SUBSTITUTED PYRIMIDINES AND THEIR USE AS JNK MODULATORS

The present invention relates to a method for modulating c-Jun N-terminal kinases (JNK), and a method for treating a subject afflicted with a disease or condition that can be alleviated by modulating JNKs with heterocyclic compounds. The invention further relates to novel heterocyclic compounds and pharmaceutical compositions comprising said compound.

The c-Jun N-terminal kinases (JNKs) are members of mitogen-activated protein kinase family along with p38 and extracellular signal-regulated kinases (ERKs). Three distinct genes (jnk1, jnk2 and jnk3) encoding 10 splice variants have been identified (Y.T. Ip and R.J. Davis, *Curr. Opin. Cell Biol.* (1998) **10**:205-19). JNK1 and JNK2 are expressed in a wide variety of tissues, whereas JNK3 is mainly expressed in neurons, and to a lesser extent in heart and testes (D.D. Yang et al., *Nature* (1997) **389**:865-70). Members of JNK family are activated by pro-inflammatory cytokines such as tumor necrosis factor α (TNF-α) and interleukin-1β (IL-1β), as well as environmental stresses. The activation of JNKs is mediated by its upstream kinases, MKK4 and MKK7, via dual phosphorylation of Thr-183 and Tyr-185 (B. Derijard et al., *Cell* (1994) **76**:1025-37). It has been shown that MKK4 and MMK7 can be activated by the diverse upstream kinases, including MEKK1 and MEKK4, depending upon the external stimuli and cellular context (D. Boyle et al., *Arthritis Rheum* (2003) **48**:2450-24). The specificity of JNK signaling is achieved by forming a JNK-specific signaling complex containing multiple components of the kinase cascade using scaffold proteins called JNK-interacting proteins (J. Yasuda et al., *Mol. Cell. Biol.* (1999) **19**:7245-54). JNKs have been shown to play important roles in inflammation, T cell functions, apoptosis and cellular survival by phosphorylating specific substrates, including transcription factors such as c-Jun, the component of activator protein-1 (AP1) family, and ATF2, as well as non-transcription factors such as IRS-1 and Bcl-2 (A.M. Manning and R.J. Davis, *Nat. Rev. Drug Discov.* (2003) **2**:554-65). Over-activation of JNK is believed to be an important mechanism in autoimmune, inflammatory, metabolic, neurological diseases as well as cancer.

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by chronic inflammation of the joints. In addition to the joint swelling and pain caused by the inflammatory process, most RA patients ultimately develop debilitating joint damage and deformation. Several lines of compelling pharmacological and genetic evidence in cellular and animal models strongly suggest the relevance and importance of the activated JNK in the pathogenesis of RA. First, abnormal activation of JNK was detected in both human arthritic joints from RA patients (G. Schett et al., *Arthritis Rheum* (2000) **43**:2501-12) and rodent arthritic joints from animal models of arthritis (Z. Han et al., *J. Clin. Invest.* (2001) **108**:73-81). In addition, inhibition of JNK activation by selective JNK inhibitors blocked proinflammatory cytokines and MMP production in human synoviocytes, macrophages and lymphocytes (Z. Han et al., (2001) *supra*). Importantly, administration of the selective JNK inhibitors in rats with adjuvant arthritis (Z. Han et al., (2001) *supra*) or in mice with collagen-induced arthritis (P. Gaillard et al., *J Med Chem.* (2005) **14**:4596-607) effectively protected joints from destruction and significantly reduced paw swelling by inhibiting cytokine and collagenase expression. Furthermore, JNK2 deficient mice were partially protected from joint destruction, but showed little effect on paw swelling and inflammation in the passive collagen-induced arthritis model. These studies indicate that JNK2 is functionally redundant with JNK1 in regard to their roles in matrix degradation, inflammation and paw swelling. Therefore, combined inhibition of both JNK1 and JNK2 activities is required for effective therapy for RA (Z. Han et al., *Arthritis Rheum.* (2002) **46**:818-23).

Asthma is a chronic inflammatory disease of airways, characterized by the presence of a cellular inflammatory process and by bronchial hyper-responsiveness associated with structural changes of the airways (B. Bradley et al., *J. Allergy Clin. Immunol.* (1991) **88**:661-74). This disorder has been shown to be driven by many cell types in the airways, including T lymphocytes, eosinophils, mast cells, neutrophils and epithelial cells (J. Bousquet et al., *Am. J. Respir. Crit. Care Med.* (2000) **161**:1720-45). JNKs have emerged as promising therapeutic targets for asthma based upon the recent proof-of-concept studies in the cellular and animal models of asthma using selective JNK inhibitors (K. Blease et al., *Expert Opin. Emerg. Drugs* (2003) **8**:71-81). It was shown that JNK inhibitors significantly blocked RANTES production in activated human airway smooth cells (K. Kujime et al., *J. Immunol.* (2000) **164**:3222-28). More importantly, the JNK inhibitors showed good efficacy in chronic rat and mouse models for their abilities to reduce cellular infiltration, inflammation, hyper-responsiveness, smooth muscle

[illegible] IgE production (P. Nath et al., *Eur. J. Pharmacol.* (2005) **506**:273-83;

P. Eynott et al., *Br. J. Pharmacol.* (2003) **140**:1373-80). These observations suggest important roles of JNKs in the allergic inflammation, airway remodeling process associated with hyperresponsiveness. Therefore, blockade of JNK activity is expected to be beneficial for the treatment of asthma.

Type 2 diabetes is the most serious and prevalent metabolic disease characterized by insulin resistance and insulin secretion impairment as a result of chronic low-level inflammation and abnormal lipid metabolism associated with oxidative stress. It has been reported that JNK activity is abnormally elevated in various diabetic target tissues under obese and diabetic conditions (J. Hirosumi et al., *Nature* (2002) **420**:333-36; H. Kaneto, *Expert. Opin. Ther. Targets* (2005) **9**:581-92). Activation of the JNK pathway by pro-inflammatory cytokines and oxidative stresses negatively regulates insulin signaling via phosphorylation of insulin receptor substrate-1 (IRS-1) at Ser^{307}, therefore contributes to insulin resistance and glucose tolerance (J. Hirosumi et al., *Nature* (2002) *supra*; Y. Lee et al., *J. Biol. Chem.* (2003) **278**:2896-902; Y. Nakatani et al., *J. Biol. Chem.* (2004) **279**:45803-09). Compelling genetic evidence came from elegant animal model studies using $jnk^{-/-}$ mice crossed with either genetic (*ob/ob*) obese mice or dietary obese mice. Loss of JNK1($JNK1^{-/-}$), but not JNK2 functions ($jnk2^{-/-}$), protected obese mice from body gains, increased steady-state levels of blood glucose, and decreased plasma insulin levels (J. Hirosumi et al., *Nature* (2002) *supra*). Furthermore, the beneficial effects were observed in a genetic diabetic model (db/db mice) by administration of either a small molecule JNK inhibitor, CC105 (B. Bennett et al., *Curr. Opin. Pharmacol.* (2003) **3**:420-25) or a JNK inhibitory peptide I(JIP) derived from the JNK binding domain of the JNK-interacting protein-1(JIP-1) (H. Kaneto et al., *Nat. Med.* (2004) **10**:1128-32), including significant lower blood glucose and higher plasma insulin levels. More interestingly, another recent report (A. Jaeschke et al., *Proc. Natl. Acad. Sci. U S A.* (2005) **102**:6931-35) revealed that JNK2 plays an important role in type 1 diabetes caused by autoimmune destruction of insulin-producing β cells. Non-obese diabetic mice deficient in JNK2 expression showed reduced destructive insulitis and less disease progression to diabetes, probably due to biased polarization toward the Th2 phenotype. Taken together, these studies demonstrated the utility of JNK inhibitors in the treatment of obesity/type 2 diabetes.

Neurodegenerative diseases, such as Alzheimer's (AD), Parkinson's (PD) and stroke are characterized by synaptic loss, neuronal atrophy and death. The JNK pathway leading to c-Jun activation has been shown to play a causal role in apoptosis of isolated primary

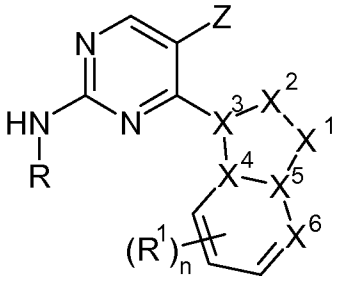
embryonic neurons and multiple neuronal cell lines upon induction of a variety of stimuli (D. Bozyczko-Coyne et al., *Curr. Drug Targets CNS Neurol. Disord.* (2002) **1**:31-49). Over-activation of JNK was observed in human brains from AD patients (J. Pei et al., *J. Alzheimers Dis.* (2001) **3**:41-48) or rodent brain sections derived from animal models of neurodegenerative diseases (M. Saporito et al., *J. Neurochem.* (2000) **75**:1200-08). For example, increased phospho-JNKs were detected in the post-mortem brains from the AD patients. Administration of JNK inhibitory peptide (JIP-1 peptide) in the rodent model of AD induced by β-amyloid peptide administration prevented the impairment of synaptic plasticity. In the animal models of PD (MPTP model), elevated phospho-MKK4 and phospho-JNKs were observed concomitantly with the neuronal cell death. Adenoviral gene transfer of JNK inhibitory peptide (JIP-1 peptide) into striatum of mice attenuated behavioral impairment by inhibiting MPTP-mediated JNK, c-Jun and caspase activation, therefore blocking neuronal cell death in the substantia nigra (X. Xia et al., *Proc. Natl. Acad. Sci. USA.* (2001) **98**:10433-38). In addition, in the animal model of ischemic stroke induced by glutamate excitotoxicity, mice deficient in JNK3, but not JNK1 or JNK2, were resistant to kainic acid (glutamate receptor agonist)-mediated seizure or neuronal death (D. D.Yang et al., *Nature* (1997) **389**:865-70). These data suggest JNK3 was mainly responsible for glutamate excitotoxicity, an important component in ischemic conditions. Taken together, the data suggests that JNKs are an attractive target for multiple CNS diseases associated with neuronal cell death.

Uncontrolled cellular growth, proliferation and migration along with de-regulated angiogenesis lead to the formation of malignant tumors. The JNK signal transduction pathway may not act exclusively in apoptosis, sustained JNK activation leading to AP1 activation has recently been implicated to contribute to the cellular survival of specific cancer types such as glial tumors and BCL-ABL transformed B lymphoblasts (M. Antonyak et al., *Oncogene* (2002) **21**:5038-46; P. Hess et al., Nat. Genet. (2002) **32**:201-05). In the case of glial tumors, enhanced JNK/AP1 activity was seen in most of the primary brain tumor samples. For the transformed B lymphoblasts, BCL-ABL was shown to activate the JNK pathway which in turn up-regulated expression of anti-apoptotic bcl-2 gene. Interestingly, the multi-drug resistance and hyper-proliferation seen in treatment-refractory AML patients has been causally linked to the sustained JNK activity present in these AML samples (L. Cripe et al., *Leukemia* (2002) **16**:799-812). Activation of JNK in leukemic cells resulted in induced expression of efflux pumps such as mdr1 and MRP1 responsible for multidrug resistance. Also, genes with a survival

benefit in response to oxidative stress including glutathione-S-transferase π and γ-glutamyl cysteine synthase were also upregulated by the activated JNK pathway.

Accordingly, JNK modulators are useful in treating a variety of diseases and/or conditions.

One aspect of the invention provides a compound of formula I:



(I)

wherein

X^1 is N, N-R^3, CHR^3, C-R^3, or O;

X^2 is N, NH, N-CH_3, CH, CH_2, $CHCH_3$ or C-CH_3;

X^3 is N, C or CH, where X^1, X^2, and X^3 are not all simultaneously N;

X^4, X^5 are each independently C, CH or N;

X^6 is N or C-R^1;

where at least two and not more than four of X^1, X^2, X^3, X^4, X^5, and X^6 are N; and where the bonds between X^1 and X^2, X^2 and X^3, X^3 and X^4, X^4 and X^5, X^5 and X^1, and X^5 and X^6 may each independently be either single, double, or form an aromatic ring, with the proviso that a chemically stable structure results;

R is –(cyclohexyl)–R^2 or –(phenyl)–R^8, where cyclohexyl and phenyl are each optionally substituted with methyl, fluoro, chloro, or hydroxy;

R^1 is halo, nitro, –CN, $–CH_2CN$, –OH, $–NH_2$, –COOH, or $–Y^1R^4$;

Y^1 is –O–, –NH–, –S–, –SO–, $–SO_2–$, $–NHSO_2–$, –NHC(O) –, –C(O)NH–, –C(O)O–, or a bond;

R^4 is C_{1-6} alkyl, acyl, phenyl, or benzyl, each of which is substituted with 0-3 hydroxy or halo;

n is 0, 1, or 2;

R^3 is H or C_{1-6} alkyl;

R^2 is H, –OH, $–SO_2NH_2$, =O, –CN, or $–Y^2–Y^3–Y^4–R^5$, where

Y^2 is –C(O)–, $–C(O)NR^a–$, $–SO_2–$, –O–, –NH–, or a bond;

Y^3 is C_{1-6} alkylene or a bond;

Y^4 is $–O–$, $–NR^a–$, –S–, $–SO_2–$, –C(O)–, $–C(O)NR^a–$, $–NR^aC(O)–$, $–NR^aC(O)O–$, $–NR^aC(O)NR^a–$, $–NHSO_2–$, $–SO_2NH–$, or a bond;

R^5 is C_{1-6} alkyl, C_{3-10} cycloalkyl, heterocyclyl, wherein R^5 is optionally substituted with –OH or $–NHR^a$; wherein each R^a is independently H or C_{1-6} alkyl;

R^8 is H, C_{1-6} alkyl, $–OR^3$, $–SO_2NH_2$, $–NHSO_2R^3$, $–COOR^3$, $–SO_2R^3$, $–NH_2$, $–CONR^aR^3$, $–NHC(O)R^3$, $–CF_3$, $–NO_2$, halo, or –CN;

Z is hydrogen, halo, C_{1-12} alkyl, or NH_2;

or a pharmaceutically acceptable salt thereof.

Preferably X^1 is N, N-R^3, C-R^3, or O;

X^2 is N, NH, N-CH_3, CH or C-CH_3;

X^3 is N or C, where X^1, X^2, and X^3 are not all simultaneously N and

X^4, X^5 are each independently C or N.

The invention also provides pharmaceutical compositions, methods of using, and methods of preparing the aforementioned compounds.

Compounds and compositions of the invention are useful in the treatment and/or prevention of a c-Jun N-terminal kinase mediated disorder, such as autoimmune disorders, inflammatory disorders, metabolic disorders, neurological diseases, and cancer. In some embodiments, compounds and compositions of the invention are useful in treating and/or preventing rheumatoid arthritis, asthma, type II diabetes, Alzheimer's disease, Parkinson's disease and/or stroke.

Definitions

Unless otherwise stated, the following terms used in this Application, including the specification and claims, have the definitions given below. It must be noted that, as used in the specification and the appended claims, the singular forms "a", "an," and "the" include plural referents unless the context clearly dictates otherwise.

"Alkyl" means the monovalent linear or branched saturated hydrocarbon moiety, consisting solely of carbon and hydrogen atoms, having from one to twelve carbon atoms. "Lower alkyl" refers to an alkyl group of one to six carbon atoms, i.e. C_1-C_6 alkyl. Examples of alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, isobutyl, sec-butyl, tert-butyl, pentyl, n-hexyl, octyl, dodecyl. "Branched alkyl" refers to an alkyl moiety having at least one branch, for example, isopropyl, isobutyl, tert-butyl. Similarly, "lower alkoxy" refers to a moiety of the form –OR, and "acyl" refers to a moiety of the form –C(O)R, where R is lower alkyl.

"Alkylene" means a linear saturated divalent hydrocarbon moiety of one to six carbon atoms or a branched saturated divalent hydrocarbon radical of three to six carbon atoms, e.g., methylene, ethylene, 2,2-dimethylethylene, propylene, 2-methylpropylene, butylene, pentylene.

"Alkylene dioxy" means a divalent moiety of the formula –O–R–O–, where R is alkylene as defined herein.

"Aryl" means a monovalent cyclic aromatic hydrocarbon moiety consisting of a mono-, bi- or tricyclic aromatic ring. The aryl group can be optionally substituted as defined herein. Examples of aryl moieties include, but are not limited to, optionally substituted phenyl, naphthyl, phenanthryl, fluorenyl, indenyl, pentalenyl, azulenyl, oxydiphenyl, biphenyl, methylenediphenyl, aminodiphenyl, diphenylsulfidyl, diphenylsulfonyl, diphenylisopropylidenyl, benzodioxanyl, benzofuranyl, benzodioxylyl, benzopyranyl, benzoxazinyl, benzoxazinonyl, benzopiperadinyl, benzopiperazinyl, benzopyrrolidinyl, benzomorpholinyl, methylenedioxyphenyl, ethylenedioxyphenyl, including partially hydrogenated derivatives thereof.

"Cycloalkyl" means a monovalent saturated carbocyclic moiety of mono- or bicyclic rings, having 3 to 10 ring carbon atoms. Preferred cycloalkyl is C_{3-7} mono-cyclic cycloalkyl. Cycloalkyl can optionally be substituted with one or more substituents,

ɔstituent is independently hydroxy, alkyl, alkoxy, halo, haloalkyl, amino,

monoalkylamino, or dialkylamino, unless otherwise specifically indicated. Examples of cycloalkyl moieties include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, including partially unsaturated derivatives thereof.

"Cycloalkylalkyl" mean a moiety of the formula $-R^a-R^b$, where R^a is alkylene and R^b is cycloalkyl as defined herein.

"Heteroalkyl" means an alkyl moiety as defined herein, including a branched C_4-C_7 alkyl, wherein one, two or three hydrogen atoms have been replaced with a substituent independently selected from the group consisting of $-OR^a$, $-NR^bR^c$, and $-S(O)_nR^d$ (where n is an integer from 0 to 2), with the understanding that the point of attachment of the heteroalkyl radical is through a carbon atom, wherein R^a is hydrogen, acyl, alkyl, cycloalkyl, or cycloalkylalkyl; R^b and R^c are independently of each other hydrogen, acyl, alkyl, cycloalkyl, or cycloalkylalkyl; and when n is 0, R^d is hydrogen, alkyl, cycloalkyl, or cycloalkylalkyl; when n is 1, R^d is alkyl, cycloalkyl, or cycloalkylalkyl; and when n is 2, R^d is alkyl, cycloalkyl, cycloalkylalkyl, amino, acylamino, monoalkylamino, or dialkylamino. Representative examples include, but are not limited to, 2-hydroxyethyl, 3-hydroxypropyl, 2-hydroxy-1-hydroxymethylethyl, 2,3-dihydroxypropyl, 1-hydroxy-methylethyl, 3-hydroxybutyl, 2,3-dihydroxybutyl, 2-hydroxy-1-methylpropyl, 2-amino-ethyl, 3-aminopropyl, 2-methylsulfonylethyl, aminosulfonylmethyl, aminosulfonylethyl, aminosulfonylpropyl, methylaminosulfonylmethyl, methylaminosulfonylethyl, methyl-aminosulfonylpropyl.

"Heteroaryl" means a monocyclic or bicyclic moiety of 5 to 12 ring atoms having at least one aromatic ring containing one, two, or three ring heteroatoms selected from N, O, or S, the remaining ring atoms being C, with the understanding that the attachment point of the heteroaryl radical will be on an aromatic ring. The heteroaryl ring may be optionally substituted as defined herein. Examples of heteroaryl moieties include, but are not limited to, optionally substituted imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, pyrazinyl, thienyl, thiophenyl, furanyl, pyranyl, pyridinyl, pyrrolyl, pyrazolyl, pyrimidyl, pyridazinyl, quinolinyl, isoquinolinyl, benzofuryl, benzofuranyl, benzothiophenyl, benzothiopyranyl, benzimidazolyl, benzoxazolyl, benzooxadiazolyl, benzothiazolyl, benzothiadiazolyl, benzopyranyl, indolyl, isoindolyl, indazolyl, triazolyl, triazinyl, quinoxalinyl, purinyl, quinazolinyl, quinolizinyl, naphthyridinyl, pteridinyl, carbazolyl, azepinyl, diazepinyl, acridinyl, including partially hydrogenated derivatives thereof.

The terms "halo," "halogen," and "halide" are used interchangeably herein and refer to a substituent fluoro, chloro, bromo, or iodo.

"Haloalkyl" means alkyl as defined herein in which one or more hydrogen has been replaced with same or different halogen. Exemplary haloalkyls include $-CH_2Cl$, $-CH_2CF_3$, $-CH_2CCl_3$, perfluoroalkyl (e.g., $-CF_3$).

"Heterocyclyl" means a monovalent saturated moiety, consisting of one to three rings, incorporating one, two, or three or four heteroatoms (chosen from nitrogen, oxygen or sulfur). A monocyclic heterocyclyl, having 3 to 8 ring atoms, is preferred. The heterocyclyl ring may be optionally substituted as defined herein. Examples of heterocyclyl moieties include, but are not limited to, optionally substituted piperidinyl, piperazinyl, homopiperazinyl, azepinyl, pyrrolidinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, pyridinyl, pyridazinyl, pyrimidinyl, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, quinuclidinyl, quinolinyl, isoquinolinyl, benzimidazolyl, thiadiazolylidinyl, benzothiazolidinyl, benzoazolylidinyl, dihydrofuryl, tetrahydrofuryl, dihydropyranyl, tetrahydropyranyl, thiamorpholinyl, thiamorpholinylsulfoxide, thiamorpholinylsulfone, dihydroquinolinyl, dihydroisoquinolinyl, tetrahydroquinolinyl, tetrahydrisoquinolinyl.

"Optionally substituted", when used in association with "aryl", "phenyl", "heteroaryl" or "heterocyclyl", means an aryl, phenyl, heteroaryl or heterocyclyl which is optionally substituted independently with one or more substituents, preferably one to four, and more preferably, one to three substituents selected from C_{1-6} alkyl, C_{1-6} heteroalkyl, oxo (i.e., =O), haloalkyl, $-(CH_2)_mCOX^1$, $-(CH_2)_mSO_2X^2$, C_{1-6} alkoxy, halogen, C_{1-6} alkylthio, C_{1-6} alkylsulfonyl, $-SO_2NR^4R^5$, cyano, nitro, and $-NR^6R^7$, where m, X^1, X^2, R^4, and R^5 are as defined herein.

"Leaving group" means a group with the meaning conventionally associated with it in synthetic organic chemistry, i.e., an atom or group displaceable under substitution reaction conditions. Examples of leaving groups include, but are not limited to, halogen, alkane- or arylenesulfonyloxy, such as methanesulfonyloxy, ethanesulfonyloxy, thiomethyl, benzenesulfonyloxy, tosyloxy, and thienyloxy, dihalophosphinoyloxy, optionally substituted benzyloxy, isopropyloxy, acyloxy.

"Optional" or "optionally" means that the subsequently described event or circumstance may but need not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not.

"Disease" and "Disease state" means any disease, condition, symptom, disorder or indication.

"Inert organic solvent" or "inert solvent" means the solvent is inert under the conditions of the reaction being described in conjunction therewith, including for example, benzene, toluene, acetonitrile, tetrahydrofuran, N,N-dimethylformamide, chloroform, methylene chloride or dichloromethane, dichloroethane, diethyl ether, ethyl acetate, acetone, methyl ethyl ketone, methanol, ethanol, propanol, isopropanol, *tert*-butanol, dioxane, pyridine. Unless specified to the contrary, the solvents used in the reactions of the present invention are inert solvents.

"Pharmaceutically acceptable" means that which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic, and neither biologically nor otherwise undesirable and includes that which is acceptable for veterinary as well as human pharmaceutical use.

"Pharmaceutically acceptable salts" of a compound means salts that are pharmaceutically acceptable, as defined herein, and that possess the desired pharmacological activity of the parent compound. Such salts include:

acid addition salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid; or formed with organic acids such as acetic acid, benzenesulfonic acid, benzoic, camphorsulfonic acid, citric acid, ethanesulfonic acid, fumaric acid, glucoheptonic acid, gluconic acid, glutamic acid, glycolic acid, hydroxynaphtoic acid, 2-hydroxyethanesulfonic acid, lactic acid, maleic acid, malic acid, malonic acid, mandelic acid, methanesulfonic acid, muconic acid, 2-naphthalenesulfonic acid, propionic acid, salicylic acid, succinic acid, tartaric acid, p-toluenesulfonic acid, trimethylacetic acid; or

salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic or inorganic base. Acceptable organic bases include diethanolamine, ethanolamine, N-methylglucamine, triethanolamine, tromethamine. Acceptable inorganic bases include aluminum hydroxide, calcium hydroxide, potassium hydroxide, sodium carbonate, sodium hydroxide.

The preferred pharmaceutically acceptable salts are the salts formed from acetic acid, hydrochloric acid, sulfuric acid, methanesulfonic acid, maleic acid, phosphoric acid, tartaric acid, citric acid, sodium, potassium, calcium, zinc, and magnesium.

"Protective group" or "protecting group" means the group which selectively blocks one reactive site in a multifunctional compound such that a chemical reaction can be carried out selectively at another unprotected reactive site in the meaning conventionally associated with it in synthetic chemistry. Certain processes of this invention rely upon the protective groups to block reactive nitrogen and/or oxygen atoms present in the reactants. For example, the terms "amino-protecting group" and "nitrogen protecting group" are used interchangeably herein and refer to those organic groups intended to protect the nitrogen atom against undesirable reactions during synthetic procedures. Exemplary nitrogen protecting groups include, but are not limited to, trifluoroacetyl, acetamido, benzyl (Bn), benzyloxycarbonyl (carbobenzyloxy, CBZ), p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, *tert*-butoxycarbonyl (BOC). Skilled persons will know how to choose a group for the ease of removal and for the ability to withstand the following reactions.

"Subject" means mammals and non-mammals. Mammals means any member of the mammalia class including, but not limited to, humans; non-human primates such as chimpanzees and other apes and monkey species; farm animals such as cattle, horses, sheep, goats, and swine; domestic animals such as rabbits, dogs, and cats; laboratory animals including rodents, such as rats, mice, and guinea pigs. Examples of non-mammals include, but are not limited to, birds. The term "subject" does not denote a particular age or sex.

"Therapeutically effective amount" means an amount of a compound that, when administered to a subject for treating a disease state, is sufficient to effect such treatment for the disease state. The "therapeutically effective amount" will vary depending on the compound, disease state being treated, the severity or the disease treated, the age and relative health of the subject, the route and form of administration, the judgment of the attending medical or veterinary practitioner, and other factors.

The terms "those defined above" and "those defined herein" when referring to a variable incorporates by reference the broad definition of the variable as well as preferred, more preferred and most preferred definitions, if any.

"Treating" or "treatment" of a disease state includes:

(i)preventing the disease state, i.e. causing the clinical symptoms of the disease state not to develop in a subject that may be exposed to or predisposed to the disease state, but does not yet experience or display symptoms of the disease state.

(ii)inhibiting the disease state, *i.e.*, arresting the development of the disease state or its clinical symptoms, or

(iii)relieving the disease state , *i.e.*, causing temporary or permanent regression of the disease state or its clinical symptoms.

The terms "treating", "contacting" and "reacting" when referring to a chemical reaction means adding or mixing two or more reagents under appropriate conditions to produce the indicated and/or the desired product. It should be appreciated that the reaction which produces the indicated and/or the desired product may not necessarily result directly from the combination of two reagents which were initially added, i.e., there may be one or more intermediates which are produced in the mixture which ultimately leads to the formation of the indicated and/or the desired product.

Nomenclature and Structures

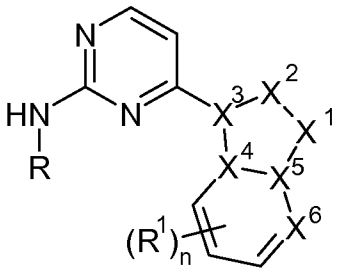
In general, the nomenclature used in this Application is based on AUTONOM™ v.4.0, a Beilstein Institute computerized system for the generation of IUPAC systematic nomenclature. Chemical structures shown herein were prepared using ISIS® version 2.2. Any open valency appearing on a carbon, oxygen or nitrogen atom in the structures herein indicates the presence of a hydrogen atom.

Whenever a chiral carbon is present in a chemical structure, it is intended that all stereoisomers associated with that chiral carbon are encompassed by the structure.

All patents and publications identified herein are incorporated herein by reference in their entirety.

General Method

One aspect of the invention provides compounds of formula I:



(I)

wherein

X^1 is N, N-R^3, C-R^3, or O;

X^2 is N, NH, N-CH_3, CH, or C-CH_3;

X^3 is N or C, where X^1, X^2, and X^3 are not all simultaneously N;

X^4, X^5 are each independently C or N;

X^6 is N or C-R^1;

where at least two and not more than four of X^1, X^2, X^3, X^4, X^5, and X^6 are N; and where the bonds between X^1 and X^2, X^2 and X^3, X^3 and X^4, X^4 and X^5, X^5 and X^1, and X^5 and X^6 may each independently be either single, double, or form an aromatic ring, with the proviso that a chemically stable structure results

(a "chemically stable structure" results where normal valences and bond numbers are not exceeded; for example, a chemically stable structure will not have double bonds between X^3-X^4, X^4-X^5, and X^5-X^1 simultaneously);

R is –(cyclohexyl)–R^2 or –(phenyl)–R^8, where cyclohexyl and phenyl are each optionally substituted with methyl, fluoro, chloro, or hydroxy;

R^1 is halo, nitro, –CN, –CH_2CN, –OH, –NH_2, –COOH, or –Y^1R^4;

Y^1 is –O–, –NH–, –S–, –SO–, –SO_2–, –$NHSO_2$–, –NHC(O) –, –C(O)NH–, –C(O)O–, or a bond;

R^4 is lower alkyl, acyl, phenyl, or benzyl, each of which is substituted with 0-3 hydroxy or halo;

n is 0, 1, or 2;

R^3 is H or lower alkyl;

R^2 is H, –OH, $–SO_2NH_2$, =O, –CN, or $–Y^2–Y^3–Y^4–R^5$, where

Y^2 is –C(O)–, $–C(O)NR^a–$, $–SO_2–$, –O–, –NH–, or a bond;

Y^3 is lower alkylene or a bond;

Y^4 is –O–, $–NR^a–$, –S–, $–SO_2–$, –C(O)–, $–C(O)NR^a–$, $–NR^aC(O)–$, $–NR^aC(O)O–$, $–NR^aC(O)NR^a–$, $–NHSO_2–$, $–SO_2NH–$, or a bond;

R^5 is lower alkyl, cycloalkyl, heterocyclyl, wherein R^5 is optionally substituted with –OH or $–NHR^a$; wherein each R^a is independently H or lower alkyl;

R^8 is H, lower alkyl, $–OR^3$, $–SO_2NH_2$, $–NHSO_2R^3$, $–COOR^3$, $–SO_2R^3$, $–NH_2$, $–CONR^aR^3$, $–NHC(O)R^3$, $–CF_3$, $–NO_2$, halo, or –CN;

Z is hydrogen, halo, alkyl, or NH_2;

or a pharmaceutically acceptable salt thereof.

In some embodiments, X^4, X^5, and X^6 are each C. In other embodiments, R is –(cyclohexyl)–R^2. In further embodiments, X^3 is N and X^1 is C. In additional embodiments, R^2 is OH. In some embodiments, R^1 is benzyloxy and n is 1. In still other embodiments, R^1 is –CN.

In some embodiments, X^2 is N. In other embodiments, R^2 is $–Y^2–Y^3–Y^4–R^5$, where Y^2 is $–C(O)NR^a–$, R^a is H, and Y^3 is lower alkylene. In other embodiments, Y^4 is $–SO_2–$. In further embodiments, R^5 is lower alkyl.

In some embodiments, Y^4 is –S–. In some embodiments, R^5 is lower alkyl.

In other embodiments, Y^4 is a bond, and R^5 is lower alkyl.

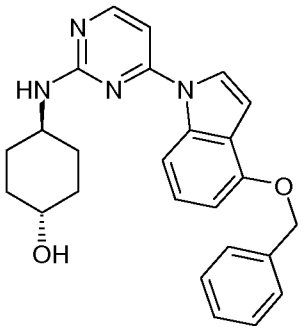
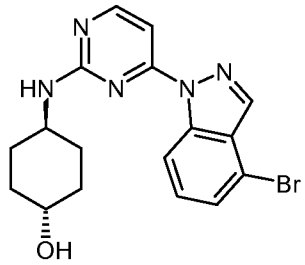
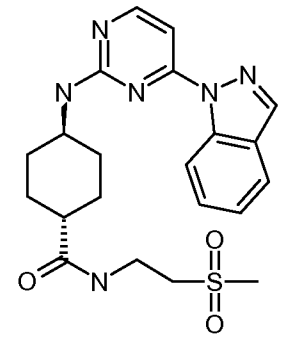
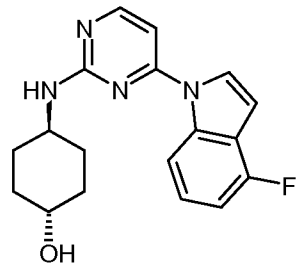
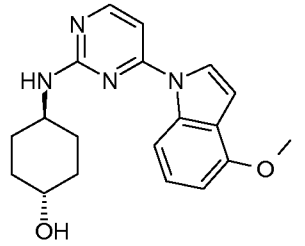
Another aspect of the invention is a method for treating inflammation, comprising administering an effective amount of a compound of the invention to a subject in need thereof.

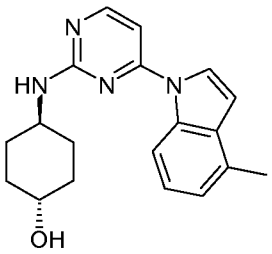
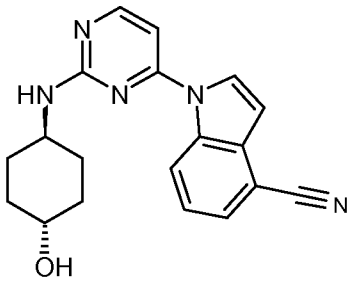
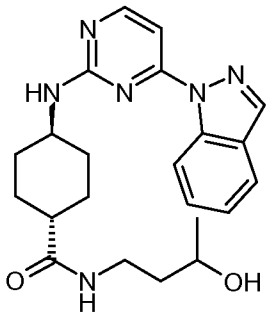
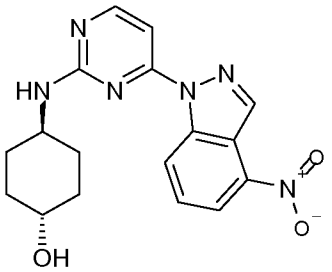
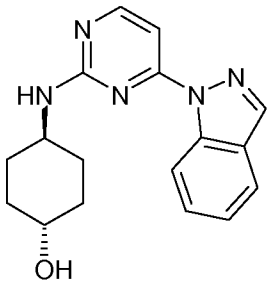
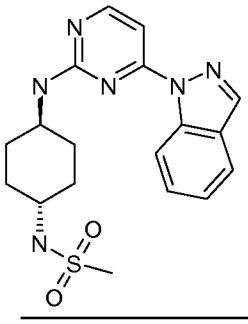
Another aspect of the invention is a pharmaceutical composition, comprising a compound of the invention and a pharmaceutically acceptable excipient.

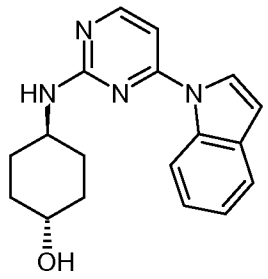
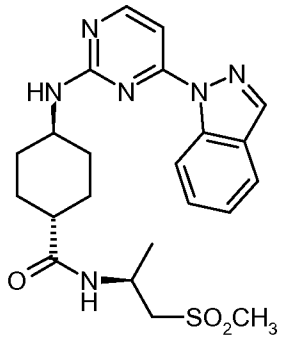
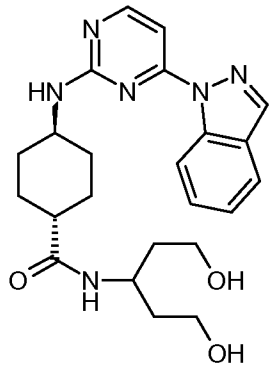
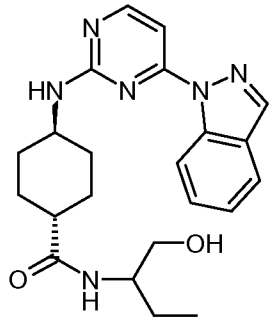
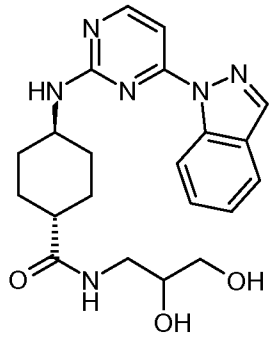
It should be appreciated that combinations of the different groups described herein may form other embodiments. In this manner, a variety of different compounds are embodied within the present invention.

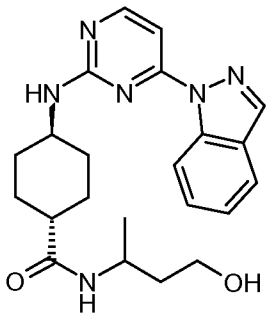
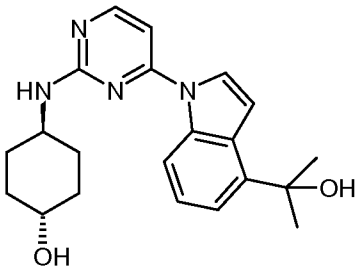
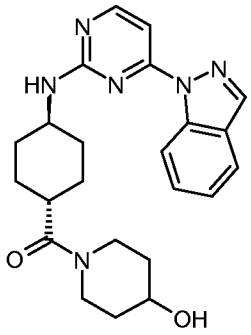
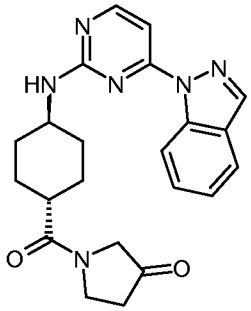
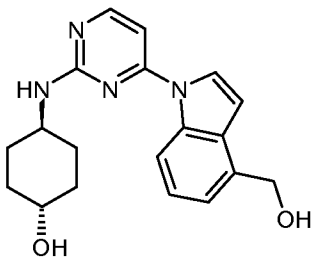
Representative compounds of the invention are shown in Table 1 below.

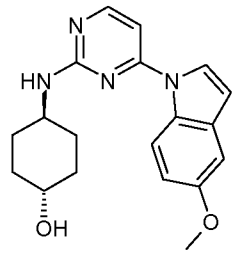
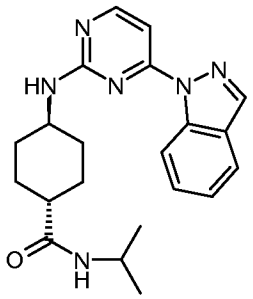
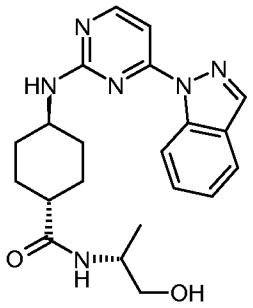
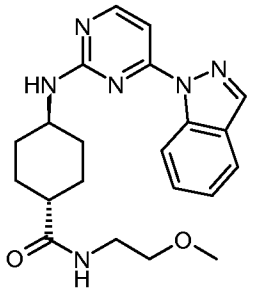
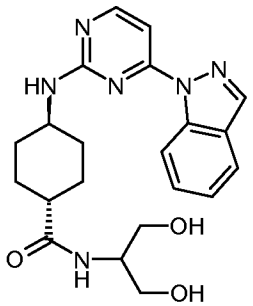
Table 1. Representative compound of Formula I.

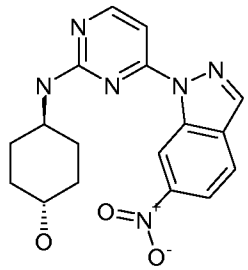
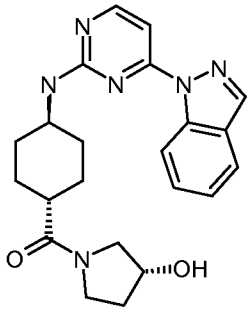
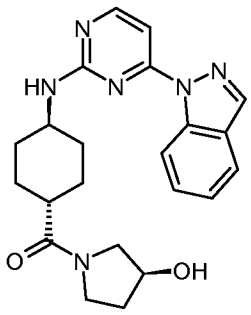
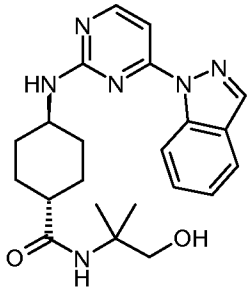
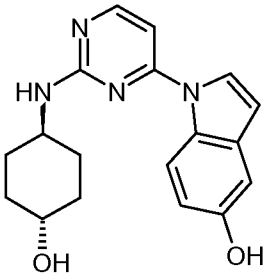
Structure	Name	Compound No.
	4-[4-(4-benzyloxy-indol-1-yl)-pyrimidin-2-ylamino]-cyclo-hexanol	1
	4-[4-(4-bromoindol-1-yl)-pyrimidin-2-yl-amino]-cyclohexanol	2
	4-(4-indol-1-yl)-pyrimidin-2-ylamino]-cyclohexane carboxylic acid (2-methane-sulfonylethyl)amide	3
	4-[4-(4-fluoroindol-1-yl)-pyrimidin-2-yl-amino]-cyclohexanol	4
	4-[4-(4-methoxy-indol-1-yl)-pyrimidin-2-ylamino]-cyclo-hexanol	5

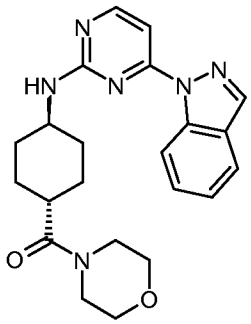
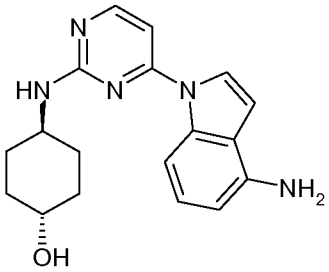
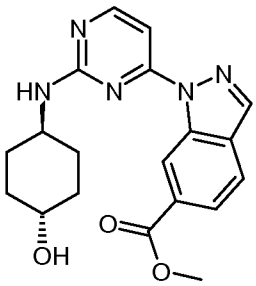
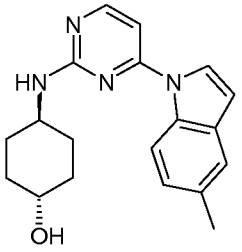
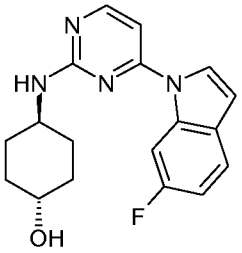
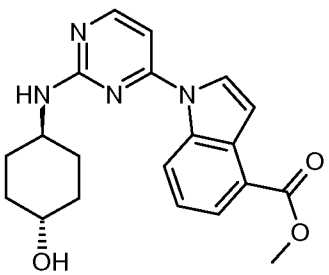
Structure	Name	Compound No.
	4-[4-(4-methyl-indol-1-yl)-pyrimidin-2-yl-amino]-cyclohexanol	6
	4-[4-(4-cyano-indol-1-yl)-pyrimidin-2-yl-amino]-cyclohexanol	7
	4-(4-indazol-1-yl)-pyrimidin-2-ylamino]-cyclohexane carboxylic acid (3-hydroxybutyl)-amide	8
	4-[4-(4-nitro-indazol-1-yl)-pyrimidin-2-yl-amino]-cyclohexanol	9
	4-(4-indazol-1-yl)-pyrimidin-2-ylamino-cyclohexanol	10
	N-[4-(4-indazol-1-yl)-pyrimidin-2-ylamino-cyclohexyl] methane-sulfonamide	11

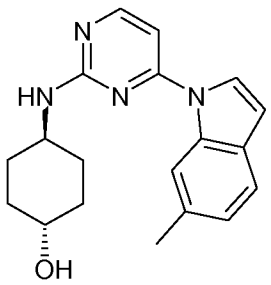
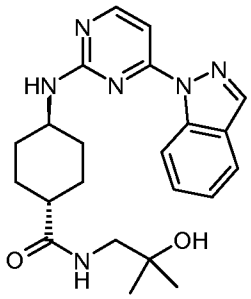
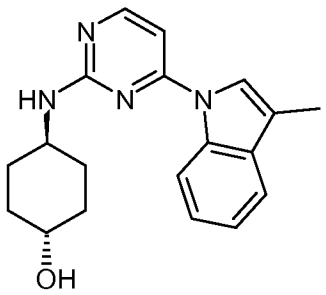
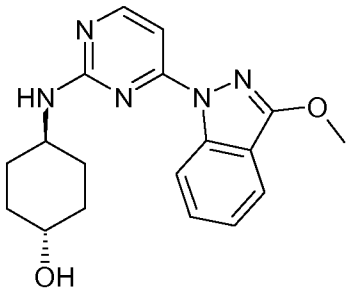
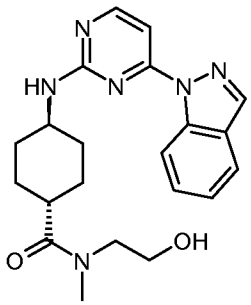
Structure	Name	Compound No.
	4-(4-indol-1-yl)-pyrimidin-2-ylamino-cyclohexanol	12
	4-(4-indazol-1-yl)-pyrimidin-2-ylamino]-cyclohexane carboxylic acid (1-methylsulfonyl-prop-2-yl)-amide	13
	4-(4-indazol-1-yl)-pyrimidin-2-ylamino]-cyclohexane carboxylic acid (1,5-dihydroxy-pent-3-yl)-amide	14
	4-(4-indazol-1-yl)-pyrimidin-2-ylamino]-cyclohexane carboxylic acid (1-hydroxy-but-2-yl)-amide	15
	4-(4-indazol-1-yl)-pyrimidin-2-ylamino]-cyclohexane carboxylic acid (2,3-dihydroxy-prop-1-yl)-amide	16

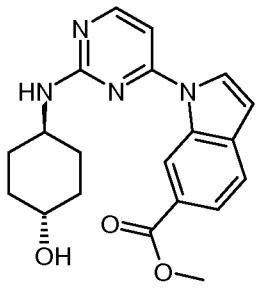
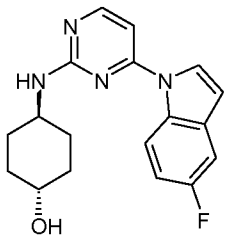
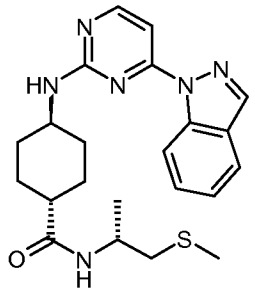
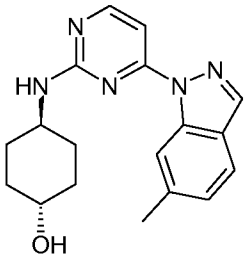
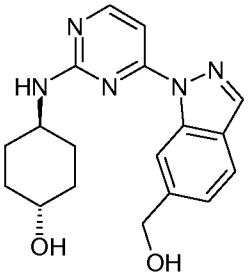
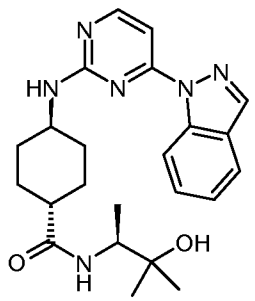
Structure	Name	Compound No.
	4-(4-indazol-1-yl)-pyrimidin-2-ylamino]-cyclohexane carboxylic acid (1-hydroxybut-3-yl)-amide	17
	4-[4-(4-(2-hydroxy-prop-2-yl)-indol-1-yl)-pyrimidin-2-ylamino]-cyclohexanol	18
	(4-hydroxypiperidin-1-yl)-[4-(4-indazol-1-yl-pyrimidin-2-ylamino)-cyclohexyl]-methanone	19
	(3-pyrrolidon-1-yl)-[4-(4-indazol-1-yl-pyrimidin-2-ylamino)-cyclohexyl]-methanone	20
	4-[4-(4-hydroxy-methylindol-1-yl)-pyrimidin-2-ylamino]-cyclohexanol	21

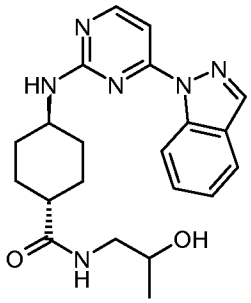
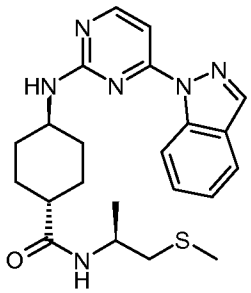
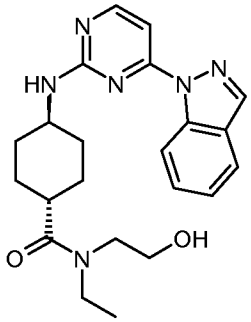
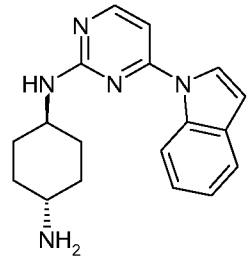
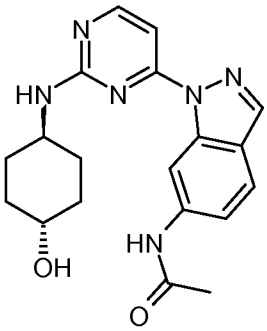
Structure	Name	Compound No.
	4-[4-(5-methoxy-indol-1-yl)-pyrimidin-2-ylamino]-cyclohexanol	22
	4-(4-indazol-1-yl-pyrimidin-2-ylamino)-cyclohexane carboxylic acid isopropylamide	23
	4-(4-indazol-1-yl-pyrimidin-2-ylamino)-cyclohexane carboxylic acid 1-hydroxyprop-2-ylamide	24
	4-(4-indazol-1-yl-pyrimidin-2-ylamino)-cyclohexane carboxylic acid 2-methoxyethy-amide	25
	4-(4-indazol-1-yl-pyrimidin-2-ylamino)-cyclohexane carboxylic acid 1,3-dihydroxy-prop-2-ylamide	26

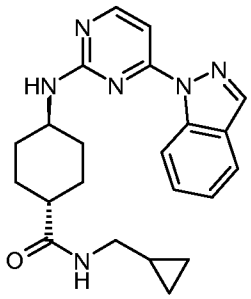
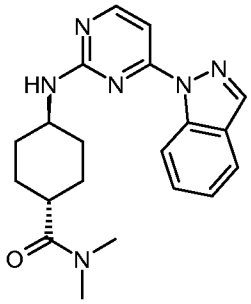
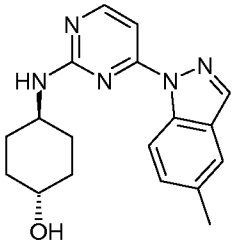
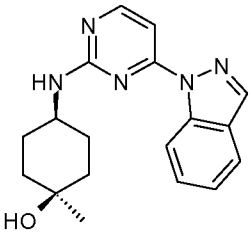
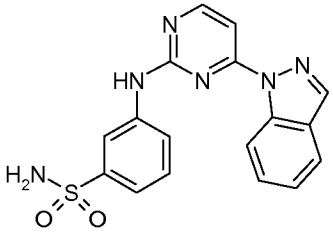
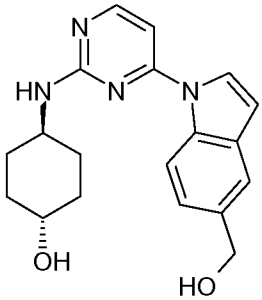
Structure	Name	Compound No.
	4-[4-(6-nitroindazol-1-ylpyrimidin-2-yl-amino)cyclohexanol	27
	(3-hydroxypyrrolidin-1-yl)-[4-(4-indazol-1-ylpyrimidin-2-yl-amino)-cyclohexyl]-methanone	28
	(3-hydroxypyrrolidin-1-yl)-[4-(4-indazol-1-ylpyrimidin-2-yl-amino)-cyclohexyl]-methanone	29
	4-(4-indazol-1-yl-pyrimidin-2-ylamino)-cyclohexane carboxylic acid 3-hydroxy-2-methylprop-2-yl-amide	30
	1-[2-(4-hydroxycyclo-hexylamino)-pyrimidin-4-yl]-1H-indol-5-ol	31

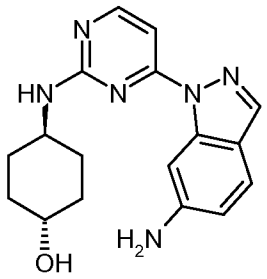
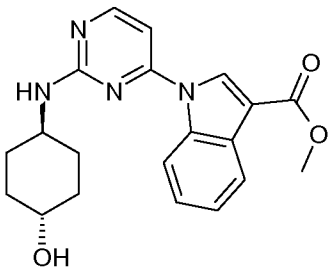
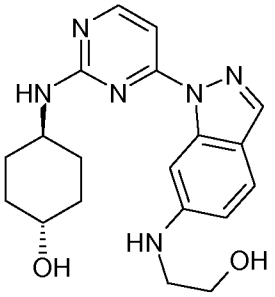
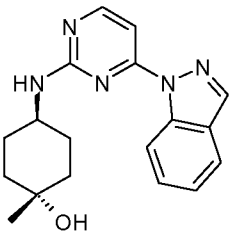
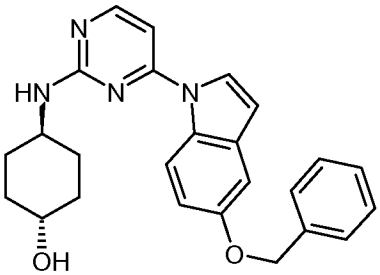
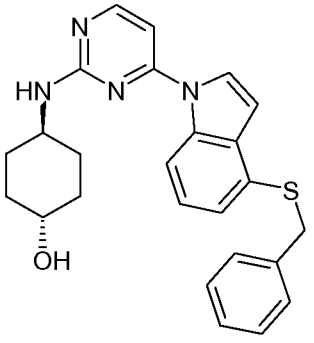
Structure	Name	Compound No.
	[4-(4-indazol-1-yl-pyrimidin-2-ylamino)-cyclohexyl]-morpholin-4-yl-methanone	32
	4-[4-(4-aminoindol-1-yl)-pyrimidin-2-yl-amino]-cyclohexanol	33
	1-[2-(4-hydroxycyclo-hexylamino)-pyrimidin-4-yl]-1H-indazole-6-carboxylic acid methyl ester	34
	4-[4-(5-methylindol-1-yl)-pyrimidin-2-yl-amino]-cyclohexanol	35
	4-[4-(6-fluoroindol-1-yl)-pyrimidin-2-yl-amino]-cyclohexanol	36
	1-[2-(4-hydroxycyclo-hexylamino)-pyrimidin-4-yl]-1H-indole-4-carboxylic acid methyl ester	37

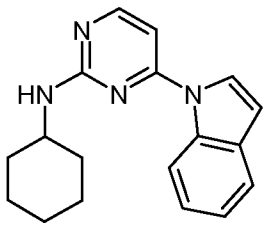
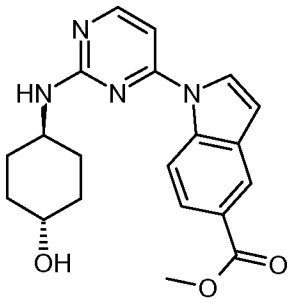
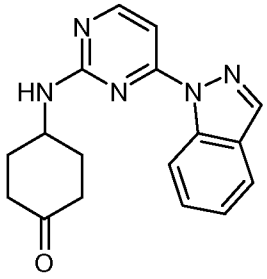
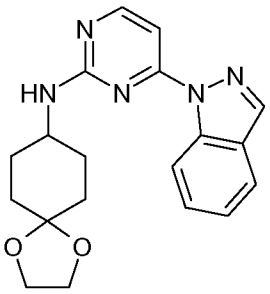
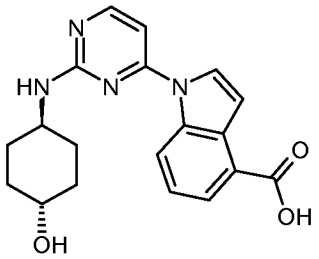
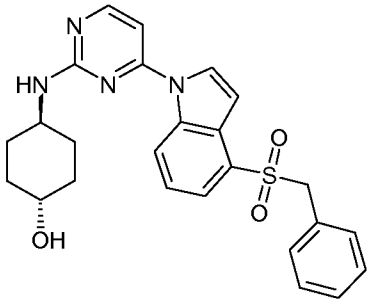
Structure	Name	Compound No.
	4-[4-(6-methylindol-1-yl)-pyrimidin-2-yl-amino]-cyclohexanol	38
	4-(4-indazol-1-yl-pyrimidin-2-ylamino)-cyclohexane carboxylic acid (2-hydroxy-2-methylpropyl)amide	39
	4-[4-(3-methylindol-1-yl)-pyrimidin-2-yl-amino]-cyclohexanol	40
	4-[4-(3-methoxy-indazol-1-yl)-pyrimidin-2-ylamino]-cyclohexanol	41
	4-(4-indazol-1-yl-pyrimidin-2-ylamino)-cyclohexane carboxylic acid (2-hydroxyethyl)-methyl-amide	42

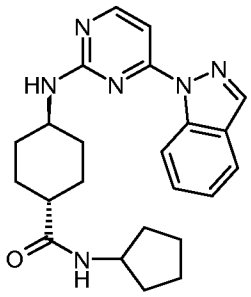
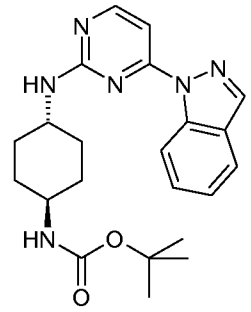
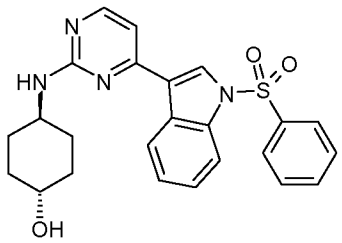
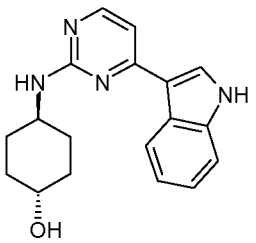
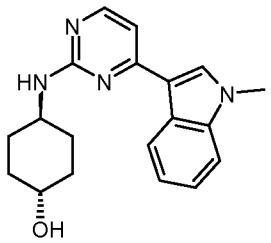
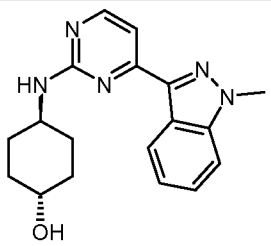
Structure	Name	Compound No.
	1-[2-(4-hydroxycyclo-hexylamino)-pyrimidin-2-yl]-1H-indole-6-carboxylic acid methyl ester	43
	4-[4-(5-fluoroindol-1-yl)-pyrimidin-2-yl-amino]-cyclohexanol	44
	4-(4-indazol-1-yl-pyrimidin-2-ylamino)-cyclohexane carboxylic acid (1-methyl-2-methylsulfanyl)ethyl-amide	45
	4-[4-(6-methylindazol-1-yl)-pyrimidin-2-yl-amino]-cyclohexanol	46
	4-[4-(6-hydroxy-methylindazol-1-yl)-pyrimidin-2-ylamino]-cyclohexanol	47
	4-(4-indazol-1-yl-pyrimidin-2-ylamino)-cyclohexane carboxylic acid (2-hydroxy-2-methylbut-3-yl)amide	48

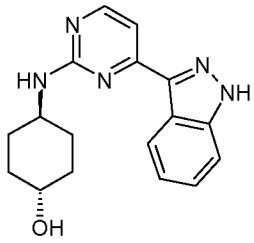
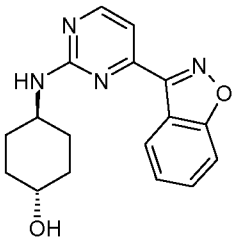
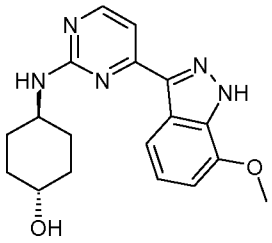
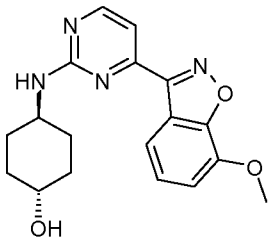
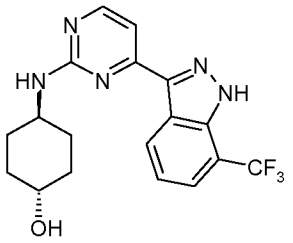
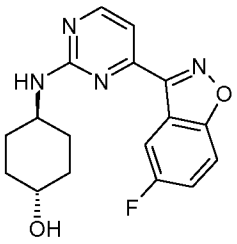
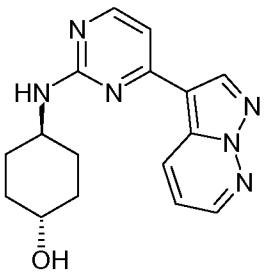
Structure	Name	Compound No.
	4-(4-indazol-1-yl-pyrimidin-2-ylamino)-cyclohexane carboxylic acid (2-hydroxy-propyl)amide	49
	4-(4-indazol-1-yl-pyrimidin-2-ylamino)-cyclohexane carboxylic acid (1-methylsulfanyl-prop-2-yl)amide	50
	4-(4-indazol-1-yl-pyrimidin-2-ylamino)-cyclohexane carboxylic acid N-(2-hydroxy-ethyl)-N-ethyl-amide	51
	N-(4-indol-1-yl-pyrimidin-2-yl)-cyclo-hexane-1,4-diamine	52
	N-(1-[2-(4-hydroxy-cyclohexylamino)-pyrimidin-4-yl]-1H-indazol-6-yl)-acet-amide	53

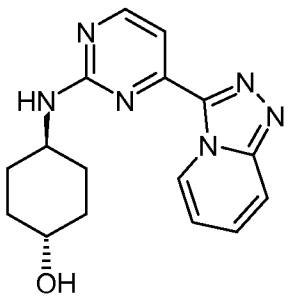
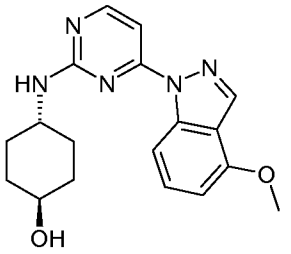
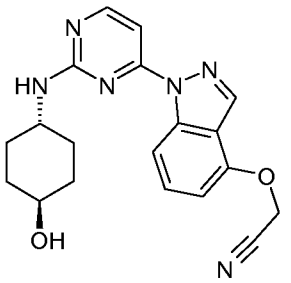
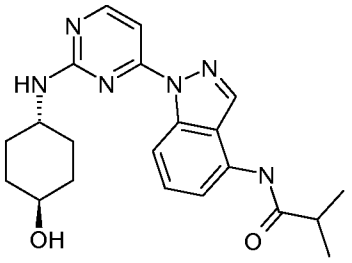
Structure	Name	Compound No.
	4-(4-indazol-1-yl-pyrimidin-2-ylamino)-cyclohexane carboxylic acid cyclopropylmethyl amide	54
	4-(4-indazol-1-yl-pyrimidin-2-ylamino)-cyclohexane carboxylic acid dimethylamide	55
	4-[4-(5-methylindazol-1-yl)-pyrimidin-2-yl-amino]-cyclohexanol	56
	4-(4-indazol-1-yl-pyrimidin-2-ylamino)-1-methylcyclohexanol	57
	3-(4-indazol-1-yl-pyrimidin-2-ylamino)-benzenesulfonamide	58
	4-[4-(5-hydroxy-methylindol-1-yl)-pyrimidin-2-ylamino]-cyclohexanol	59

Structure	Name	Compound No.
	4-[4-(6-aminoindazol-1-yl)-pyrimidin-2-yl-amino]-cyclohexanol	60
	1-[2-(4-hydroxycyclo-hexylamino)-pyrimidin-4-yl]-1H-indole-3-carboxylic acid methyl ester	61
	4-(4-[6-(2-hydroxy-ethylamino)-indazol-1-yl]-pyrimidin-2-yl-amino)-cyclohexanol	62
	4-(4-indazol-1-yl-pyrimidin-2-ylamino)-1-methyl-cyclohexanol	63
	4-[4-(5-benzyloxy-indol-1-yl)-pyrimidin-2-ylamino]-cyclo-hexanol	64
	4-[4-(4-benzylsulfanyl-indol-1-yl)-pyrimidin-2-ylamino]-cyclo-hexanol	65

Structure	Name	Compound No.
	Cyclohexyl-(4-indol-1-ylpyrimidin-2-yl)amine	66
	1-[2-(4-hydroxycyclo-hexylamino)-pyrimidin-4-yl]-1H-indole-5-carboxylic acid methyl ester	67
	4-(4-indazol-1-yl-pyrimidin-2-ylamino)-cyclohexanone	68
	(1,4-dioxaspiro[4.5]-dec-8-yl)-(4-indazol-1-ylpyrimidin-2-yl)amine	69
	1-[2-(4-hydroxycyclo-hexylamino)-pyrimidin-4-yl]-1H-indole-4-carboxylic acid	70
	4-[4-(4-benzylsulfonyl-indol-1-yl)pyrimidin-2-yl-amino]cyclohexanol	71

Structure	Name	Compound No.
	4-(4-indazol-1-yl-pyrimidin-2-ylamino)-cyclohexanecarboxylic acid cyclopentylamide	72
	[4-(4-indazol-1-yl-pyrimidin-2-ylamino)-cyclohexyl]-carbamic acid *t*-butyl ester	73
	4-[4-(1-phenylsulfonyl-1H-indol-3-yl)-pyrimidin-2-ylamino]-cyclohexanol	74
	4-[4-(1H-indol-3-yl)-pyrimidin-2-ylamino]-cyclohexanol	75
	4-[4-(1-methyl-1H-indol-3-yl)pyrimidin-2-ylamino]-cyclohexanol	76
	4-[4-(1-methyl-1H-indazol-3-yl)-pyrimidin-2-ylamino]-cyclohexanol	77

Structure	Name	Compound No.
	4-[4-(1H-indazol-3-yl)pyrimidin-2-ylamino]-cyclohexanol	78
	4-(4-benzo[d]isoxazol-3-ylpyrimidin-2-yl-amino)-cyclohexanol	79
	4-[4-(7-methoxy-1H-indazol-3-yl)-pyrimidin-2-ylamino]-cyclohexanol	80
	4-[4-(7-methoxy-benzo[d]isoxazol-3-yl)-pyrimidin-2-ylamino]-cyclohexanol	81
	4-[4-(7-methyl-1H-indazol-3-yl)-pyrimidin-2-ylamino]-cyclohexanol	82
	4-[4-(5-fluorobenzo-[d]isoxazol-3-yl)-pyrimidin-2-ylamino]-cyclohexanol	83
	4-(4-pyrazolo[1,5-b]-pyridazin-3-yl-pyrimidin-2-ylamino)-cyclohexanol	84

Structure	Name	Compound No.
	4-(4-[1,2,4]triazole-[4,3-a]pyridine-3-yl-pyrimidin-2-ylamino)-cyclohexanol	85
	4-[4-(4-methoxy-indazol-1-yl)-pyrimidin-2-ylamino]-cyclohexanol	86
	(1-[2-(4-hydroxycyclo-hexylamino)-pyrimidin-4-yl]-1H-indazol-4-yloxy)-acetonitrile	87
	N-(1-[2-(4-hydroxy-cyclohexylamino)-pyrimidin-4-yl]-1H-indazol-4-yl)-isobutyr-amide	88

Synthesis

Compounds of the present invention can be made by a variety of methods depicted in the illustrative examples shown in the Examples section below. The starting materials and reagents used in preparing these compounds generally are either available from commercial suppliers, such as Aldrich Chemical Co., or are prepared by methods known to those skilled in the art following procedures set forth in references such as *Fieser and Fieser's Reagents for Organic Synthesis*; Wiley & Sons: New York, **1991**, Volumes 1-15; *Rodd's Chemistry of Carbon Compounds*, Elsevier Science Publishers, 1989, Volumes 1-5 and Supplements; and *Organic Reactions*, Wiley & Sons: New York, **1991**, Volumes 1-40. The following synthetic reaction schemes are merely

illustrative of some methods by which the compounds of the present invention can be synthesized, and various modifications to these synthetic reaction schemes can be made and will be suggested to one skilled in the art having referred to the disclosure contained in this Application.

The starting materials and the intermediates of the synthetic reaction schemes can be isolated and purified if desired using conventional techniques, including but not limited to, filtration, distillation, crystallization, chromatography. Such materials can be characterized using conventional means, including physical constants and spectral data.

Unless specified to the contrary, the reaction described herein preferably are conducted under inert atmosphere, at atmospheric pressure, at a reaction temperature range of from about -78°C to about 230°C, and most preferably and conveniently at room (or ambient) temperature, e.g., about 20°C.

In the following schemes, if not differently specified, R^1, X^1, X^2, X^3, and the like are as defined above; while

A is Cl or SR_b

A_1 is Cl, (S=O)Me, SO_2Me or SO_2Bu

R_a is alkyl, cycloalkyl

R_b is Me or Bu

Z is N or C

X is Cl, Br, I

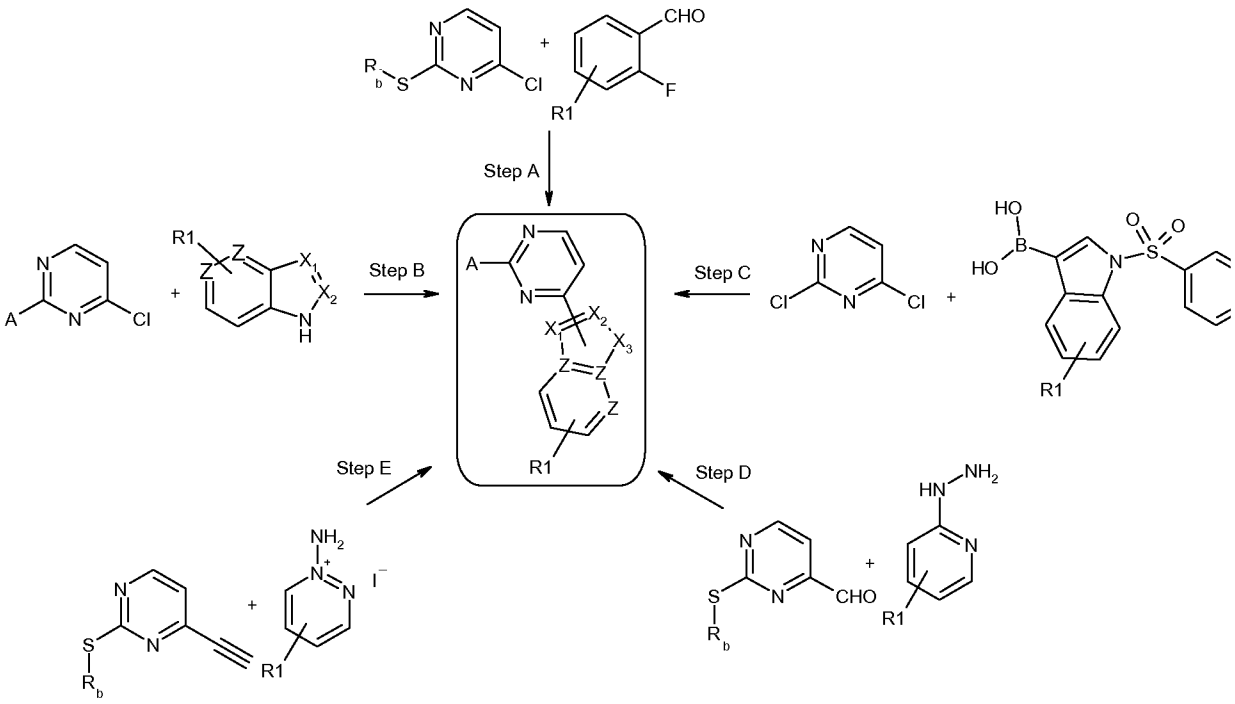
R_e and R_f are independently hydrogen, hydroxylakyl, alkoxy, alkyl, cycloalkyl hetheroalkyl, alkylsufonyl, alkylsulfinyl

R_g is lower alkyl

R_h is alkyl or cylcoalkyl

R_i is alkyl, cycloalkyl, heterocyclic

SCHEME I:



Step **A**: 1. 1,3-dimethylimidazolium iodide, NaH, 1,4-dioxane, reflux; 2. *tert*-butyl carbazate, AcOH, MeOH, reflux; or NH_2OH, EtOH, reflux; 3. DBU, THF, MW 150°C.

Step **B**: NaH, DMF; or LiHMDS or NaHMDS, acetonitrile/THF, low temp; or DIPEA, DMF 100°C.

Step **C**: tetrakis(triphenylphosphine)palladium(0), Na_2CO_3, acetonitrile, water.

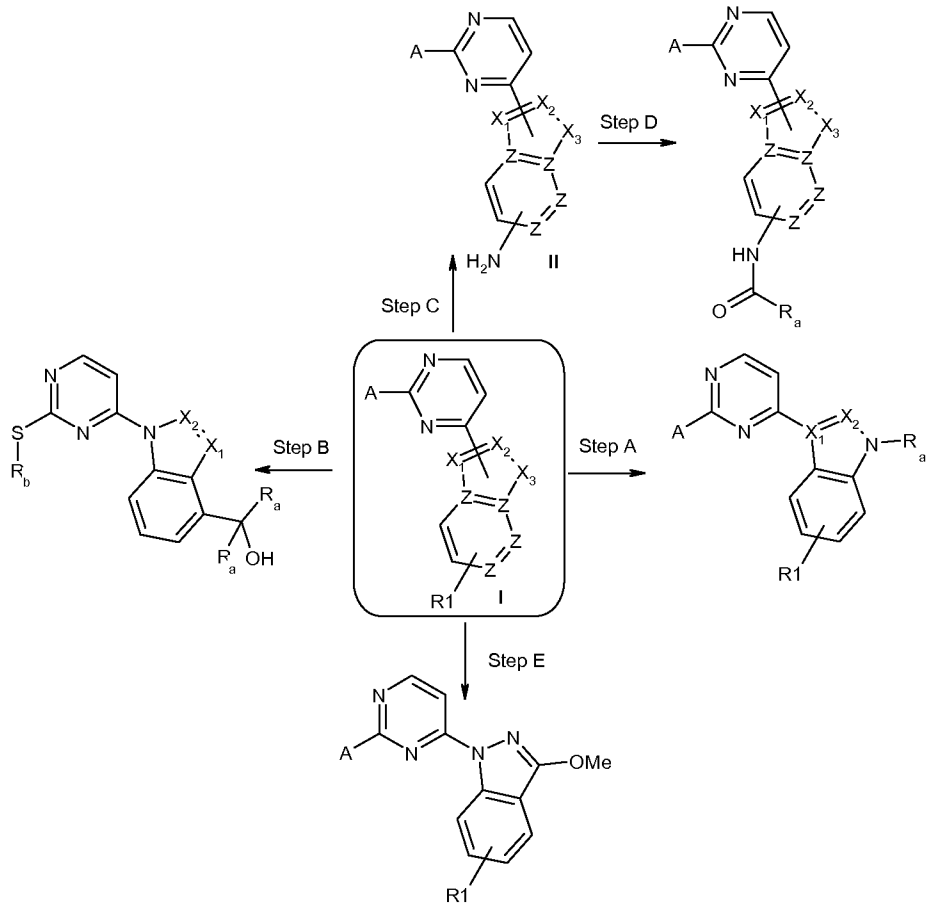
Step **D**: 1. EtOH, reflux; 2. Iodobenzene diacetate, DCM.

Step **E**: KOH, water, DCM.

In Step **A**, 4-chloro-2-methylsulfanyl-pyrimidine or 4-chloro-2-butylsulfanyl-pyrimidine reacts, by heating to reflux, in presence of a strong base, such as sodium hydride, and 1,3-dimethylimidazolium iodide with a variably substituted *o*-fluorobenzaldehyde in a polar aprotic solvent, such as 1,4-dioxane, to give the corresponding ketone. This product by treatment with *tert*-butyl carbazate, in the presence of acetic acid, in apolar protic solvent, such as methanol, by heating to reflux gives the corresponding hydrazone which, by heating under microwave conditions, in the presence of a base, such as DBU, and in a polar solvent, such as THF, cyclizes to give the corresponding indazole. When hydroxylamine is used in place of *tert*-butyl carbazate the corresponding benzoxazole is obtained. In Step **B**, 4-chloropyrimidine [illegible] 2-position a mercaptoalkyl- or chloro- moiety undergoes a S_NAr

reaction with a variably substituteed indole, indazole, azaindole or indoline in presence of a base such as NaH, LiHMDS, NaHMDS or DIPEA, in a polar solvent such as DMF, acetonitrile, THF, 1,4-dioxane or a mixture of the above, at temperature ranging from -10°C to 100°C, to afford the corresponding: *N*1-arylated indole, *N*1- or *N*2- arylated indazole, *N*1-arylated azaindole and *N*1-arylated indoline. In Step **C**, 2,4-dichloropyrimidine undergoes a Buchwald coupling with a variably substituted 3-indole boronic acid, *N1* protected, in the presence of a catalyst such as tetrakis(triphenylphosphine)palladium(0), and an inorganic base, such as Na_2CO_3, in a mixture of polar solvents, such as acetonitrile/water, affording the corresponding 2-chloro-4-arylated pyrimidine. In Step **D**, 2-methylsulfanyl-pyrimidine-4-carbaldehyde reacts with a substituted or unsubstituted pyridin-2-yl-hydrazine in a polar protic solvent, such as ethanol, by heating to reflux, to give the corresponding hydrazone, which cyclizes in the presence of iodobenzene diacetate in an apolar solvent, such as DCM, to give the corresponding variably substituted [1,2,4]triazolo[4,3-*a*]pyridine. In Step **E**, 4-ethynyl-2-methylsulfanyl-pyrimidine reacts with 1-amino-pyridazin-1-ium iodide (*J. Med. Chem.* **2004**, *47*, 4716-30) in the presence of water and an inorganic base, such as KOH, in an apolar solvent, such as DCM, to afford the corresponding 3-(2-methylsulfanyl-pyrimidin-4-yl)-pyrazolo[1,5-*b*]pyridazine.

SCHEME II:



When X^3 is NH or NSO_2Ph Step **A**: NaH, R_aX, NMP, or 1. NaOH, MeOH/THF; 2. NaH, R_aX, NMP.

When R1 is COOMe Step **B**: R_aMgCl, THF, low temp.

When R1 is NO_2 Step **C**: Fe(0), NH_4Cl, EtOH, water, heating; Step **D**: R_aCOCl, TEA, THF.

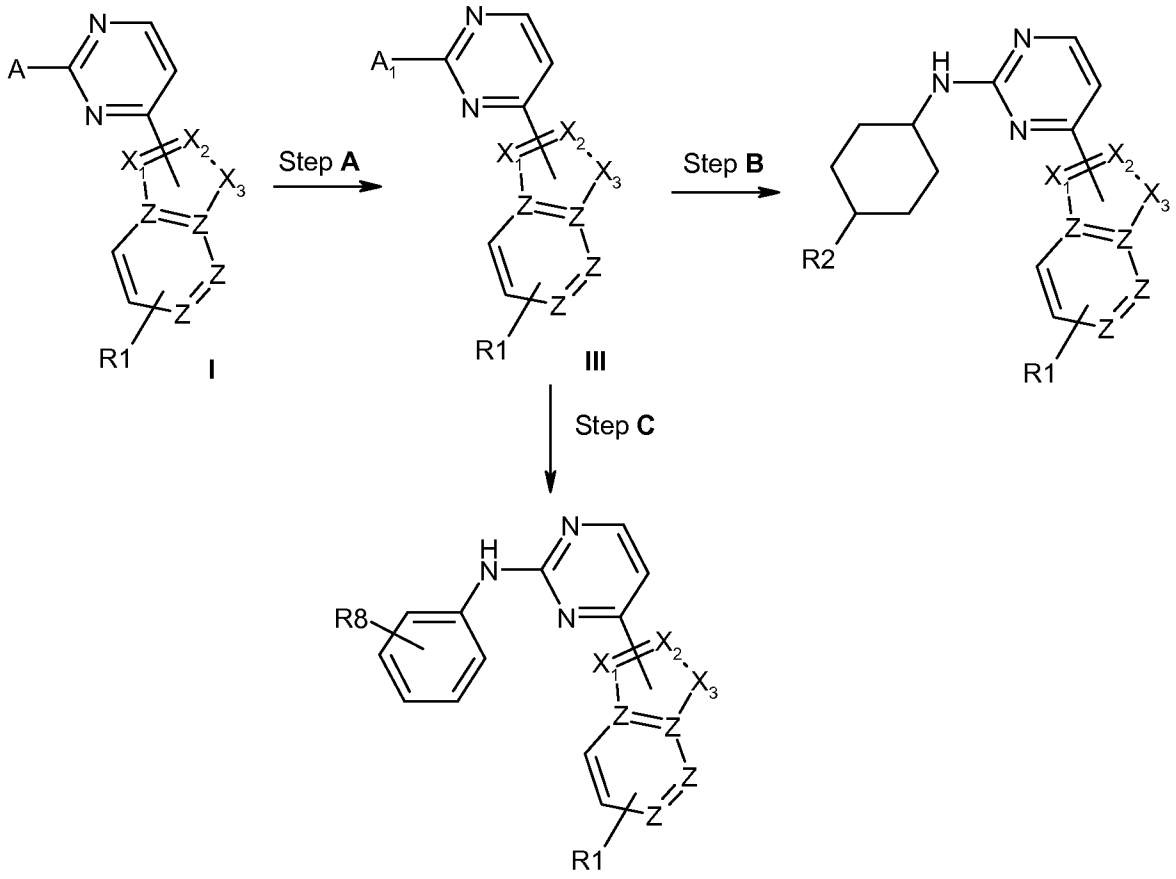
When X^1 is C=O Step **E**: NaH, R_aX, DMF, 0ºC.

In Step **A**, a compound of generic structure **I** when X^3 is NH can be alkylated by treatment with a strong base, such as NaH, and the appropriate alkyl or cycloalkyl halide such as MeI in a polar solvent such as NMP. When X^3 is a phenylsulfonylamide moiety, a compound of generic structure **I** can be firstly deprotected by treatment with a strong inorganic base, such as NaOH, in mixture of polar solvents, such as MeOH/THF, and then alkylated as previously described. In Step **B**, a compound of generic structure **I** when R1 is a methyl ester moiety can undergo a double addition by a Grignard reactant, such as MeMgCl, at low temperature, in a polar solvent, such as

he corresponding tertiary alcohol. In Step **C**, a compound of generic

structure **I** when R^1 is NO_2 can be reduced to the corresponding aniline by heating in presence of a reducing agent, such as Fe(0) Fisher, ammonium chloride and water, in a polar protic solvent such as ethanol. The aniline of generic formula **II** can subsequently be acylated by treatment with the appropriate acyl chloride in the presence of a base, such as triethylamine, in a polar solvent, such as THF, to give the corresponding secondary amide as described in Step **D**. In Step **E**, a compound of generic structure **I** when X^1 is C=O can be O-alkylated by treatment with an alkylating agent, such as MeI, after deprotonation with a strong base, such as NaH, in a polar solvent, such as DMF, at low temperature.

SCHEME III:



Step **A**: NCS, NMP or m-CPBA or $MeReO_3/H_2O_2$, DCM.

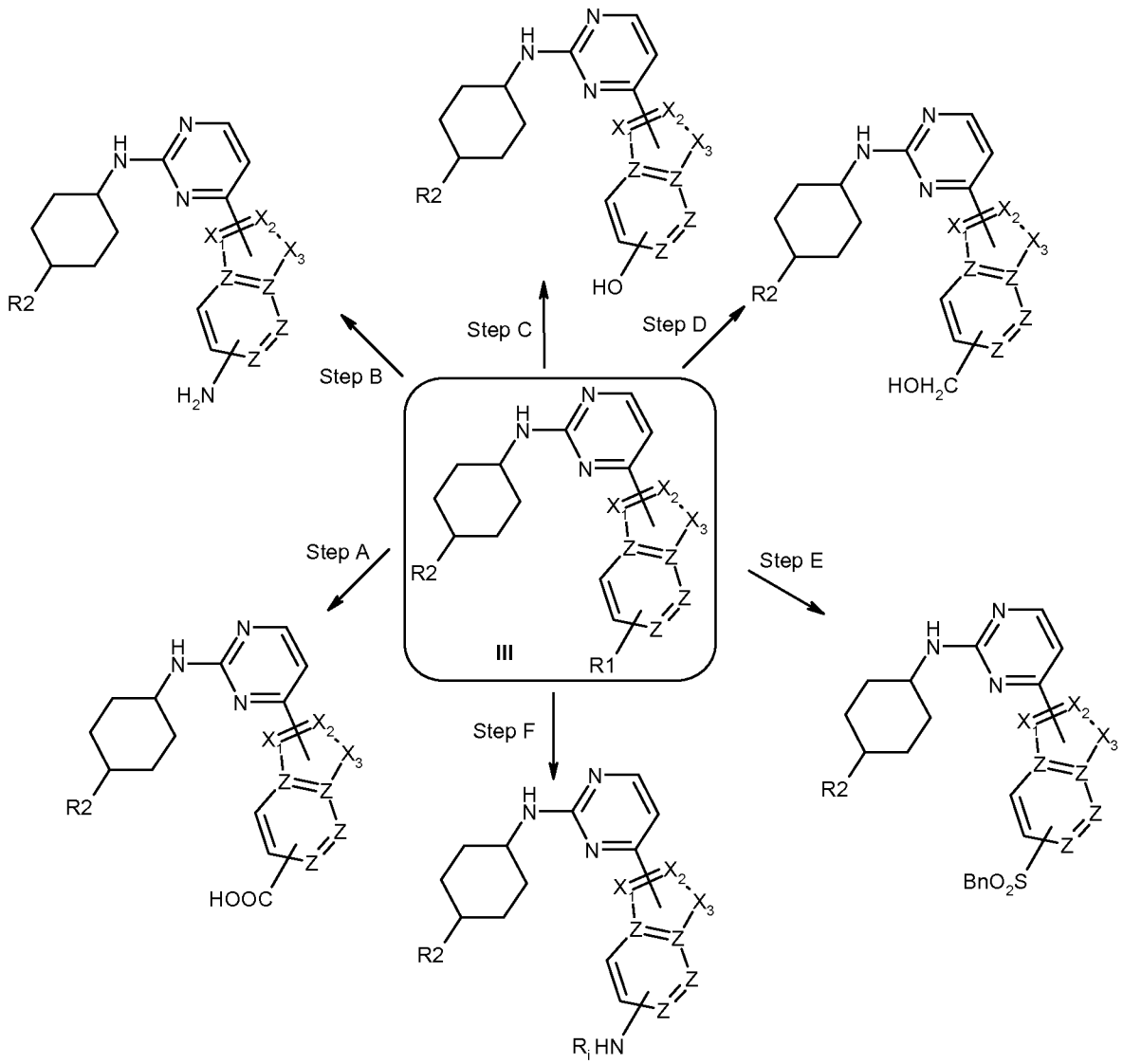
Step **B**: $R^2C_6H_{10}NH_2$, NMP, heating or $R^2C_6H_{10}NH_2$, DIPEA, NMP, heating.

Step **C**: $R^8C_6H_4NH_2$, p-TSA, i-PrOH, 150°C, MW.

In Step **A**, a compound of generic formula **I**, when A is a thiomethyl moiety, can be chlorinated in presence of N-chlorosuccinimide in a polar solvent, such as NMP, at

high temperature. Alternatively a compound of generic formula **I** can be oxidized to the corresponding sulfone or sulfoxide utilizing as oxidizer 3-chloroperoxybenzoic acid or a mixture of methyltrioxorhenium and hydrogen peroxide in an apolar solvent, such as DCM or chloroform, at temperature ranging between 0°C and room temperature. The corresponding chloride, sulfone or sulfoxide **III** can undergo a reaction of S_NAr utilizing a variably substituted or unsubstituted cyclohexylamine, as nucleophile, either with or without a base, such as diisopropylethylamine, in an apolar solvent, such as NMP, at temperature ranging between 90 and 150°C, as described in Step **B**. Alternatively a sulfoxide of generic structure **III** can react with a variably substituted or unsubstituted aniline, in the presence of *p*-toluenesulfonic acid, in a polar protic solvent, such as isopropanol, under microwave conditions at 150°C as described in Step **C**.

SCHEME IV:



When R^1 is COOMe, COOEt: Step A: LiOH or NaOH, THF/MeOH.

When R^1 is NO_2: Step B: Fe(0), NH_4Cl, EtOH, water, heating.

When R^1 is OBn: Step C: H_2, Pd/C, EtOH.

When R^1 is COOMe: Step D: LAH or $LiEt_3BH$, THF -10°C or RT.

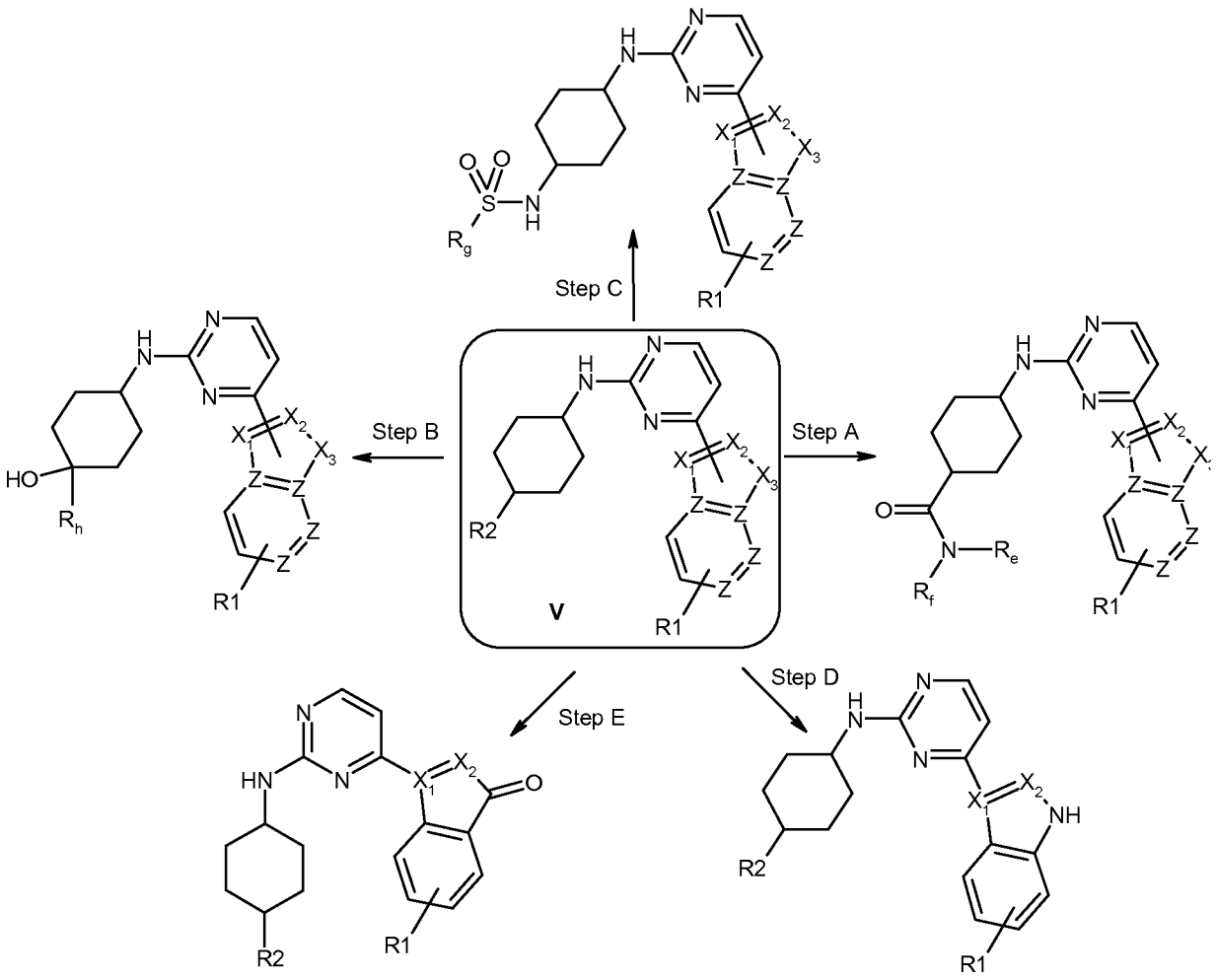
When R^1 is SBn: Step E: m-CPBA, chloroform.

When R^1 is NH_2: Step F: R_iX, Na_2CO_3, DMF, 80°C.

In Step A, a compound of generic formula **IV**, when R^1 is a methyl- or ethyl- ester moiety, can be hydrolyzed to the corresponding carboxylic acid in the presence of a strong inorganic base, such as sodium or lithium hydroxide, in a mixture of polar

solvents such as THF and MeOH. In Step **B**, a compound of generic formula **IV**, when R^1 is a nitro moiety, can be reduced to the corresponding aniline by heating in the presence of ammonium chloride and water, in a polar protic solvent, such as ethanol, utilizing a reductive agent such as iron Fisher. In Step **C**, a compound of generic formula **IV**, when R1 is a benzyloxy moiety, can be reduced to the corresponding phenol, utilizing hydrogen as reductive agent, in the presence of palladium on carbon as catalyst, in polar protic solvent such as ethanol. In Step **D**, a compound of generic formula **IV**, when R1 is a methyl- or ethyl- ester moiety, can be reduced to the corresponding benzyl alcohol, utilizing as reductive agent lithium aluminum hydride or lithium trimethylborohydride, in a polar solvent, such as THF, at temperature ranging between -10°C and room temperature. In Step **E**, a compound of generic formula **IV**, when R1 is a mercaptobenzyl moiety, can be oxidized to the corresponding sulfone, utilizing 3-chloroperoxybenzoic acid as oxidized, in an apolar solvent such as chloroform. In Step **F**, a compound of generic formula **IV**, when R^1 is an amine moiety, can be alkylated to the corresponding secondary or tertiary amine by heating, in the presence of an inorganic base, such as sodium carbonate, in a polar solvent, such as DMF, utilizing an alkyl-, cycloalkyl-, heterocyclic- halide as alkylating agent.

SCHEME V:



When R^2 is COOEt: Step **A**: 1. NaOH, THF; 2. R_eR_fNH, BOP, DIPEA, THF.

When R^2 is $O(CH_2)_2O$: Step **B**: 1. HCl, THF, heating; 2. R_hMgCl, THF, -78ºC.

When R^2 is NH_2: Step **C**: $(R_gSO_2)O$.

When X^3 is $NHSO_2Ph$: Step **D**: NaOH, MeOH.

When X^1 is C-OMe: Step **E**: TMSI, $CHCl_3$.

In Step **A**, a compound of generic formula **V**, when R^2 is an ethyl- or methyl- ester moiety, can be hydrolyzed to the corresponding carboxylic acid, in the presence of a strong inorganic base, such as sodium hydroxide, in a polar solvent such as THF. Subsequently the carboxylic acid can be coupled with a hydroxylakyl-, alkoxy-, alkyl-, cycloalkyl-, hetheroalkyl-, alkylsufonyl-, alkylsulfinyl- amine to give the corresponding amide in the presence of a coupling agent, such as BOP, and a base, such as DIPEA, in a polar solvent such as THF. In Step **B**, a compound of generic formula **V**, when R^2 is a

1,3-dioxolane moiety, can be hydrolyzed to the corresponding ketone by heating, in the presence of a strong inorganic acid, such as HCl, in a polar solvent such as THF. The ketone obtained in this manner can undergo an addition reaction by a Grignard reactant, at low temperature, in a polar solvent, such as THF, to give the corresponding tertiary alcohol. In Step **C**, a compound of generic formula **V**, when R^2 is an amine moiety, can be sulfonylated, in the presence of a sulfonylanhydride, in polar solvent, such as NMP, to give the corresponding sulfonylamide. In Step **D**, a compound of generic formula **V**, when X^3 is a phenylsulfonylamide moiety, can be hydrolyzed to the corresponding indole, indazole or benzoxazole, in the presence of an inorganic base, such as sodium hydroxide, in a polar solvent such as methanol. In Step **E**, a compound of generic formula **V**, when X^1 is a methyl ether moiety, can be oxidized to the corresponding ketone by reaction with trimethylsilyliodide in a apolar solvent

The products can then be purified, e.g., by extraction, crystallization, preparative HPLC, flash chromatography, thin layer chromatography.

The compounds of this invention are JNK modulators and as such are expected to be effective in the treatment of a wide range of JNK mediated disorders. Exemplary JNK mediated disorders include, but are not limited to, autoimmune disorder, inflammatory disorder, metabolic disorder, neurological disease, and cancer. Accordingly, compounds of the invention can be used to treat one or more of such disorders. In some embodiments, compounds of the invention can be used to treat a JNK mediated disorder such as rheumatoid arthritis, asthma, type II diabetes, Alzheimer's disease, Parkinson's disease or stroke.

Administration and Pharmaceutical Composition

The invention includes pharmaceutical compositions comprising at least one compound of the present invention, or an individual isomer, racemic or non-racemic mixture of isomers or a pharmaceutically acceptable salt or solvate thereof, together with at least one pharmaceutically acceptable carrier, and optionally other therapeutic and/or prophylactic ingredients.

In general, the compounds of the invention will be administered in a therapeutically effective amount by any of the accepted modes of administration for agents that serve similar utilities. Suitable dosage ranges are typically 1-500 mg daily, preferably 1-100 mg daily, and most preferably 1-30 mg daily, depending upon numerous factors such

as the severity of the disease to be treated, the age and relative health of the subject, the potency of the compound used, the route and form of administration, the indication towards which the administration is directed, and the preferences and experience of the medical practitioner involved. One of ordinary skill in the art of treating such diseases will be able, without undue experimentation and in reliance upon personal knowledge and the disclosure of this Application, to ascertain a therapeutically effective amount of the compounds of the present invention for a given disease.

Compounds of the invention may be administered as pharmaceutical formulations including those suitable for oral (including buccal and sub-lingual), rectal, nasal, topical, pulmonary, vaginal, or parenteral (including intramuscular, intraarterial, intrathecal, subcutaneous and intravenous) administration or in a form suitable for administration by inhalation or insufflation. The preferred manner of administration is generally oral using a convenient daily dosage regimen which can be adjusted according to the degree of affliction.

A compound or compounds of the invention, together with one or more conventional adjuvants, carriers, or diluents, may be placed into the form of pharmaceutical compositions and unit dosages. The pharmaceutical compositions and unit dosage forms may be comprised of conventional ingredients in conventional proportions, with or without additional active compounds or principles, and the unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed. The pharmaceutical compositions may be employed as solids, such as tablets or filled capsules, semisolids, powders, sustained release formulations, or liquids such as solutions, suspensions, emulsions, elixirs, or filled capsules for oral use; or in the form of suppositories for rectal or vaginal administration; or in the form of sterile injectable solutions for parenteral use. Formulations containing about one (1) mg of active ingredient or, more broadly, about 0.01 to about one hundred (100) mg, per tablet, are accordingly suitable representative unit dosage forms.

The compounds of the invention may be formulated in a wide variety of oral administration dosage forms. The pharmaceutical compositions and dosage forms may comprise a compound or compounds of the present invention or pharmaceutically acceptable salts thereof as the active component. The pharmaceutically acceptable carriers may be either solid or liquid. Solid form preparations include powders,

tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier may be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material. In powders, the carrier generally is a finely divided solid which is a mixture with the finely divided active component. In tablets, the active component generally is mixed with the carrier having the necessary binding capacity in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain from about one (1) to about seventy (70) percent of the active compound. Suitable carriers include but are not limited to magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as carrier, providing a capsule in which the active component, with or without carriers, is surrounded by a carrier, which is in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges may be as solid forms suitable for oral administration.

Other forms suitable for oral administration include liquid form preparations including emulsions, syrups, elixirs, aqueous solutions, aqueous suspensions, or solid form preparations which are intended to be converted shortly before use to liquid form preparations. Emulsions may be prepared in solutions, for example, in aqueous propylene glycol solutions or may contain emulsifying agents, for example, such as lecithin, sorbitan monooleate, or acacia. Aqueous solutions can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizers, and thickening agents. Aqueous suspensions can be prepared by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well known suspending agents. Solid form preparations include solutions, suspensions, and emulsions, and may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents.

The compounds of the invention may be formulated for parenteral administration (e.g., by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or

in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, for example solutions in aqueous polyethylene glycol. Examples of oily or nonaqueous carriers, diluents, solvents or vehicles include propylene glycol, polyethylene glycol, vegetable oils (e.g., olive oil), and injectable organic esters (e.g., ethyl oleate), and may contain formulatory agents such as preserving, wetting, emulsifying or suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilization from solution for constitution before use with a suitable vehicle, e.g., sterile, pyrogen-free water.

The compounds of the invention may be formulated for topical administration to the epidermis as ointments, creams or lotions, or as a transdermal patch. Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also containing one or more emulsifying agents, stabilizing agents, dispersing agents, suspending agents, thickening agents, or coloring agents. Formulations suitable for topical administration in the mouth include lozenges comprising active agents in a flavored base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerin or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

The compounds of the invention may be formulated for administration as suppositories. A low melting wax, such as a mixture of fatty acid glycerides or cocoa butter is first melted and the active component is dispersed homogeneously, for example, by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool, and to solidify.

The compounds of the invention may be formulated for vaginal administration. Pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

The subject compounds may be formulated for nasal administration. The solutions or suspensions are applied directly to the nasal cavity by conventional means, for example, with a dropper, pipette or spray. The formulations may be provided in a single or multidose form. In the latter case of a dropper or pipette, this may be achieved by the patient administering an appropriate, predetermined volume of the

solution or suspension. In the case of a spray, this may be achieved for example by means of a metering atomizing spray pump.

The compounds of the invention may be formulated for aerosol administration, particularly to the respiratory tract and including intranasal administration. The compound will generally have a small particle size for example of the order of five (5) microns or less. Such a particle size may be obtained by means known in the art, for example by micronization. The active ingredient is provided in a pressurized pack with a suitable propellant such as a chlorofluorocarbon (CFC), for example, dichlorodifluoromethane, trichlorofluoromethane, or dichlorotetrafluoroethane, or carbon dioxide or other suitable gas. The aerosol may conveniently also contain a surfactant such as lecithin. The dose of drug may be controlled by a metered valve. Alternatively the active ingredients may be provided in a form of a dry powder, for example a powder mix of the compound in a suitable powder base such as lactose, starch, starch derivatives such as hydroxypropylmethyl cellulose and polyvinylpyrrolidine (PVP). The powder carrier will form a gel in the nasal cavity. The powder composition may be presented in unit dose form for example in capsules or cartridges of e.g., gelatin or blister packs from which the powder may be administered by means of an inhaler.

When desired, formulations can be prepared with enteric coatings adapted for sustained or controlled release administration of the active ingredient. For example, the compounds of the present invention can be formulated in transdermal or subcutaneous drug delivery devices. These delivery systems are advantageous when sustained release of the compound is necessary and when patient compliance with a treatment regimen is crucial. Compounds in transdermal delivery systems are frequently attached to an skin-adhesive solid support. The compound of interest can also be combined with a penetration enhancer, e.g., Azone (1-dodecylazacycloheptan-2-one). Sustained release delivery systems are inserted subcutaneously into the sub-dermal layer by surgery or injection. The subdermal implants encapsulate the compound in a lipid soluble membrane, e.g., silicone rubber, or a biodegradable polymer, e.g., polylactic acid.

The pharmaceutical preparations are preferably in unit dosage forms. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and

powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

Other suitable pharmaceutical carriers and their formulations are described in *Remington: The Science and Practice of Pharmacy* 1995, edited by E. W. Martin, Mack Publishing Company, 19th edition, Easton, Pennsylvania. Representative pharmaceutical formulations containing a compound of the present invention are described below.

Additional objects, advantages, and novel features of this invention will become apparent to those skilled in the art upon examination of the following examples thereof, which are not intended to be limiting.

EXAMPLES

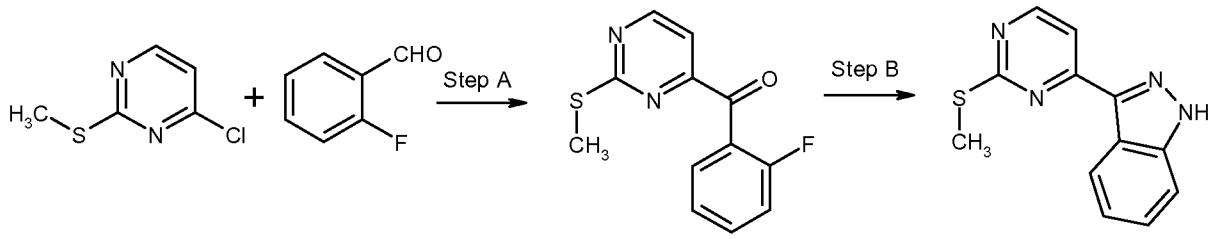
LIST OF ABBREVIATIONS

AcOH	Acetic acid
Bn	Benzyl
BOP	Benzotriazol-1-yloxytris(dimethylamIno)phosphonium hexafluorophosphate
$(BOC)_2O$	Di-*tert*-butyl dicarbonate
DBU	1,8-Diazabicyclo[5.4.0]-undec-7-ene
DCM	Dichloromethane (methylene chloride)
DEA	Diethylamine
DIPEA	Diisopropylethylamine
DMF	N,N-dimethylformamide
EDCI	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
Et_2O	Diethyl ether
EtOH	Ethanol
EtOAc	Ethyl acetate

HOBt	1-Hydroxybenzotriazole
i-PrOH	Isopropanol
LAH	Lithium aluminum hydride
m-CPBA	3-Chloroperoxybenzoic acid
MeOH	Methanol
MW	Microwaves
NCS	N-Chlorosuccinimide
NMP	1-Methyl-2-pyrrolidinone
p-TSA	p-Toluenesulfonic acid
RT	Room temperature
TEA	Triethylamine
THF	Tetrahydrofuran
TLC	Thin layer chromatography

Preparation 1: Synthesis of 3-(2-Methylsulfanyl-pyrimidin-4-yl)-1*H*-indazole

The synthesis of 3-(2-methylsulfanyl-pyrimidin-4-yl)-1*H*-indazole was carried out according to the process shown in Scheme 1.



SCHEME 1

Step A: synthesis of (2-fluoro-phenyl)-(2-methylsulfanyl-pyrimidin-4-yl)-methanone

Sodium hydride (60% dispersion in mineral oil, 598 mg, 14.94 mmol) was added to a stirring solution of 4-chloro-2-methylthiopyrimidine (1.45 mL, 12.45 mmol), 2-fluoro-benzaldehyde (1.57 mL, 14.94 mmol) and 1,3-dimethylimidazolium iodide (517 mg, 4.15

mmol) (prepared as described in *Org. Synth.* (1986) 64:9) in 1,4-dioxane (20 mL). The resulting mixture was heated at reflux for 1 hour; it was then cooled and partitioned between EtOAc and water. The organic layer was separated and dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude residue was purified by flash chromatography (hexane/EtOAc, 95/5) to give 840 mg of (2-fluorophenyl)-(2-methylsulfanyl-pyrimidin-4-yl)-methanone.

In the same manner, using the appropriate starting materials, the following compounds were prepared:

(2-Fluoro-3-methoxy-phenyl)-(2-methylsulfanyl-pyrimidin-4-yl)-methanone; and

(2,5-Difluoro-phenyl)-(2-methylsulfanyl-pyrimidin-4-yl)-methanone.

Step B: synthesis of 3-(2-methylsulfanyl-pyrimidin-4-yl)-1*H*-indazole

tert-Butylcarbazate (899 mg, 6.8 mmol) and acetic acid (0.5 mL) were added to a mixture of (2-fluoro-phenyl)-(2-methylsulfanyl-pyrimidin-4-yl)-methanone (840 mg, 3.4 mmol) in MeOH. The resulting mixture was heated at reflux for 16 h; it was then cooled to RT and partitioned between EtOAc and aqueous sodium bicarbonate. The organic layer was separated and dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was placed in a sealed tube with DBU (0.79 mL, 5.3 mmol) and THF. The resulting mixture was heated to 150°C in a microwave reactor for 30 minutes. The reaction mixture was then evaporated under reduced pressure and the crude residue was purified by flash chromatography (hexane/EtOAc, 4/1) to afford 525 mg of 3-(2-methylsulfanyl-pyrimidin-4-yl)-1*H*-indazole.

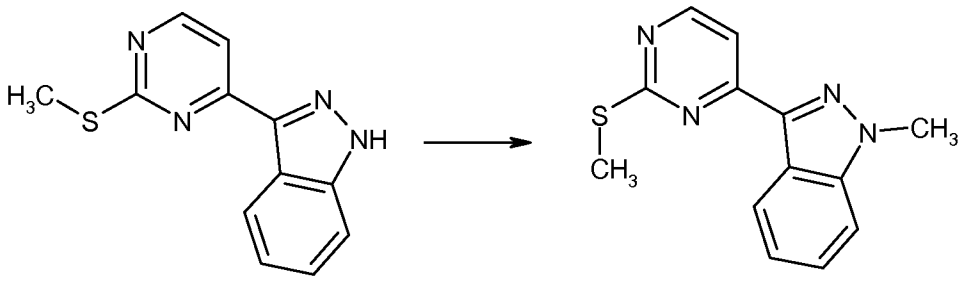
In a similar manner, utilizing the appropriate starting material, the following compounds were prepared:

7-Methoxy-3-(2-methylsulfanyl-pyrimidin-4-yl)-1*H*-indazole, and

3-(2-Methylsulfanyl-pyrimidin-4-yl)-7-trifluoromethyl-1*H*-indazole.

Preparation 2: Synthesis of 1-Methyl-3-(2-methylsulfanyl-pyrimidin-4-yl)-1*H*-indazole

The synthesis of 1-methyl-3-(2-methylsulfanyl-pyrimidin-4-yl)-1*H*-indazole was carried out according to the process shown in Scheme 2.

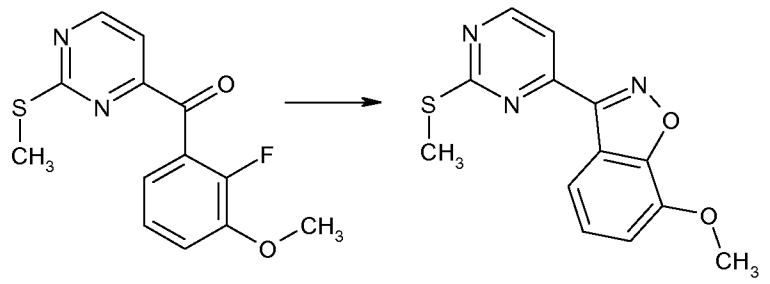


SCHEME 2

Sodium hydride (60% suspension in mineral oil, 99 mg, 2.47 mmol) was added to a stirring solution of 3-(2-methylsulfanyl-pyrimidin-4-yl)-1*H*-indazole (520 mg, 2.15 mmol) in NMP at 0°C. The mixture was stirred for 15 min and then methyliodide (0.14 mL, 2.25 mmol) was added and the resulting mixture was stirred for 2 h. The reaction mixture was then poured into water and extracted twice with EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by flash chromatography (hexane/ EtOAc, 9/1) to give 415 mg of 1-methyl-3-(2-methylsulfanyl-pyrimidin-4-yl)-1*H*-indazole.

Preparation 3: Synthesis of 7-Methoxy-3-(2-methylsulfanyl-pyrimidin-4-yl)-benzo[*d*]isoxazole

The synthesis of 7-methoxy-3-(2-methylsulfanyl-pyrimidin-4-yl)-benzo[*d*]isoxazole was carried out according to the process shown in Scheme 3.



SCHEME 3

A mixture of (2-fluoro-3-methoxy-phenyl)-(2-methylsulfanyl-pyrimidin-4-yl)-methanone (1 g, 3.59 mmol) and hydroxylamine (50% in water, 1.5 mL) in ethanol was heated to reflux overnight. The resulting mixture was cooled to RT, diluted with EtOAc and then concentrated under reduced pressure. The residue was dissolved in THF and DBU (0.84 mL, 5.6 mmol) was added, the resulting mixture was heated to 150°C in a microwave reactor for 30 min. The reaction mixture was then concentrated under reduced pressure and the residue was purified by flash chromatography (hexane/EtOAc,

95/5) to give 458 mg of 7-methoxy-3-(2-methylsulfanyl-pyrimidin-4-yl)-benzo[*d*]isoxazole.

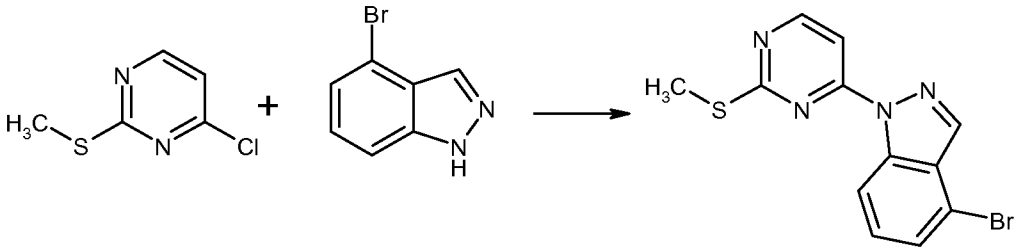
In the same manner, using the appropriate starting material, the following compounds were prepared:

3-(2-Methylsulfanyl-pyrimidin-4-yl)-benzo[*d*]isoxazole; and

5-Fluoro-3-(2-methylsulfanyl-pyrimidin-4-yl)-benzo[*d*]isoxazole.

Preparation 4: Synthesis of 3-Bromo-1-(2-methylsulfanyl-pyrimidin-4-yl)-1*H*-indazole

The synthesis of 3-bromo-1-(2-methylsulfanyl-pyrimidin-4-yl)-1*H*-indazole was carried out according to the process shown in Scheme 4.



SCHEME 4

To a solution of 4-bromo-1*H*-indazole (8.831 g, 44.82 mmol) in DMF (100 mL) was added NaH (60% suspension in mineral oil, 74.7 mmol, 2.988 g) followed by 4-chloro-2-methylsulfanyl-pyrimidine (4.34 mL, 37.35 mmol). The resulting mixture was allowed to stir at RT for 2 h; the solid precipitate was collected by filtration, washed and dried under reduced pressure to give 10.7 g (89% yield) of 3-bromo-1-(2-methylsulfanyl-pyrimidin-4-yl)-1*H*-indazole.

In a similar manner, utilizing the appropriate starting materials, the following compounds were prepared:

1-(2-Methylsulfanyl-pyrimidin-4-yl)-1*H*-indazole;

6-Methyl-1-(2-methylsulfanyl-pyrimidin-4-yl)-1*H*-indazole;

5-Methyl-1-(2-methylsulfanyl-pyrimidin-4-yl)-1*H*-indazole;

3-Methyl-1-(2-methylsulfanyl-pyrimidin-4-yl)-1*H*-indole;

6-Fluoro-1-(2-methylsulfanyl-pyrimidin-4-yl)-1*H*-indole;

4-Benzyloxy-1-(2-methylsulfanyl-pyrimidin-4-yl)-1*H*-indole;

5-Benzyloxy-1-(2-methylsulfanyl-pyrimidin-4-yl)-1*H*-indole;

1-(2-Methylsulfanyl-pyrimidin-4-yl)-1*H*-indole;

1-(2-Methylsulfanyl-pyrimidin-4-yl)-1*H*-indazole;

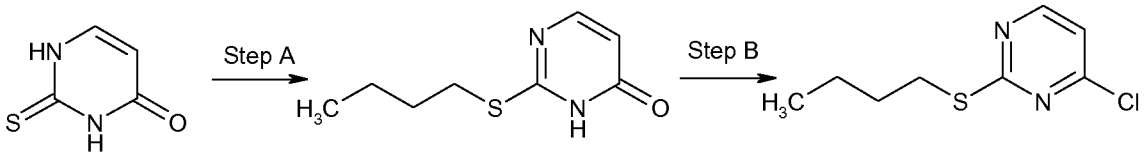
1-(2-Methylsulfanyl-pyrimidin-4-yl)-6-nitro-1*H*-indazole;

1-(2-Methylsulfanyl-pyrimidin-4-yl)-1*H*-pyrrolo[3,2-*b*]pyridine (white crystalline solid), MS = 243 $[M+H]^+$, MP = 120.1-123.0°C; and

1-(2-Methylsulfanyl-pyrimidin-4-yl)-1*H*-pyrrolo[3,2-*c*]pyridine (tan solid), MS = 243 $[M+H]^+$, MP = 167.7-169.2°C.

Preparation 5: Synthesis of 2-Butylsulfanyl-4-chloro-pyrimidine

The synthesis of 2-butylsulfanyl-4-chloro-pyrimidine was carried out according to the process shown in Scheme 5.



SCHEME 5

Step A: synthesis of 2-butylsulfanyl-3*H*-pyrimidin-4-one

2-Thioxo-2,3-dihydro-1*H*-pyrimidin-4-one (12.8 g) was added to a solution of NaOH (8.0 g) in water (70 mL). After complete dissolution of the solids butyl iodide (12.4 mL) was added to the solution and the resulting mixture was stirred at RT overnight. A second aliquot of butyl iodide (1.2 mL) was then added and the reaction mixture was stirred for 24 h. A third aliquot of butyl iodide (1.2 mL) was added and the resulting mixture was stirred for 6 days. Glacial acetic acid (5.5 mL) was added and the reaction mixture was stirred for 30 min, it was then stored at 4°C overnight. The precipitate formed was collected by filtration and dried under reduced pressure to give 12.3 g of 2-butylsulfanyl-3*H*-pyrimidin-4-one.

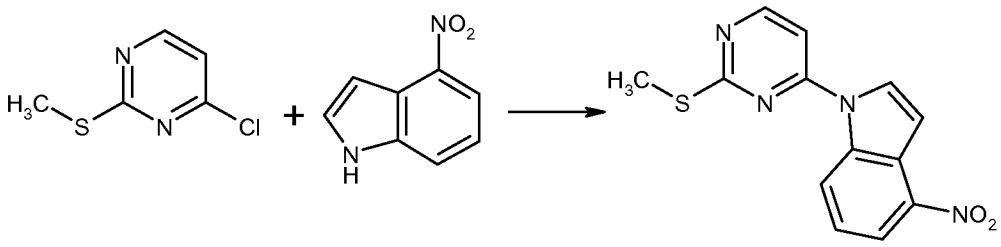
Step B: synthesis of 2-butylsulfanyl-4-chloro-pyrimidine

A mixture of 2-butylsulfanyl-3*H*-pyrimidin-4-one (3.0 g) and phosphorus oxychloride (15 mL) was heated at reflux for 3 h; it was then cooled to RT and evaporated under

reduced pressure. The residue was poured into an ice-water mixture, and the resulting mixture was extracted with DCM. The combined organic extracts were washed with a diluted aqueous solution of $NaHCO_3$, dried over Na_2SO_4, filtered and evaporated under reduced pressure to give 1.2 g of 2-butylsulfanyl-4-chloro-pyrimidine.

Preparation 6: Synthesis of 1-(2-Methylsulfanyl-pyrimidin-4-yl)-4-nitro-1*H*-indole

The synthesis of 1-(2-methylsulfanyl-pyrimidin-4-yl)-4-nitro-1*H*-indole was carried out according to the process shown in Scheme 6.



SCHEME 6

A solution of sodium(bistrimethylsilyl)amide (1 M in THF, 26.42 mL) was slowly added to a cooled (acetone/dry-ice bath) solution of 4-nitroindole (4.2 g, 25.9 mmol) in a mixture of acetonitrile/THF (2/1, 75 mL) and the resulting mixture was stirred for 1 hour. 4-Chloro-4-methylthiopyrimidine (4.202 g, 26.2 mmol) was then added and the reaction mixture was warmed to RT and stirred for 21 h. The resulting mixture was evaporated under reduced pressure and the solid residue was triturated with a mixture of hexane/EtOAc/Et_2O (5/1/1). The solid was collected by filtration, washed and dried under reduced pressure to give 2.56 g of 1-(2-methylsulfanyl-pyrimidin-4-yl)-4-nitro-1*H*-indole which was used without further purification.

In the same manner, utilizing the appropriate starting materials, the following compounds were prepared:

1-(2-Methylsulfanyl-pyrimidin-4-yl)-1*H*-indole-4-carboxylic acid methyl ester;

4-Methoxy-1-(2-methylsulfanyl-pyrimidin-4-yl)-1*H*-indole;

6-Methyl-1-(2-methylsulfanyl-pyrimidin-4-yl)-1*H*-indole

4-Methyl-1-(2-methylsulfanyl-pyrimidin-4-yl)-1*H*-indole;

4-Fluoro-1-(2-methylsulfanyl-pyrimidin-4-yl)-1*H*-indole;

5-Fluoro-1-(2-methylsulfanyl-pyrimidin-4-yl)-1*H*-indole;

1-(2-Methylsulfanyl-pyrimidin-4-yl)-1*H*-indole-3-carboxylic acid methyl ester;

1-(2-Methylsulfanyl-pyrimidin-4-yl)-1*H*-indole-5-carboxylic acid methyl ester; and

5-Methoxy-1-(2-methylsulfanyl-pyrimidin-4-yl)-1*H*-indole.

In the same manner, utilizing the appropriate starting materials and LiHMDS as a base, the following compounds were prepared:

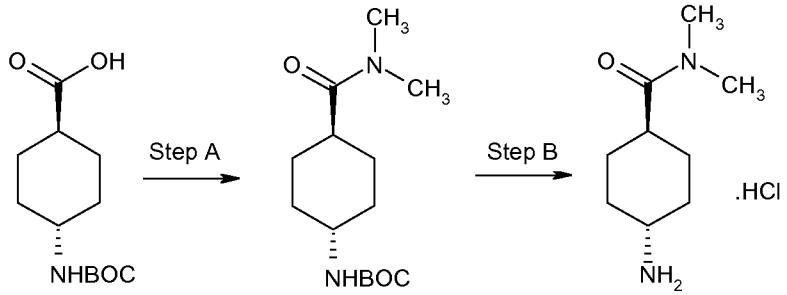
1-(2-Methylsulfanyl-pyrimidin-4-yl)-1*H*-indole-4-carbonitrile;

1-(2-Methylsulfanyl-pyrimidin-4-yl)-1*H*-indole-6-carboxylic acid methyl ester; and

5-Methyl-1-(2-methylsulfanyl-pyrimidin-4-yl)-1*H*-indole.

Preparation 7: Synthesis of 4-Amino-cyclohexanecarboxylic acid dimethylamide hydrochloride salt.

The synthesis of 4-amino-cyclohexanecarboxylic acid dimethylamide hydrochloride salt was carried out according to the process shown in Scheme 7.



SCHEME 7

Step A: synthesis of (4-dimethylcarbamoyl-cyclohexyl)-carbamic acid *tert*-butyl ester

A mixture of 4-*tert*-butoxycarbonylamino-cyclohexanecarboxylic acid (2.43 g, 10 mmol), EDCI (6.52 g, 34 mmol) and HOBt (4.59 g, 34 mmol) in NMP (20 mL) was stirred at RT for 3 h. A solution of dimethylamine (2.0 M in THF, 15 mL, 30 mmol) was added, and the resulting mixture was stirred at RT for 64 h. Water and EtOAc were then added, and the organic layer was separated and washed twice with a saturated aqueous solution of K_2CO_3, aqueous HCl (1 M), a saturated aqueous solution of K_2CO_3, and brine. The organic layer was dried over Na_2SO_4, filtered and evaporated under reduced pressure to give (4-dimethylcarbamoyl-cyclohexyl)-carbamic acid *tert*-butyl ester (1.6 g, 59% yield) as a white solid.

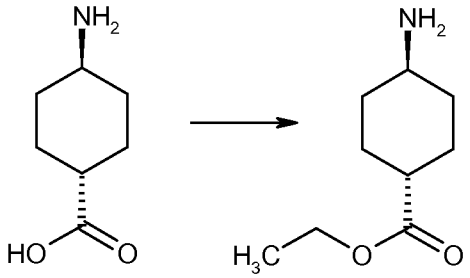
Step 2: synthesis of 4-amino-cyclohexanecarboxylic acid dimethylamide hydrochloride salt

HCl (concentrated, 7 mL) was added to a solution of (4-dimethylcarbamoyl-cyclohexyl)-carbamic acid *tert*-butyl ester (1.5 g) in 1,4-dioxane (20 mL), and the resulting mixture was stirred at RT for 5 h. Toluene was added and the reaction mixture was evaporated under reduced pressure. The oily residue was triturated with EtOAc to give 4-amino-cyclohexanecarboxylic acid dimethylamide hydrochloride salt (0.9 g).

trans-(4-Amino-cyclohexyl)-morpholin-4-yl-methanone was prepared in a similar manner, utilizing the appropriate starting materials.

Preparation 8: Synthesis of *trans*-4-Amino-cyclohexanecarboxylic acid ethyl ester

The synthesis of *trans*-4-amino-cyclohexanecarboxylic acid ethyl ester was carried out according to the process shown in Scheme 8.

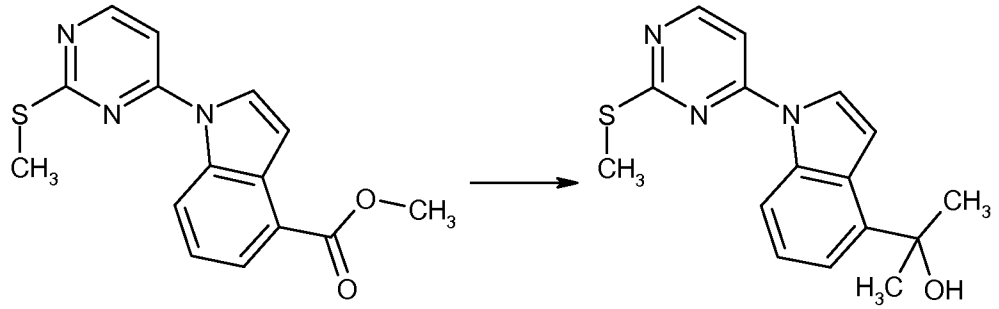


SCHEME 8

A mixture of *trans*-4-amino-cyclohexanecarboxylic acid (15 g, 83.8 mmol), sulfuric acid (9 mL) and EtOH (400 mL) was stirred at RT overnight. A saturated aqueous solution of $NaHCO_3$ and $NaHCO_3$ (solid) were added until the pH of the mixture reached 7. The solvent was then removed under reduced pressure. Aqueous K_2CO_3 (50%) was added and the resulting mixture was extracted with EtOAc, the organic extracts dried over Na_2SO_4, filtered and evaporated under reduced pressure to provide *trans*-4-amino-cyclo-hexanecarboxylic acid ethyl ester (12.81 g) as a light yellow oil.

Preparation 9: Synthesis of 2-[1-(2-Methylsulfanyl-pyrimidin-4-yl)-1*H*-indol-4-yl]-propan-2-ol

The synthesis of 2-[1-(2-methylsulfanyl-pyrimidin-4-yl)-1*H*-indol-4-yl]-propan-2-ol was carried out according to the process shown in Scheme 9.

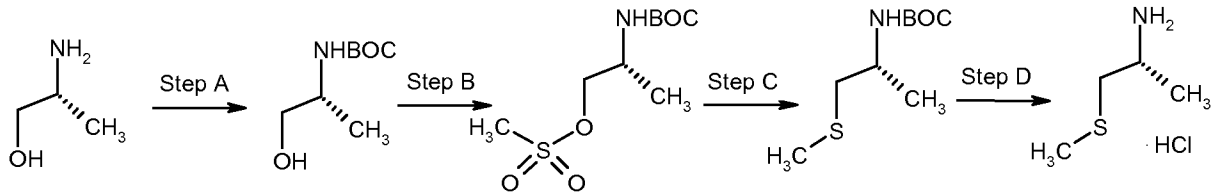


SCHEME 9

A suspension of 1-(2-methylsulfanyl-pyrimidin-4-yl)-1*H*-indole-4-carboxylic acid methyl ester (500 mg) in THF (6 mL) was added to a solution of methylmagnesium bromide (3.0 M in Et_2O, 3.51 mL) and THF (2 mL), cooled to 0°C, and the resulting mixture stirred under N_2 for 5 h. A second aliquot of methylmagnesium bromide (3.0 M in Et_2O, 1.80 mL) was then added and the reaction mixture was stirred at RT under N_2 atmosphere for 30 min. The resulting mixture was then cooled to 0°C, poured into a cold mixture of water/HCl (1 M, 1:1, 75 mL) and extracted with EtOAc. The combined organic extracts were washed once with water and twice with a saturated aqueous solution of $NaHCO_3$, dried over Na_2SO_4, filtered and evaporated under reduced pressure to give 2-[1-(2-methylsulfanyl-pyrimidin-4-yl)-1*H*-indol-4-yl]-propan-2-ol (0.48 g).

Preparation 10: Synthesis of [6-(2,4-Difluoro-phenoxy)-1*H*-pyrazolo[3,4-d]pyrimidin-3-yl]-isopropyl-amine

The synthesis of [6-(2,4-difluoro-phenoxy)-1*H*-pyrazolo[3,4-d]pyrimidin-3-yl]-isopropyl-amine was carried out according to the process shown in Scheme 10.



SCHEME 10

Step A: synthesis of (R)-2-boc-amino-propan-1-ol

(R)-2-Amino-propan-1-ol (30.0 g, 0.3994 mol) was dissolved in MeOH (800 mL), and the solution cooled in an ice bath for 30 min. A solution of di-*tert*-butyl dicarbonate (87.17 g, 0.3994 mol) in MeOH (250 mL) was added in portions to the stirring reaction mixture. The ice bath was removed, and stirring was continued for 3 h. The reaction mixture was evaporated to dryness under reduced pressure to give (R)-2-boc-amino-

ch was used without further purification.

Step B: synthesis of (R)-2-Boc-amino-1-methanesulfonyl-propan-1-ol

DCM (400 mL) and triethylamine (83.9 mL, 0.60 mol) were added to a flask containing (R)-2-boc-amino-propan-1-ol. The reaction mixture was cooled in an ice bath for 30 min, and methanesulfonyl chloride (37.0 mL, 0.478 mol) was added dropwise over a five min period. The resulting mixture was stirred for 1 hour, the ice bath removed, and the mixture stirred for 18 h at RT. The resulting mixture was washed with aqueous NaOH (10%), and the organic layer dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give (R)-2-boc-amino-1-methanesulfonyl-propan-1-ol (91.93 g).

Step C: synthesis of (R)-2-Boc-amino-1-methanesulfanyl-propane

A mixture of (R)-2-boc-amino-1-methanesulfonyl-propan-1-ol (91.93 g, 363 mmol), THF (350 mL) and sodium thiomethoxide (30.0 g, 406 mmol) was stirred at RT for 18 h. The mixture was concentrated under reduced pressure, and the residue partitioned between Et_2O and water. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give (R)-2-boc-amino-1-methanesulfanyl-propane (70.8 g).

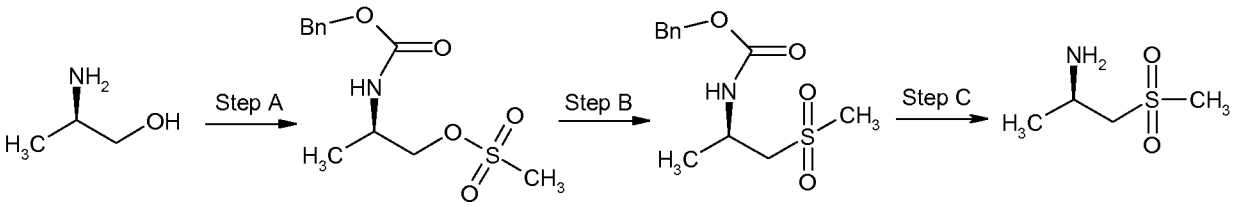
Step D: synthesis of (R)-1-methyl-2-methylsulfanyl-ethylamine

Methanol (400 mL) was cooled in an ice bath for 30 min, and acetyl chloride (100 mL) was added dropwise over a 45 min period. The resulting solution was added to (R)-2-Boc-amino-1-methanesulfanyl-propane (70.47 g, 343 mmol) with stirring at ice bath temperature. The reaction mixture was stirred for 15 min after addition was completed, the ice bath removed, and stirring continued for 2 h. The reaction mixture was concentrated to a solid under reduced pressure, then taken up in THF (700 mL). The resulting mixture was heated to reflux until all solids had dissolved, then cooled to RT, then cooled to 0°C for 30 min. The resulting precipitate was collected by filtration, washed with cold THF, and dried under reduced pressure to give (R)-1-methyl-2-methylsulfanyl-ethylamine (23.57 g). MS = 106 $[M+H]^+$.

(S)-1-Methyl-2-methylsulfanyl-ethylamine was prepared following the above described procedure utilizing the appropriate starting material.

Preparation 11: Synthesis of (R)-2-Methanesulfonyl-1-methyl-ethylamine

The synthesis of (R)-2-methanesulfonyl-1-methyl-ethylamine was carried out according to the process shown in Scheme 11.



SCHEME 11

Step A: synthesis of methanesulfonic acid (R)-2-benzyloxycarbonylamino-propyl ester

A solution of benzyl chloroformate (10.0 mL) in DCM (25 mL) was added to a stirred, cooled solution of R-(-)-2-amino-1-propanol (5.0 g) and triethylamine (6.8 g) in DCM (75 mL) at a rate to maintain the temperature below -5°C. Cooling and stirring was continued for 1 hour and then a solution of methanesulfonyl chloride (7.7 g) in DCM (25 mL) was added at a rate to maintain the temperature below -5°C. The reaction mixture was allowed to warm to 5°C, then washed twice with water (150 mL). The organic layer was filtered over anhydrous sodium sulfate and the solvent removed by vacuum distillation to yield 19.2 g of a white solid. A portion of this material (15 g) was dissolved in DCM (100 mL), and the resulting solution was distilled. The volume was maintained by addition of methyl-*t*-butyl ether. When crystallization began, the mixture was distilled to a volume of about 75 mL and heating was stopped. The resulting mixture was diluted to a volume of about 150 mL by dropwise addition of hexane. After cooling, the white crystalline solid was collected, washed with hexane/methyl-*t*-butyl ether (1:1), and dried to give methanesulfonic acid (R)-2-benzyloxycarbonylamino-propyl ester (11.1 g).

Step B: synthesis of ((R)-2-methanesulfonyl-1-methyl-ethyl)-carbamic acid benzyl ester

To a stirring mixture of methanesulfonic acid (R)-2-benzyloxycarbonylamino-propyl ester (11.1 g) in acetonitrile (72 mL) was added aqueous sodium methylmercaptide (15%, 35 mL). The resulting mixture was heated to about 55°C for 4-5 h; it was then cooled, and the lower aqueous layer separated. The organic layer was shaken with water (10 mL) and the lower layer again separated. Formic acid (15 mL) was added to the organic layer, the resulting mixture stirred, and aqueous H_2O_2 (30%, 12 g) was added dropwise. After an initial exotherm, the mixture cooled and was then heated to about 65°C. After 3 h, a second aliquot of H_2O_2 (30%, 2 mL) and formic acid (6 mL) was added to the mixture. A similar addition of the two reagents was made after 4 h. The reaction mixture was cooled [illegible]ly diluted with water (about 200 mL). A white solid crystallized during

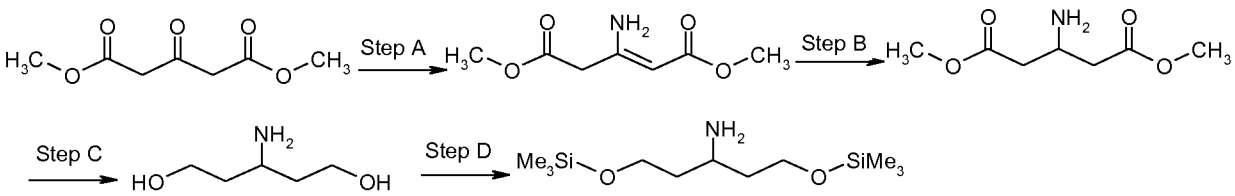
the addition. The mixture was cooled in an ice bath and the solid was collected by filtration, washed with water, and dried under reduced pressure to yield ((R)-2-methanesulfonyl-1-methyl-ethyl)-carbamic acid benzyl ester (9.2 g).

Step C: synthesis of (R)-2-methanesulfonyl-1-methyl-ethylamine

A mixture of ((R)-2-methanesulfonyl-1-methyl-ethyl)-carbamic acid benzyl ester (2.7 g), palladium hydroxide on carbon (20%, 0.3 g), and isopropanol (30 mL) was heated to about 65°C under nitrogen atmosphere. A solution of potassium formate (2.7 g) in water (4 mL) was added to the mixture over a period of about 1 hour. After 6 h the mixture was cooled and filtered. The filtrate was vacuum distilled to a viscous oil, which was dissolved in isopropanol (30 mL). The resulting solution was filtered and evaporated under reduced pressure to yield (R)-2-methanesulfonyl-1-methyl-ethylamine (1.2 g) as a viscous oil.

Preparation 12: Synthesis of 3-Trimethylsilanyloxy-1-(2-trimethylsilanyloxy-ethyl)-propylamine

The synthesis of 3-trimethylsilanyloxy-1-(2-trimethylsilanyloxy-ethyl)-propylamine was carried out according to the process shown in Scheme 12.



SCHEME 12

Step A: synthesis of dimethyl-3-aminoglutaconate

A mixture of dimethylacetone-1,3-dicaboxylate (24.55 Kg), ammonium bicarbonate (22.9 Kg) and MeOH (81.8 Kg) was stirred at RT overnight. The solids were removed by filtration, and the filtrate concentrated under reduced pressure. Isopropanol (27.2 Kg) was added and the water of reaction was removed by azeotropic distillation. The remaining solvent was distilled off to provide dimethyl-3-aminoglutaconate (24.705 Kg, 99% yield) as an oil.

Step B: synthesis of 3-amino-pentanedioic acid dimethyl ester

A diluted alcoholic sulfuric acid solution is prepared by adding sulfuric acid (20.69 Kg) to isopropanol (51.7 Kg) at 0-5°C. The resulting solution was slowly added to a solution of *tert*-butylamine borane (9.19 Kg) in THF (69.3 Kg), maintaining the temperature below -5°C. Dimethyl-3-aminoglutaconate (18.28 Kg) was slowly added to the resulting mixture, maintaining the temperature below 0°C. The resulting reaction mixture was stirred between 0°C and 15°C overnight, then quenched by slow addition to water (166 Kg) while maintaining the temperature below 10°C and the pH between 5 and 7 by adding concentrated aqueous NaOH. The pH of the mixture was then adjusted to about 9-10 by adding concentrated aqueous NaOH at the end of the quenching process. The phases were separated and the aqueous phase was extracted with DCM. The combined organic extracts were washed with brine (20.6 Kg), filtered through a cotton cartridge and concentrated under reduced pressure to give 3-amino-pentanedioic acid dimethyl ester (17.87 Kg, 97% yield).

Step C: synthesis of 3-amino-pentane-1,5-diol

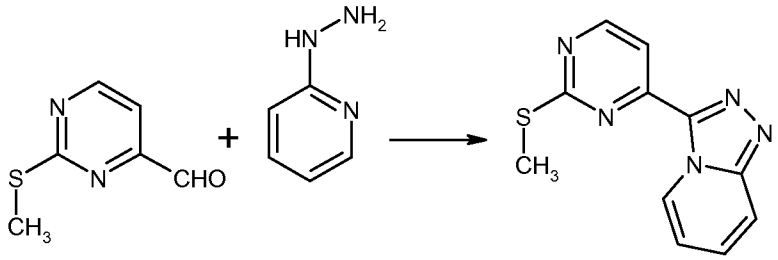
A solution of 3-amino-pentanedioic acid dimethyl ester (17.67 Kg) in THF (101.5 Kg) was added to a solution of LAH (1.0 M in THF, 90.2 Kg) at a pot temperature between 10-30°C, and the resulting mixture stirred at 25°C for 14-20 h. The reaction was quenched by slowly adding water and THF (1:1). The solids were filtered and washed with iPrOH/THF/DEA/propylamine. The filtrate was evaporated under reduced pressure to give 3-aminopentane-1,5-diol (9.55 Kg, 72% yield) as a thick oil.

Step D: synthesis of 3-trimethylsilanyloxy-1-(2-trimethylsilanyloxy-ethyl)-propylamine

A slurry of 3-aminopentane-1,5-diol (18.29 Kg) in i-PrOH (16.91 Kg) was added to a reactor, and the solvent evaporated under reduced pressure. Hexamethyldisilazane (31.985 Kg) in THF (55.3 Kg) and trimethylsilylchloride (35.57 Kg) in THF (172.03 Kg) were then added and the resulting mixture refluxed overnight. The reaction mixture was cooled, the solvent evaporated under reduced pressure, and the residue was purified by distillation (97-99°C) to give 3-trimethylsilanyloxy-1-(2-trimethylsilanyloxyethyl)-propylamine (24.36 Kg).

Preparation 13: Synthesis of 3-(2-Methylsulfanyl-pyrimidin-4-yl)-[1,2,4]triazolo[4,3-*a*]-pyridine

The synthesis of 3-(2-methylsulfanyl-pyrimidin-4-yl)-[1,2,4]triazolo[4,3-*a*]pyridine was carried out according to the process shown in Scheme 13.

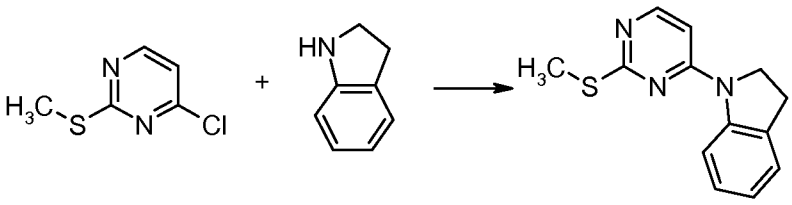


SCHEME 13

A mixture of 2-methylsulfanyl-pyrimidine-4-carbaldehyde (1.00 g) (US 6218537) and 2-hydrazinopyridine (0.71 g) in EtOH (20 mL) was heated to reflux for 24 h, then cooled to RT and the resulting solid collected by filtration to give *N*-[1-(2-methylsulfanyl-pyrimidin-4-yl)-meth-(E)-ylidene]-*N'*-pyridin-2-yl-hydrazine (1.26 g). A mixture of this material and DCM (20 mL) was gently heated, and a second aliquot of DCM (10 mL) and chloroform (5 mL) added to facilitate solubilization. Iodobenzene diacetate (1.65 g) was added, and the resulting mixture stirred at RT under N_2 for 17 h. The reaction mixture was then evaporated under reduced pressure and the crude residue was triturated with hot Et_2O. Once the mixture cooled to RT, the solid was collected by filtration to afford 3-(2-methylsulfanyl-pyrimidin-4-yl)-[1,2,4]triazolo[4,3-*a*]pyridine (1.12 g).

Preparation 14: Synthesis of 1-(2-Methylsulfanyl-pyrimidin-4-yl)-2,3-dihydro-1*H*-indole

The synthesis of 1-(2-methylsulfanyl-pyrimidin-4-yl)-2,3-dihydro-1*H*-indole was carried out according to the process shown in Scheme 14.

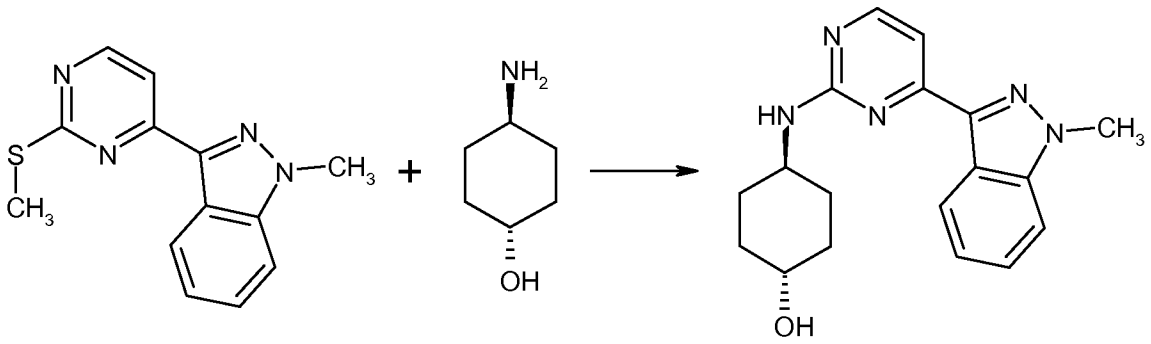


SCHEME 14

A mixture of 4-chloro-2-methylthiopyrimidine (4.02 g, 25 mmol), 2,3-dihydro-1*H*-indole (4.0 mL, 36 mmol) and N,N-diisopropyl ethyl amine (4 mL, 22 mmol) in DMF (10 mL) was heated to 100°C under N_2 for 16 h. The solidified reaction mixture was cooled, diluted with EtOAc, and filtered. The collected solids were dissolved in DCM and MeOH and recrystallized from DCM/EtOAc to give 1-(2-methylsulfanyl-pyrimidin-4-yl)-2,3-dihydro-1*H*-indole (2.32 g, 38% yield) as a light-yellow solid. MS = 244$[M+H]^+$.

Example 1: Synthesis of *trans*-4-[4-(1-Methyl-1*H*-indazol-3-yl)-pyrimidin-2-ylamino]-cyclohexanol

The synthesis of *trans*-4-[4-(1-methyl-1*H*-indazol-3-yl)-pyrimidin-2-ylamino]-cyclohexanol was carried out according to the process shown in Scheme 15.



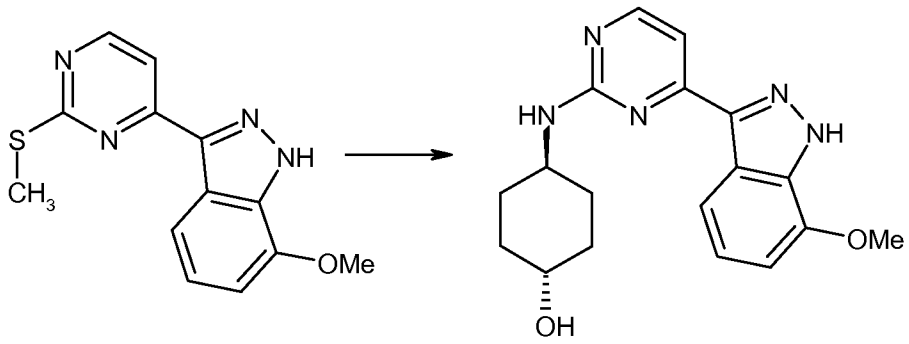
SCHEME 15

N-Chlorosuccinimide (239 mg, 1.77 mmol) was added to a solution of 1-methyl-3-(2-methylsulfanyl-pyrimidin-4-yl)-1*H*-indazole (413 mg, 1.6 mmol) in NMP, and the resulting mixture was stirred at 85°C for 15 min. *trans*-Aminocyclohexanol was then added, the reaction mixture stirred for 1 h, then poured into water and extracted twice with EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude residue was purified by preparative TLC to give *trans*-4-[4-(1-methyl-1*H*-indazol-3-yl)-pyrimidin-2-ylamino]-cyclohexanol. MS = 324 $[M+H]^+$; MP = 180-183.3°C.

trans-4-[4-(4-Bromo-indazol-1-yl)-pyrimidin-2-ylamino]-cyclohexanol (white solid) was prepared in the same manner, utilizing the appropriate starting material. MS = 388 $[M+H]^+$; MP = 200.5-201.9°C.

Example 2: Synthesis of *trans*-4-[4-(7-Methoxy-1*H*-indazol-3-yl)-pyrimidin-2-ylamino]-cyclohexanol

The synthesis of *trans*-4-[4-(7-methoxy-1*H*-indazol-3-yl)-pyrimidin-2-ylamino]-cyclohexanol was carried out according to the process shown in Scheme 16.



SCHEME 16

3-Chloroperoxybenzoic acid (77%, 407 mg, 1.82 mmol) was added to a solution of 7-methoxy-3-(2-methylsulfanyl-pyrimidin-4-yl)-1*H*-indazole (225 mg, 0.8 mmol) in DCM at 0°C, and the resulting mixture stirred for 3 h. The reaction mixture was then diluted with DCM, washed with aqueous $NaHCO_3$ (5%), dried over Na_2SO_4, filtered and evaporated under reduced pressure to give 3-(2-methanesulfonyl-pyrimidin-4-yl)-7-methoxy-1*H*-indazole, which was used without further purification. To a solution of this material in NMP was added *trans*-aminocyclohexanol (190 mg), and the resulting mixture was heated in a sealed tube to 120°C for 1.5 hour. The reaction mixture was cooled to RT, water added and the resulting suspension stirred for 30 min. The solid precipitate was collected by filtration, washed with water, and dried under reduced pressure overnight to give *trans*-4-[4-(7-methoxy-1*H*-indazol-3-yl)-pyrimidin-2-yl-amino]-cyclohexanol. MS = 341 $[M+H]^+$; MP = 243.3-244.9°C.

In a similar manner, utilizing the appropriate starting material, the following compounds were prepared:

trans-4-[4-(1*H*-Indazol-3-yl)-pyrimidin-2-ylamino]-cyclohexanol, MS = 310 $[M+H]^+$;

trans-4-(4-Benzo[*d*]isoxazol-3-yl-pyrimidin-2-ylamino)-cyclohexanol, MS = 311 $[M+H]^+$;

trans-1-[2-(4-Hydroxy-cyclohexylamino)-pyrimidin-4-yl]-1*H*-indole-4-carboxylic acid methyl ester (yellow solid), MS = 367 $[M+H]^+$; MP = 206.7-208.3°C;

Cyclohexyl-(4-indol-1-yl-pyrimidin-2-yl)-amine (off-white crystalline solid), MS = 293 $[M+H]^+$; MP = 192.5-193.0°C;

trans-4-(4-Indol-1-yl-pyrimidin-2-ylamino)-cyclohexanol (off-white solid), MS = 309 $[M+H]^+$; MP = 202.4-204.4°C;

trans-*N*-(4-Indol-1-yl-pyrimidin-2-yl)-cyclohexane-1,4-diamine (off-white solid), MS = 308 $[M+H]^+$; MP = 270.1-273.3°C;

trans-4-(4-Indazol-2-yl-pyrimidin-2-ylamino)-cyclohexanol (white needles), MS = 310 $[M+H]^+$; MP = 214.7-216.0°C;

trans-4-(4-Indazol-1-yl-pyrimidin-2-ylamino)-cyclohexanol (white solid), MS = 310 $[M+H]^+$; MP = 232.6-233.7°C;

trans-4-[4-(6-Nitro-indazol-1-yl)-pyrimidin-2-ylamino]-cyclohexanol (yellow powder), MS = 355 $[M+H]^+$; MP = 221.8-223.0°C;

trans-4-(4-[1,2,4]Triazolo[4,3-*a*]pyridin-3-yl-pyrimidin-2-ylamino)-cyclohexanol (off-white solid), MS = 311 $[M+H]^+$; MP = 253.4-255.7°C; and

trans-4-(4-Pyrazolo[1,5-*b*]pyridazin-3-yl-pyrimidin-2-ylamino)-cyclohexanol (white needles), (the starting material 3-(2-methylsulfanyl-pyrimidin-4-yl)-pyrazolo[1,5-*b*]pyridazine was prepared accordingly to the procedure described in *J. Med. Chem.* **2004**, *47*, 4716-30), MS = 311 $[M+H]^+$; MP = 214.9-215.6°C;

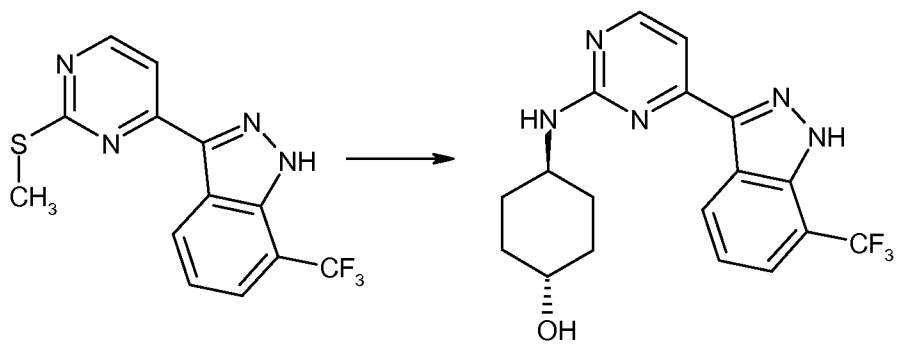
trans-4-(4-Pyrrolo[3,2-*b*]pyridin-1-yl-pyrimidin-2-ylamino)-cyclohexanol (white solid), MS = 310 $[M+H]^+$, MP = 198.9-200.3°C;

trans-4-(4-Pyrrolo[3,2-*c*]pyridin-1-yl-pyrimidin-2-ylamino)-cyclohexanol (white crystalline solid), MS = 310 $[M+H]^+$, MP = 229.9-230.2°C; and

trans-4-[4-(2,3-Dihydro-indol-1-yl)-pyrimidin-2-ylamino]-cyclohexanol (white solid), MS = 311 $[M+H]^+$, MP = 230.5-231.2°C.

Example 3: Synthesis of *trans*-4-[4-(7-Trifluoromethyl-1*H*-indazol-3-yl)-pyrimidin-2-yl-amino]-cyclohexanol

The synthesis of *trans*-4-[4-(7-trifluoromethyl-1*H*-indazol-3-yl)-pyrimidin-2-ylamino]-cyclohexanol was carried out according to the process shown in Scheme 17.



SCHEME 17

3-Chloroperoxybenzoic acid (77%, 318 mg, 0.64 mmol) was added to a solution of 3-(2-methylsulfanyl-pyrimidin-4-yl)-7-trifluoromethyl-1*H*-indazole (200 mg, 0.64 mmol) in DCM at 0°C, and the resulting mixture stirred for 2 h. The reaction mixture was then diluted with DCM, washed with aqueous $NaHCO_3$ (5%), dried over Na_2SO_4, filtered, and evaporated under reduced pressure to give 3-(2-methanesulfonyl-pyrimidin-4-yl)-7-trifluoromethyl-1*H*-indazole which was used without further purification. To a solution of this material in NMP was added *trans*-aminocyclohexanol (148 mg) followed by DIPEA (0.11 mL, 0.64 mmol), the resulting mixture stirred at 120°C for 1 hour, then cooled to RT and water added. The resulting suspension was stirred for 30 min, the solid precipitate collected by filtration, washed with water, and dried under reduced pressure overnight. The solid material was washed with hot EtOAc, filtered and dried under reduced pressure to give *trans*-4-[4-(7-methoxy-1*H*-indazol-3-yl)-pyrimidin-2-ylamino]-cyclohexanol (75 mg). MS = 378 $[M+H]^+$; MP = 265.5-270°C.

In the same manner, using the appropriate starting material, the following compounds were prepared:

trans-4-[4-(5-Fluoro-benzo[*d*]isoxazol-3-yl)-pyrimidin-2-ylamino]-cyclohexanol, MS = 329 $[M+H]^+$; MP = 172-173.9°C;

(1,4-Dioxa-spiro[4.5]dec-8-yl)-(4-indazol-1-yl-pyrimidin-2-yl)-amine (white solid), MS = 352 $[M+H]^+$; MP = 207.5-208.8°C;

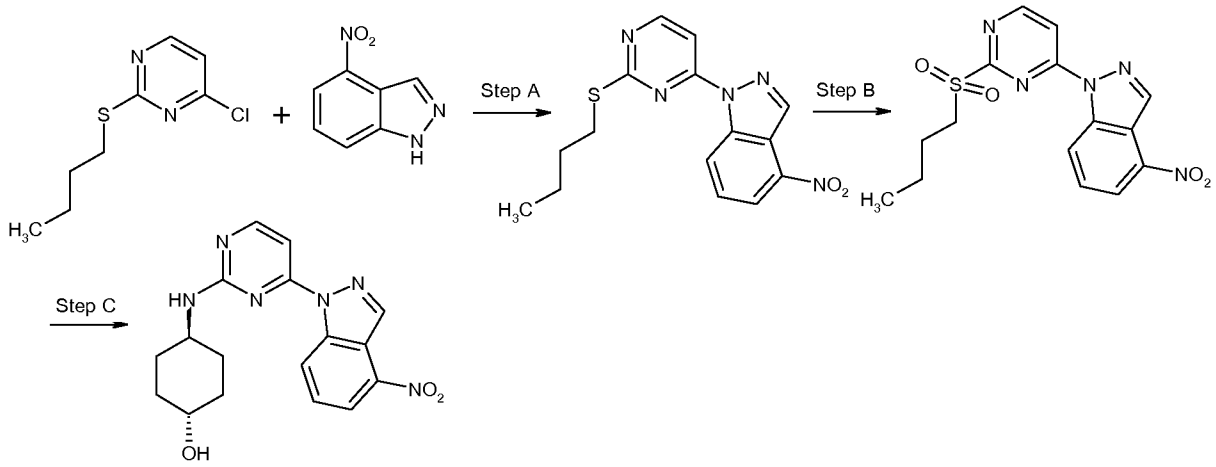
trans-4-[4-(6-Methoxy-indazol-1-yl)-pyrimidin-2-ylamino]-cyclohexanol (pink powder); MS = 340 $[M+H]^+$; MP = 166.8-167.3°C;

trans-1-[2-(4-Hydroxy-cyclohexylamino)-pyrimidin-4-yl]-1*H*-indazole-6-carbonitrile (white powder); MS = 335 $[M+H]^+$; MP = 212.0-212.6°C; and

trans-1-[2-(4-Hydroxy-cyclohexylamino)-pyrimidin-4-yl]-1*H*-indazole-6-carboxylic acid methyl ester (light yellow powder); MS = 368 $[M+H]^+$; MP = 214.9-216.3°C.

Example 4: Synthesis of *trans*-(4-Methyl-cyclohexyl)-[4-(4-nitro-indazol-1-yl)-pyrimidin-2-yl]-amine

The synthesis of *trans*-(4-methyl-cyclohexyl)-[4-(4-nitro-indazol-1-yl)-pyrimidin-2-yl]-amine was carried out according to the process shown in Scheme 18.



SCHEME 18

Step A: synthesis of 1-(2-butylsulfanyl-pyrimidin-4-yl)-4-nitro-1*H*-indazole

To a flask loaded with 2-butylsulfanyl-4-chloro-pyrimidine (202 mg) was added 4-nitro-1*H*-indazole (228 mg), followed by NaH (60% dispersion in mineral oil, 84 mg) and NMP (4 mL). The resulting mixture was stirred at RT overnight, water added, and the mixture extracted with EtOAc. The combined organic extracts were washed with water, dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude residue was purified by flash chromatography (hexane/EtOAc, 80:20) to give 1-(2-butylsulfanyl-pyrimidin-4-yl)-4-nitro-1*H*-indazole (156 mg).

In a similar manner, utilizing the appropriate starting materials, the following compounds were prepared:

1-(2-Butylsulfanyl-pyrimidin-4-yl)-1*H*-indazole-6-carbonitrile (the starting material, 1*H*-indazole-6-carbonitrile, was prepared following the method described in *J. Med. Chem.* **2000**, 43(23):4398-415);

1-(2-Butylsulfanyl-pyrimidin-4-yl)-6-methoxy-1*H*-indazole (the starting material, 6-methoxy-1*H*-indazole, was prepared following the method described in *Annalen der Chemie* **1980**, 908-27); and

1-(2-Butylsulfanyl-pyrimidin-4-yl)-1*H*-indazole-6-carboxylic acid methyl ester (the starting material, 1*H*-indazole-6-carboxylic acid methyl ester, was prepared following the method described in *J. Med. Chem.* **2000**, 43, 47).

Step B: synthesis of 1-[2-(butane-1-sulfonyl)-pyrimidin-4-yl]-4-nitro-1*H*-indazole

To a solution of 1-(2-butylsulfanyl-pyrimidin-4-yl)-4-nitro-1*H*-indazole (660 mg) in DCM cooled to 0°C was added methyltrioxorhenium (30 mg), followed by aqueous H_2O_2

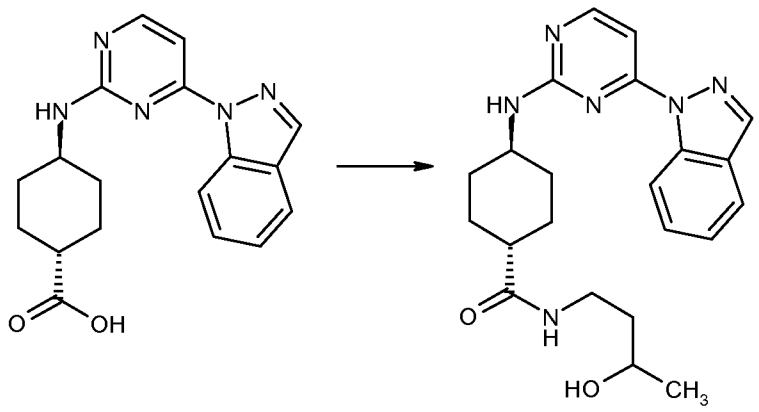
(30%, 1.3 mL). The reaction mixture was stirred at RT for 2 h, then poured into a mixture of water and DCM. The organic layer was separated, and the aqueous layer was extracted with DCM. The combined organic extracts were washed twice with aqueous Na_2SO_3, once with brine, dried over Na_2SO_4, filtered and evaporated under reduced pressure to give 1-[2-(butane-1-sulfonyl)-pyrimidin-4-yl]-4-nitro-1*H*-indazole (680 mg).

Step C: synthesis of *trans*-(4-methyl-cyclohexyl)-[4-(4-nitroindazol-1-yl)-pyrimidin-2-yl]-amine

A mixture of 1-[2-(butane-1-sulfonyl)-pyrimidin-4-yl]-4-nitro-1*H*-indazole (480 mg) and *trans*-aminocyclohexanol (500 mg) was heated neat to 120°C. After the formation of a precipitate, NMP (0.8 mL) was added. The reaction mixture was stirred for 2 h, then cooled to RT and poured into a mixture of water and DCM. The solid precipitate was collected by filtration and dried under reduced pressure to give *trans*-(4-methyl-cyclohexyl)-[4-(4-nitroindazol-1-yl)-pyrimidin-2-yl]-amine (160 mg) as a yellow powder. MS = 355 $[M+H]^+$; MP = 253.9-254.8°C.

Example 5: Synthesis of *trans*-4-(4-Indazol-1-ylpyrimidin-2-ylamino)-cyclohexane-carboxylic acid (3-hydroxy-butyl)-amide

The synthesis of *trans*-4-(4-indazol-1-yl-pyrimidin-2-ylamino)-cyclohexanecarboxylic acid (3-hydroxy-butyl)-amide was carried out according to the process shown in Scheme 19.



SCHEME 19

A mixture of *trans*-4-(4-indazol-1-ylpyrimidin-2-ylamino)-cyclohexanecarboxylic acid (100 mg, 0.30 mmol), 2-amino-2-butanol (39.2 mg, 0.44 mmol), BOP (194.6 mg, 0.44 mmol), DIPEA (77.4 mg, 0.60 mmol) in THF (8 mL) was stirred at RT overnight. Water (20 mL) was added to the resulting suspension: the solids first dissolved, then precipitated with the addition of more water (100 mL). The precipitate was collected by filtration,

washed with water and Et_2O, and dried under reduced pressure to give *trans*-4-(4-indazol-1-yl-pyrimidin-2-ylamino)-cyclohexanecarboxylic acid (3-hydroxy-butyl)amide (78 mg) as white solid. MS = 409 $[M+H]^+$.

In the same manner, utilizing the appropriate starting materials, the following compounds were prepared:

trans-4-(4-Indazol-1-ylpyrimidin-2-ylamino)-cyclohexanecarboxylic acid (2-methanesulfonyl-ethyl)-amide (light brown solid), MS = 443 $[M+H]^+$; MP = 229.6-231.2°C;

trans-4-(4-Indazol-1-ylpyrimidin-2-ylamino)-cyclohexanecarboxylic acid ((R)-2-methanesulfonyl-1-methylethyl)-amide (white powder), MS = 457 $[M+H]^+$; MP = 289.0-291.0°C;

trans-4-(4-Indazol-1-ylpyrimidin-2-ylamino)-cyclohexanecarboxylic acid [3-hydroxy-1-(2-hydroxyethyl)propyl]-amide (white solid), MS = 439 $[M+H]^+$; MP = 215.0-217.8°C;

trans-4-(4-Indazol-1-ylpyrimidin-2-ylamino)-cyclohexanecarboxylic acid (1-hydroxymethyl-propyl)amide (white powder), MS = 409 $[M+H]^+$; MP = 222.0-224.7°C;

trans-4-(4-Indazol-1-ylpyrimidin-2-ylamino)-cyclohexanecarboxylic acid (2,3-dihydroxy-propyl)-amide (white powder), MS = 411 $[M+H]^+$; MP = 243.3-245.1°C;

trans-4-(4-Indazol-1-ylpyrimidin-2-ylamino)-cyclohexanecarboxylic acid (3-hydroxy-1-methyl-propyl)-amide (white solid), MS = 409 $[M+H]^+$; MP = 231.9-234.4°C;

trans-(4-Hydroxypiperidin-1-yl)-[4-(4-indazol-1-ylpyrimidin-2-ylamino)-cyclohexyl]-methanone (light brown solid), MS = 421 $[M+H]^+$; MP = 125.5-128.8°C;

trans-1-[4-(4-Indazol-1-ylpyrimidin-2-ylamino)-cyclohexanecarbonyl]-pyrrolidin-3-one (light brown powder) (the amine starting material was prepared by a standard BOC deprotection of the commercially available 3-oxo-pyrrolidine-1-carboxylic acid *tert*-butyl ester), MS = 405 $[M+H]^+$; MP = 172.6-174.8°C;

trans-4-(4-Indazol-1-ylpyrimidin-2-ylamino)-cyclohexanecarboxylic acid isopropylamide (white solid), MS = 379 $[M+H]^+$; MP = 270.0-271.0°C;

trans-4-(4-Indazol-1-ylpyrimidin-2-ylamino)-cyclohexanecarboxylic acid ((S)-2-hydroxy-1-methylethyl)amide (white powder), MS = 395 $[M+H]^+$; MP = 254.6-256.9°C;

trans-4-(4-Indazol-1-ylpyrimidin-2-ylamino)-cyclohexanecarboxylic acid (2-methoxyethyl)-amide (white powder), MS = 395 $[M+H]^+$; MP = 216.9-219.1°C;

trans-4-(4-Indazol-1-ylpyrimidin-2-ylamino)-cyclohexanecarboxylic acid (2-hydroxy-1-hydroxymethylethyl)-amide (white powder), MS = 411 $[M+H]^+$; MP = 239.1-240.9°C;

trans-((R)-3-Hydroxypyrrolidin-1-yl)-[4-(4-indazol-1-ylpyrimidin-2-ylamino)-cyclohexyl]-methanone (white powder), MS = 407 $[M+H]^+$; MP = 203.3-204.0°C;

trans-((S)-3-Hydroxypyrrolidin-1-yl)-[4-(4-indazol-1-ylpyrimidin-2-ylamino)-cyclohexyl]-methanone (white solid), MS = 407 $[M+H]^+$; MP = 201.7-202.7°C;

trans-4-(4-Indazol-1-ylpyrimidin-2-ylamino)-cyclohexanecarboxylic acid (2-hydroxy-1,1-dimethylethyl)-amide (white powder), MS = 409 $[M+H]^+$; MP = 256.5-259.5°C;

trans-4-(4-Indazol-1-ylpyrimidin-2-ylamino)-cyclohexanecarboxylic acid (2-hydroxy-2-methylpropyl)amide (white solid) (the amine starting material was prepared following *J. Med. Chem.* **1998**, 41, 3347), MS = 409 $[M+H]^+$; MP = 224.2-225.9°C;

trans-4-(4-Indazol-1-ylpyrimidin-2-ylamino)-cyclohexanecarboxylic acid (2-hydroxyethyl)-methyl-amide (white solid), MS = 395 $[M+H]^+$; MP = 168.1-169.6°C;

trans-4-(4-Indazol-1-ylpyrimidin-2-ylamino)-cyclohexanecarboxylic acid ((R)-1-methyl-2-methylsulfanylethyl)-amide (white solid), MS = 425 $[M+H]^+$; MP = 215.1-218.8°C;

trans-4-(4-Indazol-1-ylpyrimidin-2-ylamino)-cyclohexanecarboxylic acid ((S)-2-hydroxy-1,2-dimethylpropyl)amide (light brown powder) (the amine starting material was synthesized as described in WO 2002064594), MS = 423 $[M+H]^+$; MP = 214.2-215.2°C;

trans-4-(4-Indazol-1-ylpyrimidin-2-ylamino)-cyclohexanecarboxylic acid (2-hydroxypropyl)-amide (off-white powder), MS = 395 $[M+H]^+$; MP = 234.0-236.6°C;

trans-4-(4-Indazol-1-ylpyrimidin-2-ylamino)-cyclohexanecarboxylic acid ((S)-1-methyl-2-methylsulfanyl-ethyl)-amide (white solid), MS = 425 $[M+H]^+$; MP = 221.5-222.5°C;

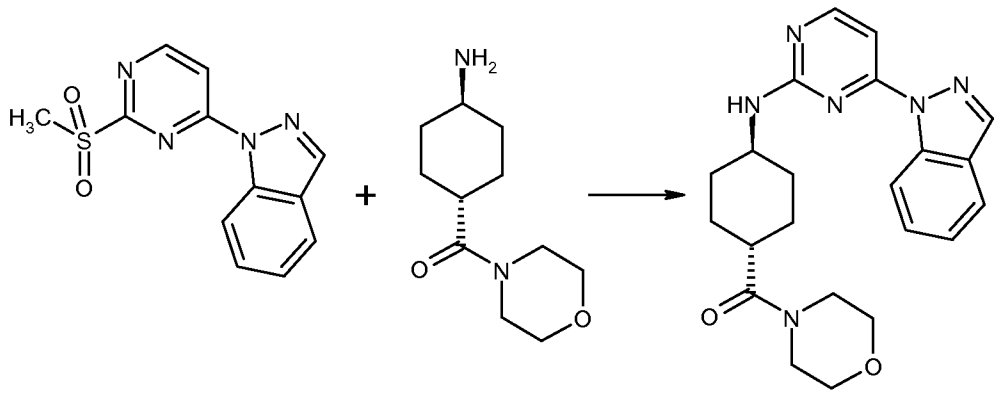
trans-4-(4-Indazol-1-ylpyrimidin-2-ylamino)-cyclohexanecarboxylic acid ethyl-(2-hydroxyethyl)amide (white solid), MS = 409 $[M+H]^+$; MP = 111.5-113.0°C;

trans-4-(4-Indazol-1-ylpyrimidin-2-ylamino)-cyclohexanecarboxylic acid cyclopropylmethyl-amide (white solid), MS = 391 $[M+H]^+$; MP = 248.5-252.5°C; and

trans-4-(4-Indazol-1-ylpyrimidin-2-ylamino)-cyclohexanecarboxylic acid cyclopentylamide (white powder), MS = 405 $[M+H]^+$; MP = 272.2-274.4°C.

Example 6: Synthesis of *trans*-[4-(4-Indazol-1-yl-pyrimidin-2-ylamino)-cyclohexyl]-morpholin-4-yl-methanone

The synthesis of *trans*-[4-(4-indazol-1-ylpyrimidin-2-ylamino)cyclohexyl]-morpholin-4-yl-methanone was carried out according to the process shown in Scheme 20.



SCHEME 20

A sealable (5 mL) tube was loaded with *trans*-(4-amino-cyclohexyl)-morpholin-4-yl-methanone (89.3 mg, 0.36 mmol), DIPEA (0.19 mL, 1.10 mmol) and NMP (1 mL). A second sealable (10 mL) tube was loaded with 1-(2-methanesulfonyl-pyrimidin-4-yl)-1*H*-indazole (100 mg, 0.36 mmol) and NMP (1 mL). Both mixtures were heated to 120°C, until complete dissolution of the solids. The solution of 1-(2-methanesulfonyl-pyrimidin-4-yl)-1*H*-indazole was then transferred via cannula into the vial containing the amine mixture, and the resulting mixture was heated to 120°C for 3 h. The reaction mixture was then cooled to RT and stirred for 2 days, then partitioned between aqueous NH_4Cl (saturated) and DCM. The organic layer was separated and the aqueous layer was extracted with DCM. The combined organic extracts were dried over Na_2SO_4, filtered and

evaporated under reduced pressure to give an amber colored oil. This crude material was recrystallized from Et_2O, the supernatant decanted away, and the resulting crystals were washed with Et_2O. The crystalline material was recrystallized from DCM to give 57 mg of a pale beige crystalline material which was purified by flash chromatography (EtOAc/hexane, gradient from 50:50 to 70:30) to give *trans*-[4-(4-indazol-1-ylpyrimidin-2-ylamino)-cyclohexyl]-morpholin-4-yl-methanone (34 mg) as an off-white powder. MS = 407 $[M+H]^+$; MP = 191.0-192.0°C.

In a similar manner, utilizing the appropriate starting materials, the following compounds were prepared:

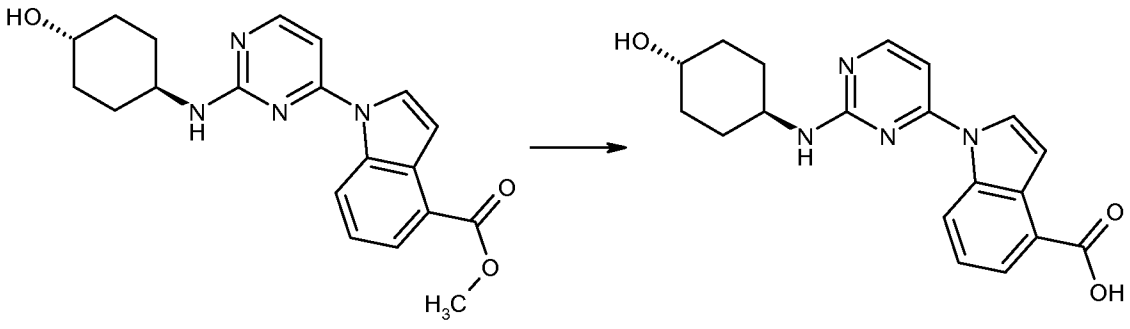
trans-4-[4-(6-Methylindazol-1-yl)-pyrimidin-2-ylamino]-cyclohexanol (yellow powder), MS = 324 $[M+H]^+$; MP = 211.0-212.5°C;

trans-4-(4-Indazol-1-ylpyrimidin-2-ylamino)-cyclohexanecarboxylic acid dimethylamide (white powder), MS = 365 $[M+H]^+$; MP = 223.0-225.0°C; and

trans-4-[4-(5-Methylindazol-1-yl)-pyrimidin-2-ylamino]-cyclohexanol (off-white powder), MS = 324 $[M+H]^+$; MP = 221.5-223.5°C.

Example 7: Synthesis of *trans*-1-[2-(4-Hydroxy-cyclohexylamino)-pyrimidin-4-yl]-1*H*-indole-4-carboxylic acid

The synthesis of *trans*-1-[2-(4-hydroxycyclohexylamino)-pyrimidin-4-yl]-1*H*-indole-4-carboxylic acid was carried out according to the process shown in Scheme 21.



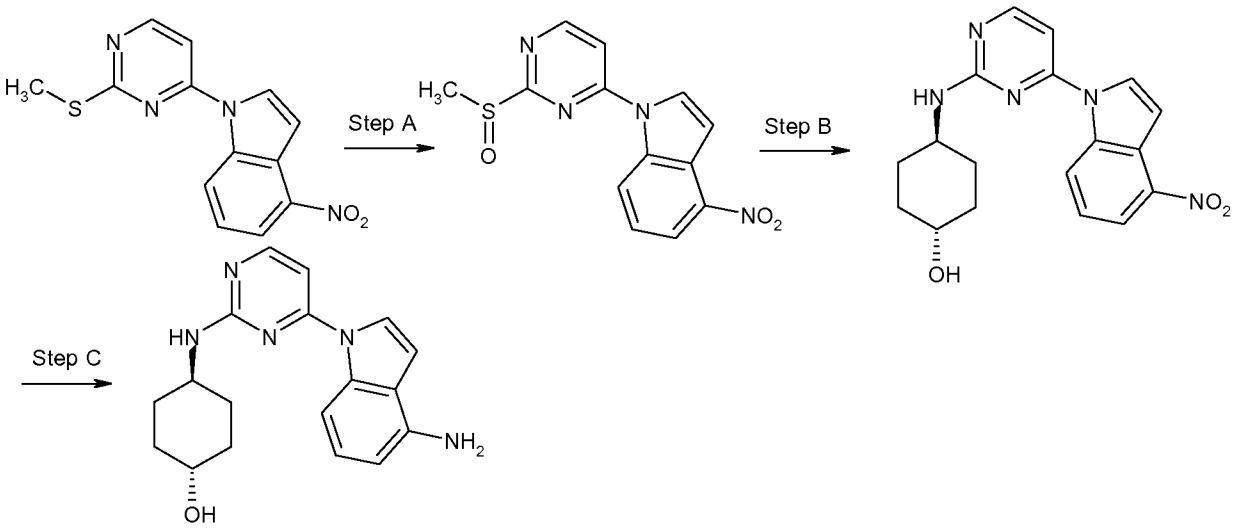
SCHEME 21

LAH (327 mg, 13.6 mmol) was added to a suspension of 1-[2-(4-hydroxycyclohexylamino)-pyrimidin-4-yl]-1*H*-indole-4-carboxylic acid methyl ester (1.0 g, 2.7 mmol) in a mixture of THF (4 mL), water (4 mL) and MeOH (1 mL). The reaction mixture was stirred at RT for 16 h, then evaporated under reduced pressure to give a beige solid. Aqueous HCl (1 M, 14 mL) was added to the residue, and the resulting mixture was [illegible]orated under reduced pressure. The residue was triturated with MeOH to

give *trans*-1-[2-(4-hydroxycyclohexylamino)-pyrimidin-4-yl]-1*H*-indole-4-carboxylic acid (700 mg) as an off-white solid. MS = 353 $[M+H]^+$; MP = 259.0-261.0°C.

Example 8: Synthesis of *trans*-4-[4-(4-Aminoindol-1-yl)-pyrimidin-2-ylamino]-cyclohexanol

The synthesis of *trans*-4-[4-(4-aminoindol-1-yl)-pyrimidin-2-ylamino]-cyclohexanol was carried out according to the process shown in Scheme 22.



SCHEME 22

Step A: synthesis of 1-(2-methanesulfinylpyrimidin-4-yl)-4-nitro-1*H*-indole

A suspension of 3-chloroperoxybenzoic acid (77%, 3.11 g) in $CHCl_3$ (40 mL) was slowly added at 0°C under N_2 to a mixture of 1-(2-methylsulfanylpyrimidin-4-yl)-4-nitro-1*H*-indole (3.93 g, 14.0 mmol) in $CHCl_3$ (50 mL). The resulting mixture was allowed to warm up to RT, and stirred overnight. The reaction mixture was then diluted with DCM (200 mL) and washed with aqueous $NaHCO_3$ (saturated). The resulting yellow precipitate was collected by filtration and dried under reduced pressure to give 1-(2-methanesulfinyl-pyrimidin-4-yl)-4-nitro-1*H*-indole (2.36 g). The mother liquors were dried over Na_2SO_4, filtered and evaporated under reduced pressure to give a second aliquot (690 mg).

Step B: synthesis of *trans*-4-[4-(4-nitroindol-1-yl)-pyrimidin-2-ylamino]-cyclohexanol

A round bottom flask loaded with 1-(2-methanesulfinylpyrimidin-4-yl)-4-nitro-1*H*-indole (3.02 g) and *trans*-aminocyclohexanol (2.87 g) was placed in an oil bath at 75°C, and NMP (5 mL) was added. The resulting mixture was heated to 105°C for 20 min, then stirred at RT overnight. The resulting solid was triturated 3 times with hexane/Et_2O (1:1, 50 mL), the supernatant discarded, and the residual solvent evaporated under reduced

lid residue was suspended in water (70 mL) with stirring, then collected

by filtration and dried under reduced pressure to give *trans*-4-[4-(4-nitroindol-1-yl)-pyrimidin-2-ylamino]-cyclohexanol (2.47 g), which was used without further purification.

In the same manner, utilizing the appropriate starting material, the following compounds were prepared:

trans-4-[4-(4-Methoxyindol-1-yl)-pyrimidin-2-ylamino]-cyclohexanol (off-white solid), MS = 339 $[M+H]^+$; MP = 208.0-209.8°C;

trans-4-[4-(3-Methylindol-1-yl)-pyrimidin-2-ylamino]-cyclohexanol (white solid), MS = 323 $[M+H]^+$; MP = 213.9-215.7°C;

trans-4-[4-(6-Fluoroindol-1-yl)-pyrimidin-2-ylamino]-cyclohexanol (white solid), MS = 327 $[M+H]^+$; MP = 188.0-190.0°C;

trans-4-[4-(4-Benzyloxyindol-1-yl)-pyrimidin-2-ylamino]-cyclohexanol (light yellow solid), MS = 415 $[M+H]^+$; MP = 171.1-173.2°C;

trans-4-[4-(5-Benzyloxyindol-1-yl)-pyrimidin-2-ylamino]-cyclohexanol (off-white solid), MS = 415 $[M+H]^+$; MP = 185.1-186.7°C;

trans-4-[4-(6-Methylindol-1-yl)-pyrimidin-2-ylamino]-cyclohexanol (white solid), MS = 323 $[M+H]^+$; MP = 207.0-208.0°C;

trans-4-[4-(4-Methylindol-1-yl)-pyrimidin-2-ylamino]-cyclohexanol (off-white solid), MS = 323 $[M+H]^+$; MP = 205.5-205.9°C;

trans-4-[4-(4-Fluoroindol-1-yl)-pyrimidin-2-ylamino]-cyclohexanol (white solid), MS = 327 $[M+H]^+$; MP = 210.5-212.0°C;

trans-4-[4-(5-Fluoroindol-1-yl)-pyrimidin-2-ylamino]-cyclohexanol (white solid), MS = 327 $[M+H]^+$; MP = 217.2-217.8°C;

trans-1-[2-(4-Hydroxycyclohexylamino)-pyrimidin-4-yl]-1*H*-indole-3-carboxylic acid methyl ester (off-white solid), MS = 367 $[M+H]^+$; MP = 177.5-178.8°C;

trans-1-[2-(4-Hydroxycyclohexylamino)-pyrimidin-4-yl]-1*H*-indole-5-carboxylic acid methyl ester (white solid), MS = 367 $[M+H]^+$; MP = 238.5-239.2°C;

trans-4-[4-(5-Methoxyindol-1-yl)-pyrimidin-2-ylamino]-cyclohexanol (off-white powder), MS = 339 $[M+H]^+$; MP = 203.6-204.0°C;

trans-1-[2-(4-Hydroxycyclohexylamino)-pyrimidin-4-yl]-1*H*-indole-4-carbonitrile (off-white solid), MS = 334 $[M+H]^+$; MP = 234.9-235.3°C;

trans-1-[2-(4-Hydroxycyclohexylamino)-pyrimidin-4-yl]-1*H*-indole-6-carboxylic acid methyl ester (light yellow solid), MS = 367 $[M+H]^+$; MP = 232.2-234.5°C;

trans-4-[4-(5-Methylindol-1-yl)-pyrimidin-2-ylamino]-cyclohexanol (off-white solid), MS = 323 $[M+H]^+$; MP = 202.5-203.5°C; and

trans-4-{4-[4-(1-Hydroxy-1-methylethyl)-indol-1-yl]-pyrimidin-2-ylamino}-cyclohexanol (off-white solid), MS = 367 $[M+H]^+$; MP = 168.0-169.0°C.

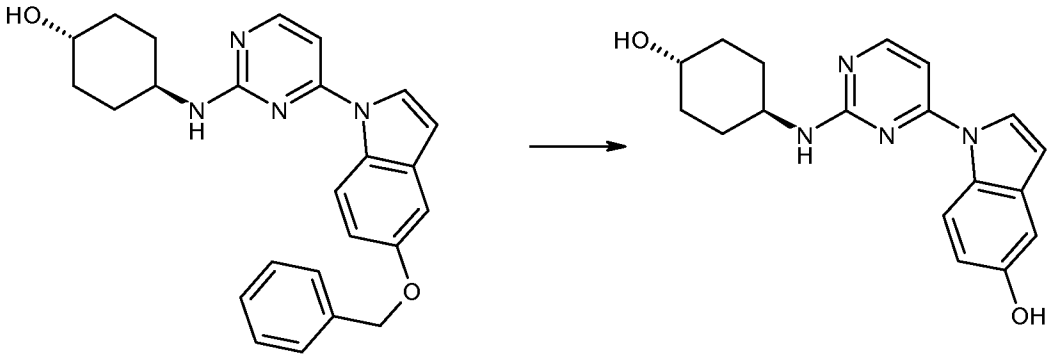
Step C: synthesis of *trans*-4-[4-(4-aminoindol-1-yl)-pyrimidin-2-ylamino]-cyclohexanol

A mixture of *trans*-4-[4-(4-nitroindol-1-yl)-pyrimidin-2-ylamino]-cyclohexanol (2.44 g), EtOH (35 mL) and water (11 mL) was heated to 80°C. To the hot suspension was added ammonium chloride (1.46 g) followed by iron (0) (Fisher, 1.55 g) and the resulting mixture heated to 80°C for 2 h, then to 50°C for an additional 24 h. The reaction mixture was filtered through a CELITE™ pad, the filter cake washed with EtOAc/MeOH (3:2), and the filtrate evaporated under reduced pressure. The crude residue was purified by flash chromatography (MeOH/DCM, gradient from 2.5:97.5 to 10:90) to give *trans*-4-[4-(4-aminoindol-1-yl)-pyrimidin-2-ylamino]-cyclohexanol as a light yellow solid. MS = 324 $[M+H]^+$; MP = 218.9-220.1°C.

trans-4-[4-(6-Amino-indazol-1-yl)-pyrimidin-2-ylamino]-cyclohexanol was prepared in the same manner, utilizing the appropriate starting material. MS = 325 $[M+H]^+$; MP = 236.5-237.5°C.

Example 9: Synthesis of *trans*-1-[2-(4-Hydroxycyclohexylamino)-pyrimidin-4-yl]-1*H*-indol-5-ol

The synthetic procedure described in this Example was carried out according to the process shown in Scheme 23.

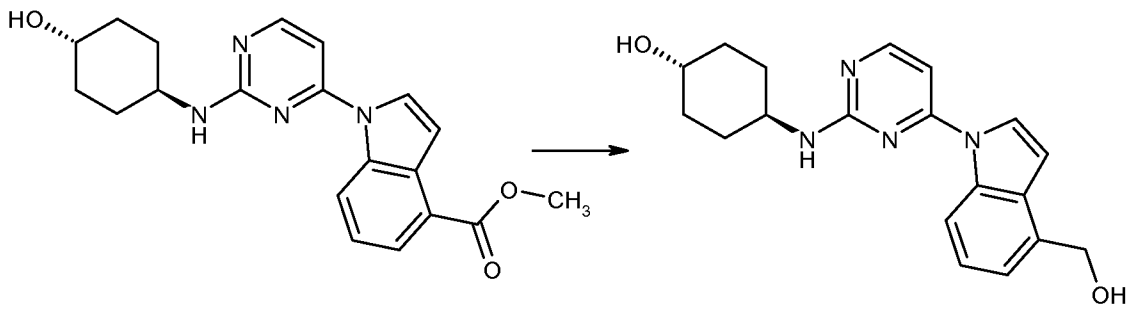


SCHEME 23

A mixture of 4-[4-(5-benzyloxyindol-1-yl)-pyrimidin-2-ylamino]-cyclohexanol (70 mg) and Pd/C (15%, 38 mg) in EtOH was stirred under H_2 (balloon pressure) at RT for 4 days. The reaction mixture was then filtered through a CELITE™ pad, the filter cake washed with EtOH, and the filtrate evaporated under reduced pressure. The residue was purified by flash chromatography (DCM/MeOH, 95:5) to give *trans*-1-[2-(4-hydroxy-cyclohexylamino)-pyrimidin-4-yl]-1*H*-indol-5-ol (51 mg) as an off-white solid. MS = 325 $[M+H]^+$; MP = 246.5-248.0°C.

Example 10: Synthesis of *trans*- 4-[4-(4-Hydroxymethylindol-1-yl)-pyrimidin-2-ylamino]-cyclohexanol

The synthesis of *trans*- 4-[4-(4-hydroxymethylindol-1-yl)-pyrimidin-2-ylamino]-cyclohexanol was carried out according to the process shown in Scheme 24.



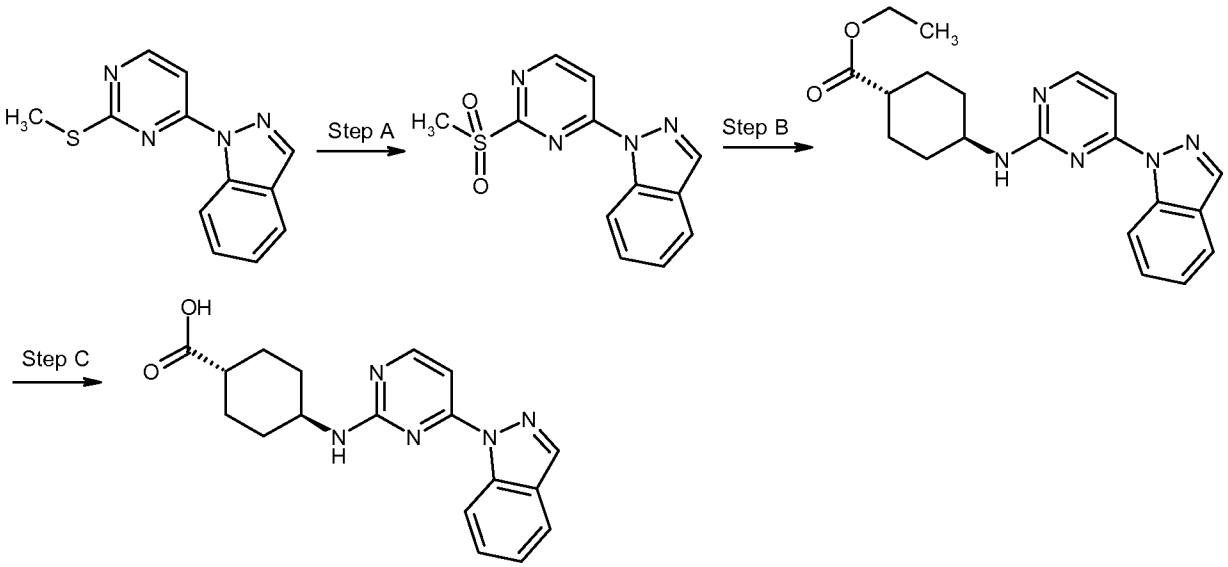
SCHEME 24

A solution of LAH (1 M in THF, 0.57 mL) was slowly added at -10°C under argon atmosphere to a solution of 1-[2-(4-hydroxycyclohexylamino)-pyrimidin-4-yl]-1*H*-indole-4-carboxylic acid methyl ester (100 mg) in THF (0.3 mL). The resulting mixture was stirred at -10°C for 30 min, and at RT overnight. The reaction mixture was then cooled to 0°C and water (20 µL) was added, followed by aqueous NaOH (15%, 20 µL) and a second aliquot of water (70 µL). The resulting mixture was stirred for 30 min, then filtered through a CELITE™ pad. The inorganic salts were triturated, the supernatant added to the filtrate, and the solution evaporated under reduced pressure to give *trans*-4-[4-(4-hydroxymethylindol-1-yl)-pyrimidin-2-ylamino]-cyclohexanol (32.5 g, 35% yield) as a white solid. MS = 339 $[M+H]^+$; MP = 212.0-213.3°C.

trans-4-[4-(5-Hydroxymethylindol-1-yl)-pyrimidin-2-ylamino]-cyclohexanol (white solid) was prepared in a similar manner, utilizing the appropriate starting materials. MS = 339 $[M+H]^+$; MP = 232.0-233.9°C.

Example 11: Synthesis of *trans*-4-(4-indazol-1-ylpyrimidin-2-ylamino)-cyclohexane-carboxylic acid

The synthesis of *trans*-4-(4-indazol-1-ylpyrimidin-2-ylamino)-cyclohexanecarboxylic acid was carried out according to the process shown in Scheme 25.



SCHEME 25

Step A: synthesis of 1-(2-methanesulfonyl-pyrimidin-4-yl)-1*H*-indazole

3-Chloroperoxybenzoic acid (77%, 14.97 g, 86.7 mmol) was added to a solution of 1-(2-methylsulfanyl-pyrimidin-4-yl)-1*H*-indazole (10 g, 41.3 mmol) in $CHCl_3$ (50 mL) cooled in an ice/acetone bath, and the resulting mixture stirred overnight. The reaction mixture was washed with aqueous sodium bisulfite (10%). The resulting solid was filtered off, and the filtrate phases separated. The aqueous layer was extracted with DCM, the combined organic extracts washed with aqueous NaOH, aqueous $NaHCO_3$ (saturated), dried over $MgSO_4$, filtered and evaporated under reduced pressure to give 1-(2-methanesulfonyl-pyrimidin-4-yl)-1*H*-indazole (6.4 g) as an orange solid, used without further purification. MS = 275 $[M+H]^+$; MP = 177.0-181.1°C.

In the same manner, utilizing the appropriate starting materials, the following compounds where prepared:

1-(2-Methanesulfonylpyrimidin-4-yl)-6-methyl-1*H*-indazole; and

1-(2-Methanesulfonylpyrimidin-4-yl)-5-methyl-1*H*-indazole.

Step B: synthesis of *trans*-4-(4-indazol-1-ylpyrimidin-2-ylamino)-cyclohexanecarboxylic acid ethyl ester

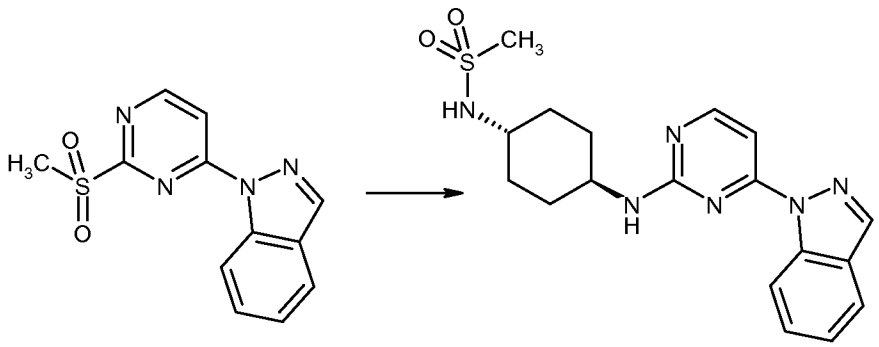
1-(2-Methanesulfonylpyrimidin-4-yl)-1*H*-indazole (6.4 g) was suspended in THF and the mixture heated to 60°C until complete dissolution of the solids. *trans*-4-Amino-cyclohexanecarboxylic acid ethyl ester (7.99 g, 46.6 mmol) was added, followed by TEA (9.7 mL, 69.9 mmol), and the resulting mixture stirred overnight. The reaction mixture was concentrated under reduced pressure until solids started to precipitate, and was then heated to 60°C for 24 h. THF (4 mL) was added, and the reaction mixture stirred for 64 h at 60°C. The resulting mixture was extracted with EtOAc, the combined organic extracts washed with water, dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The crude residue was purified by flash chromatography (DCM/MeOH, 98:2) and the brown solid obtained was triturated with Et_2O to give *trans*-4-(4-indazol-1-ylpyrimidin-2-ylamino)-cyclohexanecarboxylic acid ethyl ester (2.883 g) as a white solid.

Step C: synthesis of *trans*-4-(4-indazol-1-ylpyrimidin-2-ylamino)cyclohexanecarboxylic acid

A mixture of *trans*-4-(4-indazol-1-ylpyrimidin-2-ylamino)-cyclohexanecarboxylic acid ethyl ester (2.88 g, 7.9 mmol), aqueous NaOH (2 M, 65 mL) and THF (65 mL) was stirred overnight. MeOH (40 mL) was added, and the reaction mixture stirred for an additional 105 min. Aqueous HCl (1M) was added to reach pH 3, and the resulting solid collected by filtration to give *trans*-4-(4-indazol-1-yl-pyrimidin-2-ylamino)-cyclohexanecarboxylic acid (2.739 g) without further purification.

Example 12: Synthesis of *trans*-*N*-[4-(4-Indazol-1-ylpyrimidin-2-ylamino)-cyclohexyl]-methanesulfonamide

The synthesis of *trans*-*N*-[4-(4-indazol-1-ylpyrimidin-2-ylamino)-cyclohexyl]-methanesulfonamide was carried out according to the process shown in Scheme 26.



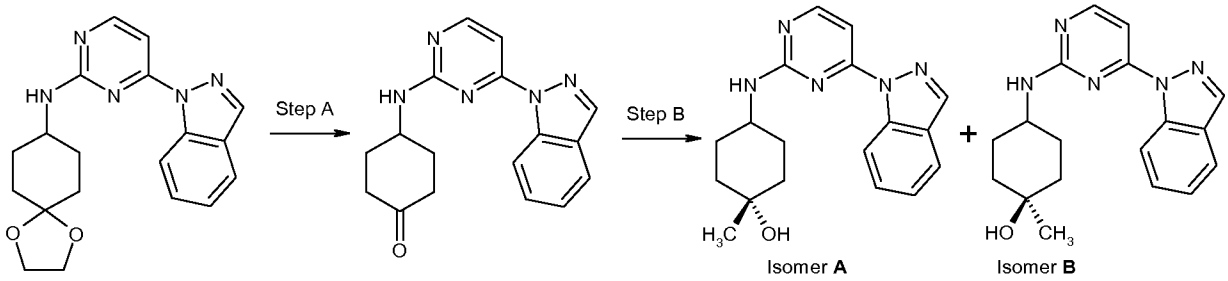
SCHEME 26

A mixture of *trans*-cyclohexane-1,4-diamine (0.62 g, 5.5 mmol) and NMP (10 mL) was heated to 120°C for 5 min, then 1-(2-methanesulfonyl-pyrimidin-4-yl)-1*H*-indazole (300

mg) in NMP (10 mL) was added dropwise and the resulting mixture was stirred for 15 min. Methanesulfonic anhydride (1.88 g, 10.8 mmol) was slowly added, and the reaction mixture stirred for 30 min. The solvent was evaporated by distillation under vacuum, EtOAc added to the residue, and the resulting solution washed with water. The organic layer was dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude residue was purified by trituration with hot DCM/MeOH (90:10) to give *trans-N*-[4-(4-indazol-1-yl-pyrimidin-2-ylamino)-cyclohexyl]-methanesulfonamide (38.0 mg) as a white solid. MS = 387 $[M+H]^+$; MP = 269.6-270.4°C.

Example 13: Synthesis of 4-(4-Indazol-1-ylpyrimidin-2-ylamino)-1-methylcyclohexanol

The synthesis of 4-(4-indazol-1-ylpyrimidin-2-ylamino)-1-methylcyclohexanol was carried out according to the process shown in Scheme 27.



SCHEME 27

Step A: synthesis of 4-(4-indazol-1-ylpyrimidin-2-ylamino)-cyclohexanone

Aqueous HCl (3 M, 40 mL) was added to (1,4-dioxaspiro[4.5]dec-8-yl)-(4-indazol-1-yl-pyrimidin-2-yl)-amine (1.89 g, 5 mmol) in THF (40 mL), and the resulting mixture heated to 80°C for 1 h. The reaction mixture was cooled and poured onto a mixture of ice and aqueous NaOH (1 M, 120 mL), and the resulting suspension filtered. The collected solids were washed with water, taken up in DCM/MeOH, and a portion of the solvent evaporated under reduced pressure. The resulting suspension was filtered, the collected solids washed with hexanes, and dried under reduced pressure to give 4-(4-indazol-1-ylpyrimidin-2-ylamino)-cyclohexanone (1.57 g, 95% yield) as a white powder. MS = 308 $[M+H]^+$; MP = 211.8-213.2°C.

Step B: synthesis of 4-(4-indazol-1-yl-pyrimidin-2-ylamino)-1-methyl-cyclohexanol

A solution of methylmagnesium chloride (3 M in THF, 2.4 mL, 7.2 mmol) was slowly added to a suspension of 4-(4-indazol-1-ylpyrimidin-2-ylamino)-cyclohexanone (600 mg, 2 mmol) in THF (100 mL) at -78°C under N_2. The reaction mixture was stirred for 15 min, a second aliquot of methylmagnesium chloride (3 M in THF, 1.0 mL, 3 mmol)

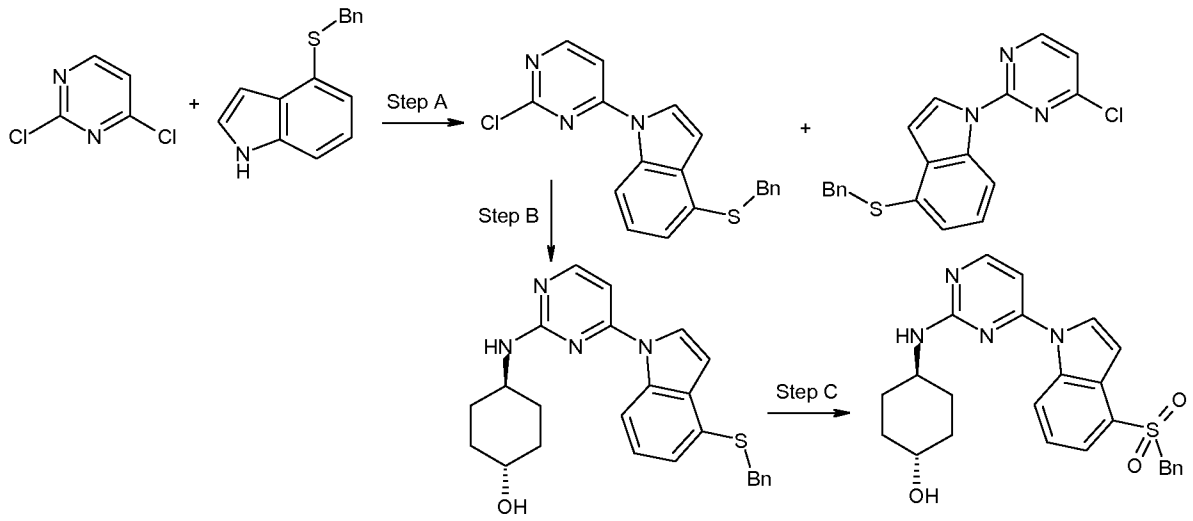
added, and the resulting mixture stirred at -78°C for 30 min. The reaction mixture was then warmed to RT and stirred for 4 h, then poured onto a mixture of ice and aqueous NH_4Cl (saturated). The resulting mixture was extracted with EtOAc, the combined organic extracts washed with brine, dried over $MgSO_4$, filtered, and evaporated under reduced pressure to give a white solid (609 mg, 96% yield). This crude material was purified by flash chromatography twice (MeOH/DCM, gradient from 3:97 to 5:95,) to give 4-(4-indazol-1-yl-pyrimidin-2-ylamino)-1-methyl-cyclohexanol (123 mg, 19% yield of the less-polar isomer as a white solid; and 360 mg, 57% yield of the more polar isomer as a white solid). Both isomers were recrystallized from DCM/hexanes (about 1:1) to give a white solid for the less polar isomer **A** (100 mg) and a crystalline free-flowing solid for the more polar isomer **B** (290 mg).

Isomer **A**: MS = 324 $[M+H]^+$; MP = 211.9-213.3°C.

Isomer **B**: MS = 324 $[M+H]^+$; MP = 168.1-170.1°C.

Example 14: Synthesis of *trans*-4-[4-(4-Phenylmethanesulfonylindol-1-yl)-pyrimidin-2-ylamino]-cyclohexanol

The synthesis of *trans*-4-[4-(4-phenylmethanesulfonylindol-1-yl)-pyrimidin-2-ylamino]-cyclohexanol was carried out according to the process shown in Scheme 28



SCHEME 28

Step A: Synthesis of 4-benzylsulfanyl-1-(2-chloro-pyrimidin-4-yl)-1*H*-indole and 4-benzylsulfanyl-1-(4-chloro-pyrimidin-2-yl)-1*H*-indole

4-Benzylsulfanyl-1*H*-indole (5.00 g, 21 mmol) (*Can. J. Chem. 1962, 40, 511*) was slowly added to a suspension of NaH (60% dispersion in mineral oil, 1.37 g, 34 mmol) in DMF

(40 mL) at 0°C. The reaction mixture was stirred for 15 min until the gas evolution ceased, then 2,4-dichloropyrimidine (3.03 g, 20 mmol) was added portionwise, followed by an additional aliquot of DMF (10 mL). The resulting mixture was slowly warmed to RT, then poured onto a slurry of ice and water and extracted with EtOAc. The organic layer was washed twice with a mixture of water and brine, dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude residue was purified by flash chromatography (EtOAc/hexanes, gradient from 10:90 to 50:50) to give 4-benzylsulfanyl-1-(4-chloropyrimidin-2-yl)-1*H*-indole (979 mg, 14% yield) as a pale-yellow waxy solid and a mixture of 4-benzylsulfanyl-1-(2-chloropyrimidin-4-yl)-1*H*-indole and the bisubstituted product (691 mg) after precipitation from DCM/EtOAc. This mixture was repurified by flash chromatography (EtOAc/hexanes, 20:80) to give 4-benzylsulfanyl-1-(2-chloropyrimidin-4-yl)-1*H*-indole (270 mg, 4% yield) as an off-white solid. MS = 352 $[M+H]^+$; MP = 159.0-161.2°C.

Step B: synthesis of *trans*-4-[4-(4-benzylsulfanylindol-1-yl)-pyrimidin-2-ylamino]-cyclohexanol

trans-4-Aminocyclohexanol (1.37 g, 12 mmol) was added to a solution of 4-benzylsulfanyl-1-(2-chloro-pyrimidin-4-yl)-1*H*-indole and the disubstituted product (673 mg, 2 mmol) in NMP (10 mL), and the resulting mixture heated to 110°C for 4 h. The reaction mixture was cooled and partitioned between water and EtOAc, the organic layer washed twice with water, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude residue was purified by flash chromatography (EtOAc/hexanes, from 10:90 to 20:80) to give after recrystallization from DCM/hexanes/EtOAc *trans*-4-[4-(4-benzylsulfanyl-indol-1-yl)-pyrimidin-2-ylamino]-cyclohexanol (309 mg, 38% yield) as a white solid. An additional aliquot of the product was recovered from the mother liquor. MS = 431 $[M+H]^+$; MP = 150.2-150.9°C.

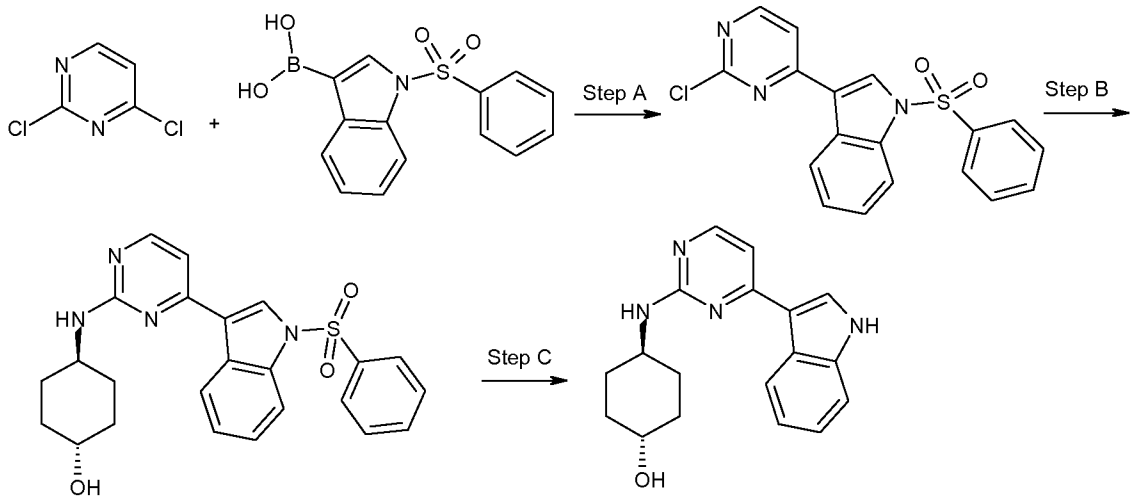
Step C: synthesis of *trans*-4-[4-(4-phenylmethanesulfonylindol-1-yl)-pyrimidin-2-ylamino]-cyclohexanol

3-Chloroperoxybenzoic acid (0.55 g, 2.5 mmol) was added to *trans*-4-[4-(4-benzylsulfanylindol-1-yl)-pyrimidin-2-ylamino]-cyclohexanol (397 mg, 0.9 mmol) in chloroform (25 mL), and the resulting mixture stirred at RT for 1 hour. A second aliquot of 3-chloroperoxybenzoic acid (150 mg) was added, the reaction mixture heated briefly; then cooled and concentrated under reduced pressure. The residue was partitioned between aqueous $NaHCO_3$ and EtOAc. The organic layer was separated, washed twice with aqueous $NaHCO_3$ and water, dried over Na_2SO_4, filtered, and evaporated under

reduced pressure onto silica gel. The residue was purified by flash chromatography (MeOH/DCM, 5:95) to give *trans*-4-[4-(4-phenylmethanesulfonylindol-1-yl)-pyrimidin-2-ylamino]-cyclohexanol (30 mg, 7% yield) as a light-yellow solid. MS = 463 $[M+H]^+$; MP = 132.1-134.5°C.

Example 15: Synthesis of *trans*-4-[4-(1*H*-Indol-3-yl)-pyrimidin-2-ylamino]-cyclohexanol

The synthesis of *trans*-4-[4-(1*H*-indol-3-yl)-pyrimidin-2-ylamino]-cyclohexanol was carried out according to the process shown in Scheme 29.



SCHEME 29

Step A: synthesis of 1-benzenesulfonyl-3-(2-chloropyrimidin-4-yl)-1*H*-indole

A solution of 2,4-dichloropyrimidine (2.42 g, 16 mmol), 1-(phenylsulfonyl)-1*H*-indol-3-ylboronic acid (3.89 g, 13 mmol) and sodium carbonate (5.03 g, 47 mmol) in acetonitrile/water (2:1, 60 mL) was degassed with argon, then tetrakis(triphenylphosphine)palladium (300 mg, 1.6 mol) was added. The resulting mixture was heated to reflux for 2 h while a white suspension formed. The precipitate was cooled and filtered through a CELITE™/silica gel plug. The filter cake was washed with EtOAc, the organic layer separated, washed with brine, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was recrystallized from EtOAc/ hexanes to give 1-benzenesulfonyl-3-(2-chloro-pyrimidin-4-yl)-1*H*-indole as a light-pink solid. The solid filtrate from the reaction mixture was dissolved in DCM, dried over Na_2SO_4, filtered, and combined with the previous batch of product. The collected solids were dissolved in DCM, the solvent was evaporated under reduced pressure and EtOAc was added to form a suspension, the product was filtered and washed with hexanes, to give 1-

benzenesulfonyl-3-(2-chloro-pyrimidin-4-yl)-1*H*-indole (2.0 g, 33% yield) as a light-pink solid. An additional 0.45 g of product was obtained from the mother liquors.

Step B: synthesis of *trans*-4-[4-(1-benzenesulfonyl-1*H*-indol-3-yl)-pyrimidin-2-ylamino]-cyclohexanol

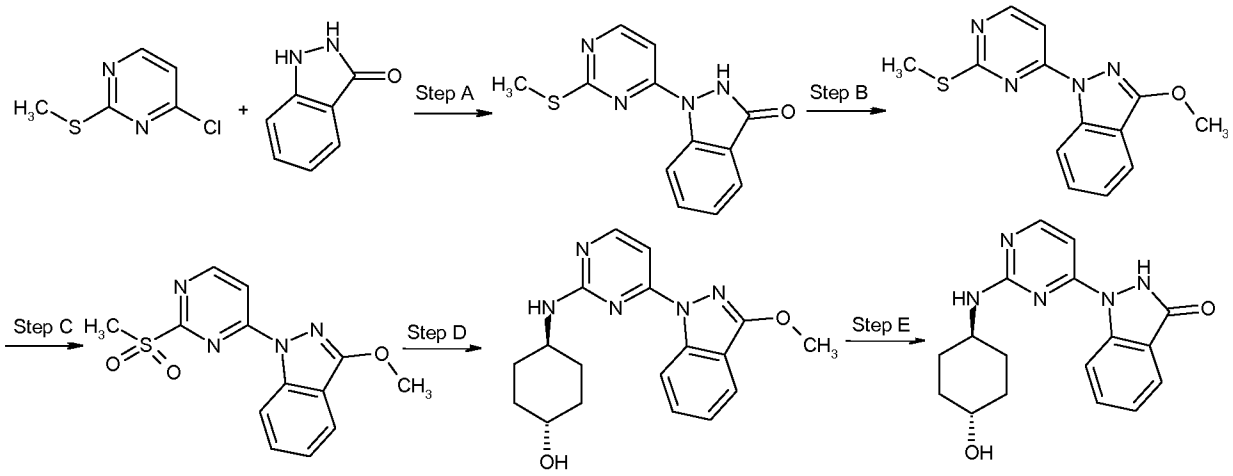
A solution of 1-benzenesulfonyl-3-(2-chloropyrimidin-4-yl)-1*H*-indole (0.45 g, 1 mmol) and *trans*-4-aminocyclohexanol (0.50 g, 4 mmol) in NMP (8 mL) was heated to 120°C for 3 h under N_2. The mixture was then cooled and partitioned between water and EtOAc, the organic layer separated, washed twice with brine, dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude residue was purified by flash chromatography (MeOH/DCM, 5:95) to give 405 mg of a yellow foam. This material was dissolved into EtOAc, washed twice with water, dried over Na_2SO_4, filtered and evaporated under reduced pressure. The solid residue was triturated with hexanes and dried under high vacuum to give *trans*-4-[4-(1-benzenesulfonyl-1*H*-indol-3-yl)-pyrimidin-2-ylamino]-cyclohexanol (365 mg, 19% yield) as a light-yellow amorphous solid. MS = 449 $[M+H]^+$; MP = 132.1-133.3°C.

Step C: synthesis of *trans*-4-[4-(1*H*-indol-3-yl)-pyrimidin-2-ylamino]-cyclohexanol

NaOH (200 mg, 5 mmol) was added to a solution of *trans*-4-[4-(1-benzenesulfonyl-1*H*-indol-3-yl)-pyrimidin-2-ylamino]-cyclohexanol (296 mg, 0.66 mmol) in MeOH (15 mL), and the resulting mixture stirred at RT for 6 h. The reaction mixture was concentrated under reduced pressure, the residue neutralized by addition of aqueous HCl (1 M), and then partitioned between water and EtOAc. The organic layer was separated, washed with water, dried over Na_2SO_4, filtered and evaporated under reduced pressure to give a crude yellow solid. This crude material was purified by flash chromatography (MeOH/DCM, 5:95) to give *trans*-4-[4-(1*H*-indol-3-yl)-pyrimidin-2-ylamino]-cyclohexanol (115 mg, 57% yield) as a white powder. MS = 309 $[M+H]^+$; MP = 258.1-259.9°C.

Example 16: Synthesis of *trans*-1-[2-(4-hydroxycyclohexylamino)-pyrimidin-4-yl]-1,2-dihydroindazol-3-one

The synthesis of *trans*-1-[2-(4-hydroxycyclohexylamino)-pyrimidin-4-yl]-1,2-dihydro-indazol-3-one was carried out according to the process shown in Scheme 30.



SCHEME 30

Step A: synthesis of 1-(2-methylsulfanylpyrimidin-4-yl)-1,2-dihydroindazol-3-one

3-Indazolinone (5.07 g, 38 mmol) was added portionwise at 0°C to a suspension of NaH (~ 60% dispersion in mineral oil, 2.18 g, 55 mmol) in DMF (50 mL), and the resulting mixture stirred for 20 min, until gas evolution ceased. 4-Chloro-2-methylthiopyrimidine (6.10 g, 38 mmol) was added, and the reaction mixture warmed to RT, then heated to 100°C for 3 h. The resulting mixture was cooled, poured into water (150 mL), neutralized with aqueous HCl (1 M), and EtOAc added. The resulting insoluble suspension was filtered and dried to give 1-(2-methylsulfanylpyrimidin-4-yl)-1,2-dihydroindazol-3-one (7.05 g, 72% yield) as an off-white solid. MS = 259 $[M+H]^+$; MP = 277.0-280.9°C.

Step B: synthesis of 3-methoxy-1-(2-methylsulfanylpyrimidin-4-yl)-1*H*-indazole

NaH (~ 60% dispersion in mineral oil, 0.75 g, 19 mmol) was added to 1-(2-methylsulfanylpyrimidin-4-yl)-1,2-dihydroindazol-3-one (2.70 g, 10 mmol) in DMF (30 mL) at 0°C, and the resulting mixture stirred until the gas evolution ceased. Iodomethane (0.90 mL, 14 mmol) was added, the mixture stirred for 30 min, then poured into water (100 mL) and extracted with EtOAc (100 mL). The combined organics were washed twice with water (100 mL), dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude residue was purified by flash chromatography (EtOAc/hexanes, from 20:80 to 50:50) and recrystallized from hexanes to give 3-methoxy-1-(2-methylsulfanyl-pyrimidin-4-yl)-1*H*-indazole (286 mg, 10% yield) as a white solid. MS = 272.9 $[M+H]^+$.

Step C: synthesis of 1-(2-methanesulfonylpyrimidin-4-yl)-3-methoxy-1*H*-indazole

3-Chloroperoxybenzoic acid (about 77%, 2.86 g, 18 mmol) was added to a solution of 3-methoxy-1-(2-methylsulfanylpyrimidin-4-yl)-1*H*-indazole (1.34 g, 5 mmol) in chloroform (30 mL) and the reaction mixture stirred at RT for 20 min. The resulting mixture was poured into aqueous $NaHCO_3$, stirred for 1 hour, then extracted with DCM. The combined organic extracts were washed twice with aqueous $NaHCO_3$ and with water, dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude residue was purified by flash chromatography (EtOAc/hexanes, gradient from 50:50 to 100:0) and recrystallized from DCM/hexanes/EtOAc to give 2 crops of 1-(2-methanesulfonylpyrimidin-4-yl)-3-methoxy-1*H*-indazole as an off-white solid (927 mg, 62% yield). An additional amount of product was recovered from the mother liquor as a yellow solid (0.44 g, 29% yield). MS = 305 $[M+H]^+$; MP = 206.3-207.8°C.

Step D: synthesis of *trans*-4-[4-(3-methoxyindazol-1-yl)-pyrimidin-2-ylamino]-cyclohexanol

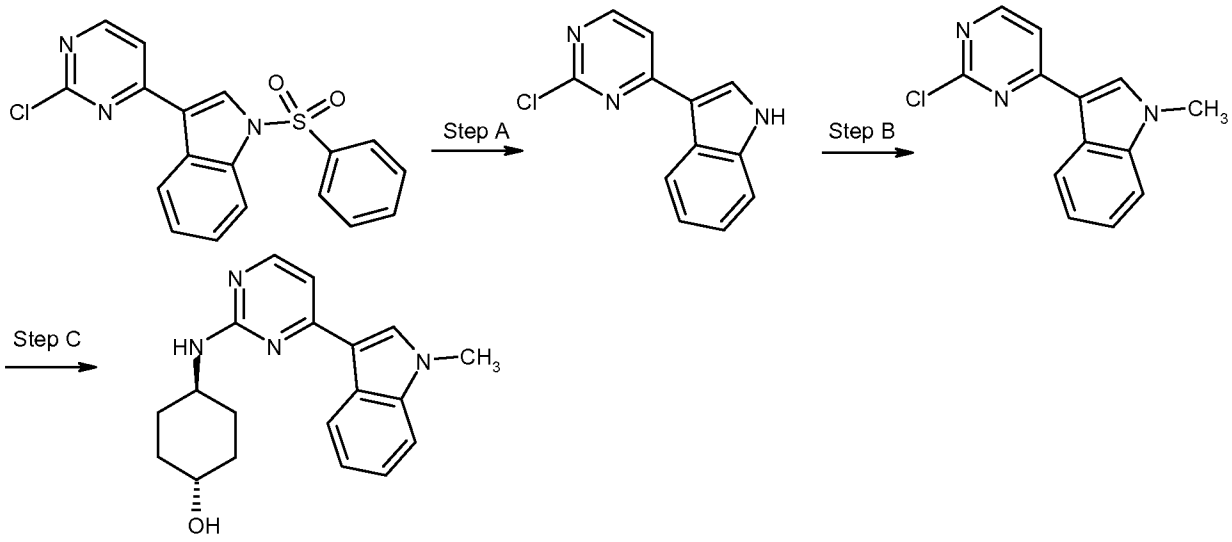
trans-4-Aminocyclohexanol (870 mg, 8 mmol) was added to 1-(2-methanesulfonyl-pyrimidin-4-yl)-3-methoxy-1*H*-indazole (440 mg, 1 mmol) in NMP (15 mL), and the resulting mixture heated to 120°C for 3 h. The reaction mixture was cooled and partitioned between EtOAc and water. The organic layer was separated, washed with water, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a crude yellow solid. This crude material was purified by flash chromatography (MeOH/DCM, 5:95) and recrystallized from DCM/hexanes to give *trans*-4-[4-(3-methoxy-indazol-1-yl)-pyrimidin-2-ylamino]-cyclohexanol (181 mg (37% yield) as a white solid. MS = 340 $[M+H]^+$; MP = 202.3-205.1°C.

Step E: synthesis of *trans*-1-[2-(4-hydroxycyclohexylamino)-pyrimidin-4-yl]-1,2-dihydro-indazol-3-one

Trimethylsilyliodide (0.80 mL, 5.6 mmol) was added under N_2 to a suspension of *trans*-4-[4-(3-methoxyindazol-1-yl)-pyrimidin-2-ylamino]-cyclohexanol (251 mg, 0.7 mmol) in chloroform (10 mL). The reaction mixture immediately became homogeneous, but within 1 hour a suspension formed, and the resulting mixture was stirred for 3 days. An additional aliquot of trimethylsilyliodide (2 mL, 14 mmol) was added, and the resulting mixture was heated to reflux overnight and stirred at RT for one day. The reaction mixture was then poured onto ice water and extracted with DCM. The insoluble solids were filtered and dissolved in a mixture of MeOH and DCM, the combined organic layers dried over Na_2SO_4, filtered and concentrated under reduced pressure onto silica gel. The residue was purified by flash chromatography (MeOH/DCM, gradient from 3:97 to 5:95) to give *trans*-1-[2-(4-hydroxycyclohexylamino)-pyrimidin-4-yl]-1,2-dihydroindazol-3-one (71 mg, 30% yield) as an off-white solid. MS = 326 $[M+H]^+$; MP = 263.5-264.4°C.

Example 17: Synthesis of *trans*- 4-[4-(1-Methyl-1*H*-indol-3-yl)-pyrimidin-2-ylamino]-cyclohexanol

The synthetic procedure described in this Example was carried out according to the process shown in Scheme 31.



SCHEME 31

Step A: synthesis of 3-(2-chloro-pyrimidin-4-yl)-1*H*-indole

A suspension of freshly crushed NaOH (740 mg) in MeOH (20 mL) was added at 0°C to a suspension of 1-benzenesulfonyl-3-(2-chloropyrimidin-4-yl)-1*H*-indole (0.91 g, 2 mmol) in MeOH/THF (1:1, 40 mL). The reaction mixture was warmed to RT and stirred

for 2 h until homogeneous. The resulting mixture was neutralized with aqueous HCl (1 M), and concentrated under reduced pressure. The residue was partitioned between water and EtOAc, the organic layer separated, washed with water, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a bright yellow solid (0.63 g). This crude material was purified by flash chromatography (1:1 EtOAc/hexanes) to give 3-(2-chloro-pyrimidin-4-yl)-1*H*-indole (502 mg, 89% yield) as a yellow solid.

Step B: synthesis of 3-(2-chloro-pyrimidin-4-yl)-1-methyl-1*H*-indole

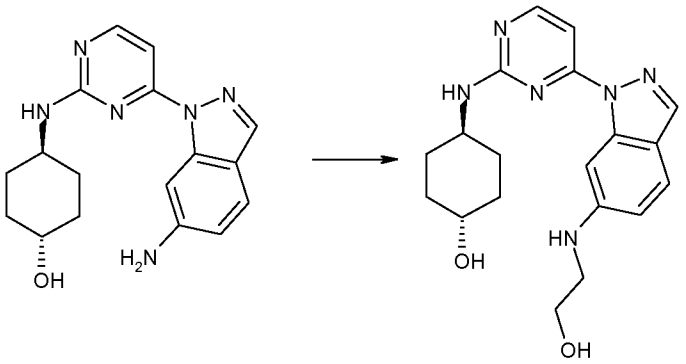
NaH (60% dispersion in mineral oil, 0.16 g, 7 mmol) was added at 0°C to 3-(2-chloro-pyrimidin-4-yl)-1*H*-indole (0.24 g, 1 mmol) in DMF (8 mL). The resulting mixture was stirred for 10 min, then iodomethane (0.20 mL, 3.2 mmol) was added, and the reaction mixture was warmed to RT and poured onto ice water. The resulting mixture was extracted with EtOAc, the combined organics washed twice with water, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give 3-(2-chloro-pyrimidin-4-yl)-1-methyl-1*H*-indole (270 mg) as a yellow solid.

Step C: synthesis of *trans*-4-[4-(1-methyl-1*H*-indol-3-yl)-pyrimidin-2-ylamino]-cyclohexanol

trans-4-Aminocyclohexanol (0.45 g, 4 mmol) was added to 3-(2-chloropyrimidin-4-yl)-1-methyl-1*H*-indole (0.23 g, 1 mmol) in NMP (8 mL), and the resulting mixture heated to 120°C for 3 h. A second aliquot of *trans*-4-aminocyclohexanol (0.16 g, 1 mmol) was added, and the resulting mixture was heated to 130°C. The reaction mixture was cooled and partitioned between water and EtOAc, the organic layer separated, washed twice with water, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was recrystallized from DCM/EtOAc/hexanes to give *trans*- 4-[4-(1-methyl-1*H*-indol-3-yl)-pyrimidin-2-ylamino]-cyclohexanol (148 mg, 46% yield) as a light-yellow solid. MS = 323 $[M+H]^+$; MP = 194.5-195.3°C.

Example 18: Synthesis of *trans*-4-{4-[6-(2-Hydroxyethylamino)-indazol-1-yl]-pyrimidin-2-ylamino}-cyclohexanol

The synthesis of *trans*-4-{4-[6-(2-hydroxy-ethylamino)-indazol-1-yl]-pyrimidin-2-ylamino}-cyclohexanol was carried out according to the process shown in Scheme 32.

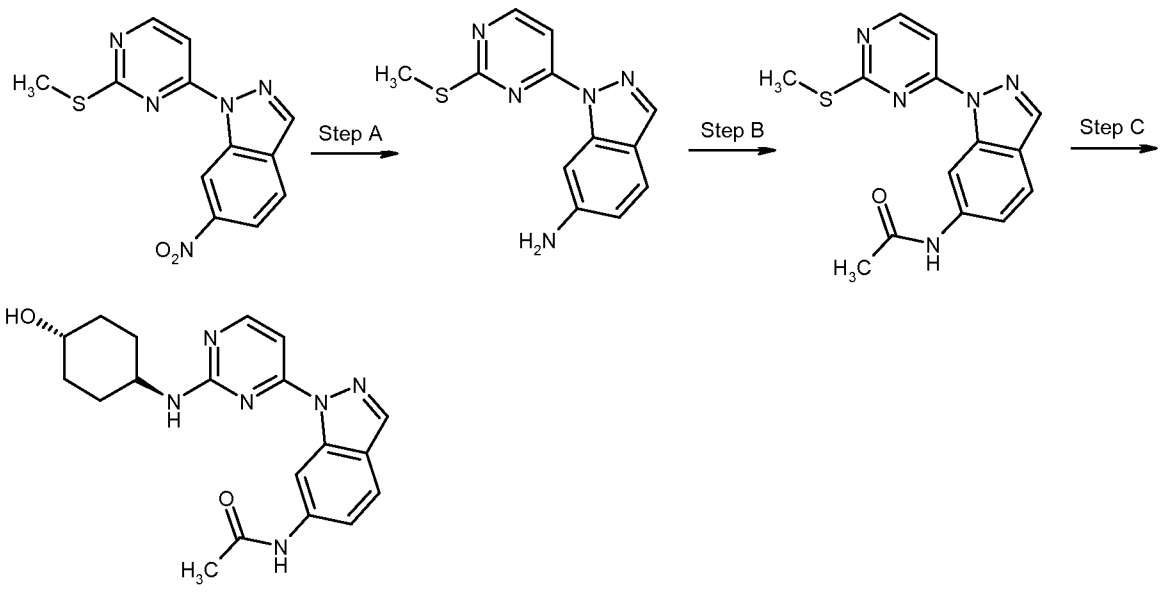


SCHEME 32

2-Bromoethanol (42 μL, 0.6 mmol) was added to a mixture of *trans*-4-[4-(6-amino-indazol-1-yl)-pyrimidin-2-ylamino]-cyclohexanol (100 mg, 0.30 mmol) and sodium bicarbonate (25 mg, 0.30 mmol) in acetonitrile (1 mL), and the resulting mixture heated to 80°C for 2 h. DMF (0.5 mL) was added, and the resulting mixture heated to 80°C overnight. A second aliquot of 2-bromoethanol (20 μL) was added, and heating continued for 3 days. The resulting mixture was diluted with MeOH, and Et_2O was added. The gummy residue which crashed out of solution was purified by preparative TLC to give *trans*-4-{4-[6-(2-hydroxyethylamino)-indazol-1-yl]-pyrimidin-2-ylamino}-cyclohexanol (29 mg) as a yellow solid. MS = 369 $[M+H]^+$.

Example 19: Synthesis of *trans*-*N*-{1-[2-(4-Hydroxycyclohexylamino)-pyrimidin-4-yl]-1H-indazol-6-yl}-acetamide

The synthesis of *trans*-*N*-{1-[2-(4-hydroxycyclohexylamino)-pyrimidin-4-yl]-1H-indazol-6-yl}-acetamide was carried out according to the process shown in Scheme 33.



SCHEME 33

Step A: Synthesis of 1-(2-methylsulfanylpyrimidin-4-yl)-1*H*-indazol-6-ylamine

1-(2-Methylsulfanylpyrimidin-4-yl)-6-nitro-1*H*-indazole was reduced following the procedure described in Example 8.

Step B: Synthesis of *N*-[1-(2-methylsulfanylpyrimidin-4-yl)-1*H*-indazol-6-yl]-acetamide

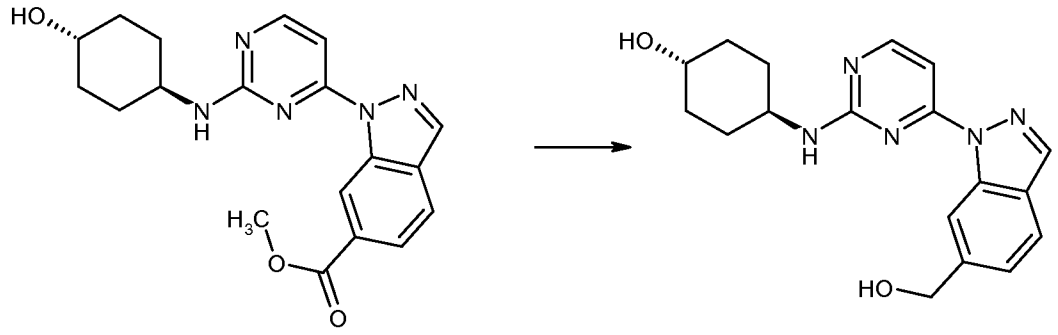
Acetyl chloride (10 drops) was added dropwise at RT to 1-(2-methylsulfanylpyrimidin-4-yl)-1*H*-indazol-6-ylamine (0.13 g, 0.5 mmol) and triethylamine (15 drops) in THF (5 mL), and the resulting mixture stirred for 30 min. The reaction mixture was diluted with DCM and MeOH, washed twice with aqueous $NaHCO_3$ and once with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was treated with Et_2O and hexane, and the precipitate was collected by filtration to give *N*-[1-(2-methylsulfanylpyrimidin-4-yl)-1*H*-indazol-6-yl]-acetamide (146 mg) as an off-white solid.

Step C: synthesis of *trans*-*N*-{1-[2-(4-hydroxycyclohexylamino)-pyrimidin-4-yl]-1H-indazol-6-yl}-acetamide

3-Chloroperoxybenzoic acid (77%, 200 mg, 0.87 mmol) was added to a slurry of *N*-[1-(2-methylsulfanylpyrimidin-4-yl)-1*H*-indazol-6-yl]-acetamide (0.43 mmol, 0.13 g) in chloroform (5 mL), and the resulting mixture stirred at RT overnight. The reaction mixture was diluted with DCM/MeOH (4:1, 25 mL), washed with aqueous NaOH (0.1 M) and with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was triturated with Et_2O to give *N*-[1-(2-methanesulfonyl-pyrimidin-4-yl)-1*H*-indazol-6-yl]-acetamide (120 mg) as an off-white solid. A portion of this material (100 mg) was mixed with *trans*-4-aminocyclohexanol (0.12 g) and the mixture was heated to 130°C for 85 min. The residue was treated with DCM/MeOH and the solvent evaporated under reduced pressure. The residue was treated with MeOH (5 mL) and Et_2O, the liquid supernatant decanted away, and the gummy solid which formed was treated with a second aliquot of MeOH (5 mL) and EtOAc (15 mL). The resulting fine precipitate was collected by filtration to give *trans*-*N*-{1-[2-(4-hydroxycyclohexylamino)-pyrimidin-4-yl]-1H-indazol-6-yl}-acetamide (72 mg, 65% yield) as an off-white solid. MS = 367 $[M+H]^+$; MP = 288.0-289.5°C.

Example 20: Synthesis of *trans*-4-[4-(6-Hydroxymethylindazol-1-yl)-pyrimidin-2-ylamino]-cyclohexanol

The synthesis of *trans*-4-[4-(6-hydroxymethylindazol-1-yl)-pyrimidin-2-ylamino]-cyclohexanol was carried out according to the process shown in Scheme 34.

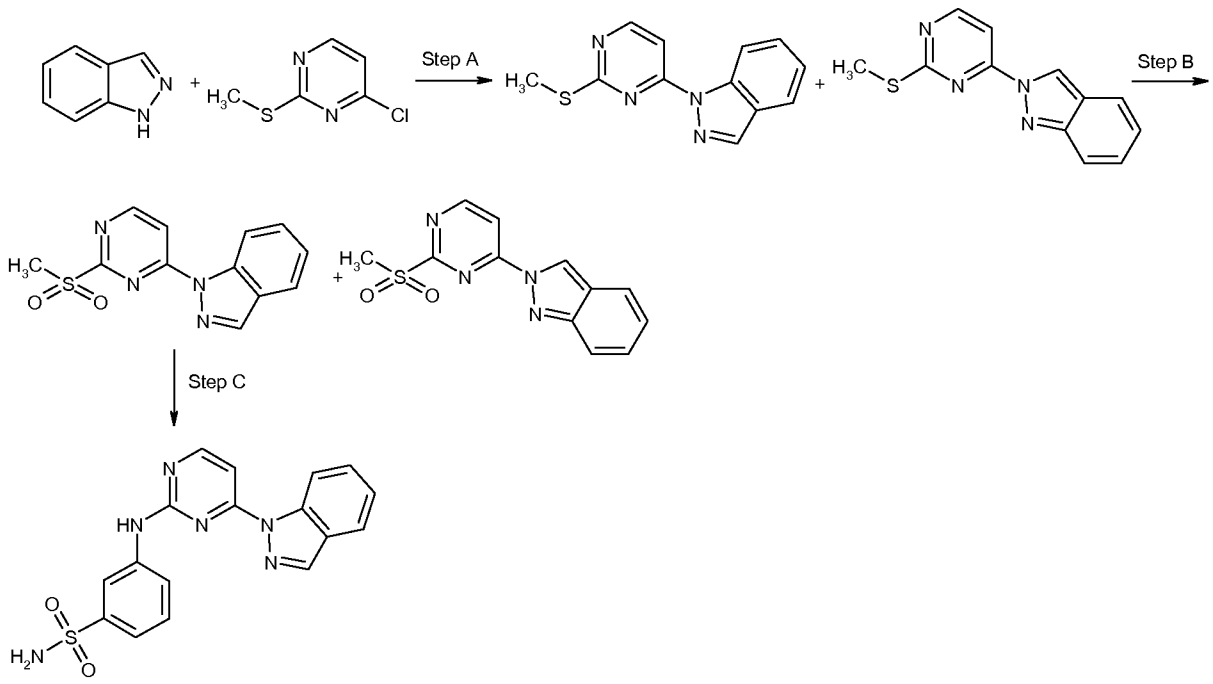


SCHEME 34

A solution of lithium triethylborohydride (1 M in THF, 0.8 mL) was slowly added at RT to *trans*-1-[2-(4-hydroxycyclohexylamino)-pyrimidin-4-yl]-1*H*-indazole-6-carboxylic acid methyl ester (100 mg) in THF (3 mL). The resulting mixture was stirred for 30 min, and AcOH/ EtOH (1:1, 2 mL) was added. The reaction mixture was stirred for 30 min, then poured onto aqueous HCl (0.1 M). The resulting mixture was basified to pH 8 with aqueous NaOH and aqueous $NaHCO_3$, then extracted with DCM. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by preparative TLC (DCM/MeOH, 95:5) to give of *trans*-4-[4-(6-hydroxymethyl-indazol-1-yl)-pyrimidin-2-ylamino]-cyclohexanol (22 mg) as a white solid. MS = 340 $[M+H]^+$; MP = 216.0 -217.7°C.

Example 21: Synthesis of 3-(4-Indazol-1-ylpyrimidin-2-ylamino)-benzenesufonamide

The synthesis of 3-(4-indazol-1-ylpyrimidin-2-ylamino)-benzenesufonamide was carried out according to the process shown in Scheme 35.



SCHEME 35

Step A: Synthesis of 1-(2-methylsulfanyl-pyrimidin-4-yl)-1*H*-indazole and 2-(2-methyl-sulfanylpyrimidin-4-yl)-2*H*-indazole

A solution of 1*H*-indazole (2.36 g, 20.0 mmol) in anhydrous DMF (100 mL) was treated with NaH (60% dispersion in mineral oil, 1.60 g, 40.0 mmol) at RT for 10 min. 4-Chloro-2-methylthiopyrimidine (2.55 ml, 22.0 mmol) was then added in one portion at RT, and the resulting mixture stirred at 70°C for 2.5 h. The reaction mixture was cooled to RT, quenched with aqueous HCl (1 M), and extracted with EtOAc. The layers were separated, the organic layer washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was absorbed onto silica gel and purified by flash chromatography (ethyl acetate/hexane, gradient from 5:95 to 25:75) to afford a mixture of 1-(2-methylsulfanyl-pyrimidin-4-yl)-1*H*-indazole and 2-(2-methylsulfanyl-pyrimidin-4-yl)-2*H*-indazole (3.77 g, 78% yield) as a beige solid.

Step B: Synthesis of 1-(2-methanesulfonylpyrimidin-4-yl)-1*H*-indazole and 2-(2-methanesulfonyl-pyrimidin-4-yl)-2*H*-indazole

A mixture of 1-(2-methylsulfanyl-pyrimidin-4-yl)-1*H*-indazole and 2-(2-methylsulfanyl-pyrimidin-4-yl)-2*H*-indazole (3.77 g, 15.55 mmol) in chloroform (80 mL) was treated with 3-chloroperoxybenzoic acid (80%, 7.37 g, 34.21 mmol). The reaction mixture was stirred at 50°C for 1.5 hour, then quenched with aqueous NaOH (1 M). The resulting mixture was extracted with DCM, the layers separated, and the organic layer washed with

brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was absorbed onto silica gel and purified by flash chromatography (DCM/ethyl acetate, gradient from 0:100 to 5:95) to afford 1-(2-methylsulfanyl-pyrimidin-4-yl)-1*H*-indazole (less polar isomer) (1.92 g, 45% yield) and 2-(2-methylsulfanyl-pyrimidin-4-yl)-2*H*-indazole (more polar isomer) (1.04 g, 24% yield).

Step C: synthesis of 3-(4-indazol-1-ylpyrimidin-2-ylamino)-benzenesufonamide

A solution of 1-(2-methylsulfonyl-pyrimidin-4-yl)-1*H*-indazole (100 mg, 0.36 mmol) and p-toluenesulfonic acid (139 mg, 0.73 mmol) in i-PrOH (4 ml) was treated with 3-aminobenzenesulfonamide (251 mg, 1.46 mmol) in a microwave synthesizer at 150°C for 20 min. The mixture was partitioned between water and ethyl acetate, the organic layer separated, washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude residue was absorbed on silica gel and purified by flash chromatography (EtOAc/hexane, gradient from 30:70 to 50:50) to afford the title compound. This residue was triturated with aqueous NaOH (1 M), the solid collected by filtration, washed with water and dried under vacuum to afford 3-(4-indazol-1-ylpyrimidin-2-ylamino)-benzenesufonamide (50 mg, 37% yield). MS = 367 $[M+H]^+$.

4-(4-Indazol-1-yl-pyrimidin-2-ylamino)-cyclohexyl]-carbamic acid tert-butyl ester (white solid) was prepared in the same manner, utilizing the appropriate starting materials. MS = 409.2 $[M+H]^+$.

Example 22: Formulations

Pharmaceutical preparations for delivery by various routes are formulated as shown in the following Tables. "Active ingredient" or "Active compound" as used in the Tables means one or more of the Compounds of Formula I.

Composition for Oral Administration

Ingredient	% wt./wt.
Active ingredient	20.0%
Lactose	79.5%
Magnesium stearate	0.5%

The ingredients are mixed and dispensed into capsules containing about 100 mg each; one capsule would approximate a total daily dosage.

Composition for Oral Administration

Ingredient	% wt./wt.
Active ingredient	20.0%
Magnesium stearate	0.5%
Crosscarmellose sodium	2.0%
Lactose	76.5%
PVP (polyvinylpyrrolidine)	1.0%

The ingredients are combined and granulated using a solvent such as methanol. The formulation is then dried and formed into tablets (containing about 20 mg of active compound) with an appropriate tablet machine.

Composition for Oral Administration

Ingredient	Amount
Active compound	1.0 g
Fumaric acid	0.5 g
Sodium chloride	2.0 g
Methyl paraben	0.15 g
Propyl paraben	0.05 g
Granulated sugar	25.5 g
Sorbitol (70% solution)	12.85 g
Veegum K (Vanderbilt Co.)	1.0 g
Flavoring	0.035 ml
Colorings	0.5 mg
Distilled water	q.s. to 100 ml

The ingredients are mixed to form a suspension for oral administration.

Parenteral Formulation

Ingredient	% wt./wt.
Active ingredient	0.25 g
Sodium Chloride	qs to make isotonic
Water for injection	100 ml

The active ingredient is dissolved in a portion of the water for injection. A sufficient quantity of sodium chloride is then added with stirring to make the solution isotonic. The solution is made up to weight with the remainder of the water for injection, filtered through a 0.2 micron membrane filter and packaged under sterile conditions.

Suppository Formulation

Ingredient	% wt./wt.
Active ingredient	1.0%
Polyethylene glycol 1000	74.5%
Polyethylene glycol 4000	24.5%

The ingredients are melted together and mixed on a steam bath, and poured into molds containing 2.5 g total weight.

Topical Formulation

Ingredients	grams
Active compound	0.2-2
Span 60	2
Tween 60	2
Mineral oil	5
Petrolatum	10
Methyl paraben	0.15
Propyl paraben	0.05
BHA (butylated hydroxy anisole)	0.01
Water	q.s. 100

All of the ingredients, except water, are combined and heated to about 60°C with stirring. A sufficient quantity of water at about 60°C is then added with vigorous stirring to emulsify the ingredients, and water then added q.s. about 100 g.

Nasal Spray Formulations

Several aqueous suspensions containing from about 0.025-0.5 percent active compound are prepared as nasal spray formulations. The formulations optionally contain inactive ingredients such as, for example, microcrystalline cellulose, sodium carboxymethyl-cellulose, dextrose. Hydrochloric acid may be added to adjust pH. The nasal spray formulations may be delivered via a nasal spray metered pump typically delivering about 50-100 μL of formulation per actuation. A typical dosing schedule is 2-4 sprays every 4-12 h.

Example 23: JNK Assay in vitro

JNK activity was measured by phosphorylation of GST-ATF2 (19-96) with [γ-^{33}P] ATP. The enzyme reaction was conducted at Km concentrations of ATP and the substrate at final volume of 40 μl in buffer containing 25 mM HEPES, pH 7.5, 2 mM dithiothreitol, 150 mM NaCl, 10 mM $MgCl_2$, 0.001% Tween® 20, 0.1% BSA and 10% DMSO. Human

JNK2α2 assay contains 1nM enzyme, 1 μM ATF2, 8 μM ATP with 1uCi [γ-^{33}P] ATP. Human JNK1α1 assay contains 2 nM enzyme, 1μM ATF2, 6 μM ATP with 1 μCi [γ-^{33}P] ATP. Human JNK3 (Upstate Biotech #14-501M) assay contains 2 nM enzyme, 1 μM ATF2, 4 μM ATP with 1 μCi [γ-^{33}P] ATP. The enzyme assay was carried out in the presence or absence of several compound concentrations. JNK and compound were pre-incubated for 10 min., followed by initiation of the enzymatic reaction by adding ATP and the substrate. The reaction mixture was incubated at 30°C for 30 min. At the end of incubation, the reaction was terminated by transferring 25 μl of the reaction mixture to 150 μl of 10% glutathione Sepharose® slurry (Amersham # 27-4574-01) containing 135 mM EDTA. The reaction product was captured on the affinity resin, and washed on a filtration plate (Millipore, MABVNOB50) with phosphate buffered saline for six times to remove free radionucleotide. The incorporation of ^{33}P into ATF2 was quantified on a microplate scintillation counter (Packard Topcount). Compound inhibition potency on JNK was measured by IC_{50} value generated from ten concentration inhibition curves fitted into the 3-parameter model: % inhibition = Maximum/(1+ (IC_{50}/[Inhibitor])^{slope}). Data were analyzed on Microsoft Excel for parameter estimation. The results are shown in Table 2 below:

Table 2: p(IC_{50})

Compound	JNK1 (μM)	JNK2 (μM)	c-jun (μM)
3	0.0412	0.4578	ND
15	0.0678	0.4583	1.286
16	0.0708	0.5924	4.133
18	0.0735	0.3375	1.9533
26	0.085	0.6949	1.894
86	0.0228	0.1777	ND
87	0.0297	0.1908	1.706
88	0.0709	0.4803	ND

Example 24: Rat *in vivo* TNFα-induced IL-6 Production assay

Female Wistar-Han rats procured from Charles River Laboratories were allowed to acclimate for one week prior to use and achieve an approximate body weight of 95-130 g. Rats were administered test compound via oral gavage 30 min prior to an

intraperitoneal challenge of 0.5 μg recombinant rat TNF-α (Biosource). Blood was collected via cardiocentesis 90 min after TNF-α challenge. Plasma was prepared using lithium heparin separation tubes (BD microtainer) and frozen at -80°C until analyzed. IL-6 levels were determined using a rat specific IL-6 ELISA kit (Biosource). The percent inhibition and ED_{50} values (calculated as the dose of compound at which TNF-α production is 50% of the control value) were determined. The results are shown in Table 3 below:

Table 3: Inhibition of IL-6 Production

Compound	Dose (mg/Kg)	IL-6 Inhibition (%)
16	30	47.4%
26	30	59.6%
87	10	64%

Example 25: Rodent Collagen-induced Arthritis

Female Lewis rats procured from Harlan Laboratories at 7-8 weeks of age are allowed to acclimate for one week prior to use and achieve an approximate body weight of 120-140 g . On day 0 of study, rats are primed intradermally (i.d.) on several sites on the back with an emulsion of 100 μg Bovine Type II Collagen (Chondrex) in Incomplete Freund's adjuvant (IFA; total of 0.1 ml in 2-3 sites). Arthritis induction is generally observed 12-14 days from priming; however a booster injection of 100 μg collagen/IFA is given around days 7-10 (i.d. up to 0.1 ml total) at the base of the tail or an alternate site on back to synchronize disease induction. Compound dosing can be prophylactic (starting at time of boost or 1-2 days prior) or therapeutic (beginning after boost and coinciding with initial disease scores of 1-2 –see clinical scoring below). Animals are evaluated for the development and progression of disease over the next 21 days.

Rats are evaluated using a scoring system (described below), paw volume measurements using a plethysmometer for each paw, or measuring paw or joint thickness with a caliper. Baseline measurements are performed on day 0, and starting again at the first signs of swelling for up to three times per week until the end of the experiment. Scoring is evaluated as follows for each paw:

1= swelling and/or redness of paw or one digit.

- welling in two or more joints.

3= gross swelling of the paw with more than two joints involved.

4= severe arthritis of the entire paw and digits.

The arthritic index for each rat is evaluated by adding the four scores of the individual paws, giving a maximum score of 16. In order to serially measure disease onset and progression, the paw volume of the hind paws is also determined through the use of a plethysmometer.

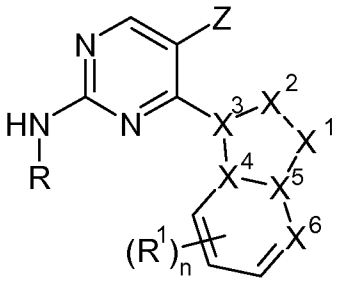
At the end of the study, the hind paws (and other tissues) are harvested for weight determination, histology, cellular and/or molecular analysis. Additionally, blood is collected via cardiocentesis, plasma is prepared using lithium heparin separation tubes (BD microtainer) and frozen at -70°C until analyzed. Inflammatory cytokine levels (e.g., TNF-α, IL-1 and IL-6) from the plasma or from homogenized joint tissue are determined using rat-specific ELISA kits (R&D). The level of disease protection or inhibition is determined as a composite of changes in clinical scores, paw volumes and histopathology compared to control animals.

Example 26: IL-8 Production Assay in TNFα-induced Human Chondrosarcoma SW1353 cells

SW1353 cells are purchased from the American Tissue Culture Collection and maintained in growth media consisting of DMEM medium (Invitrogen) with 10% fetal bovine serum (Invitrogen), ascorbic acids (Sigma) and penicillin (Invitrogen) under the culture condition of 37°C in 5% CO_2. Cells are plated at a density of 1.0×10^4 cells per well in 100 µl of media 48 hours before the compound treatment. Immediately before the compound treatment, media is replaced with 160 µl of fresh media. Compound stock (10 mM) is diluted in growth media and added to each well as a 10× concentrated solution in a volume of 20 µl, mixed and allowed to pre-incubate with cells for 30 min. The compound vehicle (DMSO) is maintained at a final concentration of 1% in all samples. After 30 min, the cells are activated with 10 ng/ml of TNF-α (Roche Biochem). TNF-α is added as a 10× concentrated solution made up in growth media and added in a volume of 20 µl per well. Cell plates are cultured for 5 h. Cell media are harvested and stored at -20°C. Media aliquots are analyzed by sandwich ELISA for the presence of IL-8 as per the manufacturer's instructions (BD Bioscience). The IC_{50} values are calculated as the concentration of the compound at which the IL-8 production was reduced to 50% of the control value using Xlfit3 in Microsoft Excel program. Certain compounds have an IC_{50} [illegible] om 0.1-20 µM in this assay.

Claims

1. A compound of formula I:



(I)

wherein

X^1 is N, N-R^3, CHR^3, C-R^3, or O;

X^2 is N, NH, N-CH_3, CH, CH_2, $CHCH_3$ or C-CH_3;

X^3 is N, C or CH, where X^1, X^2, and X^3 are not all simultaneously N;

X^4, X^5 are each independently C, CH or N;

X^6 is N or C-R^1;

where at least two and not more than four of X^1, X^2, X^3, X^4, X^5, and X^6 are N; and where the bonds between X^1 and X^2, X^2 and X^3, X^3 and X^4, X^4 and X^5, X^5 and X^1, and X^5 and X^6 may each independently be either single, double, or form an aromatic ring, with the proviso that a chemically stable structure results;

R is –(cyclohexyl)–R^2 or –(phenyl)–R^8, where cyclohexyl and phenyl are each optionally substituted with methyl, fluoro, chloro, or hydroxy;

R^1 is halo, nitro, –CN, –CH_2CN, –OH, –NH_2, –COOH, or –Y^1R^4;

Y^1 is –O–, –NH–, –S–, –SO–, –SO_2–, –$NHSO_2$–, –NHC(O) –, –C(O)NH–, –C(O)O–, or a bond;

R^4 is C_{1-6} alkyl, acyl, phenyl, or benzyl, each of which is substituted with 0-3 hydroxy or halo;

n is 0, 1, or 2;

R^3 is H or C_{1-6} alkyl;

R^2 is H, –OH, $–SO_2NH_2$, =O, –CN, or $–Y^2–Y^3–Y^4–R^5$, where

Y^2 is –C(O)–, $–C(O)NR^a–$, $–SO_2–$, –O–, –NH–, or a bond;

Y^3 is C_{1-6} alkylene or a bond;

Y^4 is –O–, $–NR^a–$, –S–, $–SO_2–$, –C(O)–, $–C(O)NR^a–$, $–NR^aC(O)–$, $–NR^aC(O)O–$, $–NR^aC(O)NR^a–$, $–NHSO_2–$, $–SO_2NH–$, or a bond;

R^5 is C_{1-6} alkyl, C_{3-10} cycloalkyl, heterocyclyl, wherein R^5 is optionally substituted with –OH or $–NHR^a$; wherein each R^a is independently H or C_{1-6} alkyl;

R^8 is H, C_{1-6} alkyl, $–OR^3$, $–SO_2NH_2$, $–NHSO_2R^3$, $–COOR^3$, $–SO_2R^3$, $–NH_2$, $–CONR^aR^3$, $–NHC(O)R^3$, $–CF_3$, $–NO_2$, halo, or –CN;

Z is hydrogen, halo, C_{1-12} alkyl, or NH_2;

or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, wherein

X^1 is N, N-R^3, C-R^3, or O;

X^2 is N, NH, N-CH_3, CH or C-CH_3;

X^3 is N or C, where X^1, X^2, and X^3 are not all simultaneously N and

X^4, X^5 are each independently C or N.

3. The compound of claim 1 or 2, wherein X^4 , X^5, and X^6 are each C-R^1.

4. The compound of any one of claims 1 to 3, wherein R is –(cyclohexyl)–R^2.

5. The compound of any one of claims 1 to 4, wherein X^3 is N and X^1 is CR^3.

6. The compound of any one of claims 1 to 5, wherein R^2 is OH.

7. The compound of any one of claims 1 to 5, wherein R^1 is benzyloxy and n is 1.

8. The compound of any one of claims 1 to 5, wherein X^2 is N.

9. The compound of any one of claims 1 to 5, wherein R^2 is $-Y^2-Y^3-Y^4-R^5$, where Y^2 is $-C(O)NR^a-$, R^a is H, and Y^3 is C_{1-6} alkylene.

10. The compound of any one of claims 1 to 9, wherein Y^4 is $-SO_2-$.

11. The compound of any one of claims 1 to 10, wherein R^5 is C_{1-6} alkyl.

12. The compound of any one of claims 1 to 9, wherein Y^4 is –S–.

13. The compound of any one of claims 1 to 12, wherein R^5 is C_{1-6} alkyl.

14. The compound of any one of claims 1 to 9, wherein Y^4 is a bond, and R^5 is C_{1-6} alkyl.

15. The compound of claim 3, wherein R^1 is –CN.

16. A compound selected from the group consisting of:

4-[4-(4-benzyloxy-indol-1-yl)-pyrimidin-2-ylamino]-cyclohexanol;
4-[4-(4-bromoindol-1-yl)-pyrimidin-2-ylamino]-cyclohexanol;
4-(4-indol-1-yl)-pyrimidin-2-ylamino]-cyclohexane carboxylic acid (2-methane-sulfonylethyl)amide;
4-[4-(4-fluoroindol-1-yl)-pyrimidin-2-ylamino]-cyclohexanol;
4-[4-(4-methoxy-indol-1-yl)-pyrimidin-2-ylamino]-cyclohexanol;
4-[4-(4-methyl-indol-1-yl)-pyrimidin-2-ylamino]-cyclohexanol;
4-[4-(4-cyano-indol-1-yl)-pyrimidin-2-ylamino]-cyclohexanol;
4-(4-indazol-1-yl)-pyrimidin-2-ylamino]-cyclohexane carboxylic acid (3-hydroxy-butyl)-amide;
4-[4-(4-nitro-indazol-1-yl)-pyrimidin-2-ylamino]-cyclohexanol;
4-(4-indazol-1-yl)-pyrimidin-2-ylamino-cyclohexanol;
N-[4-(4-indazol-1-yl)-pyrimidin-2-ylamino-cyclohexyl] methanesulfonamide;
4-(4-indol-1-yl)-pyrimidin-2-ylamino-cyclohexanol;
4-(4-indazol-1-yl)-pyrimidin-2-ylamino]-cyclohexane carboxylic acid (1-methylsulfonyl-prop-2-yl)-amide;
4-(4-indazol-1-yl)-pyrimidin-2-ylamino]-cyclohexane carboxylic acid (1,5-dihydroxy-pent-3-yl)-amide;
4-(4-indazol-1-yl)-pyrimidin-2-ylamino]-cyclohexane carboxylic acid (1-hydroxy-but-2-yl)-amide;
4-(4-indazol-1-yl)-pyrimidin-2-ylamino]-cyclohexane carboxylic acid (2,3-dihydroxy-prop-1-yl)-amide;

4-(4-indazol-1-yl)-pyrimidin-2-ylamino]-cyclohexane carboxylic acid (1-hydroxybut-3-yl)-amide;

4-[4-(4-(2-hydroxyprop-2-yl)-indol-1-yl)-pyrimidin-2-ylamino]-cyclohexanol;

(4-hydroxypiperidin-1-yl)-[4-(4-indazol-1-yl-pyrimidin-2-ylamino)-cyclohexyl]-methanone ;

(3-pyrrolidon-1-yl)-[4-(4-indazol-1-yl-pyrimidin-2-ylamino)-cyclohexyl]-methanone ;

4-[4-(4-hydroxymethylindol-1-yl)-pyrimidin-2-ylamino]-cyclohexanol;

4-[4-(5-methoxy-indol-1-yl)-pyrimidin-2-ylamino]-cyclohexanol;

4-(4-indazol-1-ylpyrimidin-2-ylamino)cyclohexane carboxylic acid isopropylamide;

4-(4-indazol-1-ylpyrimidin-2-ylamino)cyclohexane carboxylic acid 1-hydroxyprop-2-ylamide;

4-(4-indazol-1-ylpyrimidin-2-ylamino)cyclohexane carboxylic acid 2-methoxyethyamide;

4-(4-indazol-1-ylpyrimidin-2-ylamino)cyclohexane carboxylic acid 1,3-dihydroxy-prop-2-ylamide;

4-[4-(6-nitroindazol-1-ylpyrimidin-2-ylamino)cyclohexanol ;

(3-hydroxypyrrolidin-1-yl)-[4-(4-indazol-1-ylpyrimidin-2-ylamino)-cyclohexyl]-methanone ;

(3-hydroxypyrrolidin-1-yl)-[4-(4-indazol-1-ylpyrimidin-2-ylamino)-cyclohexyl]-methanone ;

4-(4-indazol-1-ylpyrimidin-2-ylamino)cyclohexane carboxylic acid 3-hydroxy-2-methylprop-2-yl-amide;

1-[2-(4-hydroxycyclohexylamino)-pyrimidin-4-yl]-1H-indol-5-ol;

[4-(4-indazol-1-yl-pyrimidin-2-ylamino)-cyclohexyl]-morpholin-4-yl-methanone;

4-[4-(4-aminoindol-1-yl)-pyrimidin-2-ylamino]-cyclohexanol;

1-[2-(4-hydroxycyclohexylamino)-pyrimidin-4-yl]-1H-indazole-6-carboxylic acid methyl ester;

4-[4-(5-methylindol-1-yl)-pyrimidin-2-ylamino]-cyclohexanol;

4-[4-(6-fluoroindol-1-yl)-pyrimidin-2-ylamino]-cyclohexanol;

1-[2-(4-hydroxycyclohexylamino)-pyrimidin-4-yl]-1H-indole-4-carboxylic acid methyl ester;

4-[4-(6-methylindol-1-yl)-pyrimidin-2-ylamino]-cyclohexanol;

4-(4-indazol-1-yl-pyrimidin-2-ylamino)-cyclohexane carboxylic acid (2-hydroxy-2-methylpropyl)amide;

4-[4-(3-methylindol-1-yl)-pyrimidin-2-ylamino]-cyclohexanol;

4-[4-(3-methoxyindazol-1-yl)pyrimidin-2-ylamino]-cyclohexanol;

4-(4-indazol-1-ylpyrimidin-2-ylamino)-cyclohexane carboxylic acid (2-hydroxyethyl)-methyl-amide;

1-[2-(4-hydroxycyclohexylamino)-pyrimidin-2-yl]-1H-indole-6-carboxylic acid methyl ester;

4-[4-(5-fluoroindol-1-yl)-pyrimidin-2-ylamino]-cyclohexanol;

4-(4-indazol-1-ylpyrimidin-2-ylamino)-cyclohexane carboxylic acid (1-methyl-2-methylsulfanyl)ethylamide;

4-[4-(6-methylindazol-1-yl)-pyrimidin-2-ylamino]-cyclohexanol;

4-[4-(6-hydroxymethylindazol-1-yl)-pyrimidin-2-ylamino]-cyclohexanol;

4-(4-indazol-1-yl-pyrimidin-2-ylamino)-cyclohexane carboxylic acid (2-hydroxy-2-methylbut-3-yl)amide;

4-(4-indazol-1-ylpyrimidin-2-ylamino)-cyclohexane carboxylic acid (2-hydroxy-propyl)amide;

4-(4-indazol-1-ylpyrimidin-2-ylamino)-cyclohexane carboxylic acid (1-methylsulfanylprop-2-yl)amide;

4-(4-indazol-1-ylpyrimidin-2-ylamino)-cyclohexane carboxylic acid N-(2-hydroxy-ethyl)-N-ethyl-amide;

N-(4-indol-1-ylpyrimidin-2-yl)-cyclohexane-1,4-diamine;

N-(1-[2-(4-hydroxycyclohexylamino)-pyrimidin-4-yl]-1H-indazol-6-yl)-acet-amide;

4-(4-indazol-1-ylpyrimidin-2-ylamino)-cyclohexane carboxylic acid cyclopropylmethyl amide;

4-(4-indazol-1-ylpyrimidin-2-ylamino)-cyclohexane carboxylic acid dimethylamide;

4-[4-(5-methylindazol-1-yl)-pyrimidin-2-ylamino]-cyclohexanol;

4-(4-indazol-1-ylpyrimidin-2-ylamino)-1-methylcyclohexanol;

3-(4-indazol-1-ylpyrimidin-2-ylamino)-benzenesulfonamide;

4-[4-(5-hydroxymethylindol-1-yl)pyrimidin-2-ylamino]-cyclohexanol;

4-[4-(6-aminoindazol-1-yl)-pyrimidin-2-ylamino]-cyclohexanol;

1-[2-(4-hydroxycyclohexylamino)-pyrimidin-4-yl]-1H-indole-3-carboxylic acid methyl ester;

4-(4-[6-(2-hydroxyethylamino)-indazol-1-yl]-pyrimidin-2-ylamino)-cyclohexanol;

4-(4-indazol-1-ylpyrimidin-2-ylamino)-1-methyl-cyclohexanol;

4-[4-(5-benzyloxyindol-1-yl)-pyrimidin-2-ylamino]-cyclohexanol;

4-[4-(4-benzylsulfanyl-indol-1-yl)-pyrimidin-2-ylamino]-cyclohexanol;

Cyclohexyl-(4-indol-1-ylpyrimidin-2-yl)amine;

1-[2-(4-hydroxycyclohexylamino)-pyrimidin-4-yl]-1H-indole-5-carboxylic acid methyl ester;

4-(4-indazol-1-yl-pyrimidin-2-ylamino)-cyclohexanone;

(1,4-dioxaspiro[4.5]dec-8-yl)-(4-indazol-1-ylpyrimidin-2-yl)amine;

1-[2-(4-hydroxycyclohexylamino)-pyrimidin-4-yl]-1H-indole-4-carboxylic acid;

4-[4-(4-benzylsulfonyl-indol-1-yl)pyrimidin-2-ylamino]cyclohexanol;

4-(4-indazol-1-yl-pyrimidin-2-ylamino)-cyclohexanecarboxylic acid cyclopentylamide;

[4-(4-indazol-1-ylpyrimidin-2-ylamino)-cyclohexyl]-carbamic acid *t*-butyl ester;

4-[4-(1-phenylsulfonyl-1H-indol-3-yl)-pyrimidin-2-ylamino]-cyclohexanol;

4-[4-(1H-indol-3-yl)pyrimidin-2-ylamino]-cyclohexanol;

4-[4-(1-methyl-1H-indol-3-yl)pyrimidin-2-ylamino]-cyclohexanol;

4-[4-(1-methyl-1H-indazol-3-yl)pyrimidin-2-ylamino]-cyclohexanol;

4-[4-(1H-indazol-3-yl)pyrimidin-2-ylamino]-cyclohexanol;

4-(4-benzo[d]isoxazol-3-ylpyrimidin-2-ylamino)-cyclohexanol;

4-[4-(7-methoxy-1H-indazol-3-yl)-pyrimidin-2-ylamino]-cyclohexanol;

4-[4-(7-methoxybenzo[d]isoxazol-3-yl)-pyrimidin-2-ylamino]-cyclohexanol;

4-[4-(7-methyl-1H-indazol-3-yl)-pyrimidin-2-ylamino]-cyclohexanol;

4-[4-(5-fluorobenzo[d]isoxazol-3-yl)-pyrimidin-2-ylamino]-cyclohexanol;

4-(4-pyrazolo[1,5-b]pyridazin-3-ylpyrimidin-2-ylamino)-cyclohexanol;

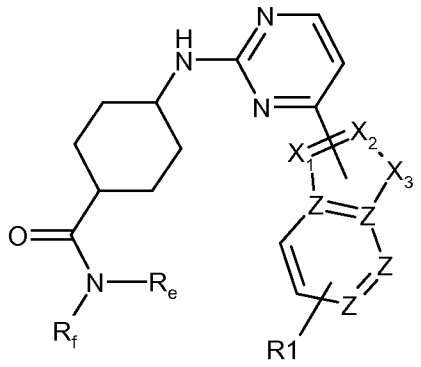
4-(4-[1,2,4]triazole[4,3-a]pyridine-3-ylpyrimidin-2-ylamino)-cyclohexanol;

4-[4-(4-methoxyindazol-1-yl)-pyrimidin-2-ylamino]-cyclohexanol;

(1-[2-(4-hydroxycyclohexylamino)-pyrimidin-4-yl]-1H-indazol-4-yloxy)-acetonitrile; and

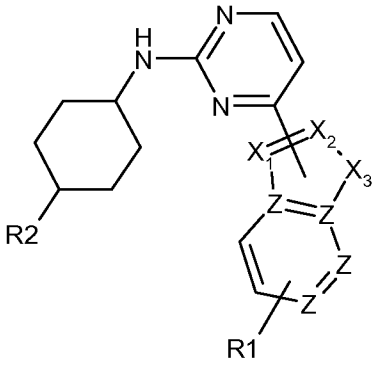
N-(1-[2-(4-hydroxycyclohexylamino)-pyrimidin-4-yl]-1H-indazol-4-yl)-isobutyramide.

17. A process for manufacturing compounds of formula (I'),



(I')

comprising a step of hydrolyzing compounds of formula (V) to the corresponding carboxylic acid,



(V), and

a step of coupling said carboxylic acid with a hydroxyl C_{1-6} akyl-, C_{1-6} alkoxy-, C_{1-6} alkyl-, C_{3-10} cycloalkyl-, heteroalkyl-, C_{1-6} alkylsufonyl- or C_{1-6} alkylsulfinyl- amine;

, wherein R^2 is COOMt or COOEt, R_e and R_f are independently hydrogen, hydroxyl C_{1-6} akyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{3-10} cycloalkyl heteroalkyl, C_{1-6} alkylsufonyl or C_{1-6} alkylsulfinyl, Z is N or C and X^1, X^2, X^3 and R^1 are as defined in claim 1.

18. Pharmaceutical compositions comprising a compound according to any one of claims 1 to 16 and a pharmaceutically acceptable excipient.

19. The compounds according to any one of claims 1 to 16 for use as therapeutic active substances.

20. Use of compounds according to any of claims 1 to 16 for the preparation of medicaments for the therapeutic and/or prophylactic treatment of a c-Jun N-terminal kinase mediated disorder.

21. The use according to claim 20, wherein the c-Jun N-terminal kinase mediated disorder is autoimmune disorder, inflammatory disorder, metabolic disorder, neurological disease, or cancer

22. The use according to claim 20, wherein the c-Jun N-terminal kinase mediated disorder is rheumatoid arthritis, asthma, type II diabetes, Alzheimer's disease, Parkinson's disease or stroke.

23. The invention as hereinbefore defined, particularly with reference to the new compounds, intermediates, medicaments, uses and processes.

***