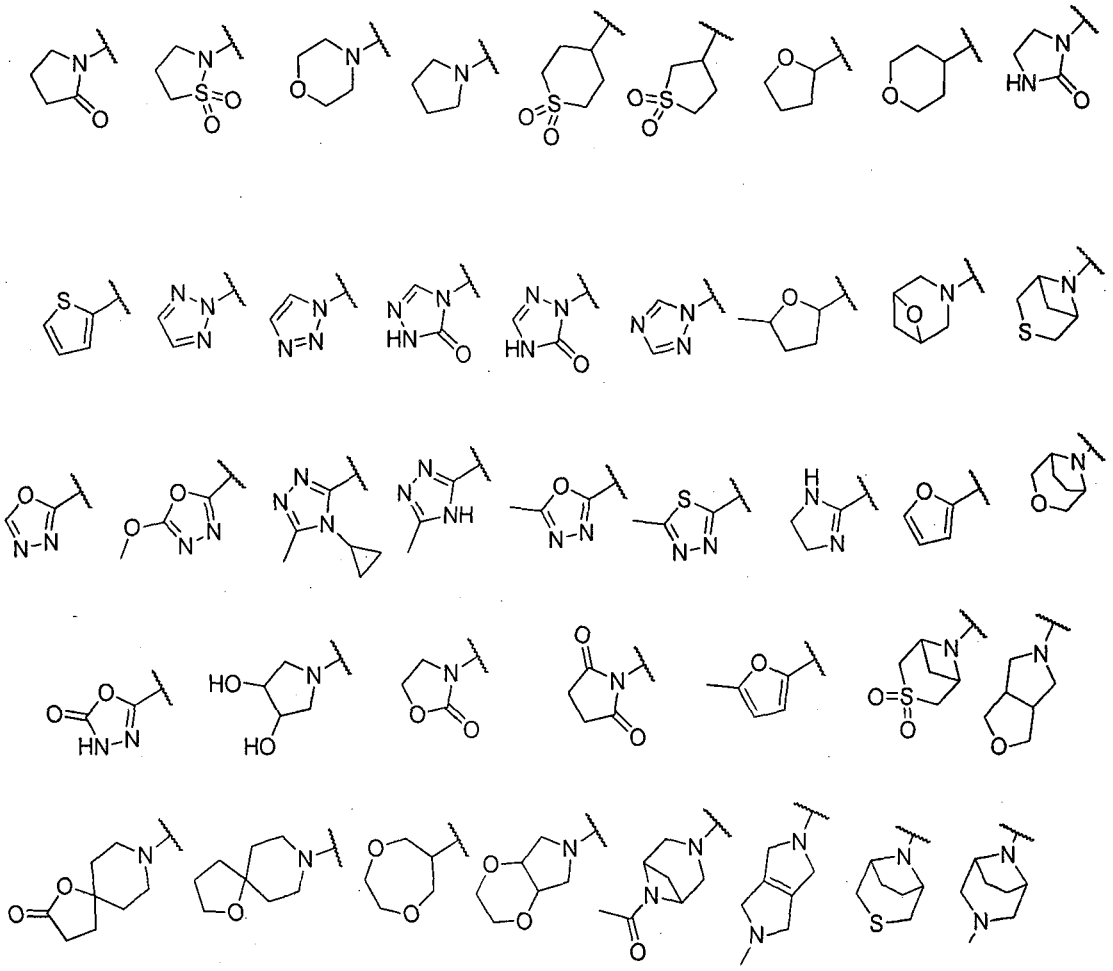
X at each occurrence is independently selected from N or CH;

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-$(CH_2)_{0-4}OC_1$-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,

$(CH_2)_{1-6}N(R_1)_2$, $(CH_2)_{1-6}NHC(=O)OR_1$, $(CH_2)_{1-6}NHC(=O)R_1$, $C(=O)OR_1$ 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.

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.

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

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

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 ^{0}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

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

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.

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-(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;

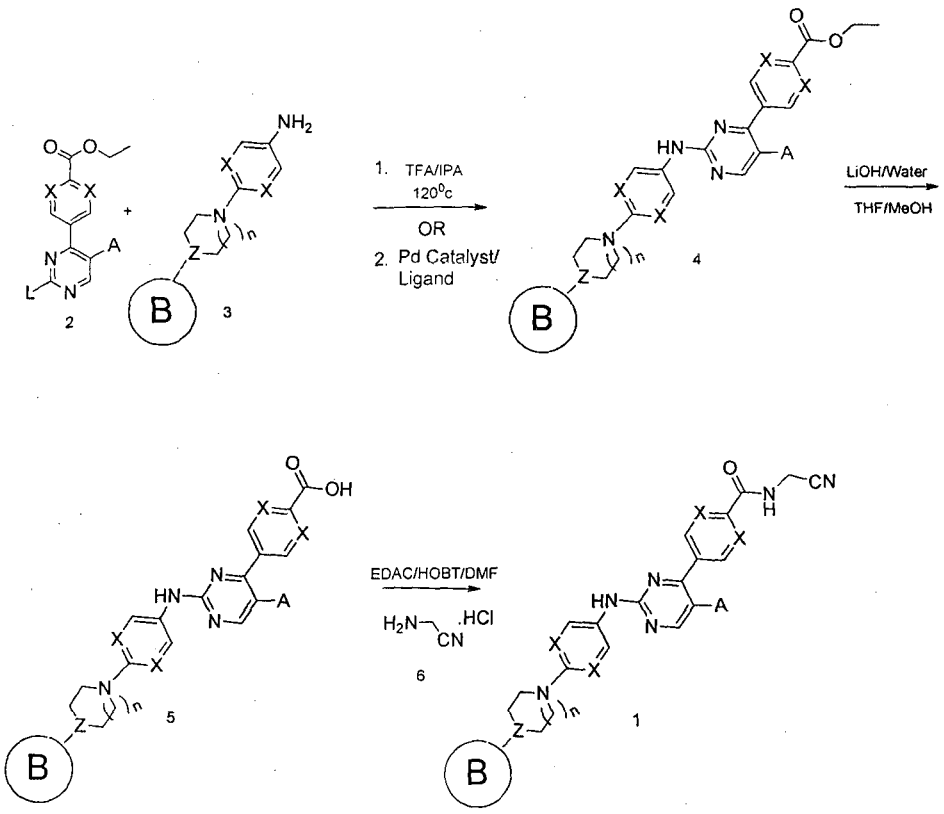
4-(2-((4-(4-(3-Thia-6-azabicyclo[3.1.1]heptan-6-yl)piperidin-1-yl)phenyl)amino)-5-methylpyrimidin-4-yl)-N-(cyanomethyl)benzamide;

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;

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:



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.

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.

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.

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.

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

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

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.

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.

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.

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

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
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)piperidin-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

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

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.

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.

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

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

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

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

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

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

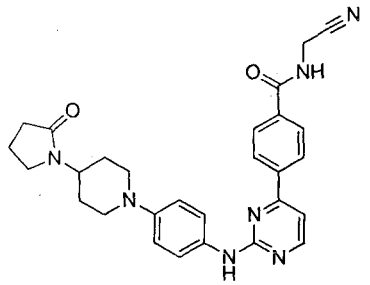
Prepared similar to the procedure described in Amine 1 but using 8-(piperidin-4-yl)-3-oxa-8-azabicyclo[3.2.1]octane [Ref.: WO2005108402].

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

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].

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.



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

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 ^{0}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

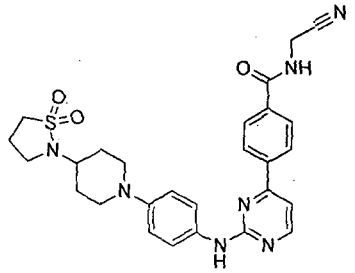
(25.0 g, 51.5 mmol) was dissolved in 3:1 methanol/THF(100 mL). To this lithium hydroxide (9.86 g, 412 mmol) in water (25 mL) was added and mixture was refluxed for 2 h., cooled, concentrated and acidified with dil HCl. The dark precipitate was filtered, washed with water and dried under vacuum to give 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

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 ^{0}C. The resulting reaction mixture was stirred at 25 ^{0}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%). ^{1}H 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.

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.

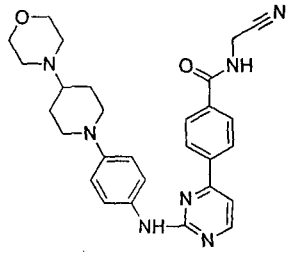
Example 2 : Preparation of N-(cyanomethyl)-4-(2-((4-(4-(1,1-dioxido isothiazolidin-2-yl) piperidin-1-yl) phenyl)amino)pyrimidin-4-yl)benzamide.



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,

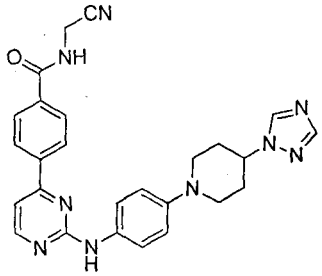
d, J = 5.2 Hz), 8.26 (2H, d, J = 8.4 Hz), 8.01 (2H, d, J = 8.4 Hz), 7.64 (2H, d, J = 9.2 Hz), 7.40 (1H, d, J = 5.2 Hz), 6.93 (2H, d, J = 8.8 Hz), 4.35 (2H, d, J = 5.6 Hz), 3.64 (2H, d, J = 13.2 Hz), 3.42-3.17 (4H, m), 2.67-2.66 (3H, m), 2.30-2.10 (2H, m), 1.85-1.70 (4H, m). ESI-MS: 531.90 $(M+H)^+$. 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.



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.

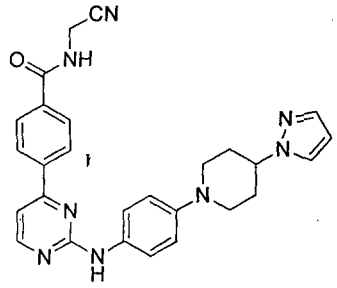
Example 4 : Preparation of 4-(2-((4-(4-(1H-1,2,4-triazol-1-yl)piperidin-1-yl) phenyl)amino) pyrimidin-4-yl)-N-(cyanomethyl)benzamide.



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,

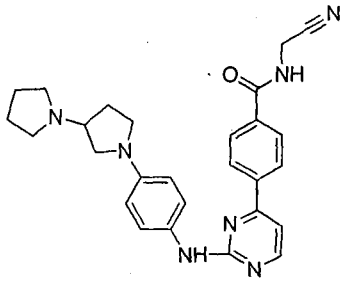
s), 8.55 (1H, d, J = 5.2 Hz), 8.28 (2H, d, J = 8.4 Hz), 8.02 (2H, d, J = 8.4 Hz), 7.91 (1H, S), 7.65 (2H, d, J = 8.8 Hz), 7.41 (1H, d, J = 5.2 Hz), 7.0 (2H, d, J = 8.8 Hz), 4.4 (1H, m), 4.35 (1H, d, J = 5.6 Hz), 3.74-3.71 (2H, m), 2.9-2.8 (2H, m), 2.3 -2.1 (4H, m). ESI-MS : 480.20 $(M+H)^+$. UPLC t_{ret} : 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.



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.

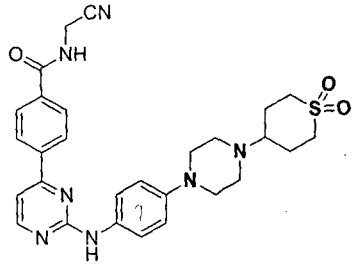
Example 6 : Preparation of 4-(2-((4-([1,3'-Bipyrrolidin]-1'-yl)phenyl) amino)pyrimidin-4-yl)-N-(cyanomethyl) benzamide.



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

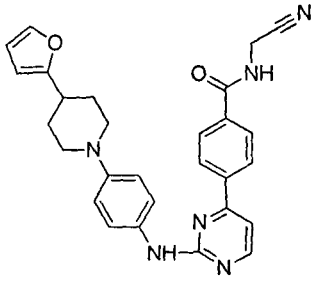
(1H, d, J = 5.2 Hz), 8.25 (2H, d, J = 8.8 Hz), 8.01 (2H, d, J = 8.8 Hz), 7.56 (2H, d, J = 8.8 Hz), 7.35 (1H, d, J = 5.2 Hz), 6.53 (2H, d, J = 9.2 Hz), 4.35 (2H, d, J = 5.2 Hz), 3.41-3.43 (1H, m), 3.32-3.26 (2H, m), 3.09-3.05 (1H, m), 2.85-2.81 (1H, m), 2.70-2.69 (4H, m), 2.16-2.14 (1H, m), 1.92-1.85 (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.



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.

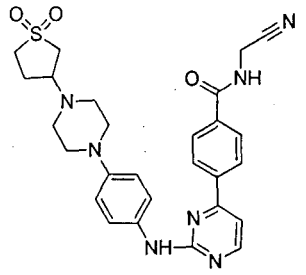
Example 8 : Preparation of N-(cyanomethyl)-4-(2-((4-(4-(furan-2-yl)piperidin-1-yl)phenyl) amino)pyrimidin-4-yl)benzamide.



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

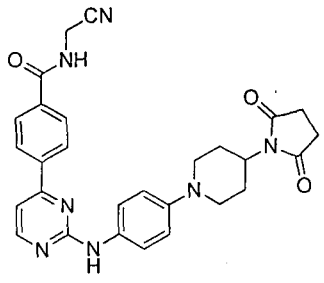
(1H, d, J = 5.2 Hz), 8.02 (2H, d, J = 8.4 Hz), 7.65 (2H, d, J = 9.2 Hz), 7.53 (1H, t, J = 1.6 Hz), 7.39 (1H, d, J = 5.2 Hz), 6.95 (2H, d, J = 9.2 Hz), 6.38-6.36 (1H, m), 6.13 (1H, d, J = 3.2 Hz), 4.35 (2H, d, J = 5.6 Hz), 3.65-3.62 (2H, m), 2.78-2.74 (3H, m), 2.10-1.97 (2H, m), 1.82-1.62 (2H, m). ESI-MS : 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.



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.

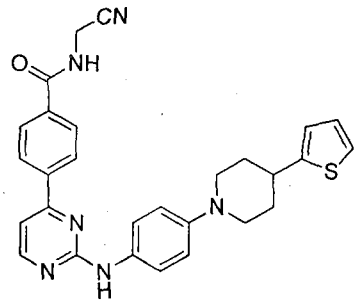
Example 10 : Preparation of N-(cyanomethyl)-4-(2-((4-(4-(2,5-dioxopyrrolidin-1-yl)piperidin-1-yl)phenyl) amino)pyrimidin-4-yl)benzamide.



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.

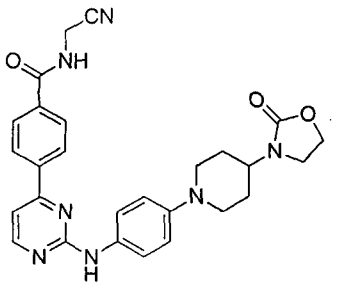
^{1}H NMR (400 MHz, d_6-DMSO) : 9.49 (1H, s), 9.34 (1H, t, J = 5.6 Hz), 8.53 (1H, d, J = 5.2 Hz), 8.26 (2H, d, J = 8.8 Hz), 8.02 (2H, d, J = 8.8 Hz), 7.63 (2H, d, J = 5.2 Hz), 7.40 (1H, d, J = 5.2 Hz), 6.93 (2H, d, J = 9.2 Hz), 4.35 (2H, d, J = 5.6 Hz), 3.99 (1H, m), 3.68 (2H, m), 2.63-2.69 (2H, m), 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.



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.

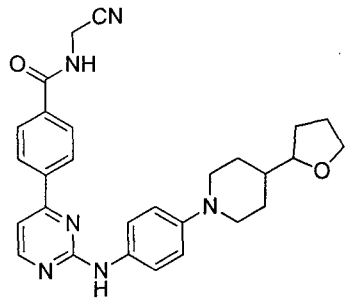
Example 12 : Preparation of N-(cyanomethyl)-4-(2-((4-(4-(2-oxooxazolidin-3-yl)piperidin-1-yl)phenyl) amino)pyrimidin-4-yl)benzamide.



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

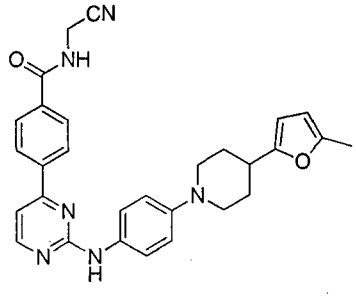
solid. ^{1}H NMR (400 MHz, d_6-DMSO) : 10.04 (1H, s), 9.41 (1H, t, J = 5.2 Hz), 8.64 (1H, d, J = 5.2 Hz), 8.28 (2H, d, J = 8.8 Hz), 8.03 (2H, d, J = 8.4 Hz), 7.65 (2H, d, J = 9.2 Hz), 7.40 (1H, d, J = 5.2 Hz), 6.96 (2H, d, J = 9.2 Hz), 4.35 (2H, d, J = 5.2 Hz), 4.26 (2H, t, J = 6.8 Hz), 3.71-3.63 (3H, 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.



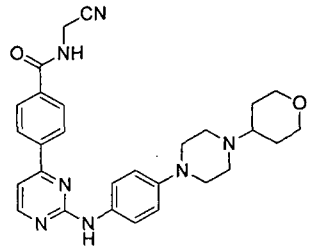
Prepared similar to the procedure described in Example 1 but using **Ester 1** and **Amine 13** as starting material. The title compound was obtained as light yellow solid. ^{1}H NMR (400 MHz, d_6-DMSO) : 9.46 (1H, s), 9.35 (1H, t, J = 5.6 Hz), 8.53 (1H, d, J = 5.2 Hz), 8.26 (2H, d, J = 8.4 Hz), 8.02 (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.



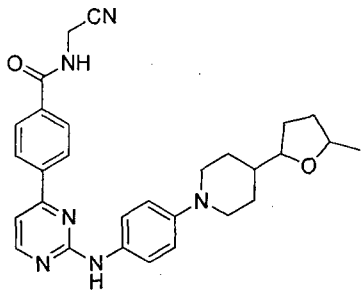
Prepared similar to the procedure described in Example 1 but using **Ester 1** and **Amine 14** as starting material. The title compound was obtained as light yellow solid. ^{1}H NMR (400 MHz, d_6-DMSO) : 9.48 (1H, s), 9.34 (1H, t, J = 4.8 Hz), 8.54 (1H, d, J = 5.2 Hz), 8.27 (2H, d, J = 8.4 Hz), 8.03 (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.



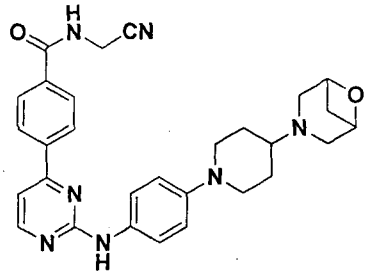
Prepared similar to the procedure described in Example 1 but using **Ester 1** and **Amine 15** as starting material. The title compound was obtained as light yellow solid. ^{1}H NMR (400 MHz, d_6-DMSO) : 9.46 (s, 1H), 9.33 (1H, t, J = 5.6 Hz), 8.52 (1H, d , J = 4.8 Hz), 8.25 (2H, d , J = 8.4 Hz), 8.01 (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.



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.



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.

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 $(M+H)^+$.

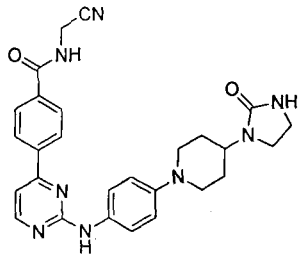
Step II : Preparation of 4-(2-((4-(4-(6-oxa-3-azabicyclo[3.1.1]heptan-3-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzoic acid.

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.

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 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.

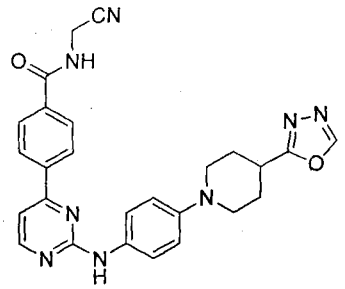
Example 18 : Preparation of N-(cyanomethyl)-4-(2-((4-(4-(2-oxoimidazolidin-1-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide.



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,

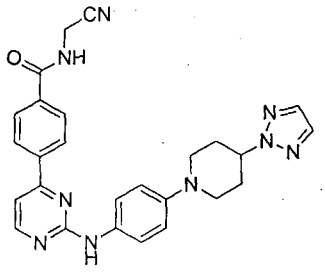
J = 4.8 Hz), 3.58-3.68 (3H, m), 3.21-3.23 (2H, m), 2.64-2.70 (2H, m), 1.70-1.78 (2H, m), 1.61-1.64 (2H, m). ESI-MS : 497.40 $(M+H)^+$. UPLC t_{ret} : 2.48 min.

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.



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.

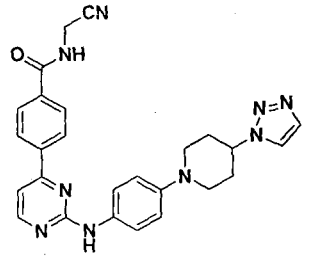
Example 20 : Preparation of 4-(2-((4-(4-(2H-1,2,3-triazol-2-yl)piperidin-1-yl) phenyl)amino) pyrimidin-4-yl)-N-(cyanomethyl)benzamide.



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),

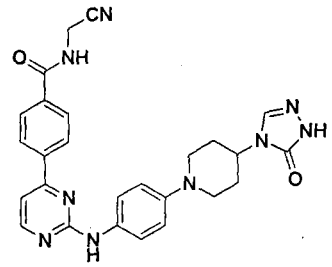
4.70 (1H, m), 4.36 (2H, d, J = 5.2 Hz), 3.71-3.68 (2H, m), 2.94-2.88 (2H, m), 2.11-2.18 (4H, m). ESI-MS : 479.85 $(M+H)^+$. UPLC t_{ret} : 2.85 min.

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.



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.

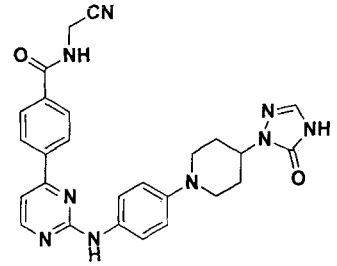
Example 22 : Preparation of N-(cyanomethyl)-4-(2-((4-(4-(5-oxo-1H-1,2,4-triazol-4(5H)-yl) piperidin-1-yl) phenyl)amino)pyrimidin-4-yl)benzamide.



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

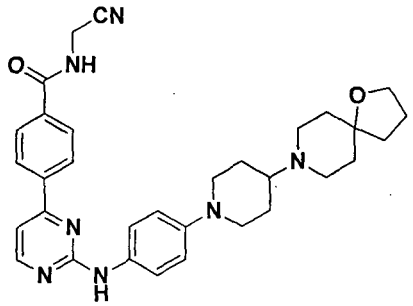
(1H, m), 4.35 (2H, d, J = 8.8 Hz), 3.42-3.31 (2H,m), 3.00-2.95 (2H, m), 2.10-2.08 (2H, m), 1.80-1.77 (2H, m). ESI-MS : 518.18 $(M+Na)^+$. UPLC t_{ret} : 2.49 min

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.



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.

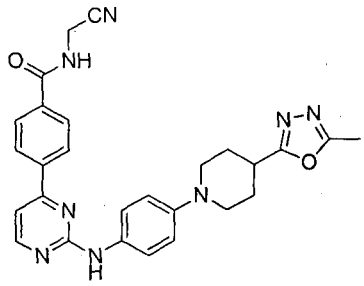
Example 24 : Preparation of 4-(2-((4-(4-(1-oxa-8-azaspiro[4.5]decan-8-yl)piperidin-1-yl) phenyl) amino)pyrimidin-4-yl)-N-(cyanomethyl)benzamide.



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 =

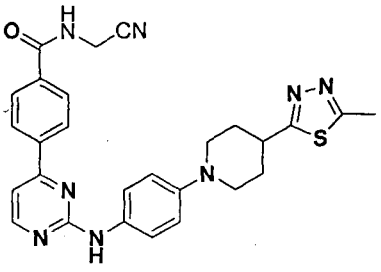
5.2 Hz), 3.68-3.65 (4H, m) 2.57-2.48 (6H, m), 1.81-1.79 (4H, m), 1.61-1.59 (3H, m), 1.51-1.49 (6H, m). ESI-MS : 552.20 $(M+H)^+$. UPLC t_{ret} : 2.63 min.

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.



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.

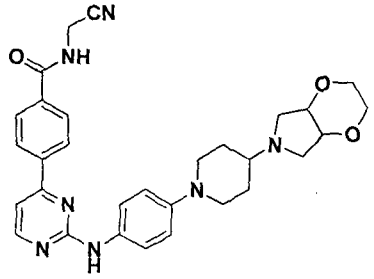
Example 26 : Preparation of N-(cyanomethyl)-4-(2-((4-(4-(5-methyl-1,3,4-thiadiazol-2-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide.



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

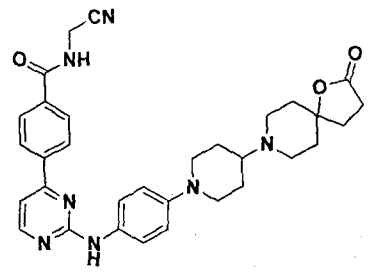
Hz), 3.65 (1H, d, J = 12.4 Hz), 3.29-3.26 (1H, m), 2.79 (2H, t, J = 10 hz), 2.69 (3H, s), 2.14-2.11 (2H, m), 1.85-1.82 (2H, m). ESI-MS : 511.50 $(M+H)^+$. UPLC t_{ret} : 2.71 min.

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.



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.

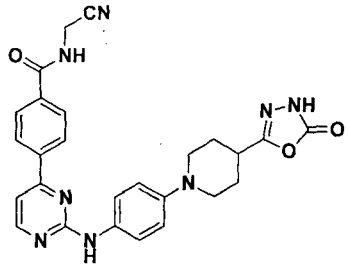
Example 28: Preparation of N-(cyanomethyl)-4-(2-((4-(4-(2-oxo-1-oxa-8-azaspiro[4.5]decan-8-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide.



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

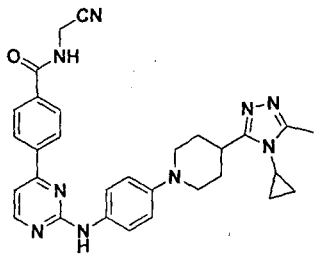
(1H, d, J = 5.2 Hz), 8.26 (2H, d, J = 8.4 Hz), 8.00 (2H, d, J = 8.4 Hz), 7.61 (2H, d, J = 9.2), 7.38 (1H, d, J = 5.2 Hz), 6.80 (2H, d, J = 9.2 Hz), 4.34 (2H, d, J = 5.6 Hz), 3.70-3.66 (2H, m), 2.50-2.49 (7H, m), 2.33-2.32 (2H, m), 1.99-1.95 (2H, m), 1.85-1.77 (4H, m), 1.62-1.52 (2H, m),1.51-1.47 (2H, 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.



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.

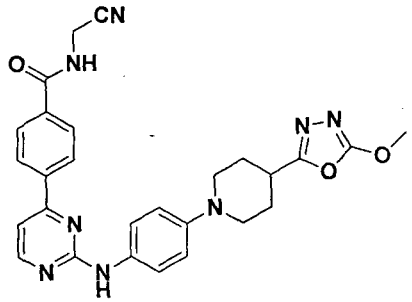
Example 30 : Preparation of N-(cyanomethyl)-4-(2-((4-(4-(4-cyclopropyl-5-methyl-4H-1,2,4-triazol-3-yl) piperidin-1-yl)phenyl)amino)pyrimidin-4-yl) benzamide.



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

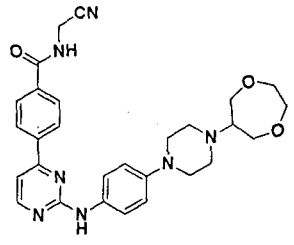
(1H, d, J = 5.2 Hz), 8.26 (2H, d, J = 8.4 Hz); 8.02 (2H, d, J = 8.8 Hz), 7.65 (2H, d, J = 9.2 Hz), 7.40 (1H, d, J = 5.2 Hz), 6.97 (2H, d, J = 9.2 Hz) 4.35 (2H, d, J = 5.6 Hz), 3.72-3.69 (2H, m), 3.17-3.13 (1H, m); 3.00-3.02 (1H, m), 2.77-2.66 (2H, m), 2.33 (3H, s), 2.04-2.01 (2H, m), 1.86-1.84 (2H, m), 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.



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.

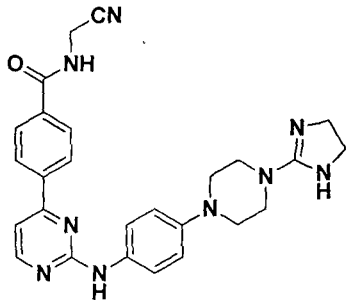
Example 32 : Preparation of 4-(2-((4-(4-(1,4-dioxepan-6-yl)piperazin-1-yl) phenyl)amino) pyrimidin-4-yl)-N-(cyanomethyl) benzamide.



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

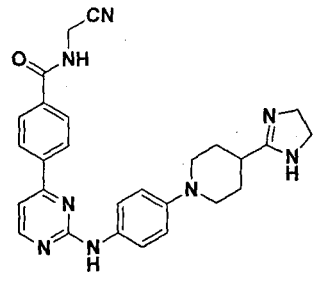
(1H, d, J = 5.2 Hz), 8.25 (2H, d, J = 8.4 Hz), 8.00 (2H, d, J = 8 Hz), 7.62 (2H, d, J = 8.8 Hz), 7.38 (1H, d, J = 5.2 Hz), 6.90 (2H, d, J = 9.2 Hz), 4.34 (2H, d, J = 5.2 Hz), 3.82-3.80 (4H, m), 3.56-3.60 (4H, m), 3.02-3.09 (4H, m), 2.71-2.73 (4H, m. ESI-MS : 514.15 $(M+H)^+$. UPLC t_{ret} : 2.66 min.

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.



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.

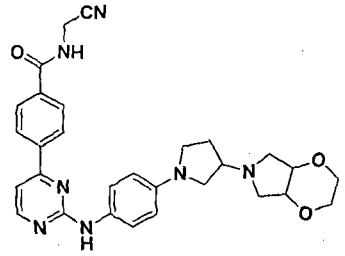
Example 34 : Preparation of N-(cyanomethyl)-4-(2-((4-(4-(4,5-dihydro-1H-imidazol-2-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide.



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),

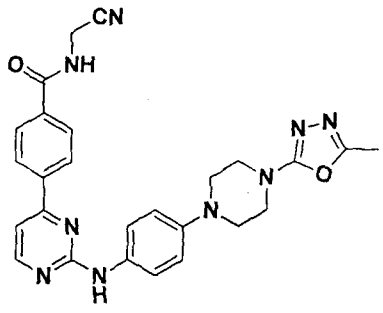
8.53 (1H, d, J = 5.2 Hz), 8.26 (2H, d, J = 8.0 Hz), 8.00 (d, J = 8.4 Hz), 7.65 (2H, d, J = 8.8 Hz), 7.40 (1H, d, J = 5.2 Hz), 6.95 (2H, d, J = 8.8 Hz), 4.35 (2H, d, J = 5.6 Hz), 4.35 (2H, m), 3.63-3.59 (2H, m), 3.09-3.07 (2H, m), 2.85-2.80 (2H, m), 2.49 (3H, s), 2.09-2.06 (2H, m), 1.85-1.82 (2H, m). 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.



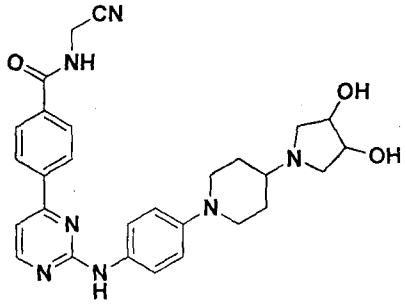
Prepared similar to the procedure described in Example 1 but using **Ester 1** and **Amine 35** as starting material. The title compound was obtained as light yellow solid. ^{1}H NMR (400 MHz, d_6-DMSO) : 9.33-9.29 (2H, m), 8.48 (1H, d, J = 4.8 Hz), 8.25 (1H, d, J = 8.4 Hz), 8.05 (2H, d, J = 8.8 Hz), 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.



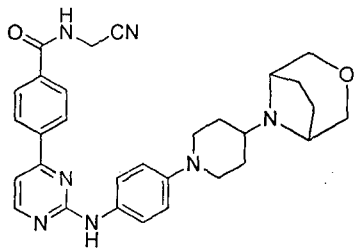
Prepared similar to the procedure described in Example 1 but using **Ester 1** and **Amine 36** as starting material. The title compound was obtained as light yellow solid. ^{1}H NMR (400 MHz, d_6-DMSO) : 9.50 (1H, s), 9.32 (1H, t, J = 5.2 Hz), 8.53 (1H, d, J = 5.2 Hz), 8.25 (2H, d, J = 8.4 Hz), 8.01 (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.



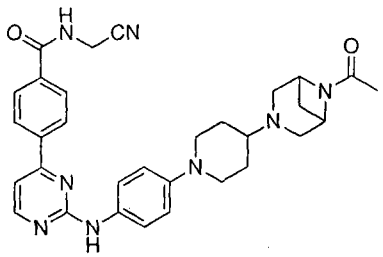
Prepared similar to the procedure described in Example 1 but using **Ester 1** and **Amine 37** as starting material. The title compound was obtained as light yellow solid. ^{1}H NMR (400 MHz, d_6-DMSO) : 9.54 (1H, s), 9.40 (1H, t, J = 5.2 Hz), 8.54 (1H, d, J = 5.2 Hz), 8.26 (2H, d, J = 8.4 Hz), 8.04 (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.



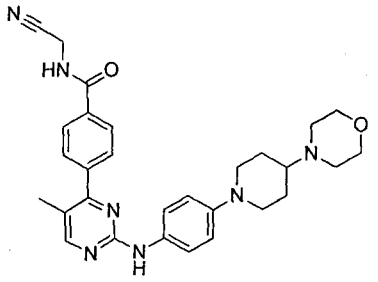
Prepared similar to the procedure described in Example 17 but using **Ester 1** and **Amine 38** as starting material. The title compound was obtained as light yellow solid. ^{1}H NMR (400 MHz, d_6-DMSO) : 9.48 (1H, s), 9.36 (1H, t, J = 5.2 Hz), 8.53 (1H, d, J = 5.2 Hz), 8.27 (2H, d, J = 8.4 Hz), 8.03 (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.



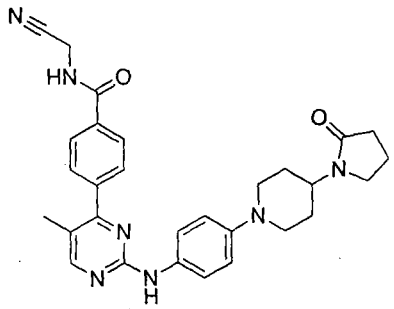
Prepared similar to the procedure described in Example 17 but using **Ester 1** and **Amine 39** as starting material. The title compound was obtained as light yellow solid. ^{1}H NMR (400 MHz, d_6-DMSO) : 9.44 (s, 1H), 9.32 (t, 1H, J = 5.2 Hz), 8.52 (d, 1H, J = 5.2 Hz), 8.25 (d, 2H, J = 8.4 Hz), 8.01 (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.



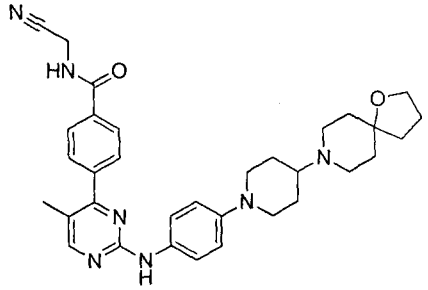
Prepared similar to the procedure described in Example 1 but using **Ester 2** and **Amine 3** as starting material. The title compound was obtained as light yellow solid. ^{1}H NMR (400 MHz, d_6-DMSO) : 9.30 (t, 2H, J = 5.2 Hz), 8.36 (s, 1H), 7.98 (d, 2H, J = 8.4 Hz), 7.77 (d, 2H, J = 8.0 Hz), 7.57 (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.



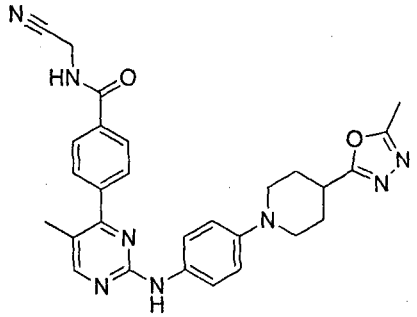
Prepared similar to the procedure described in Example 1 but using **Ester 2** and **Amine 1** as starting material. The title compound was obtained as light yellow solid. ^{1}H NMR (400 MHz, d_6-DMSO) : 9.32 (bs, 2H), 8.38 (bs, 1H), 7.99 (d, 2H, J = 7.6 Hz), 7.77 (d, 2H, J = 8.0 Hz), 7.59 (d, 2H, J = 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.



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.

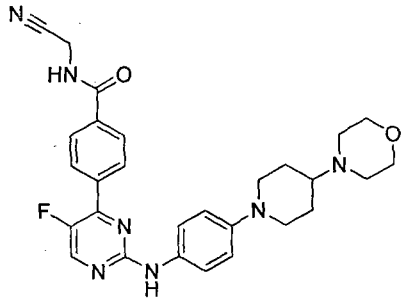
Example 43 : Preparation of N-(cyanomethyl)-4-(5-methyl-2-((4-(4-(5-methyl-1,3,4-oxadiazol-2-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide.



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_6-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

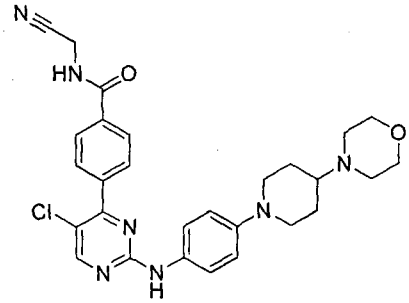
(m, 2H), 2.46 (s, 3H), 2.19 (s, 3H), 2.03-2.07 (m, 2H), 1.80-1.83 (m, 2H). ESI-MS: 509.10 $(M+H)^+$. UPLC t_{ret} : 2.86 min.

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



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.

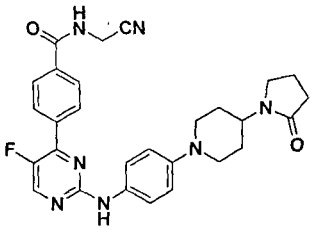


Prepared similar to the procedure described in Example 1 but using **Ester 4** and **Amine 3** as starting material. The title compound was obtained as light yellow solid. ^{1}H NMR (400 MHz, d_6-DMSO) : 9.70 (s, 1H), 9.33 (t, 1H, J = 5.6 Hz), 8.57 (s, 1H), 8.00 (d, 2H, J = 8.4 Hz), 7.90 (d, 2H, J = 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),

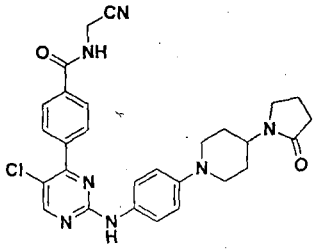
2.56-2.62 (m, 2H), 2.49-2.50 (m, 4H), 2.10-2.23 (m, 1H), 1.83-1.86 (m, 2H), 1.47-1.49 (m, 2H). ESI-MS : 532.20 $(M+H)^+$. UPLC t_{ret} : 2.75 min.

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.

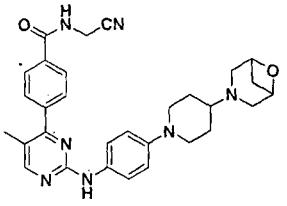
N-(Cyanomethyl)-4-(5-fluoro-2-((4-(4-(2-oxopyrrolidin-1-yl)piperidin-1-yl) phenyl)amino)pyrimidin-4-yl)benzamide.



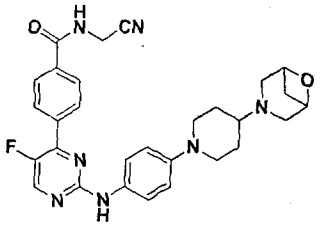
4-(5-Chloro-2-((4-(4-(2-oxopyrrolidin-1-yl)piperidin-1-yl)phenyl)amino) pyrimidin-4-yl)-N-(cyanomethyl)benzamide.



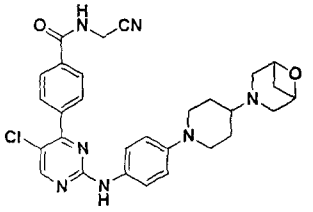
4-(2-((4-(4-(6-Oxa-3-azabicyclo[3.1.1]heptan-3-yl)piperidin-1-yl)phenyl)amino)-5-methylpyrimidin-4-yl)-N-(cyanomethyl)benzamide.



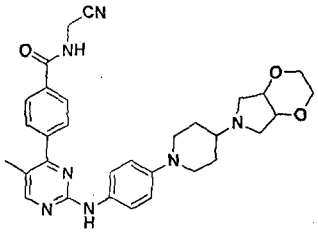
4-(2-((4-(4-(6-Oxa-3-azabicyclo[3.1.1]heptan-3-yl)piperidin-1-yl)phenyl)amino)-5-fluoropyrimidin-4-yl)-N-(cyanomethyl)benzamide.



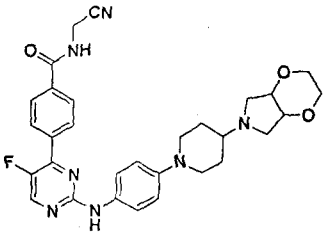
4-(2-((4-(4-(6-Oxa-3-azabicyclo[3.1.1]heptan-3-yl)piperidin-1-yl)phenyl)amino)-5-chloropyrimidin-4-yl)-N-(cyanomethyl)benzamide.



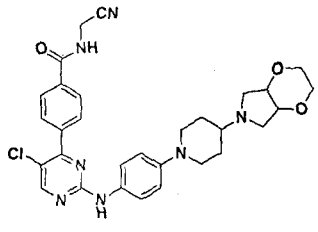
N-(Cyanomethyl)-4-(5-methyl-2-((4-(4-(tetrahydro-2H-[1,4]dioxino[2,3-c]pyrrol-6(3H)-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide.



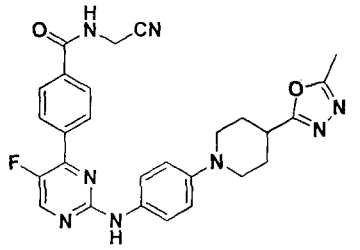
N-(Cyanomethyl)-4-(5-fluoro-2-((4-(4-(tetrahydro-2H-[1,4]dioxino[2,3-c]pyrrol-6(3H)-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide.



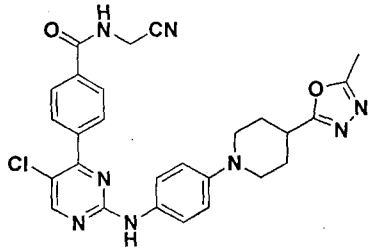
4-(5-Chloro-2-((4-(4-(tetrahydro-2H-[1,4]dioxino[2,3-c]pyrrol-6(3H)-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)-N-(cyanomethyl)benzamide.



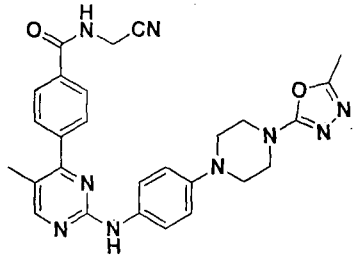
N-(Cyanomethyl)-4-(5-fluoro-2-((4-(4-(5-methyl-1,3,4-oxadiazol-2-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide.



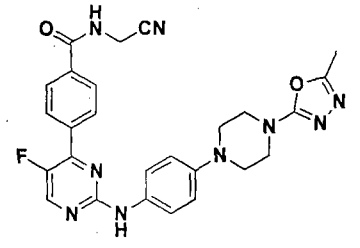
4-(5-Chloro-2-((4-(4-(5-methyl-1,3,4-oxadiazol-2-yl)piperidin-1-yl)phenyl) amino)pyrimidin-4-yl)-N-(cyanomethyl)benzamide.



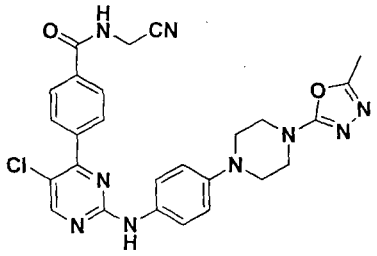
N-(Cyanomethyl)-4-(5-methyl-2-((4-(4-(5-methyl-1,3,4-oxadiazol-2-yl)piperazin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide.



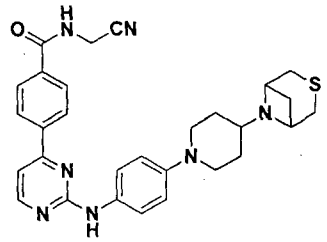
N-(Cyanomethyl)-4-(5-fluoro-2-((4-(4-(5-methyl-1,3,4-oxadiazol-2-yl)piperazin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide



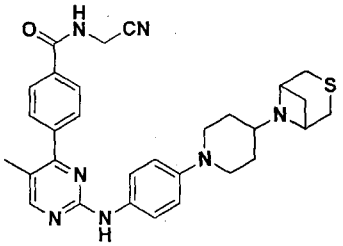
4-(5-Chloro-2-((4-(4-(5-methyl-1,3,4-oxadiazol-2-yl)piperazin-1-yl)phenyl) amino)pyrimidin-4-yl)-N-(cyanomethyl)benzamide.



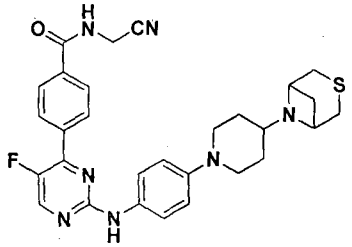
4-(2-((4-(4-(3-Thia-6-azabicyclo[3.1.1]heptan-6-yl)piperidin-1-yl)phenyl) amino)pyrimidin-4-yl)-N-(cyanomethyl)benzamide.



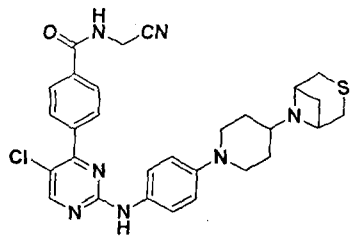
4-(2-((4-(4-(3-Thia-6-azabicyclo[3.1.1]heptan-6-yl)piperidin-1-yl)phenyl)amino)-5-methylpyrimidin-4-yl)-N-(cyanomethyl)benzamide



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.



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 and are incorporated herein as references.

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.

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.

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.

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.

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.

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.

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

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.

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
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

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.

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

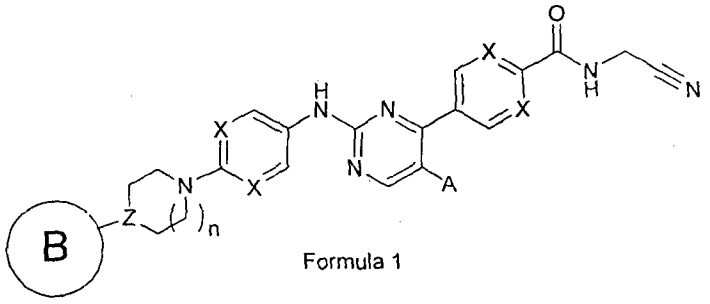
Induction and Assessment of Arthritis (Collagen-Induced Arthritis).

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.

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.

We claim:

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



Formula 1

or pharmaceutically acceptable salts thereof

Wherein

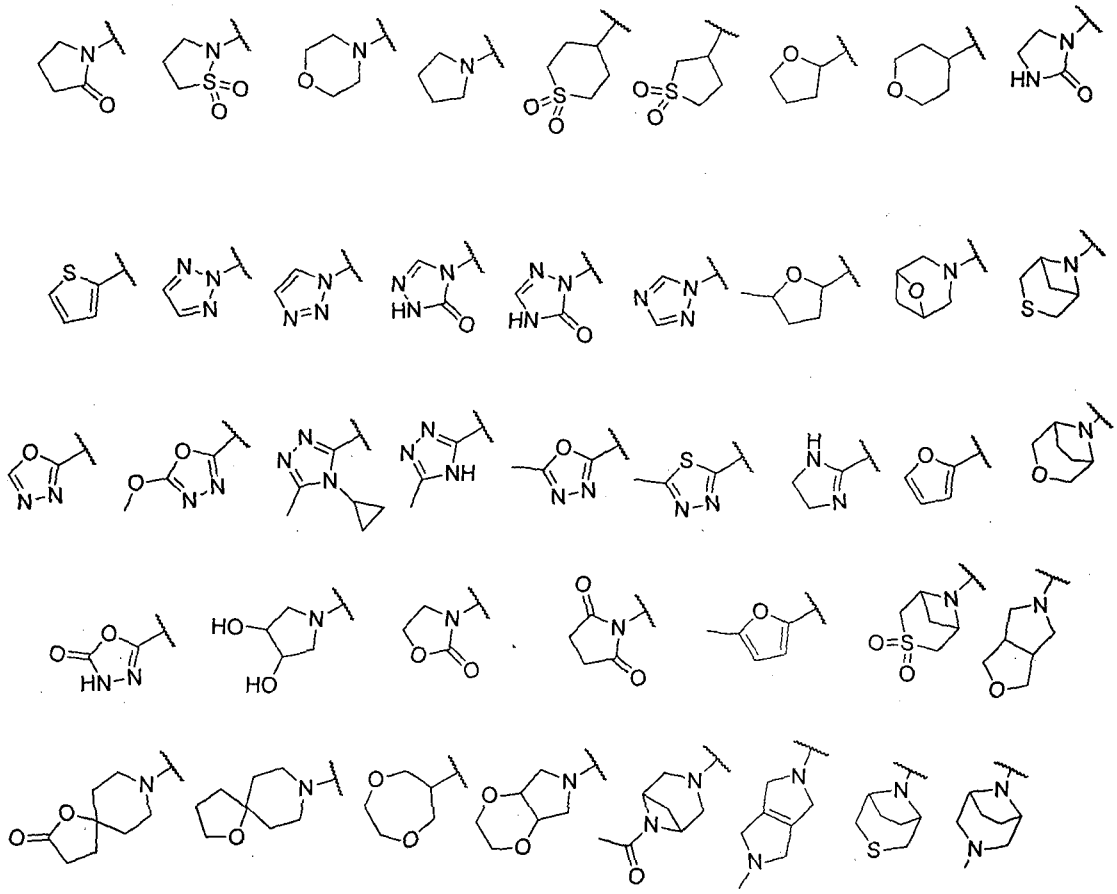
X at each occurrence is independently selected from N or CH;

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, $(CH_2)_{1-6}OC_1$-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 or –C(=O)R_1, $CH_2(CH_2)_{0-4}$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(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-(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 preferably 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(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;

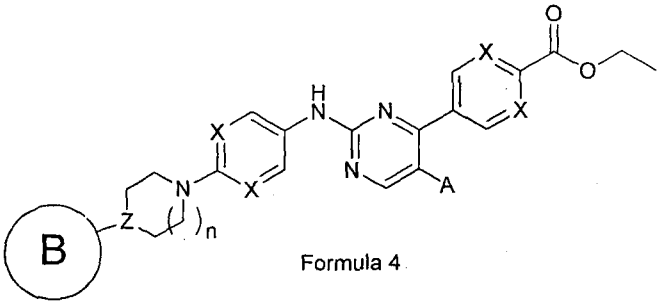
N-(Cyanomethyl)-4-(2-((4-(4-(3,4-dihydroxypyrrolidin-1-yl)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)benzamide;

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-(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 suitable as JAK inhibitors.
10. A method of treating diseases medicated by the JAK protein which comprising administering to a patient in need thereof an effective amount of a compound of Formula (**I**) as claimed in any of the preceding claims or its suitable pharmaceutical composition.
11. The use of compounds of formula **(1)** or its pharmaceutical compositions as claimed in any of the preceding claim suitable for treatment of diseases wherein the JAK kinase has a pathophysiological function.
12. The pharmaceutical composition comprising compounds of formula 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.

13. An intermediate of formula 4 and their isomers.



Formula 4

INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2014/000515

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D403/12 C07D401/14 C07D405/14 C07D413/14 C07D491/08
C07D401/12 C07D407/12 C07D407/14 C07D409/12 C07D409/14
C07D417/14 C07D471/08 C07D491/056 C07D491/107 C07D495/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2008/109943 A1 (CYTOPIA RES PTY LTD [AU]; BURNS CHRISTOPHER JOHN [AU]; DONOHUE ANDREW) 18 September 2008 (2008-09-18) claims 1, 11, 17, 19-22 compounds 39, 42 -----	1-13
X	WO 2009/029998 A1 (CYTOPIA RES PTY LTD [AU]; BURNS CHRISTOPHER JOHN [AU]; PALMER JAMES T) 12 March 2009 (2009-03-12) claims 1, 10, 14, 15 page 21; compound 34 page 22; compound 40 -----	1-13
A	WO 2009/103032 A1 (RIGEL PHARMACEUTICALS INC [US]; BHAMIDIPATI SOMASEKHAR [US]; CLOUGH JE) 20 August 2009 (2009-08-20) claims 1, 67, 68 ----- -/--	1-13

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 November 2014	01/12/2014

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Brandstetter, T

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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2014/000515

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2007/089768 A2 (EXELIXIS INC [US]; MANN GRACE [US]; AAY NAING [US]; ARCALAS ARLYN [US]) 9 August 2007 (2007-08-09) claims 1, 47, 50, 53-58 -----	1-13

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IN2014/000515

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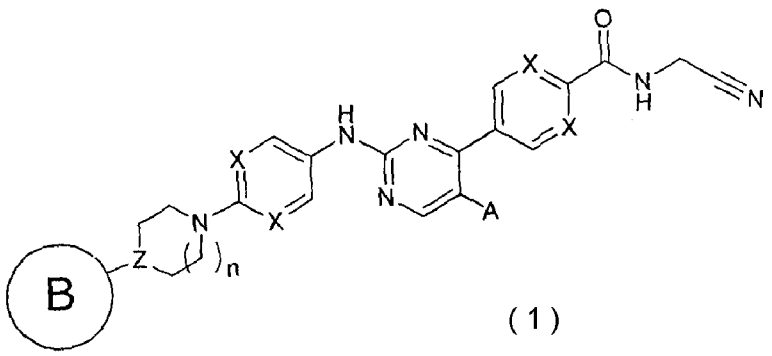
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(54) Title: N-CYANOMETHYLAMIDES AS INHIBITORS OF JANUS KINASE



(1)

(57) Abstract: 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.

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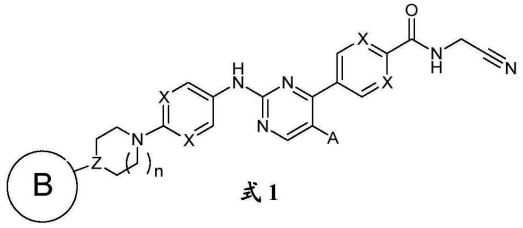
权利要求书8页 说明书42页

(54)发明名称

作为詹纳斯激酶的抑制剂的N-氰基甲基酰胺

(57)摘要

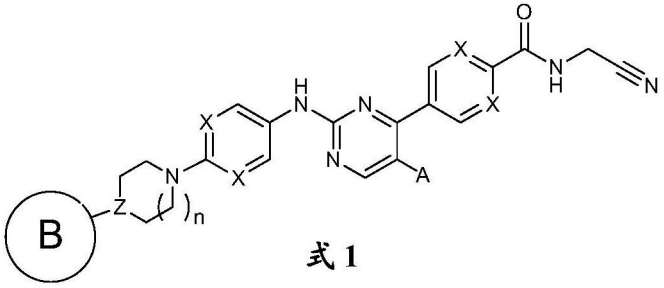
本发明涉及通式(1)的化合物,其为詹纳斯激酶(JAK)的抑制剂,詹纳斯激酶(JAK)是涉及炎性病症、自身免疫性疾病、增殖性疾病、变态反应症、移植排斥、涉及软骨转换的损伤的疾病、先天性软骨畸形和/或与IL6或干扰素类的分泌过多相关的疾病的一类酪氨酸激酶。特别地,本发明化合物抑制JAK1和/或JAK2和/或JAK3亚家族。本发明还提供了本发明化合物的制备方法、包含本发明化合物的药物组合物、它们的互变体形式以及它们的可药用盐。



式1

CN 105612154 A

1.具有通式(I)的结构的化合物或其可药用盐：



式1

其中，

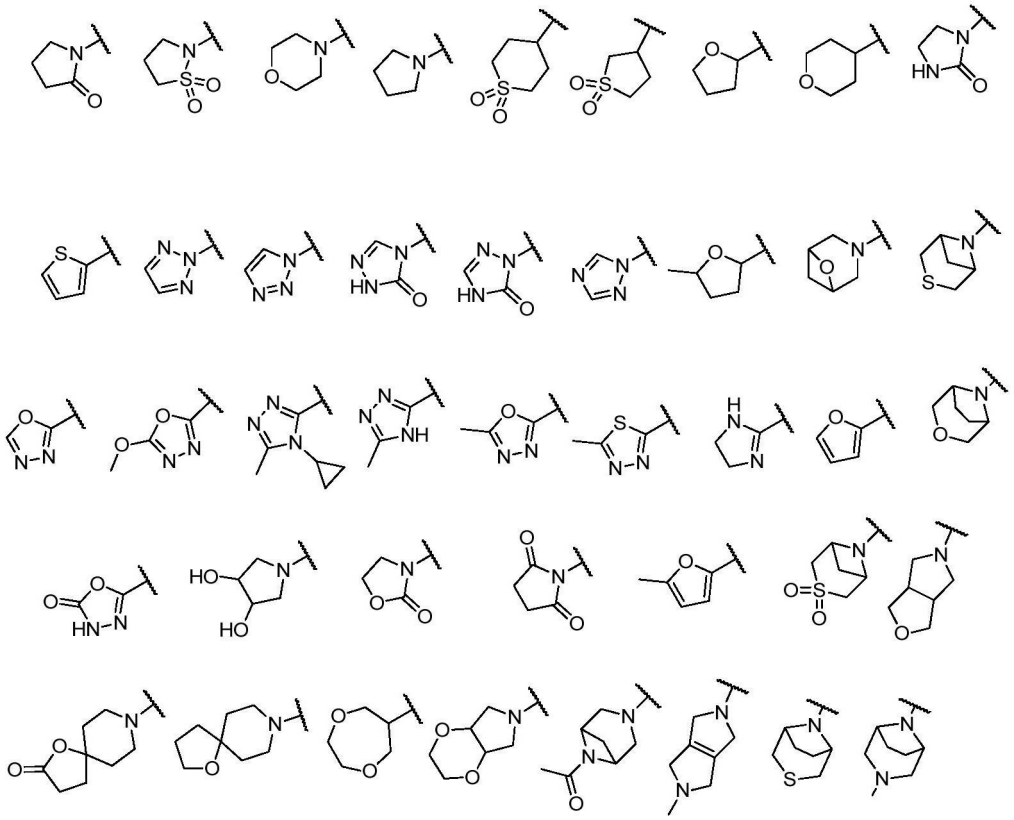
X，当存在时，独立地选自N或CH；

Z，当存在时，独立地选自N或CH；

n选自0、1；

A独立地选自氢、卤素、C_{1-4}烷基、CF_3、CN、$CON(R_1)_2$、OC_{1-4}烷基；

环B选自以下环体系，各环体系可以为经取代的：



2.权利要求1的化合物，其中环B上的取代基在适用时独立地选自H、OH、CN、NH_2、卤素、氧代基团、OCF_3、CF_3、C_1-C_6烷基、OC_1-C_6烷基、$(CH_2)_{1-6}OC_1$-C_6烷基、O-$(CH_2)_{0-4}OC_1$-C_6烷基、C(O)NHC_1-C_6烷基、$NHC(O)C_1$-C_6烷基、$S(O)_{0-2}C_1$-C_6烷基、$(CH_2)_{1-6}N(R_1)_2$、$(CH_2)_{1-6}NHC(=O)OR_1$、$(CH_2)_{1-6}NHC(=O)R_1$、$C(=O)OR_1$、$C(=O)R_1$、$(CH_2)_{1-4}C(=O)NHR_1$、$(CH_2)_{0-4}O(CH_2)_{0-4}Ar_1$、$(CH_2)_{0-4}NH(CH_2)_{0-4}Ar_1$、$(CH_2)_{0-4}Ar_1$、$(CH_2)_{0-4}C(O)(CH_2)_{0-4}Ar_1$、$(CH_2)_{0-4}C(=O)O(CH_2)_{0-4}Ar_1$、$(CH_2)_{0-4}C(=O)NR_1(CH_2)_{0-4}Ar_1$。

3.权利要求1和2的化合物，其中R_1，当存在时，独立地选自氢、C_1-C_4烷基、C_1-C_4卤代烷基、C_3-C_7环烷基。

4.权利要求2的化合物，其中Ar_1，在每次出现时，独立地选自芳环或杂环环，所述芳环或杂环环为未经取代的或者经一个、两个、三个或四个取代基取代。

5.权利要求4的化合物，其中在Ar_1上的取代基独立地选自OH、CN、NH_2、卤素、OCF_3、CF_3、C_1-C_6烷基、OC_1-C_6烷基、$(CH_2)_{1-6}OC_1$-C_6烷基、O-$(CH_2)_{0-4}OC_1$-C_6烷基、$C(O)NHC_1$-C_6烷基、$NHC(O)C_1$-C_6烷基、$S(O)_{0-2}C_1$-C_6烷基、$(CH_2)_{1-6}N(R_1)_2$、$(CH_2)_{1-6}NHC(=O)OR_1$、$(CH_2)_{1-6}NHC(=O)R_1$、$C(=O)OR_1$或-$C(=O)R_1$、$CH_2(CH_2)_{0-4}C(=O)NHR_1$。

6.权利要求1中的化合物，选自：

N-(氰基甲基)-4-(2-((4-(4-(2-氧代吡咯烷-1-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

N-(氰基甲基)-4-(2-((4-(4-(1,1-二氧代异噻唑烷-2-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

N-(氰基甲基)-4-(2-((4-(4-吗啉代哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

4-(2-((4-(4-(1H-1,2,4-三唑-1-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)-N-(氰基甲基)苯甲酰胺；

4-(2-((4-(4-(1H-吡唑-1-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)-N-(氰基甲基)苯甲酰胺；

4-(2-((4-([1,3'-联吡咯烷]-1'-基)苯基)氨基)嘧啶-4-基)-N-(氰基甲基)苯甲酰胺；

N-(氰基甲基)-4-(2-((4-(4-(1,1-二氧代四氢-2H-噻喃-4-基)哌嗪-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

N-(氰基甲基)-4-(2-((4-(4-(呋喃-2-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

N-(氰基甲基)-4-(2-((4-(4-(1,1-二氧代四氢噻吩-3-基)哌嗪-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

N-(氰基甲基)-4-(2-((4-(4-(2,5-二氧代吡咯烷-1-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

N-(氰基甲基)-4-(2-((4-(4-(噻吩-2-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

N-(氰基甲基)-4-(2-((4-(4-(2-氧代噁唑烷-3-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

N-(氰基甲基)-4-(2-((4-(4-(四氢呋喃-2-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

N-(氰基甲基)-4-(2-((4-(4-(5-甲基呋喃-2-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

N-(氰基甲基)-4-(2-((4-(4-(四氢-2H-吡喃-4-基)哌嗪-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

N-(氰基甲基)-4-(2-((4-(4-(5-甲基四氢呋喃-2-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

4-(2-((4-(4-(6-氧杂-3-氮杂双环[3.1.1]庚-3-基)哌啶-1-基)苯基)氨基)嘧啶-4-

基)-N-(氰基甲基)苯甲酰胺；

N-(氰基甲基)-4-(2-((4-(4-(2-氧代咪唑啉-1-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

4-(2-((4-(4-(1,3,4-噁二唑-2-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)-N-(氰基甲基)苯甲酰胺；

4-(2-((4-(4-(2H-1,2,3-三唑-2-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)-N-(氰基甲基)苯甲酰胺；

4-(2-((4-(4-(1H-1,2,3-三唑-1-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)-N-(氰基甲基)苯甲酰胺；

N-(氰基甲基)-4-(2-((4-(4-(5-氧代-1H-1,2,4-三唑-4(5H)-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

N-(氰基甲基)-4-(2-((4-(4-(5-氧代-4,5-二氢-1H-1,2,4-三唑-1-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

4-(2-((4-(4-(1-氧杂-8-氮杂螺[4.5]癸-8-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)-N-(氰基甲基)苯甲酰胺；

N-(氰基甲基)-4-(2-((4-(4-(5-甲基-1,3,4-噁二唑-2-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

N-(氰基甲基)-4-(2-((4-(4-(5-甲基-1,3,4-噻二唑-2-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

N-(氰基甲基)-4-(2-((4-(4-(四氢-2H-[1,4]二氧杂环己二烯并[2,3-c]吡咯-6(3H)-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

N-(氰基甲基)-4-(2-((4-(4-(2-氧代-1-氧杂-8-氮杂螺[4.5]癸-8-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

N-(氰基甲基)-4-(2-((4-(4-(5-氧代-4,5-二氢-1,3,4-噁二唑-2-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

N-(氰基甲基)-4-(2-((4-(4-(4-环丙基-5-甲基-4H-1,2,4-三唑-3-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

N-(氰基甲基)-4-(2-((4-(4-(5-甲氧基-1,3,4-噁二唑-2-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

4-(2-((4-(4-(1,4-二氧杂萘-6-基)哌嗪-1-基)苯基)氨基)嘧啶-4-基)-N-(氰基甲基)苯甲酰胺；

N-(氰基甲基)-4-(2-((4-(4-(4,5-二氢-1H-咪唑-2-基)哌嗪-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

N-(氰基甲基)-4-(2-((4-(4-(4,5-二氢-1H-咪唑-2-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

N-(氰基甲基)-4-(2-((4-(3-(四氢-2H-[1,4]二氧杂环己二烯并[2,3-c]吡咯-6(3H)-基)吡咯烷-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

N-(氰基甲基)-4-(2-((4-(4-(5-甲基-1,3,4-噁二唑-2-基)哌嗪-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

N-(氰基甲基)-4-(2-((4-(4-(3,4-二羟基吡咯烷-1-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

4-(2-((4-(4-(8-氧杂-3-氮杂双环[3.2.1]辛-3-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)-N-(氰基甲基)苯甲酰胺；

4-(2-((4-(4-(6-乙酰基-3,6-二氮杂双环[3.1.1]庚-3-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)-N-(氰基甲基)苯甲酰胺；

N-(氰基甲基)-4-(5-甲基-2-((4-(4-吗啉代哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

N-(氰基甲基)-4-(5-甲基-2-((4-(4-(2-氧代吡咯烷-1-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

4-(2-((4-(4-(1-氧杂-8-氮杂螺[4.5]癸-8-基)哌啶-1-基)苯基)氨基)-5-甲基嘧啶-4-基)-N-(氰基甲基)苯甲酰胺；

N-(氰基甲基)-4-(5-甲基-2-((4-(4-(5-甲基-1,3,4-噁二唑-2-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

N-(氰基甲基)-4-(5-氟-2-((4-(4-吗啉代哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

4-(5-氯-2-((4-(4-吗啉代哌啶-1-基)苯基)氨基)嘧啶-4-基)-N-(氰基甲基)苯甲酰胺；

N-(氰基甲基)-4-(5-氟-2-((4-(4-(2-氧代吡咯烷-1-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

4-(5-氯-2-((4-(4-(2-氧代吡咯烷-1-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)-N-(氰基甲基)苯甲酰胺；

4-(2-((4-(4-(6-氧杂-3-氮杂双环[3.1.1]庚-3-基)哌啶-1-基)苯基)氨基)-5-甲基嘧啶-4-基)-N-(氰基甲基)苯甲酰胺；

4-(2-((4-(4-(6-氧杂-3-氮杂双环[3.1.1]庚-3-基)哌啶-1-基)苯基)氨基)-5-氟嘧啶-4-基)-N-(氰基甲基)苯甲酰胺；

-(2-((4-(4-(6-氧杂-3-氮杂双环[3.1.1]庚-3-基)哌啶-1-基)苯基)氨基)-5-氯嘧啶-4-基)-N-(氰基甲基)苯甲酰胺；

N-(氰基甲基)-4-(5-甲基-2-((4-(4-(四氢-2H-[1,4]二氧杂环己二烯并[2,3-c]吡咯-6(3H)-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

N-(氰基甲基)-4-(5-氟-2-((4-(4-(四氢-2H-[1,4]二氧杂环己二烯并[2,3-c]吡咯-6(3H)-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

4-(5-氯-2-((4-(4-(四氢-2H-[1,4]二氧杂环己二烯并[2,3-c]吡咯-6(3H)-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)-N-(氰基甲基)苯甲酰胺；

N-(氰基甲基)-4-(5-氟-2-((4-(4-(5-甲基-1,3,4-噁二唑-2-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

4-(5-氯-2-((4-(4-(5-甲基-1,3,4-噁二唑-2-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)-N-(氰基甲基)苯甲酰胺；

N-(氰基甲基)-4-(5-甲基-2-((4-(4-(5-甲基-1,3,4-噁二唑-2-基)哌嗪-1-基)苯基)

氨基)嘧啶-4-基)苯甲酰胺;

N-(氰基甲基)-4-(5-氟-2-((4-(4-(5-甲基-1,3,4-噁二唑-2-基)哌嗪-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺;

4-(5-氯-2-((4-(4-(5-甲基-1,3,4-噁二唑-2-基)哌嗪-1-基)苯基)氨基)嘧啶-4-基)-N-(氰基甲基)苯甲酰胺;

4-(2-((4-(4-(3-硫杂-6-氮杂双环[3.1.1]庚-6-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)-N-(氰基甲基)苯甲酰胺;

4-(2-((4-(4-(3-硫杂-6-氮杂双环[3.1.1]庚-6-基)哌啶-1-基)苯基)氨基)-5-甲基嘧啶-4-基)-N-(氰基甲基)苯甲酰胺;

4-(2-((4-(4-(3-硫杂-6-氮杂双环[3.1.1]庚-6-基)哌啶-1-基)苯基)氨基)-5-氟嘧啶-4-基)-N-(氰基甲基)苯甲酰胺;

4-(2-((4-(4-(3-硫杂-6-氮杂双环[3.1.1]庚-6-基)哌啶-1-基)苯基)氨基)-5-氯嘧啶-4-基)-N-(氰基甲基)苯甲酰胺;

7.前述权利要求任一项中的化合物,优选地选自:

N-(氰基甲基)-4-(2-((4-(4-(2-氧代吡咯烷-1-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺;

N-(氰基甲基)-4-(2-((4-(4-(1,1-二氧代异噻唑烷-2-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺;

N-(氰基甲基)-4-(2-((4-(4-吗啉代哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺;

4-(2-((4-(4-(1H-1,2,4-三唑-1-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)-N-(氰基甲基)苯甲酰胺;

4-(2-((4-(4-(1H-吡唑-1-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)-N-(氰基甲基)苯甲酰胺;

4-(2-((4-([1,3'-联吡咯烷]-1'-基)苯基)氨基)嘧啶-4-基)-N-(氰基甲基)苯甲酰胺;

N-(氰基甲基)-4-(2-((4-(4-(1,1-二氧代四氢-2H-噻喃-4-基)哌嗪-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺;

N-(氰基甲基)-4-(2-((4-(4-(呋喃-2-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺;

N-(氰基甲基)-4-(2-((4-(4-(1,1-二氧代四氢噻吩-3-基)哌嗪-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺;

N-(氰基甲基)-4-(2-((4-(4-(2,5-二氧代吡咯烷-1-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺;

N-(氰基甲基)-4-(2-((4-(4-(噻吩-2-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺;

N-(氰基甲基)-4-(2-((4-(4-(2-氧代噁唑烷-3-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺;

N-(氰基甲基)-4-(2-((4-(4-(四氢呋喃-2-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺;

N-(氰基甲基)-4-(2-((4-(4-(5-甲基呋喃-2-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

N-(氰基甲基)-4-(2-((4-(4-(四氢-2H-吡喃-4-基)哌嗪-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

N-(氰基甲基)-4-(2-((4-(4-(5-甲基四氢呋喃-2-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

4-(2-((4-(4-(6-氧杂-3-氮杂双环[3.1.1]庚-3-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)-N-(氰基甲基)苯甲酰胺；

N-(氰基甲基)-4-(2-((4-(4-(2-氧代咪唑啉-1-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

4-(2-((4-(4-(1,3,4-噁二唑-2-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)-N-(氰基甲基)苯甲酰胺；

4-(2-((4-(4-(2H-1,2,3-三唑-2-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)-N-(氰基甲基)苯甲酰胺；

4-(2-((4-(4-(1H-1,2,3-三唑-1-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)-N-(氰基甲基)苯甲酰胺；

N-(氰基甲基)-4-(2-((4-(4-(5-氧代-1H-1,2,4-三唑-4(5H)-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

N-(氰基甲基)-4-(2-((4-(4-(5-氧代-4,5-二氢-1H-1,2,4-三唑-1-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

4-(2-((4-(4-(1-氧杂-8-氮杂螺[4.5]癸-8-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)-N-(氰基甲基)苯甲酰胺；

N-(氰基甲基)-4-(2-((4-(4-(5-甲基-1,3,4-噁二唑-2-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

N-(氰基甲基)-4-(2-((4-(4-(5-甲基-1,3,4-噻二唑-2-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

N-(氰基甲基)-4-(2-((4-(4-(四氢-2H-[1,4]二氧杂环己二烯并[2,3-c]吡咯-6(3H)-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

N-(氰基甲基)-4-(2-((4-(4-(2-氧代-1-氧杂-8-氮杂螺[4.5]癸-8-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

N-(氰基甲基)-4-(2-((4-(4-(5-氧代-4,5-二氢-1,3,4-噁二唑-2-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

N-(氰基甲基)-4-(2-((4-(4-(4-环丙基-5-甲基-4H-1,2,4-三唑-3-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

N-(氰基甲基)-4-(2-((4-(4-(5-甲氧基-1,3,4-噁二唑-2-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

4-(2-((4-(4-(1,4-二氧杂萘-6-基)哌嗪-1-基)苯基)氨基)嘧啶-4-基)-N-(氰基甲基)苯甲酰胺；

N-(氰基甲基)-4-(2-((4-(4-(4,5-二氢-1H-咪唑-2-基)哌嗪-1-基)苯基)氨基)嘧啶-

4-基)苯甲酰胺；

N-(氰基甲基)-4-(2-((4-(4-(4,5-二氢-1H-咪唑-2-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

N-(氰基甲基)-4-(2-((4-(3-(四氢-2H-[1,4]二氧杂环己二烯并[2,3-c]吡咯-6(3H)-基)吡咯烷-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

N-(氰基甲基)-4-(2-((4-(4-(5-甲基-1,3,4-噁二唑-2-基)哌嗪-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

N-(氰基甲基)-4-(2-((4-(4-(3,4-二羟基吡咯烷-1-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

4-(2-((4-(4-(8-氧杂-3-氮杂双环[3.2.1]辛-3-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)-N-(氰基甲基)苯甲酰胺；

4-(2-((4-(4-(6-乙酰基-3,6-二氮杂双环[3.1.1]庚-3-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)-N-(氰基甲基)苯甲酰胺；

N-(氰基甲基)-4-(5-甲基-2-((4-(4-吗啉代哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

N-(氰基甲基)-4-(5-甲基-2-((4-(4-(2-氧代吡咯烷-1-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

4-(2-((4-(4-(1-氧杂-8-氮杂螺[4.5]癸-8-基)哌啶-1-基)苯基)氨基)-5-甲基嘧啶-4-基)-N-(氰基甲基)苯甲酰胺；

N-(氰基甲基)-4-(5-甲基-2-((4-(4-(5-甲基-1,3,4-噁二唑-2-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

N-(氰基甲基)-4-(5-氟-2-((4-(4-吗啉代哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

4-(5-氯-2-((4-(4-吗啉代哌啶-1-基)苯基)氨基)嘧啶-4-基)-N-(氰基甲基)苯甲酰胺；

8.药物组合物，其包含治疗有效量的前述权利要求中任一项的式(I)化合物以及任选一种或多种可药用载体、稀释剂或赋形剂。

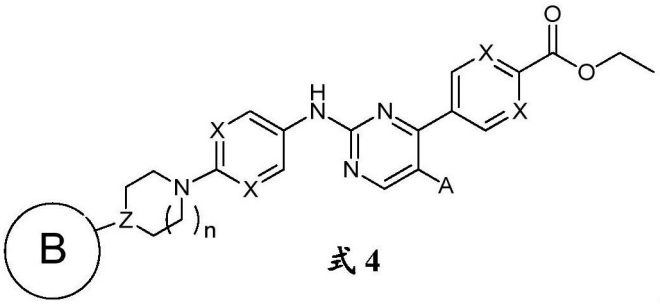
9.前述权利要求中任一项所述的化合物，其适合用作JAK抑制剂。

10.治疗由JAK蛋白质介导的疾病的方法，所述方法包括向有此需要的患者给予治疗有效量的前述权利要求中任一项的式(I)化合物或其合适的药物组合物。

11.前述权利要求中任一项式(1)化合物或其药物组合物适于治疗疾病的用途，其中所述JAK激酶具有病理生理作用。

12.药物组合物，其包含式1的化合物以及合适的赋形剂，所述药物组合物适于治疗炎性病症、自身免疫性疾病、增殖性疾病、变态反应症和移植排斥、涉及软骨转换的损伤的疾病、先天性软骨畸形和/或与IL6或干扰素类的分泌过多相关的疾病。

13.式4的中间体和它们的异构体：



式 4

。

作为詹纳斯激酶的抑制剂的N-氰基甲基酰胺

技术领域

[0001] 本发明涉及通式(1)的化合物其为詹纳斯激酶(Janus kinase,JAK)的抑制剂,詹纳斯激酶(JAK)是涉及炎性病症、自身免疫性疾病、增殖性疾病、变态反应症、移植排斥、涉及软骨转换的损伤的疾病、先天性软骨畸形和/或与IL6或干扰素类的分泌过多相关的疾病的一类酪氨酸激酶。特别地,本发明的化合物抑制JAK1和/或JAK2和/或JAK3亚家族。本发明还提供了本发明化合物的制备方法、包含本发明化合物的药物组合物、它们的互变异构体以及它们的可药用盐。

背景技术

[0002] 蛋白质激酶(PKs)调节多种生物过程,包括细胞生长、存活、分化、器官形成、器官发生、血管新生、组织修复和再生。蛋白质激酶在人类疾病的宿主中还有专门的作用,疾病例如移植排斥、类风湿性关节炎、银屑病(psoriasis)、肌萎缩性侧索硬化症(amyotrophic lateral sclerosis)和多发性硬化(multiple sclerosis)以及实体和血液恶性疾病如白血病和淋巴瘤。细胞因子影响细胞分化、增殖和活化,并且可以同时调节促炎和抗炎响应使得宿主对病原体适当地反应。细胞因子刺激的免疫和炎性反应促进疾病的发病:病变如严重的重症联合免疫缺陷(SCID)产生于免疫系统的抑制,同时过分活跃或者不合适的免疫/炎性响应促进自身免疫性疾病(例如,哮喘、全身性红斑性狼疮、甲状腺炎、心肌炎)以及疾病如硬皮病和骨关节炎的病变(Ortmann,R.A.,T.Cheng,et al.(2000)Arthritis Res 2(1):16-32)。

[0003] 很大范围的细胞因子的信号传导包括蛋白质酪氨酸激酶的詹纳斯激酶家族(JAKs)、以及信号转导与转录激活因子(STATs)。詹纳斯激酶(JAK)为经由JAK-STAT途径将细胞因子介导的信号进行转导的细胞内非受体酪氨酸激酶家族,范围为120-140kDa。JAK家族在细胞因子依赖性调节涉及免疫响应的增殖和细胞功能中扮演重要角色。目前,已知有四种哺乳动物JAK家族成员:JAK 1、JAK 2、JAK 3和TYK 2。JAK 1、JAK 2和TYK 2被普遍表达,而JAK 3表达于髓样和淋巴样细胞谱系中。

[0004] Vandeghinste等人(WO 2005/124342)发现JAK1为这样一种靶标,对其进行抑制也许与包括OA的多种疾病有治疗相关性。敲除小鼠中的JAK1基因证实了JAK1在疾病发展期间扮演必要而非多余的角色。

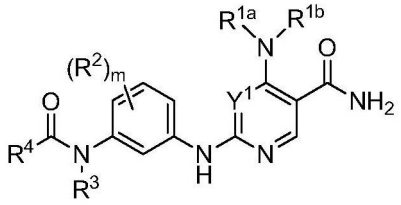
[0005] JAK2为细胞质蛋白质-酪氨酸激酶,其在信号转导分子中催化三磷酸腺苷的γ磷酸根基团至特定酪氨酸残基的羟基基团的转移。JAK2在配体诱导的受体和酶的自体磷酸化之后介导细胞因子受体下游的信号传导。JAK2的主要下游效应基因为已知为信号传导与转录活化因子(STAT)蛋白质的一类转录因子。研究已经发现活化JAK2突变(JAK2V617F)与骨髓增生性疾病(myeloproliferative disorders)之间的关联。骨髓增生性疾病是骨髓恶性肿瘤的一类亚组,是以形态学上成熟的粒细胞、红细胞(erythroid)、巨核细胞或单核细胞谱系的细胞的扩张为特征的同源干细胞疾病。骨髓增殖性疾病(MPD)包括真性红细胞增多症(PV)、特发性血小板增多症(ET)、伴有骨髓纤维变性的髓样化生(MMM)、慢性髓细胞性白

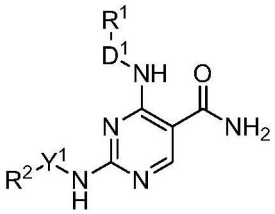
血病(CML)、慢性骨髓单核细胞性白血病(CMML)、嗜酸细胞增多综合征(HES)、青少年粒-单核细胞型白血病(JMML)和系统性肥大细胞病(SMCD)。已经认为,在信号传导机制中的异常,包括在组成上活化蛋白质赖氨酸激酶,引发了MPD。Jak2-/-小鼠胚胎由于不存在发育完全的红细胞生成而是贫血的,且在交配后约12.5天死亡。

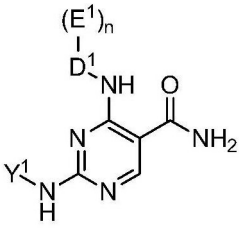
[0006] JAK3缔合下列白介素的常见细胞外受体γ链:IL-2、IL-4、IL-7、IL-9和IL-15。JAK3缺失在啮齿动物和人类中均与缺乏免疫(immune compromised)(SCID)的表型有关。SCID表型的JAK3(-/-)哺乳动物和淋巴样细胞特异性表达的JAK3为免疫抑制物的靶标的两个有利的属性。数据表明JAK3的抑制剂会阻碍T-细胞活化并且防止移植手术后的移植物的排斥,或者向患有自体免疫疾病的患者提供治疗益处。JAK3的一个重要特征在于其特异性缔合常见的细胞因子受体γ链,后者为IL-2、IL-4、IL-7、IL-9和IL-15的受体的共同组成。与其他更广泛地表达于许多哺乳动物组织中的JAK家族成员不同,JAK3表达看上去似乎主要受限于造血细胞的内质膜。JAK3通过小鼠和人基因而确认为免疫抑制靶标(O'Shea J.et al.(2004))。JAK3抑制剂成功地进入临床研发阶段,最初用于器官移植排斥,但是后来也用于其他免疫炎性指征如风湿性关节炎(RA)、银屑病和克罗恩病(Crohn's disease)。

[0007] 在JAK激酶水平阻断信号传导对于研发治疗人类癌症和关节炎是有前景的。也认为抑制JAK激酶在患有皮肤免疫病症例如银屑病和皮肤敏化的患者中具有治疗作用。很多病症被认为受益于调节JAK通路的治疗,根据这些病症,显然的是调节JAK通路的新的化合物以及使用这些化合物的方法应当向大范围的患者提供实质的治疗益处。

[0008] Portola的专利申请(WO 2010/129802,WO 2009/145856,WO 2009/136995等)记载了作为脾酪氨酸激酶(SYK)或JAK抑制剂的嘧啶类化合物。

[0009] 
WO 2011/129802

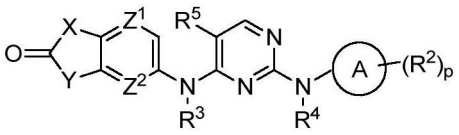

WO 2009/145856


WO 2009/136995

[0010] Rigel已经递交了诸多专利申请(WO 2011/017178,WO 2010/085684,WO 2010/078369,WO 2010/075558和WO 2010/039518等),要求保护用作JAK途径的调节剂或JAK激酶、特别是JAK-2、JAK-3或这两者的抑制剂的嘧啶类化合物。

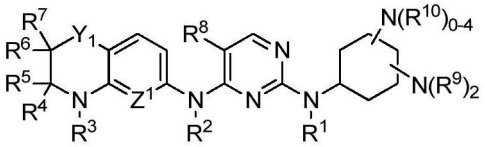


WO 2011/017178

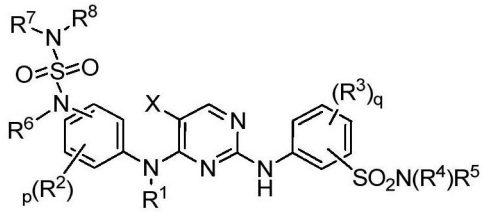


WO 2010/085684

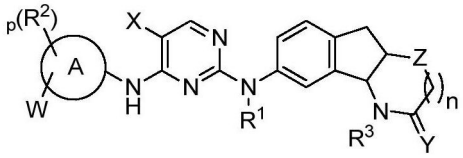
[0011]



WO 2010/078369

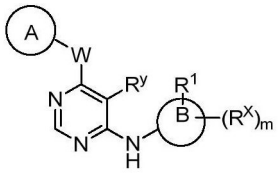


WO 2010/075558

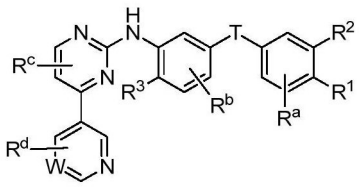


W0 2010/039518

[0012] Avila Therapeutics报道了作为蛋白质激酶抑制剂的嘧啶类化合物(WO 2010123870,WO 2009/158571,WO 2009/051822和WO 2008/151183)。

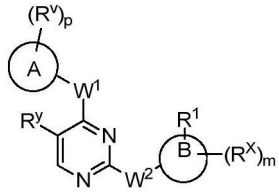


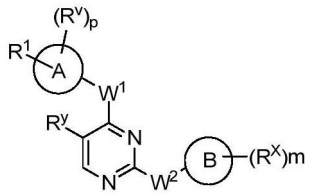
WO 2010/123870
WO 2009/051822



WO:2008151183

[0013]

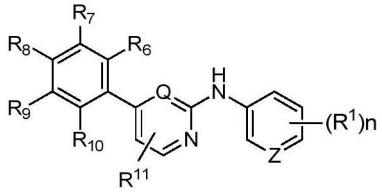




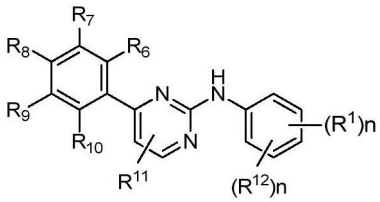
WO2009158571

[0014] Cytopia Research Pvt.Ltd报道了作为蛋白质激酶(包括JAK)抑制剂的苯基氨基嘧啶类化合物(WO 2008109943,WO 2009029998)。

[0015]

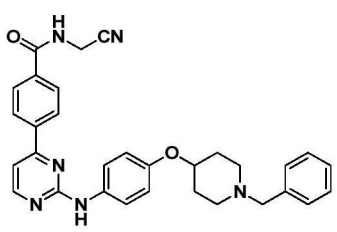


WO2008109943

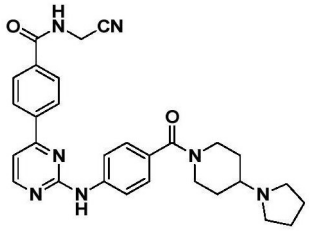


WO2009029998

[0016] Cytopia在他们的专利申请WO 2008109943中报道了两个化合物。所报道的化合物2在体外对JAK 2和JAK-3的抑制分别小于1μM和小于20μM。

[0017] 

化合物 1

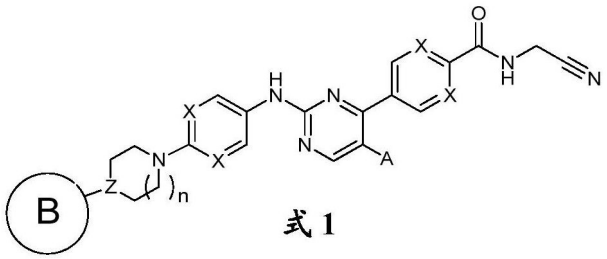


化合物 2

[0018] 然而，这些化合物都没有市场化，并且要注意这些化合物存在巨大的未满足的能力，因此需要开发以治疗有效方式调节JAK酶的化合物。本申请在下文中记载了这样的新的分子。

发明内容

[0019] 本发明描述了一组作为JAK抑制剂的新的化合物，其可用于治疗自身免疫性疾病、增殖性疾病、变态反应症、移植排斥、涉及软骨转换的损伤的疾病、先天性软骨畸形和/或与IL6或干扰素类的分泌过多相关的疾病。新的化合物由以下通式(1)定义：

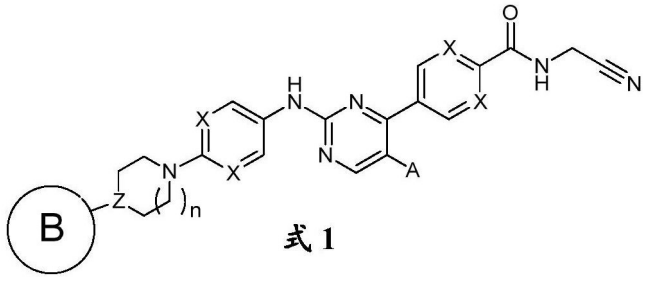
[0020] 

式 1

[0021] 本发明的化合物可用于通过调节詹纳斯激酶(JAK)治疗人体或哺乳动物体。本发明的化合物因此适合用于治疗其他自体免疫相关的疾病。

具体实施方式

[0022] 本发明的主要目的在于提供新的通式(1)化合物、在它们的合成中涉及的中间体、它们的可药用盐以及包含它们或它们的混合物作为药剂的药物组合物。

[0023] 

式 1

[0024] 在一个实施方案中提供了新的通式(1)化合物、在它们的合成中涉及的中间体、它们的可药用盐以及包含它们或它们的混合物作为药剂的药物组合物的制备方法。

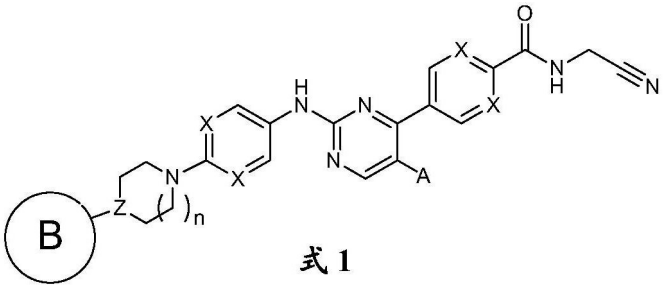
[0025] 在另一实施方案中提供了药物组合物，所述药物组合物包含通式(1)化合物、它们的可药用盐以及包含可药用载体、溶剂、稀释剂、赋形剂和其他通常用于制造药物组合物中的媒介。

[0026] 在另一实施方案中提供了本发明的新的化合物在由于JAK失调发展出的疾病状况中的用途，通过向哺乳动物给予治疗有效量且无毒性量的式(1)化合物或它们的可药用组

合物。

[0027] 发明详述

[0028] 本发明的新的化合物通过以下通式(I)定义：

[0029] 

式1

[0030] 其中

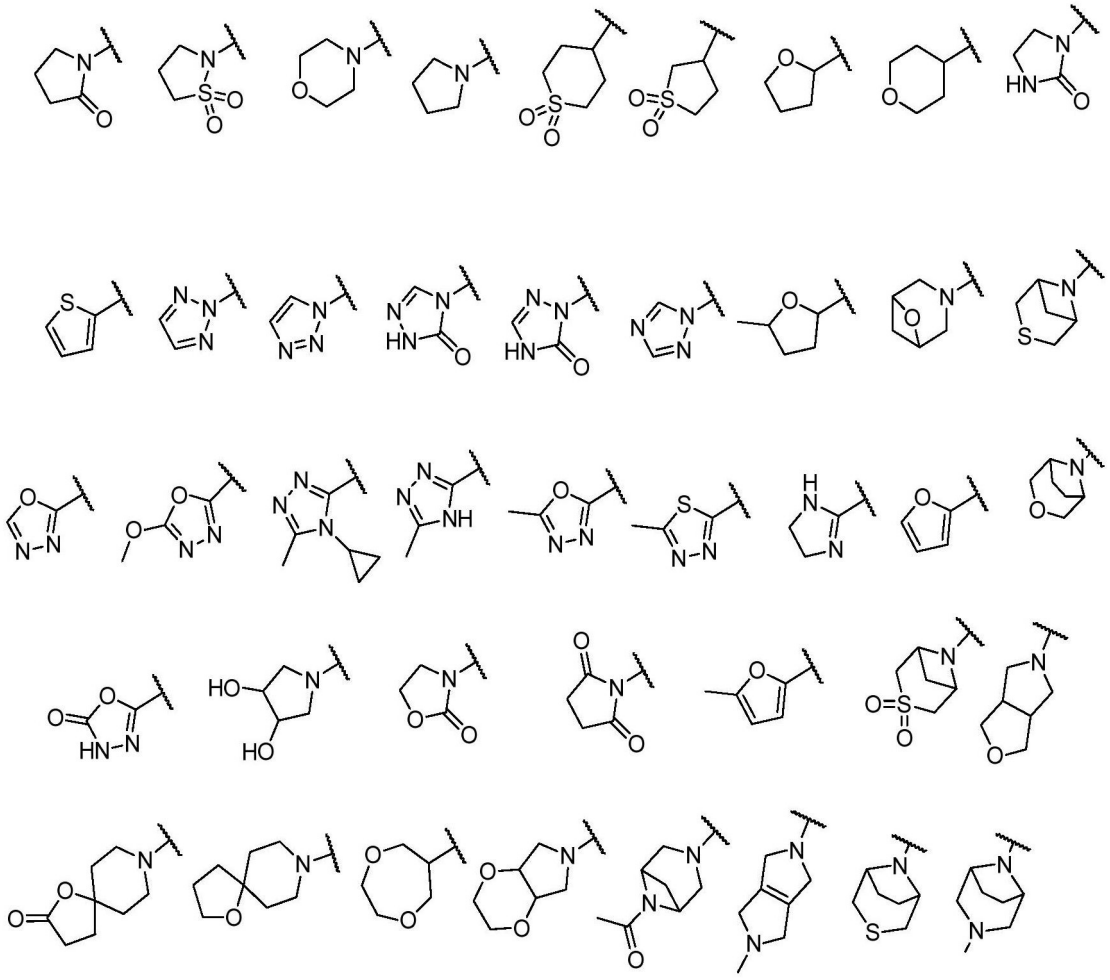
[0031] X，当存在时，独立地选自N或CH；

[0032] Z，当存在时，独立地选自N或CH；

[0033] ‘n’选自0、1。

[0034] A独立地选自氢、卤素、C_{1-4}烷基、CF_3、CN、$CON(R_1)_2$、OC_{1-4}烷基

[0035] 环B选自以下环体系：

[0036] 

[0037] 所述环B可以，当适用时，任选地取代有独立选自以下的一个或多个取代基：H、OH、CN、NH_2、卤素、氧代、OCF_3、CF_3、C_1-C_6烷基、OC_1-C_6烷基、$(CH_2)_{1-6}OC_1$-C_6烷基、O-$(CH_2)_{0-4}OC_1$-C_6烷基、$C(O)NHC_1$-C_6烷基、$NHC(O)C_1$-C_6烷基、$S(O)_{0-2}C_1$-C_6烷基、$(CH_2)_{1-6}N(R_1)_2$、$(CH_2)_{1-6}NHC(=$

O)OR_1、$(CH_2)_{1-6}NHC(=O)R_1$、$C(=O)OR_1$、$C(=O)R_1$、$(CH_2)_{1-4}C(=O)NHR_1$、$(CH_2)_{0-4}O(CH_2)_{0-4}Ar_1$、$(CH_2)_{0-4}NH(CH_2)_{0-4}Ar_1$、$(CH_2)_{0-4}Ar_1$、$(CH_2)_{0-4}C(O)(CH_2)_{0-4}Ar_1$、$(CH_2)_{0-4}C(=O)O(CH_2)_{0-4}Ar_1$、$(CH_2)_{0-4}C(=O)NR_1(CH_2)_{0-4}Ar_1$；

[0038] 术语AR_1，当存在时，独立地选自芳环或杂环环，所述芳环或杂环环为未经取代的或经一个、两个、三个或四个独立地选自以下的取代基所取代：OH、CN、NH_2、卤素、OCF_3、CF_3、C_1-C_6烷基、OC_1-C_6烷基、$(CH_2)_{1-6}OC_1$-C_6烷基、O-$(CH_2)_{0-4}OC_1$-C_6烷基、C(O)NHC_1-C_6烷基、NHC(O)C_1-C_6烷基、S(O)$_{0-2}C_1$-C_6烷基、$(CH_2)_{1-6}N(R_1)_2$、$(CH_2)_{1-6}NHC(=O)OR_1$、$(CH_2)_{1-6}NHC(=O)R_1$、$C(=O)OR_1$或-$C(=O)R_1$、$CH_2(CH_2)_{0-4}C(=O)NHR_1$；

[0039] R_1，当存在时，独立地选自氢、C_1-C_4烷基、C_1-C_4卤代烷基、C_3-C_7环烷基基团；

[0040] 如果没有特别指明的话，合适的取代基在适用时包括但不限于单独或与其他自由基组合的下列自由基：羟基、氧代基团、卤代基团、硫代基团、硝基、氨基、烷基、烷氧基、卤代烷基或卤代烷氧基；

[0041] 在进一步的实施方式中，上述的基团、自由基可以选自：

[0042] -“烷基”基团，无论是单独使用还是与其他自由基组合，表示含有一至六个碳的直链或支链的自由基，选自甲基、乙基、正丙基、异丙基、正丁基、仲丁基、叔丁基、戊基、叔戊基、正戊基、正己基等；

[0043] -本文使用的术语“卤代”或“卤素”，无论是单独使用还是与其他自由基组合，如“卤代烷基”、“全卤代烷基”，是指氟、氯、溴或碘。术语“卤代烷基”表示经一个或多个卤素取代的如上定义的烷基自由基；如氟甲基、二氟甲基、三氟甲基、氟乙基、二氟乙基、三氟乙基，单或多卤素取代的甲基、乙基、丙基、丁基、戊基或己基基团。术语“卤代烷氧基”表示如上定义的卤代烷基直接连接至氧原子，例如氟甲氧基、氯甲氧基、氟乙氧基、氯乙氧基等。

[0044] -术语″芳基″是指芳香族单碳环和多碳环体系，其中在多个环体系中的各个碳环环稠合或通过单个碳键彼此连接。合适的芳基包括苯基、萘基和联苯基。

[0045] -本文使用的术语″经取代的″表示所指定原子上的任一个或多个氢被选自所指定基团的选项取代，条件是不超过所指定原子的正常价态并且该取代生成稳定的化合物。

[0046] 式(I)化合物可以含有一种或多种不对称中心并且因此可以作为外消旋体或外消旋混合物、单个对映异构体、非对映异构体混合物和单个的非对映异构体存在。本发明是指包括所有的式(I)化合物的这些异构体形式，无论是作为单个种类还是其混合物的形式。

[0047] 本文描述的一些化合物含有烯属双键，并且如果没有另外指明，意指包括E和Z几何异构体这两者。

[0048] 本文描述的一些化合物可以存在不同的氢的连接点，称为互变异构体。这样的实例可以为酮和其烯醇形式，已知为酮-烯醇不变异构体。各个互变异构体及其混合物包括在式(I)化合物中。

[0049] 缩写列表

[0050] DMF:二甲基甲酰胺

[0051] DCM:二氯甲烷

[0052] EDAC.HCl:N-(3-二甲基氨基丙基)-N'-乙基碳二亚胺盐酸盐，

[0053] HOBT:1-羟基苯并三唑

[0054] TFA:三氟乙酸

[0055] DCC:二环已基碳二亚胺

[0056] DIPEA:二异丙基乙胺

[0057] EtOAc:乙酸乙酯

[0058] h:小时

[0059] min:分钟

[0060] t_{Ret}:保留时间

[0061] HCl:氢氯酸

[0062] RT:室温[25-30℃]

[0063] BINAP:(±)-2,2'-双(二苯基膦基)-1,1'-联萘

[0064] DPPF:[1,1'-双(二苯基膦基)二茂铁]二氯化钯与DCM的复合物

[0065] $Pd_2(dba)_3$:三(二亚苄基丙酮)二钯

[0066] $(PPh_3)_2PdCl_2$:双(三苯基膦)二氯化钯(II)

[0067] 设备描述

[0068] 质谱在LC-MS 2010-A Shimadzu上记录。

[0069] UPLC纯度通过使用Waters Sequipy设备确定。

[0070] UPLC柱:BEH C_18(2.1X100mm)1.7μ

[0071] 流动相:0.05%TFA/水:ACN梯度。

[0072] 流速:1.0ml/min。

[0073] 波长:在220nm的UV。

[0074] HPLC纯度通过使用Agilent-1100设备确定。

[0075] HPLC柱J'Sphere ODS 150*4.6mm,

[0076] 流速1.0ml/min,220min

[0077] NMR谱:Bruker Avanc 400mHz

[0078] 本发明特别有用的化合物选自:

[0079] N-(氰基甲基)-4-(2-((4-(4-(2-氧代吡咯烷-1-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺;

[0080] N-(氰基甲基)-4-(2-((4-(4-(1,1-二氧代异噻唑烷-2-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺;

[0081] N-(氰基甲基)-4-(2-((4-(4-吗啉代哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺;

[0082] 4-(2-((4-(4-(1H-1,2,4-三唑-1-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)-N-(氰基甲基)苯甲酰胺;

[0083] 4-(2-((4-(4-(1H-吡唑-1-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)-N-(氰基甲基)苯甲酰胺;

[0084] 4-(2-((4-([1,3'-联吡咯烷]-1'-基)苯基)氨基)嘧啶-4-基)-N-(氰基甲基)苯甲酰胺;

[0085] N-(氰基甲基)-4-(2-((4-(4-(1,1-二氧代四氢-2H-噻喃-4-基)哌嗪-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺;

[0086] N-(氰基甲基)-4-(2-((4-(4-(呋喃-2-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯

甲酰胺；

[0087] N-(氰基甲基)-4-(2-((4-(4-(1,1-二氧代四氢噻吩-3-基)哌嗪-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

[0088] N-(氰基甲基)-4-(2-((4-(4-(2,5-二氧代吡咯烷-1-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

[0089] N-(氰基甲基)-4-(2-((4-(4-(噻吩-2-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

[0090] N-(氰基甲基)-4-(2-((4-(4-(2-氧代噁唑烷-3-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

[0091] N-(氰基甲基)-4-(2-((4-(4-(四氢呋喃-2-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

[0092] N-(氰基甲基)-4-(2-((4-(4-(5-甲基呋喃-2-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

[0093] N-(氰基甲基)-4-(2-((4-(4-(四氢-2H-吡喃-4-基)哌嗪-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

[0094] N-(氰基甲基)-4-(2-((4-(4-(5-甲基四氢呋喃-2-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

[0095] 4-(2-((4-(4-(6-氧杂-3-氮杂双环[3.1.1]庚-3-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)-N-(氰基甲基)苯甲酰胺；

[0096] N-(氰基甲基)-4-(2-((4-(4-(2-氧代咪唑啉-1-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

[0097] 4-(2-((4-(4-(1,3,4-噁二唑-2-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)-N-(氰基甲基)苯甲酰胺；

[0098] 4-(2-((4-(4-(2H-1,2,3-三唑-2-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)-N-(氰基甲基)苯甲酰胺；

[0099] 4-(2-((4-(4-(1H-1,2,3-三唑-1-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)-N-(氰基甲基)苯甲酰胺；

[0100] N-(氰基甲基)-4-(2-((4-(4-(5-氧代-1H-1,2,4-三唑-4(5H)-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

[0101] N-(氰基甲基)-4-(2-((4-(4-(5-氧代-4,5-二氢-1H-1,2,4-三唑-1-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

[0102] 4-(2-((4-(4-(1-氧杂-8-氮杂螺[4.5]癸-8-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)-N-(氰基甲基)苯甲酰胺；

[0103] N-(氰基甲基)-4-(2-((4-(4-(5-甲基-1,3,4-噁二唑-2-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

[0104] N-(氰基甲基)-4-(2-((4-(4-(5-甲基-1,3,4-噻二唑-2-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

[0105] N-(氰基甲基)-4-(2-((4-(4-(四氢-2H-[1,4]二氧杂环己二烯并[2,3-c]吡咯-6(3H)-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

[0106] N-(氰基甲基)-4-(2-((4-(4-(2-氧代-1-氧杂-8-氮杂螺[4.5]癸-8-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

[0107] N-(氰基甲基)-4-(2-((4-(4-(5-氧代-4,5-二氢-1,3,4-噁二唑-2-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

[0108] N-(氰基甲基)-4-(2-((4-(4-(4-环丙基-5-甲基-4H-1,2,4-三唑-3-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

[0109] N-(氰基甲基)-4-(2-((4-(4-(5-甲氧基-1,3,4-噁二唑-2-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

[0110] 4-(2-((4-(4-(1,4-二氧杂萜-6-基)哌嗪-1-基)苯基)氨基)嘧啶-4-基)-N-(氰基甲基)苯甲酰胺；

[0111] N-(氰基甲基)-4-(2-((4-(4-(4,5-二氢-1H-咪唑-2-基)哌嗪-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

[0112] N-(氰基甲基)-4-(2-((4-(4-(4,5-二氢-1H-咪唑-2-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

[0113] N-(氰基甲基)-4-(2-((4-(3-(四氢-2H-[1,4]二氧杂环己二烯并[2,3-c]吡咯-6(3H)-基)吡咯烷-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

[0114] N-(氰基甲基)-4-(2-((4-(4-(5-甲基-1,3,4-噁二唑-2-基)哌嗪-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

[0115] N-(氰基甲基)-4-(2-((4-(4-(3,4-二羟基吡咯烷-1-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

[0116] 4-(2-((4-(4-(8-氧杂-3-氮杂双环[3.2.1]辛-3-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)-N-(氰基甲基)苯甲酰胺；

[0117] 4-(2-((4-(4-(6-乙酰基-3,6-二氮杂双环[3.1.1]庚-3-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)-N-(氰基甲基)苯甲酰胺；

[0118] N-(氰基甲基)-4-(5-甲基-2-((4-(4-吗啉代哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

[0119] N-(氰基甲基)-4-(5-甲基-2-((4-(4-(2-氧代吡咯烷-1-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

[0120] 4-(2-((4-(4-(1-氧杂-8-氮杂螺[4.5]癸-8-基)哌啶-1-基)苯基)氨基)-5-甲基嘧啶-4-基)-N-(氰基甲基)苯甲酰胺；

[0121] N-(氰基甲基)-4-(5-甲基-2-((4-(4-(5-甲基-1,3,4-噁二唑-2-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

[0122] N-(氰基甲基)-4-(5-氟-2-((4-(4-吗啉代哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

[0123] 4-(5-氯-2-((4-(4-吗啉代哌啶-1-基)苯基)氨基)嘧啶-4-基)-N-(氰基甲基)苯甲酰胺；

[0124] N-(氰基甲基)-4-(5-氟-2-((4-(4-(2-氧代吡咯烷-1-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

[0125] 4-(5-氯-2-((4-(4-(2-氧代吡咯烷-1-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)-N-

(氰基甲基)苯甲酰胺；

[0126] 4-(2-((4-(4-(6-氧杂-3-氮杂双环[3.1.1]庚-3-基)哌啶-1-基)苯基)氨基)-5-甲基嘧啶-4-基)-N-(氰基甲基)苯甲酰胺；

[0127] 4-(2-((4-(4-(6-氧杂-3-氮杂双环[3.1.1]庚-3-基)哌啶-1-基)苯基)氨基)-5-氟嘧啶-4-基)-N-(氰基甲基)苯甲酰胺；

[0128] -(2-((4-(4-(6-氧杂-3-氮杂双环[3.1.1]庚-3-基)哌啶-1-基)苯基)氨基)-5-氯嘧啶-4-基)-N-(氰基甲基)苯甲酰胺；

[0129] N-(氰基甲基)-4-(5-甲基-2-((4-(4-(四氢-2H-[1,4]二氧杂环己二烯并[2,3-c]吡咯-6(3H)-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

[0130] N-(氰基甲基)-4-(5-氟-2-((4-(4-(四氢-2H-[1,4]二氧杂环己二烯并[2,3-c]吡咯-6(3H)-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

[0131] 4-(5-氯-2-((4-(4-(四氢-2H-[1,4]二氧杂环己二烯并[2,3-c]吡咯-6(3H)-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)-N-(氰基甲基)苯甲酰胺；

[0132] N-(氰基甲基)-4-(5-氟-2-((4-(4-(5-甲基-1,3,4-噁二唑-2-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

[0133] 4-(5-氯-2-((4-(4-(5-甲基-1,3,4-噁二唑-2-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)-N-(氰基甲基)苯甲酰胺；

[0134] N-(氰基甲基)-4-(5-甲基-2-((4-(4-(5-甲基-1,3,4-噁二唑-2-基)哌嗪-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

[0135] N-(氰基甲基)-4-(5-氟-2-((4-(4-(5-甲基-1,3,4-噁二唑-2-基)哌嗪-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺；

[0136] 4-(5-氯-2-((4-(4-(5-甲基-1,3,4-噁二唑-2-基)哌嗪-1-基)苯基)氨基)嘧啶-4-基)-N-(氰基甲基)苯甲酰胺；

[0137] 4-(2-((4-(4-(3-硫杂-6-氮杂双环[3.1.1]庚-6-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)-N-(氰基甲基)苯甲酰胺；

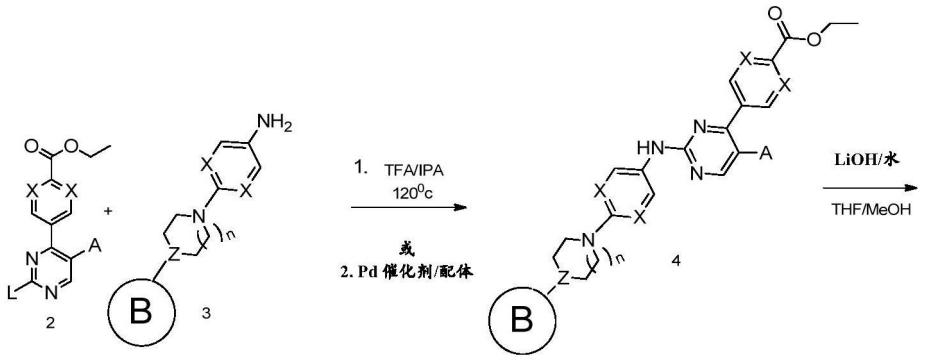
[0138] 4-(2-((4-(4-(3-硫杂-6-氮杂双环[3.1.1]庚-6-基)哌啶-1-基)苯基)氨基)-5-甲基嘧啶-4-基)-N-(氰基甲基)苯甲酰胺；

[0139] 4-(2-((4-(4-(3-硫杂-6-氮杂双环[3.1.1]庚-6-基)哌啶-1-基)苯基)氨基)-5-氟嘧啶-4-基)-N-(氰基甲基)苯甲酰胺；

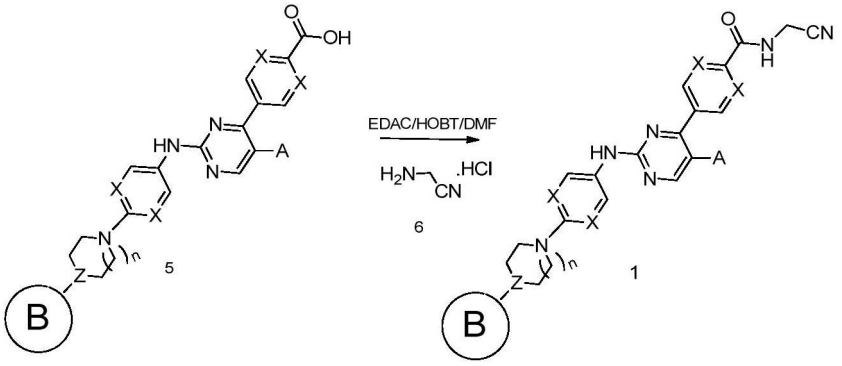
[0140] 4-(2-((4-(4-(3-硫杂-6-氮杂双环[3.1.1]庚-6-基)哌啶-1-基)苯基)氨基)-5-氯嘧啶-4-基)-N-(氰基甲基)苯甲酰胺；

[0141] 本发明的化合物可以使用下面描述的方法以及有机合成领域技术人员已知的常规技术或者本领域技术人员能理解的变化进行制备。参考方法包括但不限于下面描述的那些,其中所有的符号已经在上文进行了定义。

[0142] 一般方法1：



[0143]



[0144] 式[4]的酯衍生物可以在酸如三氟乙酸、对甲苯磺酸或碱如碳酸钾、二异丙基乙胺、三乙胺等的存在下在溶剂如异丙醇、二甲基亚砜、二甲基甲酰胺或二噁烷等中于温度25-150℃使式[2]的化合物(其中'L'为选自Cl、Br、I或$SOCH_3$等的合适的离去基团)和式[3]的合适的胺衍生物反应而合成。作为连接至胺衍生物[3]的酸敏感基团的备选,酯衍生物可以使用催化剂如DPPF、$Pd_2(dba)_3$、$(PPh_3)_2PdCl_2$等在配体BINAP等的存在下在溶剂如DMF、DMA、二噁烷中于温度80-150℃使式[2]化合物与胺衍生物[3]偶联而制备。

[0145] 酯衍生物[4]与碱如氢氧化钠、氢氧化锂在溶剂如水、甲醇、乙醇、四氢呋喃或其组合中于温度25-100℃的水解得到式[5]的酸衍生物。式[6]的乙腈衍生物可以通过使用合适的羧基活化试剂如N-(3-二甲基氨基丙基)-N'-乙基碳二亚胺盐酸盐(EDAC.HCl)、二环已基碳二亚胺等在添加剂1-羟基苯并三唑(HOBT)和碱如三乙基胺或二异丙基乙胺(DIEA)等的存在下在溶剂如二甲基甲酰胺或二氯甲烷等中于温度0-25℃使氨基乙腈[6]与式[5]的酸衍生物反应进行合成。

[0146] 式[2]的化合物可以如本领域中已知的一般方法如WO2008109943中所提及的与本领域技术人员公知的变化进行制备。胺衍生物[3]可以通过本领域技术人员已知的变化如在以下参考文献中给出的方法进行合成: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.1-9Pergamon,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;和Organic Reactions,Wiley&Sons:

New York,1991,Volumes 1-40,上述仅为已知文献方法中的一些。

[0147] 形成本发明一部分的可药用盐可以通过本领域已知的方法在合适的溶剂中以合适的酸处理式(1)化合物而制备。

[0148] 酯结构单元[2]通过下文描述的方法合成。

[0149]

酯	化学名称
酯1	4-(2-氯嘧啶-4-基)苯甲酸乙酯
酯2	4-(2-氯-5-甲基嘧啶-4-基)苯甲酸乙酯
酯3	4-(2-氯-5-氟嘧啶-4-基)苯甲酸乙酯
酯4	4-(2-氯-5-氯嘧啶-4-基)苯甲酸乙酯

[0150] 酯结构单元的合成

[0151] 酯1:制备4-(2-氯嘧啶-4-基)苯甲酸乙酯。

[0152] 向2,4-二氯嘧啶[70g,470mmol]在DMF[600mL]中的溶液添加$(PPh_3)_2PdCl_2$[9.9g,14mmol],将混合物加热至90℃保持1h。向其中添加(4-(乙氧基羰基)苯基)硼酸[91g,470mmol]并将混合物加热至90℃再保持0.5h。将碳酸氢钾[282g,2.8mol]在200mL的水中的溶液添加至反应混合物并于90℃搅拌0.5h。反应完成后,混合物在冰冷的水[500mL]中淬灭。过滤所得到的灰白色的固体,以水洗涤并真空干燥得到标题化合物[45g,37%]。

[0153] 酯2:制备4-(2-氯-5-甲基嘧啶-4-基)苯甲酸乙酯

[0154] 以类似于酯1中描述的方法制备,但是使用2,4-二氯-5-甲基嘧啶作为原料。

[0155] 酯3:制备4-(2-氯-5-氟嘧啶-4-基)苯甲酸乙酯。

[0156] 以类似于酯1中描述的方法制备,但是使用2,4-二氯-5-氟嘧啶作为原料。

[0157] 酯4:制备4-(2-氯-5-氯嘧啶-4-基)苯甲酸乙酯。

[0158] 以类似于酯1中描述的方法制备,但是使用2,4,5-三氯嘧啶作为原料。

[0159] 胺结构单元[3]通过下文描述的方法合成:

[0160]

胺	化学名称
胺 1	1-(1-(4-氨基苯基)哌啶-4-基)吡咯烷-2-酮
胺 2	2-(1-(4-氨基苯基)哌啶-4-基)异噻唑烷 1,1-二氧化物
胺 3	4-(4-吗啉代哌啶-1-基)苯胺
胺 4	4-(4-(1H-1,2,4-三唑-1-基)哌啶-1-基)苯胺
胺 5	4-(4-(1H-吡唑-1-基)哌啶-1-基)苯胺
胺 6	4-([1,3'-联吡咯烷]-1'-基)苯胺
胺 7	4-(4-(4-氨基苯基)哌嗪-1-基)四氢-2H-噻喃 1,1-二氧化物
胺 8	4-(4-(呋喃-2-基)哌啶-1-基)苯胺
胺 9	3-(4-(4-氨基苯基)哌嗪-1-基)四氢噻吩 1,1-二氧化物
胺 10	1-(1-(4-氨基苯基)哌啶-4-基)吡咯烷-2,5-二酮
胺 11	4-(4-(噻吩-2-基)哌啶-1-基)苯胺
胺 12	3-(1-(4-氨基苯基)哌啶-4-基)噁唑烷-2-酮

[0161]

胺 13	4-(4-(四氢呋喃-2-基)哌啶-1-基)苯胺
胺 14	4-(4-(5-甲基呋喃-2-基)哌啶-1-基)苯胺
胺 15	4-(4-(四氢-2H-吡喃-4-基)哌嗪-1-基)苯胺
胺 16	4-(4-(5-甲基四氢呋喃-2-基)哌啶-1-基)苯胺
胺 17	4-(4-(6-氧杂-3-氮杂双环[3.1.1]庚-3-基)哌啶-1-基)苯胺
胺 18	1-(1-(4-氨基苯基)哌啶-4-基)咪唑啉-2-酮
胺 19	4-(4-(1,3,4-噁二唑-2-基)哌啶-1-基)苯胺
胺 20	4-(4-(2H-1,2,3-三唑-2-基)哌啶-1-基)苯胺
胺 21	4-(4-(1H-1,2,3-三唑-1-基)哌啶-1-基)苯胺
胺 22	4-(1-(4-氨基苯基)哌啶-4-基)-1H-1,2,4-三唑-5(4H)-酮
胺 23	1-(1-(4-氨基苯基)哌啶-4-基)-1H-1,2,4-三唑-5(4H)-酮
胺 24	4-(4-(1-氧杂-8-氮杂螺[4.5]癸-8-基)哌啶-1-基)苯胺
胺 25	4-(4-(5-甲基-1,3,4-噁二唑-2-基)哌啶-1-基)苯胺
胺 26	4-(4-(5-甲基-1,3,4-噻二唑-2-基)哌啶-1-基)苯胺
胺 27	4-(4-(四氢-2H-[1,4]二氧杂环己二烯并[2,3-c]吡咯-6(3H)-基)哌啶-1-基)苯胺
胺 28	8-(1-(4-氨基苯基)哌啶-4-基)-1-氧杂-8-氮杂螺[4.5]癸-2-酮
胺 29	5-(1-(4-氨基苯基)哌啶-4-基)-1,3,4-噁二唑-2(3H)-酮
胺 30	4-(4-(4-环丙基-5-甲基-4H-1,2,4-三唑-3-基)哌啶-1-基)苯胺
胺 31	4-(4-(5-甲氧基-1,3,4-噁二唑-2-基)哌啶-1-基)苯胺
胺 32	4-(4-(1,4-二氧杂萘-6-基)哌嗪-1-基)苯胺
胺 33	4-(4-(4,5-二氢-1H-咪唑-2-基)哌嗪-1-基)苯胺
胺 34	4-(4-(4,5-二氢-1H-咪唑-2-基)哌啶-1-基)苯胺
胺 35	4-(3-(四氢-2H-[1,4]二氧杂环己二烯并[2,3-c]吡咯-6(3H)-基)吡咯烷-1-基)苯胺
胺 36	4-(4-(5-甲基-1,3,4-噁二唑-2-基)哌嗪-1-基)苯胺
胺 37	1-(1-(4-氨基苯基)哌啶-4-基)吡咯烷-3,4-二醇
胺 38	4-(4-(3-氧杂-8-氮杂双环[3.2.1]辛-8-基)哌啶-1-基)苯胺
胺 39	1-(3-(1-(4-氨基苯基)哌啶-4-基)-3,6-二氮杂双环[3.1.1]庚-6-基)乙酮

[0162] 胺结构单元的合成

[0163] 胺1：1-(1-(4-氨基苯基)哌啶-4-基)吡咯烷-2-酮.

[0164] 步骤1:制备1-(1-(4-硝基苯基)哌啶-4-基)吡咯烷-2-酮

[0165] 1-(哌啶-4-基)吡咯烷-2-酮(1.8g,10.7mmol)[OPRD 2007,11,482-486]于室温溶解于DMF(10.0mL)中。于室温向其中加入K_2CO_3(2.96g,21.40mmol),接着加入1-氟-4-硝基苯(1.5mL,10.7mmol)。反应混合物于80-90℃搅拌4h。反应完成后,混合物以水淬灭。得到的黄色固体经过滤,以水洗涤,真空干燥得到所需的化合物(2.5g,81%),为黄色固体。

[0166] 步骤2:制备1-(1-(4-氨基苯基)哌啶-4-基)吡咯烷-2-酮

[0167] 在500mL的青花瓶中添加在乙醇(50mL)中的1-(1-(4-硝基苯基)哌啶-4-基)吡咯烷-2-酮[2.5g,8.6mmol]。向其中添加10%Pd/C(0.372g,3.50mmol)并且将瓶置于parr氢化设备中于50psi保持8h。反应完成后,混合物经硅藻土(hyflow bed)过滤,以甲醇洗涤,并且有机挥发物真空蒸馏得到标题胺1(1.7g,76%),为棕色固体。

[0168] 胺2:2-(1-(4-氨基苯基)哌啶-4-基)异噻唑烷1,1-二氧化物.

[0169] 以类似于胺1中描述的方法制备,但是使用2-(哌啶-4-基)异噻唑烷1,1-二氧化物[参考:JMC,53(9),3517-3531,2010]。

[0170] 胺3:4-(4-吗啉代哌啶-1-基)苯胺.

[0171] 以类似于胺1中描述的方法制备,但是使用4-(哌啶-4-基)吗啉[参考:BMCL 22(9),3157-3162,2012]。

[0172] 胺4:4-(4-(1H-1,2,4-三唑-1-基)哌啶-1-基)苯胺

[0173] 以类似于胺1中描述的方法制备,但是使用4-(1H-1,2,4-三唑-1-基)哌啶[参考:WO2008060621]。

[0174] 胺5:4-(4-(1H-吡唑-1-基)哌啶-1-基)苯胺

[0175] 以类似于胺1中描述的方法制备,但是使用4-(1H-吡唑-1-基)哌啶[参考:WO2013010453]。

[0176] 胺6:4-([1,3'-联吡咯烷]-1'-基)苯胺

[0177] 以类似于胺1中描述的方法制备,但是使用1,3'-联吡咯烷[参考:WO2004039780]。

[0178] 胺7:4-(4-(4-氨基苯基)哌嗪-1-基)四氢-2H-噻喃1,1-二氧化物

[0179] 以类似于胺1中描述的方法制备,但是使用4-(哌嗪-1-基)四氢-2H-噻喃1,1-二氧化物[参考:WO20070072847]。

[0180] 胺8:4-(4-(呋喃-2-基)哌啶-1-基)苯胺

[0181] 以类似于胺1中描述的方法制备,但是使用4-(呋喃-2-基)哌啶[参考:WO9737979]。

[0182] 胺9:3-(4-(4-氨基苯基)哌嗪-1-基)四氢噻吩1,1-二氧化物.

[0183] 以类似于胺1中描述的方法制备,但是使用3-(哌嗪-1-基)四氢噻吩1,1-二氧化物[参考:US20080045517]。

[0184] 胺10:1-(1-(4-氨基苯基)哌啶-4-基)吡咯烷-2,5-二酮.

[0185] 以类似于胺1中描述的方法制备,但是使用1-(哌啶-4-基)吡咯烷-2,5-二酮.

[0186] 胺11:4-(4-(噻吩-2-基)哌啶-1-基)苯胺.

[0187] 以类似于胺1中描述的方法制备,但是使用4-(噻吩-2-基)哌啶[参考:WO9737979]。

[0188] 胺12:3-(1-(4-氨基苯基)哌啶-4-基)噁唑烷-2-酮.

[0189] 以类似于胺1中描述的方法制备，但是使用3-(哌啶-4-基)噁唑烷-2-酮[参考：Journal of Medicinal Chemsitry,2008,51,144,4150-69]。

[0190] 胺13:4-(4-(四氢呋喃-2-基)哌啶-1-基)苯胺.

[0191] 以类似于胺1中描述的方法制备，但是使用4-(四氢呋喃-2-基)哌啶[参考:WO 9737979]。

[0192] 胺14:4-(4-(5-甲基呋喃-2-基)哌啶-1-基)苯胺.

[0193] 以类似于胺1中描述的方法制备，但是使用4-(5-甲基呋喃-2-基)哌啶[参考:WO 9737979]。

[0194] 胺15:4-(4-(四氢-2H-吡喃-4-基)哌嗪-1-基)苯胺.

[0195] 以类似于胺1中描述的方法制备，但是使用1-(四氢-2H-吡喃-4-基)哌嗪.

[0196] 胺16:4-(4-(5-甲基四氢呋喃-2-基)哌啶-1-基)苯胺.

[0197] 以类似于胺1中描述的方法制备，但是使用4-(5-甲基四氢呋喃-2-基)哌啶[参考：WO 9737979]。

[0198] 胺17:4-(4-(6-氧杂-3-氮杂双环[3.1.1]庚-3-基)哌啶-1-基)苯胺.

[0199] 以类似于胺1中描述的方法制备，但是使用3-(哌啶-4-基)-6-氧杂-3-氮杂双环[3.1.1]庚烷[参考:Synthesis 2011,16,2619-2624]。

[0200] 胺18:1-(1-(4-氨基苯基)哌啶-4-基)咪唑啉-2-酮.

[0201] 以类似于胺1中描述的方法制备，但是使用1-(哌啶-4-基)咪唑啉-2-酮.

[0202] 胺19:4-(4-(1,3,4-噁二唑-2-基)哌啶-1-基)苯胺.

[0203] 以类似于胺1中描述的方法制备，但是使用2-(哌啶-4-基)-1,3,4-噁二唑[参考：Journal of Med.Chem.51,15,4430-4448,2008]。

[0204] 胺20:4-(4-(2H-1,2,3-三唑-2-基)哌啶-1-基)苯胺.

[0205] 以类似于胺1中描述的方法制备，但是使用4-(2H-1,2,3-三唑-2-基)哌啶[参考：Tetrahedron letter 53,6842-52,2012]。

[0206] 胺21:4-(4-(1H-1,2,3-三唑-1-基)哌啶-1-基)苯胺.

[0207] 以类似于胺1中描述的方法制备，但是使用4-(1H-1,2,3-三唑-1-基)哌啶[参考：Tetrahedron letter 53,6842-52,2012]。

[0208] 胺22:4-(1-(4-氨基苯基)哌啶-4-基)-1H-1,2,4-三唑-5(4H)-酮.

[0209] 以类似于胺1中描述的方法制备，但是使用4-(哌啶-4-基)-1H-1,2,4-三唑-5(4H)-酮[参考:WO 2009039257]。

[0210] 胺23:1-(1-(4-氨基苯基)哌啶-4-基)-1H-1,2,4-三唑-5(4H)-酮.

[0211] 以类似于胺1中描述的方法制备，但是使用8-(哌啶-4-基)-1-氧杂-8-氮杂螺[4.5]癸烷[参考:BMCL 12,1759,2002]。

[0212] 胺24:4-(4-(1-氧杂-8-氮杂螺[4.5]癸-8-基)哌啶-1-基)苯胺.

[0213] 以类似于胺1中描述的方法制备，但是使用8-(哌啶-4-基)-1-氧杂-8-氮杂螺[4.5]癸烷[参考:BMCL 12,1759,2002]。

[0214] 胺25:4-(4-(5-甲基-1,3,4-噁二唑-2-基)哌啶-1-基)苯胺.

[0215] 以类似于胺1中描述的方法制备，但是使用2-甲基-5-(哌啶-4-基)-1,3,4-噁二唑[参考:Journal of Medicinal Chemistry 51,15,4430-4448,2008]。

[0216] 胺26:4-(4-(5-甲基-1,3,4-噻二唑-2-基)哌啶-1-基)苯胺.

[0217] 以类似于胺1中描述的方法制备,但是使用2-甲基-5-(哌啶-4-基)-1,3,4-噻二唑[参考:Org.Lett.2006,8,1625-28]。

[0218] 胺27:4-(4-(四氢-2H-[1,4]二氧杂环己二烯并[2,3-c]吡咯-6(3H)-基)哌啶-1-基)苯胺.

[0219] 以类似于胺1中描述的方法制备,但是使用6-(哌啶-4-基)六氢-2H-[1,4]二氧杂环己二烯并[2,3-c]吡咯[参考:Synthesis 1995,795-800]。

[0220] 胺28:8-(1-(4-氨基苯基)哌啶-4-基)-1-氧杂-8-氮杂螺[4.5]癸-2-酮.

[0221] 以类似于胺1中描述的方法制备,但是使用8-(哌啶-4-基)-1-氧杂-8-氮杂螺[4.5]癸-2-酮[参考:WO 0187838,BMCL 12,1759,2002]。

[0222] 胺29:5-(1-(4-氨基苯基)哌啶-4-基)-1,3,4-噁二唑-2(3H)-酮.

[0223] 以类似于胺1中描述的方法制备,但是使用5-(哌啶-4-基)-1,3,4-噁二唑-2(3H)-酮[参考:WO 2013093940]。

[0224] 胺30:4-(4-(4-环丙基-5-甲基-4H-1,2,4-三唑-3-基)哌啶-1-基)苯胺.

[0225] 以类似于胺1中描述的方法制备,但是使用4-(4-环丙基-5-甲基-4H-1,2,4-三唑-3-基)哌啶[参考:BMCL 21,5684-87,2011]。

[0226] 胺31:4-(4-(5-甲氧基-1,3,4-噁二唑-2-基)哌啶-1-基)苯胺.

[0227] 以类似于胺1中描述的方法制备,但是使用2-甲氧基-5-(哌啶-4-基)-1,3,4-噁二唑[参考:US 20020111358]。

[0228] 胺32:4-(4-(1,4-二氧杂萘-6-基)哌嗪-1-基)苯胺.

[0229] 以类似于胺1中描述的方法制备,但是使用1-(1,4-二氧杂萘-6-基)哌嗪[参考:WO 20101139717]。

[0230] 胺33:4-(4-(4,5-二氢-1H-咪唑-2-基)哌嗪-1-基)苯胺.

[0231] 以类似于胺1中描述的方法制备,但是使用1-(4,5-二氢-1H-咪唑-2-基)哌嗪[参考:WO 2002036562]。

[0232] 胺34:4-(4-(4,5-二氢-1H-咪唑-2-基)哌啶-1-基)苯胺.

[0233] 以类似于胺1中描述的方法制备,但是使用4-(4,5-二氢-1H-咪唑-2-基)哌啶[参考:BMCL 21,2244-51,2011]。

[0234] 胺35:4-(3-(四氢-2H-[1,4]二氧杂环己二烯并[2,3-c]吡咯-6(3H)-基)吡咯烷-1-基)苯胺。

[0235] 以类似于胺1中描述的方法制备,但是使用6-(吡咯烷-3-基)六氢-2H-[1,4]二氧杂环己二烯并[2,3-c]吡咯[参考:Synthesis 795-800,1995]。

[0236] 胺36:4-(4-(5-甲基-1,3,4-噁二唑-2-基)哌嗪-1-基)苯胺.

[0237] 以类似于胺1中描述的方法制备,但是使用2-甲基-5-(哌嗪-1-基)-1,3,4-噁二唑。

[0238] 胺37:1-(1-(4-氨基苯基)哌啶-4-基)吡咯烷-3,4-二醇.

[0239] 以类似于胺1中描述的方法制备,但是使用1-(哌啶-4-基)吡咯烷-3,4-二醇。

[0240] 胺38:4-(4-(3-氧杂-8-氮杂双环[3.2.1]辛-8-基)哌啶-1-基)苯胺.

[0241] 以类似于胺1中描述的方法制备,但是使用8-(哌啶-4-基)-3-氧杂-8-氮杂双环

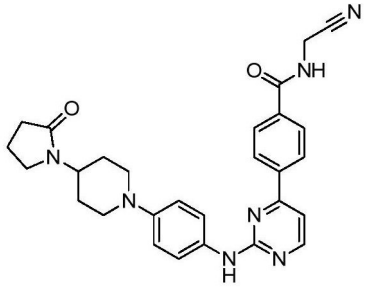
[3.2.1]辛烷[参考:WO2005108402]。

[0242] 胺39:1-(3-(1-(4-氨基苯基)哌啶-4-基)-3,6-二氮杂双环[3.1.1]庚-6-基)乙酮.

[0243] 以类似于胺1中描述的方法制备,但是使用1-(3-(哌啶-4-基)-3,6-二氮杂双环[3.1.1]庚-6-基)乙酮[参考:WO2011120854]。

[0244] 本发明通过以下实施例进一步示例,这些实施例提供了本发明的一些优选的实施方案。这些实施例仅作为代表性实施方案提供,并且不应当以任何方式理解为限制本发明的范围。

[0245] 实施例1:制备N-(氰基甲基)-4-(2-((4-(4-(2-氧代吡咯烷-1-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺.

[0246] 

[0247] 步骤1:制备4-(2-((4-(4-(2-氧代吡咯烷-1-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酸乙酯。

[0248] 将4-(2-氯嘧啶-4-基)苯甲酸乙酯(7.09g,27.0mmol)在异丙醇[100mL]中的溶液添加至1-(1-(4-氨基苯基)哌啶-4-基)吡咯烷-2-酮(7.0 g,27.0 mmol)。向其中添加三氟乙酸(4.62g,40.0mmol)并且混合物于120℃在密封试管中加热16h。反应完成后,混合物在水中淬灭,以氨水溶液碱化并以乙酸乙酯萃取。有机层以水洗涤,经硫酸钠干燥并减压除去得到粗的灰白色固体化合物。通过柱色谱的方式完成粗产物的纯化(SiO_2,己烷至30%EtOAc/己烷)得到固体化合物(10.7g,82%)。标题化合物通过光谱分析表征。ESI-MS:486.2$(M+H)^+$.

[0249] 步骤2:制备4-(2-((4-(4-(2-氧代吡咯烷-1-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酸.

[0250] 4-(2-((4-(4-(2-氧代吡咯烷-1-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酸乙酯

[0251] (25.0g,51.5mmol)溶解于3:1甲醇/THF(100mL)中。向其中加入在水(25mL)中的氢氧化锂(9.86g,412mmol)并且混合物回流2h,冷却,浓缩并以稀HCl酸化。深色的沉淀经过滤,以水洗涤并真空干燥得到标题化合物(20.0g,85%)。标题化合物通过光谱分析表征ESI-MS:458.2$(M+H)^+$。

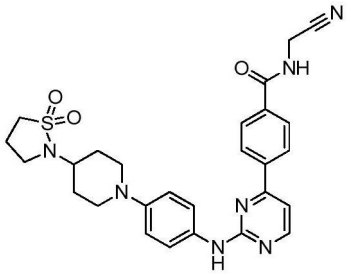
[0252] 步骤3:N-(氰基甲基)-4-(2-((4-(4-(2-氧代吡咯烷-1-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺

[0253] 向4-(2-((4-(4-(2-氧代吡咯烷-1-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酸[20.0g,43.7mmol]在200mL DMF中的溶液添加HOBt[8.03g,52.5mmol]。在N_2下于0-5℃向该反应混合物中添加EDAC.HCl[10.06g,52.5mmol]、2-氨基乙腈盐酸盐[8.09g,87mmol]和三乙胺[26.5g,262mmol]。所得反应混合物于25℃搅拌16h。混合物以水稀释。水层以EtOAc萃

取。有机层以盐水洗涤，经硫酸钠干燥并真空浓缩得到半固体化合物。通过柱色谱完成粗产物的纯化(SiO_2,$CHCl_3$至4％MeOH/$CHCl_3$)得到黄色固体化合物(600mg,46％)。^{1}H NMR(400MHz,d_6-DMSO):9.47(s,1H),9.33(1H,t,J＝5.8Hz,),8.53(1H,d,J＝5.2Hz),8.26(2H,d,J＝8.4Hz),8.02(2H,d,J＝8.4Hz),7.64(2H,d,J＝8.8Hz),7.39(1H,d,J＝5.2Hz),6.94(2H,d,J＝9.2Hz),4.35(2H,d,J＝5.6Hz),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}:2.57min.

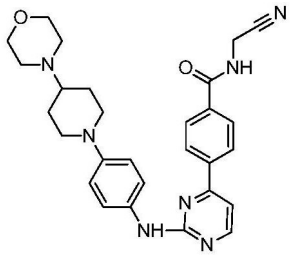
[0254] 本发明的一些化合物根据下述方法以及技术人员能力范围内的合适的调节、变化等来制备。

[0255] 实施例2:制备N-(氰基甲基)-4-(2-((4-(4-(1,1-二氧代异噻唑烷-2-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺.

[0256] 

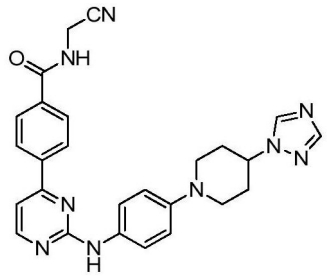
[0257] 以类似于实施例1描述的类似方法制备，但是使用酯1和胺2作为原料。得到标题化合物，为黄色固体。^{1}H NMR(400MHz,d_6-DMSO):9.47(1H,s),9.33(1H,t,J＝5.2Hz),8.53(1H,d,J＝5.2Hz),8.26(2H,d,J＝8.4Hz),8.01(2H,d,J＝8.4Hz),7.64(2H,d,J＝9.2Hz),7.40(1H,d,J＝5.2Hz),6.93(2H,d,J＝8.8Hz),4.35(2H,d,J＝5.6Hz),3.64(2H,d,J＝13.2Hz),3.42-3.17(4H,m),2.67-2.66(3H,m),2.30-2.10(2H,m),1.85-1.70(4H,m).ESI-MS:531.90$(M+H)^+$.UPLC t_{ret}:2.73min.

[0258] 实施例3:制备N-(氰基甲基)-4-(2-((4-(4-吗啉代哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺.

[0259] 

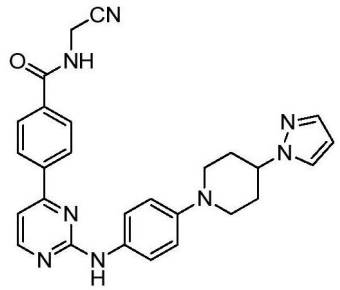
[0260] 以类似于实施例1描述的类似方法制备，但是使用酯1和胺3作为原料。得到标题化合物，为黄色固体。^{1}H NMR(400MHz,d_6-DMSO):9.47(1H,s),9.33(1H,t,J＝5.2Hz),8.53(1H,d,J＝5.2Hz),8.26(2H,d,J＝8.4Hz),8.02(2H,d,J＝8.4Hz),7.63(2H,d,J＝8.8Hz),7.44(1H,d,J＝5.2Hz),6.92(2H,d,J＝9.2Hz),4.35(2H,d,J＝5.6Hz),3.65-3.56(6H,m),2.73-2.52(2H,m),2.50-2.47(4H,m),2.23(1H,t,J＝3.6Hz),1.87-1.85(2H,m),1.52-1.45(2H,m).ESI-MS:＝514.20$(M+NH_4)^+$.UPLC t_{ret}:2.37min.

[0261] 实施例4:制备4-(2-((4-(4-(1H-1,2,4-三唑-1-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)-N-(氰基甲基)苯甲酰胺.

[0262] 

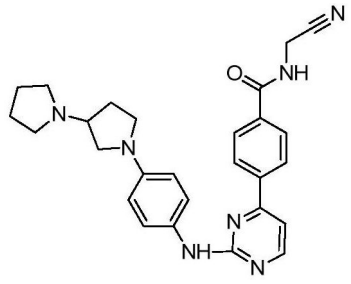
[0263] 以类似于实施例1描述的类似方法制备，但是使用酯1和胺4作为原料。得到标题化合物，为黄色固体。^{1}H NMR(400MHz,d_6-DMSO):9.51(1H,s),9.35(1H,t,J＝5.2Hz),8.61(1H,s),8.55(1H,d,J＝5.2Hz),8.28(2H,d,J＝8.4Hz),8.02(2H,d,J＝8.4Hz),7.91(1H,S),7.65(2H,d,J＝8.8Hz),7.41(1H,d,J＝5.2Hz),7.0(2H,d,J＝8.8Hz),4.4(1H,m),4.35(1H,d,J＝5.6Hz),3.74-3.71(2H,m),2.9-2.8(2H,m),2.3-2.1(4H,m).ESI-MS:480-20$(M+H)^+$.UPLC t_{ret}:2.56min

[0264] 实施例5：制备4-(2-((4-(4-(1H-吡唑-1-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)-N-(氰基甲基)苯甲酰胺.

[0265] 

[0266] 以类似于实施例1描述的类似方法制备，但是使用酯1和胺5作为原料。得到标题化合物，为浅黄色固体。^{1}H NMR(400MHz,d_6-DMSO):9.50(1H,s),9.34(1H,t,J＝5.2Hz),8.54(1H,d,J＝5.2Hz),8.27(2H,d,J＝8.4Hz),8.02(2H,d,J＝8.4Hz),7.81(1H,d,J＝2.0Hz),7.66(2H,d,J＝8.8Hz),7.45(1H,d,J＝4Hz),7.40(1H,d,J＝5.2Hz),6.98(2H,d,J＝8.8Hz),6.24(1H,t,J＝2Hz),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}:2.83min.

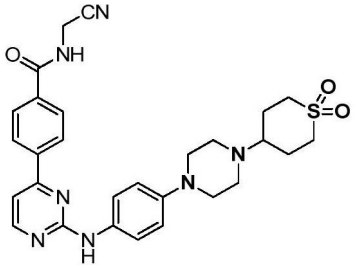
[0267] 实施例6：制备4-(2-((4-([1,3'-联吡咯烷]-1'-基)苯基)氨基)嘧啶-4-基)-N-(氰基甲基)苯甲酰胺.

[0268] 

[0269] 以类似于实施例1描述的类似方法制备，但是使用酯1和胺6作为原料。得到标题化合物，为深黄色固体。^{1}H NMR(400MHz,d_6-DMSO):9.32(2H,t,J＝5.2Hz),9.30(1H,s),8.49(1H,d,J＝5.2Hz),8.25(2H,d,J＝8.8Hz),8.01(2H,d,J＝8.8Hz),7.56(2H,d,J＝8.8Hz),7.35(1H,d,J＝5.2Hz),6.53(2H,d,J＝9.2Hz),4.35(2H,d,J＝5.2Hz),3.41-3.43(1H,m),

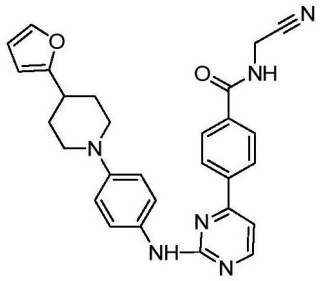
3.32-3.26(2H,m),3.09-3.05(1H,m),2.85-2.81(1H,m),2.70-2.69(4H,m),2.16-2.14(1H,m),1.92-1.85(1H,m),1.75-1.70(4H,m).ESI-MS:468.12$(M+H)^+$.UPLC t_{ret}:2.56min.

[0270] 实施例7:制备N-(氰基甲基)-4-(2-((4-(4-(1,1-二氧代四氢-2H-噻喃-4-基)哌嗪-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺.

[0271] 

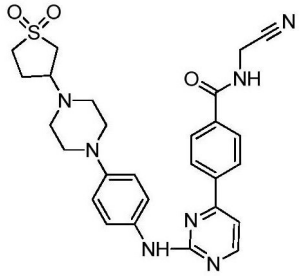
[0272] 以类似于实施例1描述的类似方法制备,但是使用酯1和胺7作为原料。得到标题化合物,为浅黄色固体。^{1}H NMR(400MHz,d_6-DMSO):9.48(1H,s),9.33(1H,t,J=5.6Hz),8.53(1H,d,J=4.8Hz),8.26(2H,d,J=8.4Hz),8.02(2H,d,J=8.4Hz),7.64(2H,d,J=8.8Hz),7.40(1H,d,J=5.2Hz),6.92(2H,d,J=8.8Hz),4.35(2H,d,J=5.6Hz),3.08(8H,m),2.67-2.66(4H,m),2.04(4H,m).ESI-MS:545.95$(M+H)^+$.UPLC t_{ret}:2.51min.

[0273] 实施例8:制备N-(氰基甲基)-4-(2-((4-(4-(呋喃-2-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺.

[0274] 

[0275] 以类似于实施例1描述的类似方法制备,但是使用酯1和胺8作为原料。得到标题化合物,为浅黄色固体。^{1}H NMR(400MHz,d_6-DMSO):9.43(1H,s),9.33(1H,t,J=5.6Hz),8.53(1H,d,J=5.2Hz),8.02(2H,d,J=8.4Hz),7.65(2H,d,J=9.2Hz),7.53(1H,t,J=1.6Hz),7.39(1H,d,J=5.2Hz),6.95(2H,d,J=9.2Hz),6.38-6.36(1H,m),6.13(1H,d,J=3.2Hz),4.35(2H,d,J=5.6Hz),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}:3.24min.

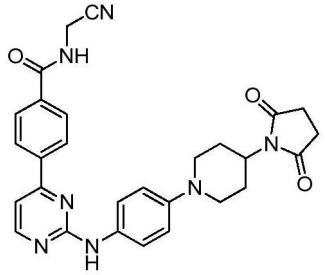
[0276] 实施例9:制备N-(氰基甲基)-4-(2-((4-(4-(1,1-二氧代四氢噻吩-3-基)哌嗪-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺.

[0277] 

[0278] 以类似于实施例1描述的类似方法制备,但是使用酯1和胺9作为原料。得到标题化合物,为浅黄色固体。^{1}H NMR(400MHz,d_6-DMSO):9.48(1H,s),9.33(1H,t,J=5.6Hz),8.53

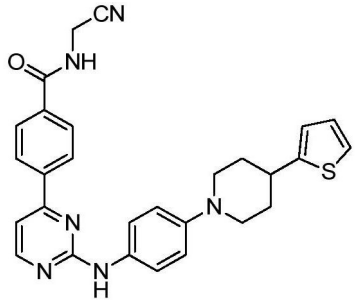
(1H,d,J＝5.2Hz),8.26(2H,d,J＝8.8Hz),8.02(2H,d,J＝8.8Hz),7.65(2H,d,J＝8.8Hz),7.39(1H,d,J＝5.2Hz),6.92(2H,d,J＝9.2Hz),4.32(2H,d,J＝5.6Hz),3.40-3.35(1H,m),3.28-3.25(2H,m),3.12-3.07(5H,m),3.04-2.97(1H,m),2.68-2.58(4H,m),2.36-2.32(1H,m),2.02-1.97(1H,m).ESI-MS:532.08$(M+H)^+$.UPLC t_{ret}:2.52min.

[0279] 实施例10:制备N-(氰基甲基)-4-(2-((4-(4-(2,5-二氧代吡咯烷-1-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺.

[0280] 

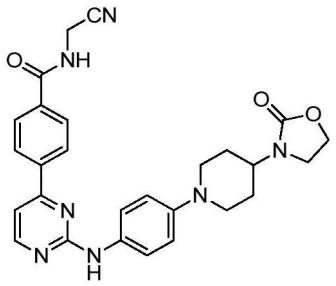
[0281] 以类似于实施例1描述的类似方法制备,但是使用酯1和胺10作为原料。得到标题化合物,为黄色固体。^{1}H NMR(400MHz,d_6-DMSO):9.49(1H,s),9.34(1H,t,J＝5.6Hz),8.53(1H,d,J＝5.2Hz),8.26(2H,d,J＝8.8Hz),8.02(2H,d,J＝8.8Hz),7.63(2H,d,J＝5.2Hz),7.40(1H,d,J＝5.2Hz),6.93(2H,d,J＝9.2Hz),4.35(2H,d,J＝5.6Hz),3.99(1H,m),3.68(2H,m),2.63-2.69(2H,m),2.52(4H,s),2.32-2.43(2H,m),1.56-1.59(2H,m).ESI-MS:510.35$(M+H)^+$.

[0282] 实施例11:制备N-(氰基甲基)-4-(2-((4-(4-(噻吩-2-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺.

[0283] 

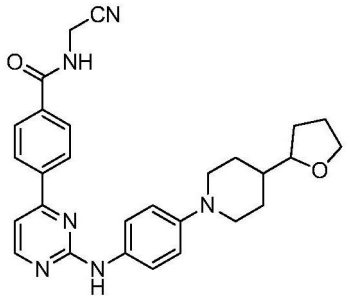
[0284] 以类似于实施例1描述的类似方法制备,但是使用酯1和胺11作为原料。得到标题化合物,为棕色固体。^{1}H NMR(400MHz,d_6-DMSO):9.49(1H,s),9.34(1H,t,J＝5.6Hz),8.54(1H,d,J＝5.2Hz),8.27(2H,d,J＝8.4Hz),8.02(2H,d,J＝8.4Hz),7.65(2H,d,J＝9.2Hz),7.40(1H,d,J＝5.2Hz),7.35(1H,d,J＝5.2Hz),6.98-6.93(4H,m),4.36(2H,d,J＝5.2Hz),3.70(2H,d,J＝12.4Hz),3.11-2.97(1H,m),),2.77-2.72(2H,m),2.07-2.03(2H,d,J＝12.8Hz),1.77-1.73(2H,m).ESI-MS:495.25$(M+H)^+$.UPLC t_{ret}:3.39min.

[0285] 实施例12:制备N-(氰基甲基)-4-(2-((4-(4-(2-氧代噁唑烷-3-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺.

[0286] 

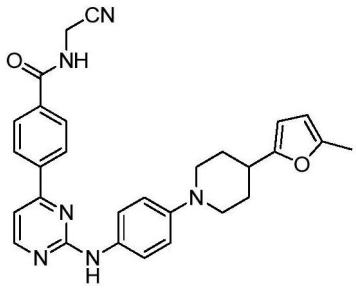
[0287] 以类似于实施例1描述的类似方法制备，但是使用酯1和胺12作为原料。得到标题化合物，为浅黄色固体。^{1}H NMR(400MHz,d_6-DMSO):10.04(1H,s),9.41(1H,t,J＝5.2Hz),8.64(1H,d,J＝5.2Hz),8.28(2H,d,J＝8.8Hz),8.03(2H,d,J＝8.4Hz),7.65(2H,d,J＝9.2Hz),7.40(1H,d,J＝5.2Hz),6.96(2H,d,J＝9.2Hz),4.35(2H,d,J＝5.2Hz),4.26(2H,t,J＝6.8Hz),3.71-3.63(3H,m),3.53(2H,t,J＝6.8Hz),2.73-2.67(2H,m),1.80-1.74(4H,m).ESI-MS:498.30$(M+H)^+$.UPLC t_{ret}:2.58min.

[0288] 实施例13:制备N-(氰基甲基)-4-(2-((4-(4-(四氢呋喃-2-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺.

[0289] 

[0290] 以类似于实施例1描述的类似方法制备，但是使用酯1和胺13作为原料。得到标题化合物，为浅黄色固体。^{1}H NMR(400MHz,d_6-DMSO):9.46(1H,s),9.35(1H,t,J＝5.6Hz),8.53(1H,d,J＝5.2Hz),8.26(2H,d,J＝8.4Hz),8.02(2H,d,J＝8.4Hz),7.63(2H,d,J＝9.2Hz),7.40(1H,d,J＝5.2Hz),6.92(2H,d,J＝8.8Hz),4.35(2H,d,J＝7.2Hz),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}:2.88min.

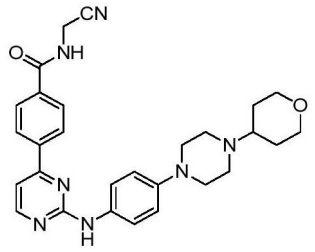
[0291] 实施例14:制备N-(氰基甲基)-4-(2-((4-(4-(5-甲基呋喃-2-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺.

[0292] 

[0293] 以类似于实施例1描述的类似方法制备，但是使用酯1和胺14作为原料。得到标题化合物，为浅黄色固体。^{1}H NMR(400MHz,d_6-DMSO):9.48(1H,s),9.34(1H,t,J＝4.8Hz),8.54(1H,d,J＝5.2Hz),8.27(2H,d,J＝8.4Hz),8.03(2H,d,J＝8.4Hz),7.64(2H,d,J＝8.8Hz),

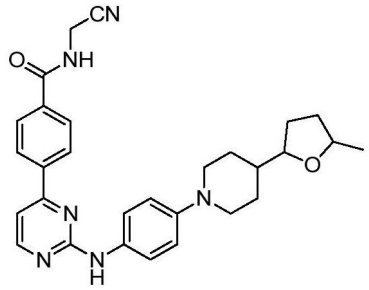
7.40(1H,d,J＝5.2Hz),6.95(2H,d,J＝9.2Hz),5.96(2H,t,J＝2.8Hz),4.36(2H,d,J＝5.6Hz),2.67-2.60(2H,m),2.76-2.67(3H,m),2.33(3H,s),2.01-1.98(2H,m),1.72-1.65(2H,m).ESI-MS:493.20$(M+H)^+$.UPLC t_{ret}:3.42min.

[0294] 实施例15:制备N-(氰基甲基)-4-(2-((4-(4-(四氢-2H-吡喃-4-基)哌嗪-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺.

[0295] 

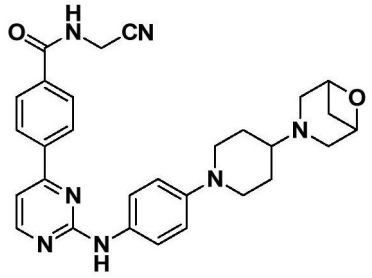
[0296] 以类似于实施例1描述的类似方法制备,但是使用酯1和胺15作为原料。得到标题化合物,为浅黄色固体。^{1}H NMR(400MHz,d_6-DMSO):9.46(s,1H),9.33(1H,t,J＝5.6Hz),8.52(1H,d,J＝4.8Hz),8.25(2H,d,J＝8.4Hz),8.01(2H,d,J＝8.4Hz),7.63(2H,d,J＝8.8Hz),7.39(1H,d,J＝5.2Hz),6.92(2H,d,J＝9.2Hz),4.34(2H,d,J＝5.6Hz),3.88-3.91(2H,m),3.29(2H,m),3.07(4H,m),2.63(4H,m)2.49(1H,m),1.73(2H,m),1.41(2H,m).ESI-MS:498.25$(M+H)^+$.UPLC t_{ret}:2.52min.

[0297] 实施例16:制备N-(氰基甲基)-4-(2-((4-(4-(5-甲基四氢呋喃-2-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺.

[0298] 

[0299] 以类似于实施例1描述的类似方法制备,但是使用酯1和胺16作为原料。得到标题化合物,为浅黄色固体。^{1}H NMR(400MHz,d_6-DMSO):9.44(1H,s),9.32(1H,bs),8.51(1H,d,J＝4.8Hz),8.24(2H,d,J＝8Hz),7.9(2H,d,J＝8.4Hz),7.61(2H,d,J＝8.8Hz),7.38(1H,d,J＝6Hz),6.90(2H,d,J＝8.4Hz),4.34(2H,d,J＝5.2Hz),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}:3.10min.

[0300] 实施例17:制备4-(2-((4-(4-(6-氧杂-3-氮杂双环[3.1.1]庚-3-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)-N-(氰基甲基)苯甲酰胺.

[0301] 

[0302] 步骤I:制备4-(2-((4-(4-(6-氧杂-3-氮杂双环[3.1.1]庚-3-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酸乙基酯。

[0303] 4-(2-氯嘧啶-4-基)苯甲酸乙酯[4.37g,16.64mmol]置于圆底烧瓶中,接着添加DMA[60mL]。于25℃在N_2气氛下向其中添加4-(4-(6-氧杂-3-氮杂双环[3.1.1]庚-3-基)哌啶-1-基)苯胺(胺17)[3.5g,12.80mmol]、碳酸铯[6.26g,19.20mmol]、BINAP[1.19g,1.92mmol]和双(三苯基)膦Pd(II)二氯化物[1.34g,1.92mmol]。将混合物加热90℃保持16h。反应完成后,混合物在水中淬灭,化合物以乙酸乙酯淬灭(50mL X 4)。合并有机层并以水和盐水溶液洗涤。有机层经Na_2SO_4干燥,过滤并减压浓缩得到所需的产物,为浅黄色固体。标题化合物通过光谱分析表征。ESI-MS:500.30$(M+H)^+$。

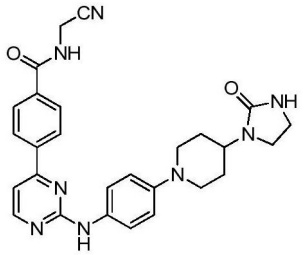
[0304] 步骤II:制备4-(2-((4-(4-(6-氧杂-3-氮杂双环[3.1.1]庚-3-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酸.

[0305] 4-(2-((4-(4-(6-氧杂-3-氮杂双环[3.1.1]庚-3-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酸通过根据实施例1步骤II中描述的方法使用4-(2-((4-(4-(6-氧杂-3-氮杂双环[3.1.1]庚-3-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酸乙酯制备。

[0306] 步骤III.制备4-(2-((4-(4-(6-氧杂-3-氮杂双环[3.1.1]庚-3-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)-N-(氰基甲基)苯甲酰胺.

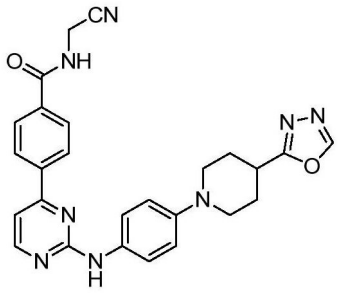
[0307] 4-(2-((4-(4-(6-氧杂-3-氮杂双环[3.1.1]庚-3-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)-N-(氰基甲基)苯甲酰胺通过根据实施例1步骤II中描述的方法使用4-(2-((4-(4-(6-氧杂-3-氮杂双环[3.1.1]庚-3-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酸合成。得到标题化合物,为绿色固体。^{1}H NMR(400MHz,d_6-DMSO):9.47(s,1H),9.33(1H,t,J=5.2Hz),8.53(1H,d,J=5.2Hz),8.26(2H,d,J=8.8Hz),8.32(2H,d,J=8.8Hz),7.63(2H,d,J=9.2Hz),7.39(1H,d,J=5.2Hz),6.93(2H,d,J=9.2Hz),4.44-4.43(2H,m),4.35(2H,d,J=5.2Hz),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}:2.35min.

[0308] 实施例18:制备N-(氰基甲基)-4-(2-((4-(4-(2-氧代咪唑啉-1-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺.

[0309] 

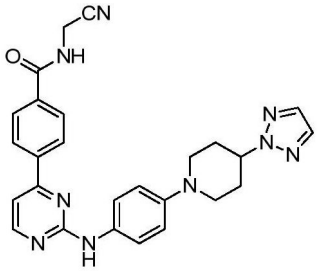
[0310] 以类似于实施例17描述的类似方法制备,但是使用酯1和胺18作为原料。得到标题化合物,为浅黄色固体。^{1}H NMR(400MHz,d_6-DMSO):9.47(1H,s),9.43(1H,bs),8.53(1H,d,J=4.8Hz),8.26(2H,d,J=8.0Hz),8.02(2H,d,J=8.0Hz)7.64(2H,d,J=8.8Hz),7.40(1H,d,J=4.8Hz),6.94(2H,d,J=8.4Hz)6.26(1H,s),4.36(2H,d,J=4.8Hz),3.58-3.68(3H,m),3.21-3.23(2H,m),2.64-2.70(2H,m),1.70-1.78(2H,m),1.61-1.64(2H,m).ESI-MS:497.40$(M+H)^+$.UPLC t_{ret}:2.48min.

[0311] 实施例19:制备4-(2-((4-(4-(1,3,4-噁二唑-2-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)-N-(氰基甲基)苯甲酰胺.

[0312] 

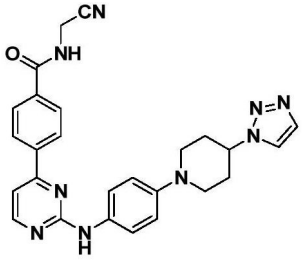
[0313] 以类似于实施例1描述的类似方法制备,但是使用酯1和胺19作为原料。得到标题化合物,为浅黄色固体。^{1}H NMR(400MHz,d_6-DMSO):9.47(1H,s),9.34(1H,t,J=5.2Hz),9.16(1H,s),8.53(1H,d,J=5.2Hz),8.26(2H,d,J=8.4Hz),8.02(2H,d,J=8.4Hz),7.44(2H,d,J=8.8Hz),7.40(1H,d,J=5.2Hz),6.98(2H,d,J=5.2Hz),4.35(2H,d,J=5.2Hz),3.63-3.60(2H,s),3.14-3.19(1H,m),2.83-2.80(2H,m),2.13-2.19(2H,m),1.88-1.85(2H,m).ESI-MS:481.05$(M+H)^+$.UPLC t_{ret}:2.52min.

[0314] 实施例20:制备4-(2-((4-(4-(2H-1,2,3-三唑-2-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)-N-(氰基甲基)苯甲酰胺.

[0315] 

[0316] 以类似于实施例17描述的类似方法制备,但是使用酯1和胺20作为原料。得到标题化合物,为浅黄色固体。^{1}H NMR(400MHz,d_6-DMSO):9.50(1H,s),9.34(1H,t,J=5.6Hz),8.55(1H,d,J=5.2Hz),8.28(2H,d,J=8.4Hz),8.03(2H,d,J=8.8Hz),7.80(2H,s),7.67(2H,d,J=9.2Hz),7.41(1H,d,J=5.2Hz),7.00(2H,d,J=9.2Hz),4.70(1H,m),4.36(2H,d,J=5.2Hz),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}:2.85min.

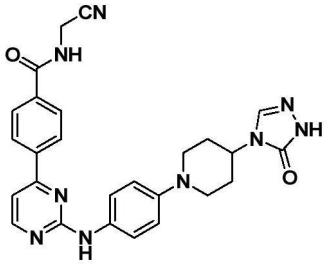
[0317] 实施例21:制备4-(2-((4-(4-(1H-1,2,3-三唑-1-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)-N-(氰基甲基)苯甲酰胺.

[0318] 

[0319] 以类似于实施例1描述的类似方法制备,但是使用酯1和胺21作为原料。得到标题化合物,为浅黄色固体。^{1}H NMR(400MHz,d_6-DMSO):9.5(1H,s),9.34(1H,t,J=5.2Hz),8.55(1H,d,J=5.2Hz),8.28(2H,d,J=8.4Hz),8.27(1H,s),8.03(2H,d,J=8.8Hz),7.80(1H,

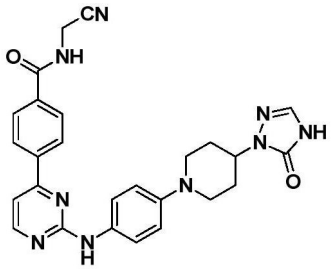
s),7.67(2H,d,J＝9.2Hz),7.41(1H,d,J＝5.2Hz),7.00(2H,d,J＝9.2Hz),4.70-4.67(1H,m),4.36(2H,d,J＝5.2Hz),3.75-3.72(2H,m),2.88-2.94(2H,m),2.11-2.18(4H,m).ESI-MS:479.85$(M+H)^+$.UPLC t_{ret}:2.85min.

[0320] 实施例22:制备N-(氰基甲基)-4-(2-((4-(4-(5-氧代-1H-1,2,4-三唑-4(5H)-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺.

[0321] 

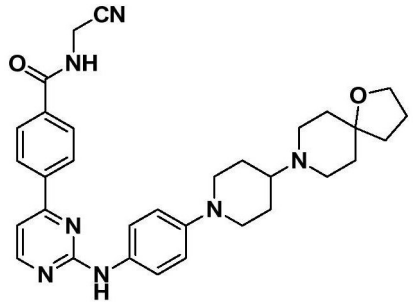
[0322] 以类似于实施例1描述的类似方法制备,但是使用酯1和胺22作为原料。得到标题化合物,为黄色固体。^{1}H NMR(400MHz,d_6-DMSO):13.28(1H,s)9.48(1H,s),9.33(1H,t,J＝5.2Hz),8.54(1H,d,J＝5.2Hz),8.27-8.22(3H,m)8.00(2H,d,J＝8.8Hz),7.64(2H,d,J＝8.8Hz),7.40(1H,d,J＝5.2Hz),6.96(2H,d,J＝8.8Hz),4.74-4.73(1H,m),4.35(2H,d,J＝8.8Hz),3.42-3.31(2H,m),3.00-2.95(2H,m),2.10-2.08(2H,m),1.80-1.77(2H,m).ESI-MS:518.18$(M+Na)^+$.UPLC t_{ret}:2.49min

[0323] 实施例23:制备N-(氰基甲基)-4-(2-((4-(4-(5-氧代-4,5-二氢-1H-1,2,4-三唑-1-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺.

[0324] 

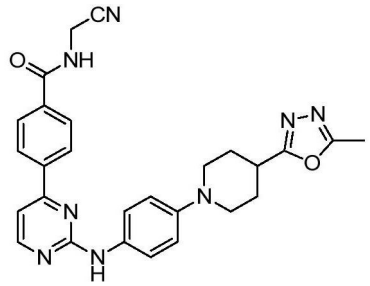
[0325] 以类似于实施例1描述的类似方法制备,但是使用酯1和胺23作为原料。得到标题化合物,为浅黄色固体。^{1}H NMR(400MHz,d_6-DMSO):11.65(1H,s)9.50(1H,s),9.34(1H,t,J＝5.2Hz),8.54(1H,d,J＝5.2Hz),8.27-8.22(3H,m)8.00(2H,d,J＝8.8Hz),7.64(2H,d,J＝8.8Hz),7.4(1H,d,J＝5.2Hz),6.96(2H,d,J＝8.8Hz),4.74-4.73(1H,m),4.35(2H,d,J＝8.8Hz),3.42-3.31(2H,m),3.00-2.95(2H,m),2.10-2.08(2H,m),1.80-1.77(2H,m).ESI-MS:518.18$(M+Na)^+$.UPLC t_{ret}:2.49min.

[0326] 实施例24:制备4-(2-((4-(4-(1-氧杂-8-氮杂螺[4.5]癸-8-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)-N-(氰基甲基)苯甲酰胺.

[0327] 

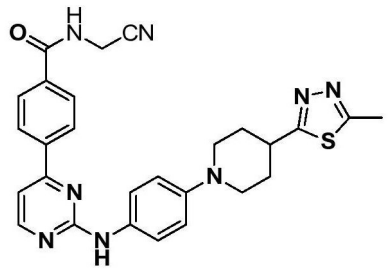
[0328] 以类似于实施例1描述的类似方法制备，但是使用酯1和胺24作为原料。得到标题化合物，为浅黄色固体。^{1}H NMR(400MHz,d_6-DMSO):9.44(1H,s),9.32(1H,t,J＝5.2Hz),8.51(1H,d,J＝5.2Hz),8.25(2H,d,J＝8.4Hz),7.99(2H,d,J＝8.4Hz),7.62(2H,d,J＝8.8Hz),7.39(1H,d,J＝5.2Hz),6.91(2H,d,J＝8.8Hz),4.33(2H,t,J＝5.2Hz),3.68-3.65(4H,m)2.57-2.48(6H,m),1.81-1.79(4H,m),1.61-1.59(3H,m),1.51-1.49(6H,m).ESI-MS:552.20$(M+H)^+$.UPLC t_{ret}:2.63min.

[0329] 实施例25：制备N-(氰基甲基)-4-(2-((4-(4-(5-甲基-1,3,4-噁二唑-2-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺.

[0330] 

[0331] 以类似于实施例17描述的类似方法制备，但是使用酯1和胺25作为原料。得到标题化合物，为浅黄色固体。^{1}H NMR(400MHz,d_6-DMSO):9.48(s,1H);9.33(1H,t,J＝5.2Hz),8.53(1H,d,J＝5.2Hz),8.26(2H,d,J＝8.0Hz),8.00(2H,d,J＝8.4Hz),7.65(2H,d,J＝8.8Hz),7.40(1H,d,J＝5.2Hz),6.95(2H,d,J＝8.8Hz),4.35(2H,d,J＝5.6Hz),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}:2.65min.

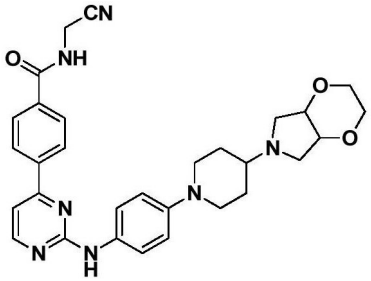
[0332] 实施例26：制备N-(氰基甲基)-4-(2-((4-(4-(5-甲基-1,3,4-噻二唑-2-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺.

[0333] 

[0334] 以类似于实施例17描述的类似方法制备，但是使用酯1和胺26作为原料。得到标题化合物，为浅黄色固体。^{1}H NMR(400MHz,d_6-DMSO):9.49(1H,s),9.42(1H,t,J＝5.2Hz),8.52(1H,d,J＝5.2Hz),8.25(2H,d,J＝8.4Hz),8.01(2H,d,J＝8.4Hz),7.64(2H,d,J＝8.4Hz),7.39(1H,d,J＝5.2Hz),6.95(2H,d,J＝9.2Hz),4.34(2H,d,J＝5.2Hz),3.65(1H,d,J＝

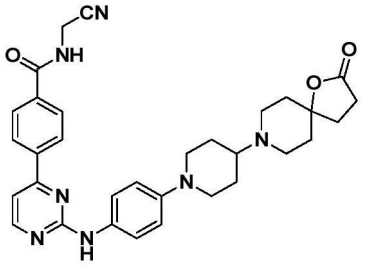
12.4Hz),3.29-3.26(1H,m),2.79(2H,t,J＝10hz),2.69(3H,s),2.14-2.11(2H,m),1.85-1.82(2H,m).ESI-MS:511.50(M+H)$^+$.UPLC t_{ret}:2.71min.

[0335] 实施例27:制备N-(氰基甲基)-4-(2-((4-(4-(四氢-2H-[1,4]二氧杂环己二烯并[2,3-c]吡咯-6(3H)-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺.

[0336] 

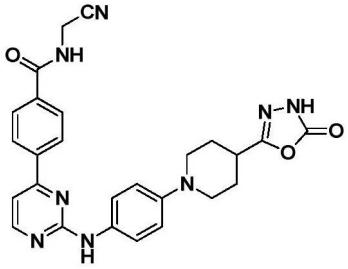
[0337] 以类似于实施例1描述的类似方法制备,但是使用酯1和胺27作为原料。得到标题化合物,为浅黄色固体。^{1}H NMR(400MHz,d_6-DMSO):9.46(1H,s),9.33(1H,t,J＝5.6Hz),8.52(1H,d,J＝5.2Hz),8.25(2H,d,J＝8.4Hz),8.01(2H,d,J＝8.8Hz),7.61(2H,d,J＝9.2Hz),7.39(1H,d,J＝5.2Hz),6.90(2H,d,J＝9.2Hz),4.34(2H,d,J＝5.6Hz),3.91-3.97(2H,m),3.68-2.65(2H,m),3.45-2.57(4H,m),2.87-2.84(2H,m),2.66-2.64(2H,m),2.63-2.53(3H,m),1.90-1.88(2H,m),1.55-1.53(2H,m).ESI-MS:540.35(M+H)$^+$.UPLC t_{ret}:2.46min.

[0338] 实施例28:制备N-(氰基甲基)-4-(2-((4-(4-(2-氧代-1-氧杂-8-氮杂螺[4.5]癸-8-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺.

[0339] 

[0340] 以类似于实施例1描述的类似方法制备,但是使用酯1和胺28作为原料。得到标题化合物,为浅黄色固体。^{1}H NMR(400MHz,d_6-DMSO):9.46(1H,s),9.33(1H,t,J＝5.2Hz),8.52(1H,d,J＝5.2Hz),8.26(2H,d,J＝8.4Hz),8.00(2H,d,J＝8.4Hz),7.61(2H,d,J＝9.2),7.38(1H,d,J＝5.2Hz),6.80(2H,d,J＝9.2Hz),4.34(2H,d,J＝5.6Hz),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}:2.50min.

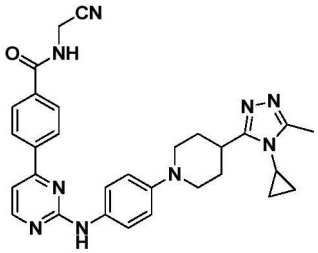
[0341] 实施例29:制备N-(氰基甲基)-4-(2-((4-(4-(5-氧代-4,5-二氢-1,3,4-噁二唑-2-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺.

[0342] 

[0343] 以类似于实施例17描述的类似方法制备,但是使用酯1和胺29作为原料。得到标题

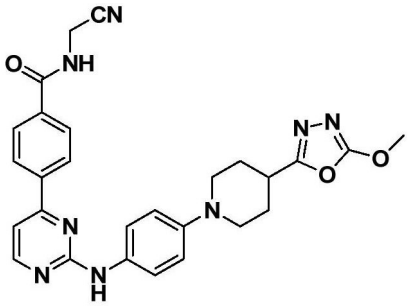
化合物，为浅黄色固体。^{1}H NMR(400MHz,d_6-DMSO):12.10(1H,s),9.48(1H,s),9.33(1H,t,J＝5.6Hz),8.53(1H,d,J＝5.2Hz),8.26(2H,d,J＝8.0Hz),8.02(2H,d,J＝8.8Hz),7.64(2H,d,J＝9.2Hz),7.40(1H,d,J＝5.2Hz),6.95(2H,d,J＝9.2Hz),4.35(2H,d,J＝5.2Hz),3.60-3.57(2H,m),2.80-2.74(3H,m),2.00-1.98(2H,m),1.74-1.71(2H,m).ESI-MS:497.10(M+H)$^+$.UPLC t_{ret}:2.67min.

[0344] 实施例30：制备N-(氰基甲基)-4-(2-((4-(4-(4-环丙基-5-甲基-4H-1,2,4-三唑-3-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺.

[0345] 

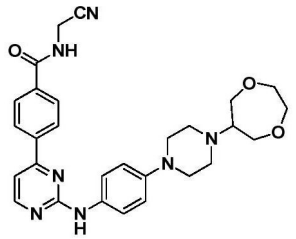
[0346] 以类似于实施例1描述的类似方法制备，但是使用酯1和胺30作为原料。得到标题化合物，为浅黄色固体。^{1}H NMR(400MHz,d_6-DMSO):9.48(1H,s),9.33(1H,t,J＝5.2Hz),8.53(1H,d,J＝5.2Hz),8.26(2H,d,J＝8.4Hz);8.02(2H,d,J＝8.8Hz),7.65(2H,d,J＝9.2Hz),7.40(1H,d,J＝5.2Hz),6.97(2H,d,J＝9.2Hz)4.35(2H,d,J＝5.6Hz),3.72-3.69(2H,m),3.17-3.13(1H,m);3.00-3.02(1H,m),2.77-2.66(2H,m),2.33(3H,s),2.04-2.01(2H,m),1.86-1.84(2H,m),1.10-1.09(2H,m),1.0-0.98(2H,m).ESI-MS:543.30(M+H)$^+$.UPLC t_{ret}:2.59min.

[0347] 实施例31：制备N-(氰基甲基)-4-(2-((4-(4-(5-甲氧基-1,3,4-噁二唑-2-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺.

[0348] 

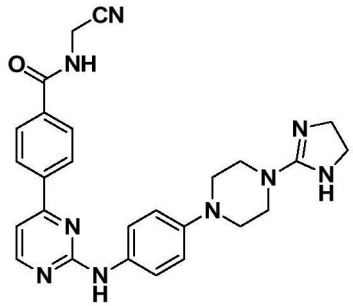
[0349] 以类似于实施例1描述的类似方法制备，但是使用酯1和胺31作为原料。得到标题化合物，为浅黄色固体。^{1}H NMR(400MHz,d_6-DMSO):9.48(1H,s),9.33(1H,t,J＝5.6Hz),8.53(1H,d,J＝5.2Hz),8.26(2H,d,J＝8.4Hz),8.02(2H,d,J＝8.8Hz),7.64(2H,d,J＝8.8Hz),7.40(1H,d,J＝5.2Hz),6.94(2H,d,J＝9.2Hz),4.35(2H,d,J＝5.2Hz),3.62-3.58(2H,m),3.28(3H,s),2.83-2.66(3H,m)2.01-1.98(2H,m)1.74-1.72(2H,m).ESI-MS:511.25(M+H)$^+$.UPLC t_{ret}:2.83min.

[0350] 实施例32：制备4-(2-((4-(4-(1,4-二氧杂萘-6-基)哌嗪-1-基)苯基)氨基)嘧啶-4-基)-N-(氰基甲基)苯甲酰胺.

[0351] 

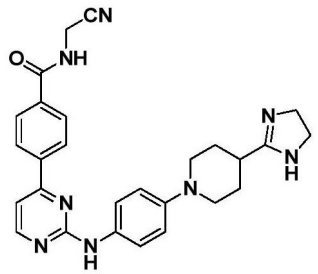
[0352] 以类似于实施例1描述的类似方法制备，但是使用酯1和胺32作为原料。得到标题化合物，为浅黄色固体。^{1}H NMR(400MHz,d_6-DMSO):9.47(1H,s),9.32(1H,t,J＝5.2Hz),8.52(1H,d,J＝5.2Hz),8.25(2H,d,J＝8.4Hz),8.00(2H,d,J＝8Hz),7.62(2H,d,J＝8.8Hz),7.38(1H,d,J＝5.2Hz),6.90(2H,d,J＝9.2Hz),4.34(2H,d,J＝5.2Hz),3.82-3.80(4H,m),3.56-3.60(4H,m),3.02-3.09(4H,m),2.71-2.73(4H,m.ESI-MS:514.15$(M+H)^+$.UPLC t_{ret}:2.66min.

[0353] 实施例33:制备N-(氰基甲基)-4-(2-((4-(4-(4,5-二氢-1H-咪唑-2-基)哌嗪-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺.

[0354] 

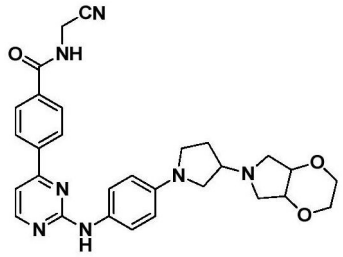
[0355] 以类似于实施例1描述的类似方法制备，但是使用酯1和胺33作为原料。得到标题化合物，为浅黄色固体。^{1}H NMR(400MHz,d_6-DMSO):9.52(1H,s),9.37(1H,t,J＝4Hz),8.54-8.53(3H,m),8.26(2H,d,J＝8.4Hz),8.02(2H,d,J＝8.4Hz),7.68(2H,d,J＝8.8Hz),7.41(1H,d,J＝5.2Hz),7.09-7.07(2H,m),4.34(2H,d,J＝5.6Hz),3.66(4H,s),3.59-3.57(4H,m),3.19-3.15(4H,m).ESI-MS:482.05$(M+H)^+$.UPLC t_{ret}:2.60min.

[0356] 实施例34:制备N-(氰基甲基)-4-(2-((4-(4-(4,5-二氢-1H-咪唑-2-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺.

[0357] 

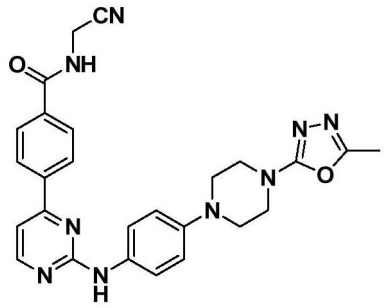
[0358] 以类似于实施例1描述的类似方法制备，但是使用酯1和胺34作为原料。得到标题化合物，为浅黄色固体。^{1}H NMR(400MHz,d_6-DMSO):9.48(1H,s),9.33(1H,t,J＝5.2Hz),8.53(1H,d,J＝5.2Hz),8.26(2H,d,J＝8.0Hz),8.00(d,J＝8.4Hz),7.65(2H,d,J＝8.8Hz),7.40(1H,d,J＝5.2Hz),6.95(2H,d,J＝8.8Hz),4.35(2H,d,J＝5.6Hz),4.35(2H,m),3.63-3.59(2H,m),3.09-3.07(2H,m),2.85-2.80(2H,m),2.49(3H,s),2.09-2.06(2H,m),1.85-1.82(2H,m).ESI-MS:495.25$(M+H)^+$.UPLC t_{ret}:2.28min.

[0359] 实施例35:制备N-(氰基甲基)-4-(2-((4-(3-(四氢-2H-[1,4]二氧杂环己二烯并[2,3-c]吡咯-6(3H)-基)吡咯烷-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺.

[0360] 

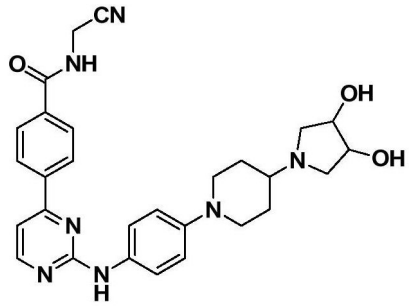
[0361] 以类似于实施例1描述的类似方法制备,但是使用酯1和胺35作为原料。得到标题化合物,为浅黄色固体。^{1}H NMR(400MHz,d_6-DMSO):9.33-9.29(2H,m),8.48(1H,d,J=4.8Hz),8.25(1H,d,J=8.4Hz),8.05(2H,d,J=8.8Hz),7.55(2H,d,J=8.8Hz),7.34(1H,d,J=5.2Hz),6.51(2H,d,J=8.8Hz),4.34(2H,d,J=5.2Hz),4.01-4.03(2H,m),3.71-3.72(2H,m),3.62-3.57(1H,m),3.45-3.47(1H,m),3.22-3.19(2H,m),3.01-3.08(2H,m),2.94-2.90(2H,m),2.86-2.89(2H,m),2.09-2.10(2H,m),1.82-1.90(1H,m).ESI-MS:526.35(M+H)$^+$.UPLC t_{ret}:2.60min.

[0362] 实施例36:制备N-(氰基甲基)-4-(2-((4-(4-(5-甲基-1,3,4-噁二唑-2-基)哌嗪-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺.

[0363] 

[0364] 以类似于实施例1描述的类似方法制备,但是使用酯1和胺36作为原料。得到标题化合物,为浅黄色固体。^{1}H NMR(400MHz,d_6-DMSO):9.50(1H,s),9.32(1H,t,J=5.2Hz),8.53(1H,d,J=5.2Hz),8.25(2H,d,J=8.4Hz),8.01(2H,d,J=8.4Hz),7.67(2H,d,J=8.4Hz),7.40(1H,d,J=5.2Hz),6.95(2H,d,J=9.2Hz),4.34(2H,d,J=5.2Hz),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}:2.93min.

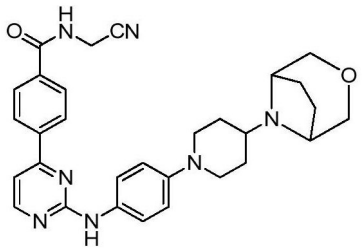
[0365] 实施例37:制备N-(氰基甲基)-4-(2-((4-(4-(3,4-二羟基吡咯烷-1-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺.

[0366] 

[0367] 以类似于实施例1描述的类似方法制备,但是使用酯1和胺37作为原料。得到标题化合物,为浅黄色固体。^{1}H NMR(400MHz,d_6-DMSO):9.54(1H,s),9.40(1H,t,J=5.2Hz),8.54

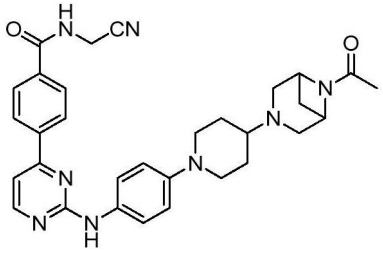
(1H,d,J＝5.2Hz),8.26(2H,d,J＝8.4Hz),8.04(2H,d,J＝8.4Hz),7.69(2H,d,J＝8Hz),7.42(1H,d,J＝5.2Hz),7.09-7.07(2H,m),4.34(2H,d,J＝5.2Hz),4.22-4.01(2H,m),3.73-3.65(6H,m),2.8-2.69(2H,m),2.13-2.11(2H,m),1.63(1H,m),1.9-1.68(2H,m),1.28-1.22(2H,m).ESI-MS:514.15$(M+H)^+$.UPLC t_{ret}:2.34min.

[0368] 实施例38:制备4-(2-((4-(4-(8-氧杂-3-氮杂双环[3.2.1]辛-3-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)-N-(氰基甲基)苯甲酰胺.

[0369] 

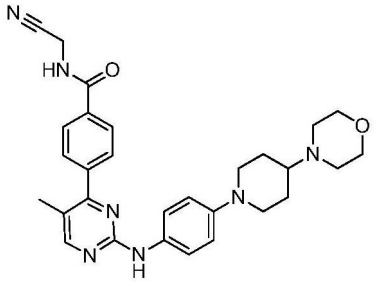
[0370] 以类似于实施例17描述的类似方法制备,但是使用酯1和胺38作为原料。得到标题化合物,为浅黄色固体。^1H NMR(400MHz,d_6-DMSO):9.48(1H,s),9.36(1H,t,J＝5.2Hz),8.53(1H,d,J＝5.2Hz),8.27(2H,d,J＝8.4Hz),8.03(2H,d,J＝8.4Hz),7.66(2H,d,J＝8.8Hz),7.41(1H,d,J＝4.8Hz),6.98(2H,d,J＝9.2Hz),4.35(2H,d,J＝5.2Hz),4.20(2H,m),3.89(1H,m),3.80(2H,m),3.71(2H,m),2.66(1H,m)2.03-1.96(4H,m),2.01(3H,m),1.68(2H,m).ESI-MS:524.25$(M+H)^+$.UPLC t_{ret}:2.48min.

[0371] 实施例39:制备4-(2-((4-(4-(6-乙酰基-3,6-二氮杂双环[3.1.1]庚-3-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)-N-(氰基甲基)苯甲酰胺.

[0372] 

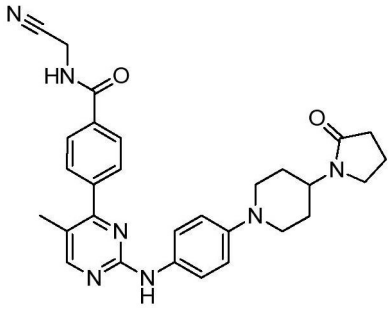
[0373] 以类似于实施例17描述的类似方法制备,但是使用酯1和胺39作为原料。得到标题化合物,为浅黄色固体。^1H NMR(400MHz,d_6-DMSO):9.44(s,1H),9.32(t,1H,J＝5.2Hz),8.52(d,1H,J＝5.2Hz),8.25(d,2H,J＝8.4Hz),8.01(d,2H,J＝8.4Hz),7.61(d,2H,J＝9.2Hz),7.38(d,1H,J＝5.2Hz),6.90(d,2H,J＝9.2Hz),4.34(d,2H,J＝5.6Hz),3.73-3.76(m,1H),3.61-3.62(m,2H),3.40-3.49(m,4H),3.34-3.38(m,1H),2.69-2.78(m,3H),2.31-2.34(m,1H),2.00(s,3H),1.70-1.80(m,2H),1.22-1.38(m,3H).ESI-MS:551.25$(M+H)^+$.UPLC t_{ret}:2.38min.

[0374] 实施例40:制备N-(氰基甲基)-4-(5-甲基-2-((4-(4-吗啉代哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺.

[0375] 

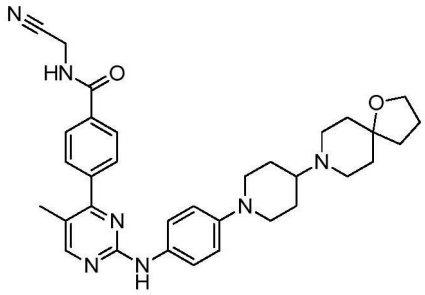
[0376] 以类似于实施例1描述的类似方法制备，但是使用酯2和胺3作为原料。得到标题化合物，为浅黄色固体。^{1}H NMR(400MHz,d_6-DMSO):9.30(t,2H,J＝5.2Hz),8.36(s,1H),7.98(d,2H,J＝8.4Hz),7.77(d,2H,J＝8.0Hz),7.57(d,2H,J＝8.8Hz),6.85(d,2H,J＝8.8Hz),4.34(d,2H,J＝5.6Hz),3.57-3.60(m,6H),2.54-2.59(m,2H),2.19(s,3H),1.82-1.85(m,2H),1.47-1.49(m,2H).,ESI-MS:512.25$(M+H)^+$.UPLC t_{ret}:2.50min.

[0377] 实施例41：制备N-(氰基甲基)-4-(5-甲基-2-((4-(4-(2-氧代吡咯烷-1-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺.

[0378] 

[0379] 以类似于实施例1描述的类似方法制备，但是使用酯2和胺1作为原料。得到标题化合物，为浅黄色固体。^{1}H NMR(400MHz,d_6-DMSO):9.32(bs,2H),8.38(bs,1H),7.99(d,2H,J＝7.6Hz),7.77(d,2H,J＝8.0Hz),7.59(d,2H,J＝7.6Hz),6.88(d,2H,J＝8.8Hz),4.34(d,2H,J＝4.8Hz),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}:2.71min.

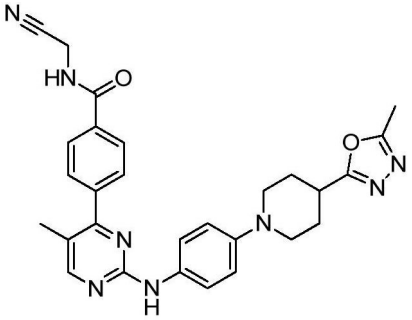
[0380] 实施例42：制备4-(2-((4-(4-(1-氧杂-8-氮杂螺[4.5]癸-8-基)哌啶-1-基)苯基)氨基)-5-甲基嘧啶-4-基)-N-(氰基甲基)苯甲酰胺.

[0381] 

[0382] 以类似于实施例1描述的类似方法制备，但是使用酯2和胺24作为原料。得到标题化合物，为浅黄色固体。^{1}H NMR(400MHz,d_6-DMSO):9.43(1H,s),9.30(1H,t,J＝5.6Hz),8.37(1H,s),8.00(2H,d,J＝8.4Hz),7.77(2H,d,J＝8.4Hz),7.60(2H,d,J＝9.2Hz),6.89(2H,d,J＝9.2Hz),4.35(2H,d,J＝5.6Hz),3.77-3.70(4H,m),3.42-3.40(2H,m),3.06-3.03(2H,

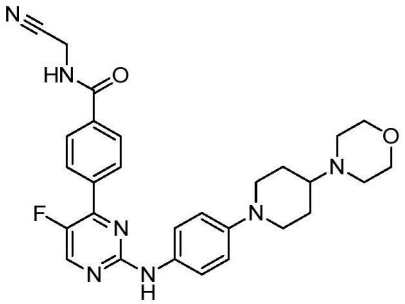
m),2.66-2.59(2H,m),2.18(3H,s),2.11-2.08(2H,m),1.91-1.85(2H,m),1.80-1.69(6H,m).ESI-MS:566.22(M+H)$^+$.UPLC t_{ret}:2.80min.

[0383] 实施例43:制备N-(氰基甲基)-4-(5-甲基-2-((4-(4-(5-甲基-1,3,4-噁二唑-2-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺.

[0384] 

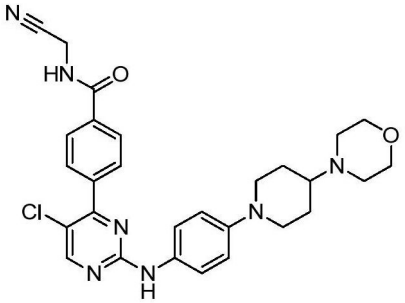
[0385] 以类似于实施例17描述的类似方法制备,但是使用酯2和胺25作为原料。得到标题化合物,为浅黄色固体。^{1}H NMR(400MHz,d_6-DMSO):9.30-9.32(m,2H),8.37(s,1H),7.99(d,2H,J=8.4Hz),7.77(d,2H,J=8.4Hz),7.60(d,2H,J=8.8Hz),6.89(d,2H,J=9.2Hz),4.34(d,2H,J=5.2Hz),3.55-3.58(m,2H),3.06(m,1H),2.75-2.82(m,2H),2.46(s,3H),2.19(s,3H),2.03-2.07(m,2H),1.80-1.83(m,2H).ESI-MS:509.10(M+H)$^+$.UPLC t_{ret}:2.86min.

[0386] 实施例44:制备N-(氰基甲基)-4-(5-氟-2-((4-(4-吗啉代哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺.

[0387] 

[0388] 以类似于实施例1描述的类似方法制备,但是使用酯3和胺3作为原料。得到标题化合物,为浅黄色固体。^{1}H NMR(400MHz,d_6-DMSO):9.30(t,2H,J=5.2Hz),8.36(s,1H),7.98(d,2H,J=8.4Hz),7.77(d,2H,J=8.0Hz),7.57(d,2H,J=8.8Hz),6.85(d,2H,J=8.8Hz),4.34(d,2H,J=5.6Hz),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}:2.50min.

[0389] 实施例45:制备4-(5-氯-2-((4-(4-吗啉代哌啶-1-基)苯基)氨基)嘧啶-4-基)-N-(氰基甲基)苯甲酰胺.

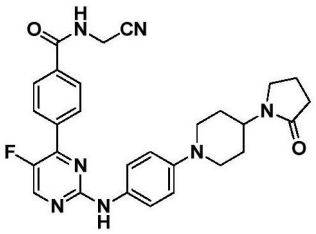
[0390] 

[0391] 以类似于实施例1描述的类似方法制备,但是使用酯4和胺3作为原料。得到标题化

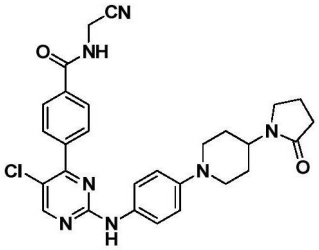
合物，为浅黄色固体。^{1}H NMR(400MHz,d_6-DMSO):9.70(s,1H),9.33(t,1H,J＝5.6Hz),8.57(s,1H),8.00(d,2H,J＝8.4Hz),7.90(d,2H,J＝8.4Hz),7.53(d,2H,J＝8.8Hz),6.88(d,2H,J＝9.2Hz),4.35(d,2H,J＝5.6Hz),3.53-3.63(m,6H),2.56-2.62(m,2H),2.49-2.50(m,4H),2.10-2.23(m,1H),1.83-1.86(m,2H),1.47-1.49(m,2H).ESI-MS:532.20$(M+H)^+$.UPLC t_{ret}:2.75min.

[0392] 下列化合物可以根据上述描述的相同方法进行合成并且被认为包括在本发明的范围内。

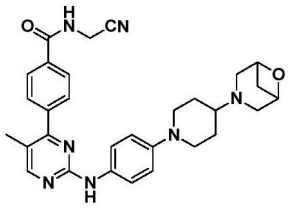
[0393] N-(氰基甲基)-4-(5-氟-2-((4-(4-(2-氧代吡咯烷-1-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺.

[0394] 

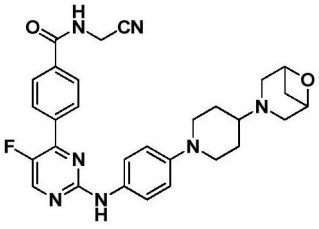
[0395] 4-(5-氯-2-((4-(4-(2-氧代吡咯烷-1-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)-N-(氰基甲基)苯甲酰胺.

[0396] 

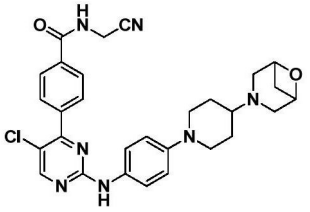
[0397] 4-(2-((4-(4-(6-氧杂-3-氮杂双环[3.1.1]庚-3-基)哌啶-1-基)苯基)氨基)-5-甲基嘧啶-4-基)-N-(氰基甲基)苯甲酰胺.

[0398] 

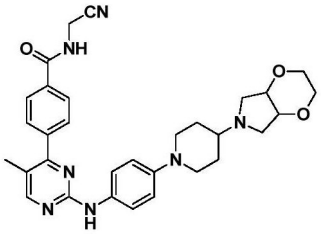
[0399] 4-(2-((4-(4-(6-氧杂-3-氮杂双环[3.1.1]庚-3-基)哌啶-1-基)苯基)氨基)-5-氟嘧啶-4-基)-N-(氰基甲基)苯甲酰胺.

[0400] 

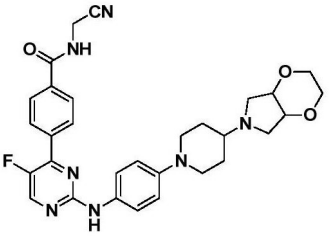
[0401] 4-(2-((4-(4-(6-氧杂-3-氮杂双环[3.1.1]庚-3-基)哌啶-1-基)苯基)氨基)-5-氯嘧啶-4-基)-N-(氰基甲基)苯甲酰胺.

[0402] 

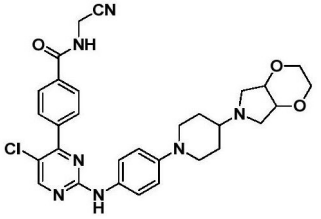
[0403] N-(氰基甲基)-4-(5-甲基-2-((4-(4-(四氢-2H-[1,4]二氧杂环己二烯并[2,3-c]吡咯-6(3H)-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺.

[0404] 

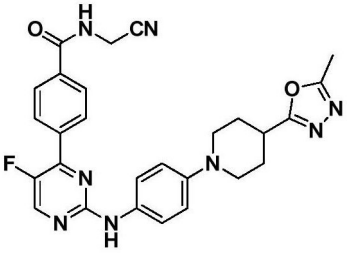
[0405] N-(氰基甲基)-4-(5-氟-2-((4-(4-(四氢-2H-[1,4]二氧杂环己二烯并[2,3-c]吡咯-6(3H)-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺.

[0406] 

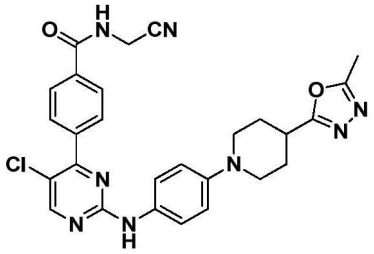
[0407] 4-(5-氯-2-((4-(4-(四氢-2H-[1,4]二氧杂环己二烯并[2,3-c]吡咯-6(3H)-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)-N-(氰基甲基)苯甲酰胺.

[0408] 

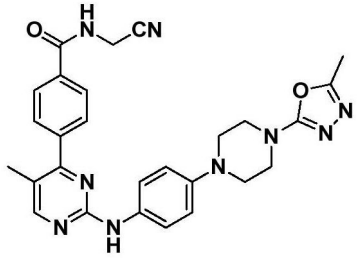
[0409] N-(氰基甲基)-4-(5-氟-2-((4-(4-(5-甲基-1,3,4-噁二唑-2-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺.

[0410] 

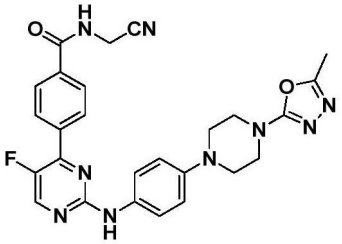
[0411] 4-(5-氯-2-((4-(4-(5-甲基-1,3,4-噁二唑-2-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)-N-(氰基甲基)苯甲酰胺.

[0412] 

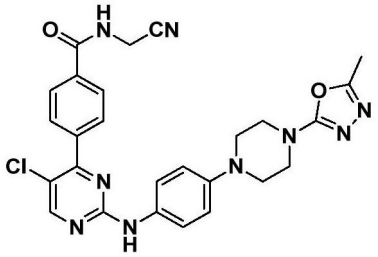
[0413] N-(氰基甲基)-4-(5-甲基-2-((4-(4-(5-甲基-1,3,4-噁二唑-2-基)哌嗪-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺.

[0414] 

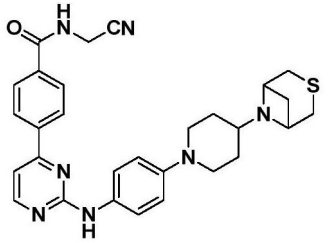
[0415] N-(氰基甲基)-4-(5-氟-2-((4-(4-(5-甲基-1,3,4-噁二唑-2-基)哌嗪-1-基)苯基)氨基)嘧啶-4-基)苯甲酰胺

[0416] 

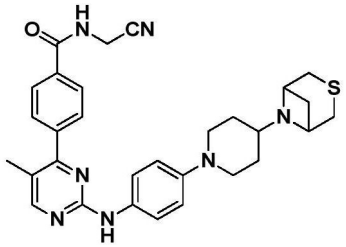
[0417] 4-(5-氯-2-((4-(4-(5-甲基-1,3,4-噁二唑-2-基)哌嗪-1-基)苯基)氨基)嘧啶-4-基)-N-(氰基甲基)苯甲酰胺.

[0418] 

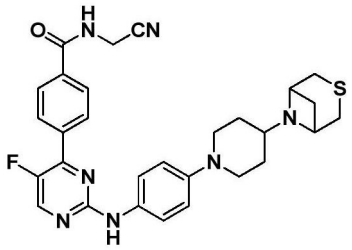
[0419] 4-(2-((4-(4-(3-硫杂-6-氮杂双环[3.1.1]庚-6-基)哌啶-1-基)苯基)氨基)嘧啶-4-基)-N-(氰基甲基)苯甲酰胺.

[0420] 

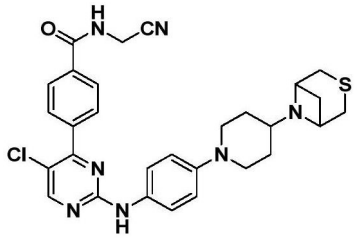
[0421] 4-(2-((4-(4-(3-硫杂-6-氮杂双环[3.1.1]庚-6-基)哌啶-1-基)苯基)氨基)-5-甲基嘧啶-4-基)-N-(氰基甲基)苯甲酰胺

[0422] 

[0423] 4-(2-((4-(4-(3-硫杂-6-氮杂双环[3.1.1]庚-6-基)哌啶-1-基)苯基)氨基)-5-氟嘧啶-4-基)-N-(氰基甲基)苯甲酰胺

[0424] 

[0425] 4-(2-((4-(4-(3-硫杂-6-氮杂双环[3.1.1]庚-6-基)哌啶-1-基)苯基)氨基)-5-氯嘧啶-4-基)-N-(氰基甲基)苯甲酰胺.

[0426] 

[0427] 应当理解,在上述反应中,在底物分子中的任何反应性基团可以根据常规化学操作进行保护。在任何上述反应中的合适保护基团是本领域常规使用的那些。形成和除去这些保护基团的方法为适合受保护分子的那些常规方法。T.W.Greene and P.G.M.Wuts "Protective groups in Organic Synthesis",John Wiley&Sons,Inc,1999,3rd Ed.,201-245以及其中的参考文献给出了这些常规方法并且结合在此用作参考。

[0428] 本发明的新的化合物可以公知的技术和方法和浓度通过与合适的赋形剂混合配制成合适的可药用组合物。

[0429] 式(1)化合物或含有它们的药用组合物用作适合人类或其他恒温哺乳动物肾素抑制剂,并且可以经口、表皮或肠胃外给药方式进行给药。

[0430] 药物组合物通过采用常规技术提供。优选地,组合物为含有有效量活性成份(即,根据本发明的式(1)化合物)的单位剂型。

[0431] 在药物组合物及其单位剂型中的活性成份(即,根据本发明的式(1)化合物)的数量可以依据具体的给药方法、具体化合物的能力和所需的浓度在大范围变化或调解。

[0432] 本发明的化合物可以单独地或与一种或多种其他熟练医药从业者可容易识别的治疗剂组合地使用。这些其他治疗剂可以根据待治疗的疾病类型、严重程度、患者服用的其他药品等进行选择。因此,例如,对于治疗类风湿性关节炎,一种或多种DMARD可以与本发明化合物组合物使用。

[0433] 生物活性:

[0434] 体外研究

[0435] JAK抑制的评估。

[0436] NCEs使用体外JAK(1、2和3)激酶实验在ADP Glo平台(Promega)上进行筛选。固定量的重组纯化人JAK(25ng的JAK1和10ng的JAK2和JAK3每反应,来自Life Technologies Ltd)使用增加浓度的NCEs在1x激酶反应缓冲液(40mM Tris-Cl,pH7.5,20mM $MgCl_2$,0.1mg/ml BSA和50μM DTT)中温育。酶反应在96孔板中通过添加底物混合物(含有50μM的ATP(最终浓度)和5μg的JAK1及2.5μg的JAK2及JAK3(polyGln$_4$TyR$_1$(Signal Chem)),总计25μl的反应)引发。反应于室温温育1hr。

[0437] 在温育1h后,添加等体积(25μl每反应)的ADP Glo并在室温温育40min。

[0438] 接着添加激酶检测试剂(50μl每反应)并在室温温育30min。最终,于500毫秒每孔的积分时间读出板上的荧光。

[0439] 将不含抑制剂的酶设为100%激酶活性来描绘数据。C_{50}值使用Graph Pad Prism软件计算。

[0440]

实施例编号	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

[0441]

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
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

[0442] *ND:未确定

[0443] 从体外数据可以清楚地看见合成的化合物对于JAK-1、JAK-2和JAK-3具有纳摩尔级的能力。同样地，合成的化合物显示了对JAK-1和JAK-2的选择性。因此，这些化合物可以用作潜在的药剂用于治疗人类癌症、关节炎和皮肤免疫疾病如银屑病。

[0444] 体内研究

[0445] 肽聚糖多糖聚合物(PGPS)关节炎。

[0446] 雌性SD大鼠以0.5mg/ml的鼠李糖在右脚踝中关节内注射20μl的PGPS而做好准备。2周时，脚踝直径以器官充满度测量器测量，并且大鼠以初始关节直径的类似分布分成各组。然后大鼠接受它们的第一次给药化合物，接着1h后在尾静脉中静脉注射0.5ml的PGPS(0.5mg/ml的鼠李糖)。化合物以10mg/kg给药并且测量脚踝直径持续3天[即第15、16、17天]。针对第16天给出数值。

[0447]

实施例编号	%爪炎症的减少，剂量为 10 mg/Kg
1	51

[0448]

3	56
4	52
17	57
24	41
25	63
29	43

[0449] 诱导和评价关节炎(胶原蛋白诱导的关节炎)

[0450] 对雄性DBA1j(8至12周大)小鼠注射天然牛II型胶原蛋白(Chondrex,Redmond,WA)(混合有弗氏完全佐剂)并在第0天和第21天皮下注射,基于(200μg的II型胶原蛋白,在100μl的乳状液中)的尾部。观察动物的临床评分并且以类似评分分配成不同的组。然后对小鼠给药并且里确定3周的临床评分。关节炎的程度基于每爪的0-4的临床评分进行确定并且对所有四个求和。很少有所合成化合物在10mg/kg BID剂量显示活性。

[0451] 本发明的化合物适合作为JAK抑制剂并用于治疗炎性病症、自身免疫性疾病、增殖性疾病、变态反应症和移植排斥、涉及软骨转换的损伤的疾病、先天性软骨畸形和/或与IL6或干扰素类的分泌过多相关的疾病。