INHIBITORS OF JNK

This invention relates generally to the fields of medicinal chemistry and treatment of inflammatory disorders. More particularly, the invention relates to JNK inhibitors, processes for making said inhibitors, and corresponding methods, formulations, and compositions for inhibiting JNK and treating JNK-mediated disorders, and the like.

JNK 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. 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. 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. It has been shown that MKK4 and MKK7 can be activated by the diverse upstream kinases, including MEKK1 and MEKK4, depending upon the external stimuli and cellular context. The specificity of JNK signaling is achieved by forming a JNK-specific signaling complex containing multiple components of the kinase cascade by use of scaffold proteins called JNK-interacting proteins. 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. 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 and rodent arthritic joints from animal models of arthritis. In addition, inhibition of JNK activation by selective JNK inhibitors blocked proinflammatory cytokines and MMP production in human synoviocytes, macrophages and lymphocytes. Importantly, administration of the selective JNK inhibitors in rats with adjuvant arthritis or in mice with collagen-induced arthritis effectively protected joints from destruction and significantly reduced paw swelling by inhibiting cytokine and collagenase expression.

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. 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. JNKs have emerged as promising therapeutic targets for asthma based upon the recent proof-of-concept studies: it has been shown that JNK inhibitors significantly blocked RANTES production in activated human airway smooth cells. 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 proliferation, and IgE production. These observations suggest important roles of JNKs in the allergic inflammation, airway remodeling process associated with hyper-responsiveness. 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. 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. 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. These studies demonstrated the potential utility of JNK inhibitor in the treatment of obesity/type 2 diabetes.

Neurodegenerative diseases, such as Alzheimer's (AD), Parkinson's (PD) and Stroke are CNS diseases characterized by synaptic loss, neuronal atrophy and death. The JNK pathway

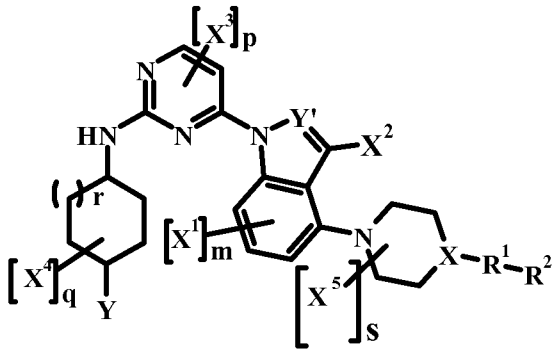
leading to c-Jun activation has been shown to play a causal role in apoptosis of isolated primary embryonic neurons and multiple neuronal cell lines upon induction of a variety of stimuli. Over-activation of JNK was observed in human brains from AD patients or rodent brain sections derived from animal models of neurodegenerative diseases. 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. 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. These data suggest JNK3 was mainly responsible for glutamate excitotoxicity, an important component in ischemic conditions. Taken together, data has emerged suggesting JNKs as 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. 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 (acute myeloid leukemia) patients has been causally linked to the sustained JNK activity present in these AML samples. 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.

Kidney diseases are characterized by loss of nephron function caused by progressive glomerulosclerosis and tubulointerstitial fibrosis. Renal disease may develop as a

consequence of many conditions including inflammation, hypertension, diabetes, or acute tissue damage caused by antibiotics, contrast agents, or other nephrotoxic substances. JNK signaling has been shown to be upregulated in pathology specimens from many human renal diseases, including immune and non-immune mediated glomerulonephritis, diabetic nephropathy, hypertension, acute injury (1), and appears to play a signaling role in polycystic kidney disease (2). Compelling evidence for a central role of JNK and the therapeutic potential of JNK inhibitors is supported by studies in animal models of renal injury. JNK was increased in a rat anti-glomerular basement membrane induced glomerulonephritis model and renal function was improved by a specific inhibitor in both acute and chronic disease paradigms (3). JNK was also increased in the Dahl salt-sensitive hypertensive rat, a model of hypertensive renal disease (4), as well as in models of renal ischemia-reperfusion injury (5,6). The cellular mechanisms by which JNK may contribute to renal injury are, in part, by up-regulation of pro-inflammatory mediators in macrophages, as well as by activation of pro-fibrotic, and pro-apoptotic pathways directly in cells of the renal glomerulus and the tubular epithelium (7). The ability to improve renal function by inhibition of JNK in multiple disease models, suggests JNKs as attractive targets for therapy of renal diseases of various etiology.

In one aspect, the application provides a compound of formula **I**



I

or a pharmaceutically acceptable salt thereof,

wherein:

Y' is CH or N;

X is CH or N;

each X^1 is independently halogen, lower alkyl, lower alkoxy, lower haloalkyl, or hydroxy;

m is 0, 1, or 2;

X^2 is H, lower alkyl, lower alkoxy, amido, lower haloalkyl, or lower haloalkoxy;

X^3 is lower alkyl, lower alkoxy, or lower haloalkyl;

p is 0 or 1;

each X^4 is independently lower alkyl, lower alkoxy, lower haloalkyl, hydroxy, lower hydroxylalkyl, $OC(=O)Z^2$, or halogen;

q is 0, 1, or 2;

X^5 is lower alkyl;

s is 0, 1 or 2;

r is 0 or 1;

Y is H, OH, $C(=O)Z^2$, $C(=O)OZ^2$, OZ^2, $OC(=O)Z^2$, $N(Z^1)C(=O)(Z^2)$, $C(Z^1)_2S(O)_2Z^2$, $N(Z^1)S(O)_2Z^2$, $N(Z^1)S(O)_2N(Z^1)(Z^2)$, $C(Z^1)_2(Z^2)$, or $(C=O)N(Z^1)(Z^2)$;

Z^1 is H or $Z^{1'}$;

$Z^{1'}$ is lower alkyl, optionally substituted with one or more $Z^{1''}$;

each $Z^{1''}$ is independently halogen, hydroxy, lower haloalkyl, dialkylamino or amino;

Z^2 is H or $Z^{2'}$;

$Z^{2'}$ is hydroxy, lower alkyl, lower alkoxy, lower hydroxyalkyl, lower haloalkyl, cycloalkyl, cycloalkyl lower alkyl, heterocycloalkyl, heterocycloalkyl lower alkyl, optionally substituted with one or more $Z^{2''}$;

each $Z^{2''}$ is independently halogen, hydroxy, lower alkyl, cycloalkyl, cyano, lower haloalkyl, amino, carboxylic acid, ester, or lower alkoxy;

R^1 is a bond, C(=O), C(=O)O, $C(=O)CH_2OC(=O)$, $C(=O)CH_2NHC(=O)O$, or $S(=O)_2$;

R^2 is H or $R^{2'}$;

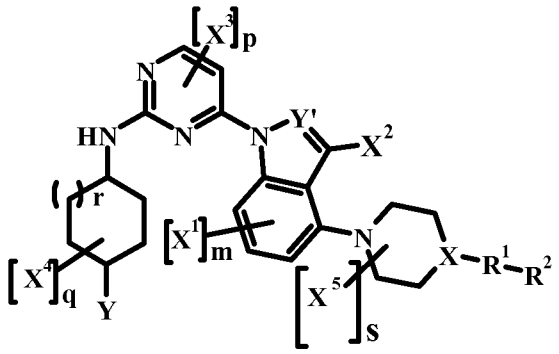
$R^{2'}$ is hydroxy, lower alkyl, $N(R^3)_2$, lower hydroxyalkyl, or lower haloalkyl, optionally substituted with one or more $R^{2''}$;

each $R^{2''}$ is independently cyano, amino, dialkylamino, hydroxy, lower hydroxyalkyl, or lower alkoxy; and

each R^3 is independently H, lower alkyl, lower cycloalkyl, phenyl, lower heterocycloalkyl, or both R^3 together form a heterocyclic ring;

with the proviso that when X is N, X^2 is H, Y' is CH, R^1 is C(=O), R^2 is methyl, r is 1, m is 0, p is 0, q is 0, Y is $N(Z^1)S(O)_2Z^2$, and Z^2 is methyl, then Z^1 is not H or hydroxyethyl.

In another aspect, the application provides a compound of formula **I**



I

or a pharmaceutically acceptable salt thereof,

wherein:

Y' is CH or N;

X is CH or N;

each X^1 is independently halogen, lower alkyl, lower alkoxy, lower haloalkyl, or hydroxy;

m is 0, 1, or 2;

X^2 is H, lower alkyl, lower alkoxy, amido, lower haloalkyl, or lower haloalkoxy;

X^3 is lower alkyl, lower alkoxy, or lower haloalkyl;

p is 0 or 1;

each X^4 is independently lower alkyl, lower alkoxy, lower haloalkyl, hydroxy, lower hydroxylalkyl, $OC(=O)Z^2$, or halogen;

q is 0, 1, or 2;

s is 0;

r is 0 or 1;

Y is H, OH, $C(=O)Z^2$, $C(=O)OZ^2$, OZ^2, $OC(=O)Z^2$, $N(Z^1)C(=O)(Z^2)$, $C(Z^1)_2S(O)_2Z^2$, $N(Z^1)S(O)_2Z^2$, $N(Z^1)S(O)_2N(Z^1)(Z^2)$, $C(Z^1)_2(Z^2)$, or $(C=O)N(Z^1)(Z^2)$;

Z^1 is H or $Z^{1'}$;

$Z^{1'}$ is lower alkyl, optionally substituted with one or more $Z^{1''}$;

each $Z^{1''}$ is independently halogen, hydroxy, lower haloalkyl, or amino;

Z^2 is H or $Z^{2'}$;

$Z^{2'}$ is lower alkyl, lower alkoxy, lower hydroxyalkyl, lower haloalkyl, cycloalkyl, cycloalkyl lower alkyl, heterocycloalkyl, heterocycloalkyl lower alkyl, optionally substituted with one or more $Z^{2''}$;

each $Z^{2''}$ is independently halogen, hydroxy, lower alkyl, cyano, lower haloalkyl, amino, carboxylic acid, ester, or lower alkoxy;

R^1 is C(=O), C(=O)O, $C(=O)CH_2OC(=O)$, $C(=O)CH_2NHC(=O)O$, or $S(=O)_2$;

R^2 is H or $R^{2'}$;

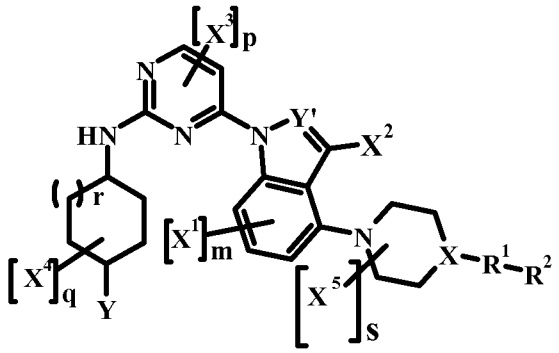
$R^{2'}$ is lower alkyl, $N(R^3)_2$, lower hydroxyalkyl, or lower haloalkyl, optionally substituted with one or more $R^{2''}$;

each $R^{2''}$ is independently cyano, amino, hydroxy, lower hydroxyalkyl, or lower alkoxy; and

each R^3 is independently H, lower alkyl, lower cycloalkyl, phenyl, lower heterocycloalkyl, or both R^3 together form a heterocyclic ring;

with the proviso that when X is N, X^2 is H, Y' is CH, R^1 is C(=O), R^2 is methyl, r is 1, m is 0, p is 0, q is 0, Y is $N(Z^1)S(O)_2Z^2$, and Z^2 is methyl, then Z^1 is not H or hydroxyethyl.

In a further aspect, the application provides a compound of formula **I**



I

or a pharmaceutically acceptable salt thereof,

wherein:

Y' is CH or N;

X is CH or N;

m is 0;

X^2 is H or amido;

p is 0

each X^4 is independently lower alkyl, hydroxy, $OC(=O)Z^2$;

q is 0 or 1;

X^5 is lower alkyl;

s is 0, 1

r is 0 or 1;

Y is H, OH, $C(=O)Z^2$, $C(=O)OZ^2$, OZ^2, $N(Z^1)C(=O)(Z^2)$, $C(Z^1)_2S(O)_2Z^2$, $N(Z^1)S(O)_2Z^2$, $N(Z^1)S(O)_2N(Z^1)(Z^2)$, $C(Z^1)_2(Z^2)$, or $(C=O)N(Z^1)(Z^2)$;

Z^1 is H or $Z^{1'}$;

$Z^{1'}$ is lower alkyl, optionally substituted with one or more $Z^{1''}$;

each $Z^{1''}$ is dialkylamino;

Z^2 is H or $Z^{2'}$;

$Z^{2'}$ is hydroxy, lower alkyl or heterocycloalkyl, optionally substituted with one or more $Z^{2''}$;

each $Z^{2''}$ is independently hydroxy, lower alkyl, cycloalkyl, cyano, or lower alkoxy;

R^1 is a bond, C(=O), $C(=O)CH_2OC(=O)$, $C(=O)CH_2NHC(=O)O$, or $S(=O)_2$;

R^2 is H or $R^{2'}$;

$R^{2'}$ is hydroxy, lower alkyl, $N(R^3)_2$, lower hydroxyalkyl, optionally substituted with one or more $R^{2''}$;

each $R^{2''}$ is independently cyano, amino or dialkylamino; and

each R^3 is H ;

with the proviso that when X is N, X^2 is H, Y' is CH, R^1 is C(=O), R^2 is methyl, r is 1, m is 0, p is 0, q is 0, Y is $N(Z^1)S(O)_2Z^2$, and Z^2 is methyl, then Z^1 is not H.

In certain embodiment of formula I, is 0.

In one variation of formula I, m is 0, X^2 is H, p is 0, q is 0, r is 0, X is N, Y' is CH, R^1 is C(=O), R^2 is $R^{2'}$, $R^{2'}$ is methylene, and $R^{2''}$ is cyano.

In one variation of formula I, m is 0, p is 0, q is 0, r is 1, X is N, Y' is CH, R^1 is C(=O), R^2 is $R^{2'}$, $R^{2'}$ is methylene, and $R^{2''}$ is cyano.

In one variation of formula I, m is 0, X^2 is H, p is 0, q is 0, r is 1, X is N, Y' is CH, R^1 is C(=O), R^2 is $R^{2'}$, and $R^{2'}$ is methyl.

In one variation of formula I, m is 0, p is 0, q is 0, r is 1, X is CH, Y' is CH, R^1 is $S(=O)_2$, R^2 is $R^{2'}$, and $R^{2'}$ is methyl.

In one variation of formula I, R^1 is C(=O), R^2 is $R^{2'}$, $R^{2'}$ is methylene, and $R^{2''}$ is cyano.

In one variation of formula I, R^1 is $S(=O)_2$, R^2 is $R^{2'}$, and $R^{2'}$ is methyl.

In one variation of formula I, wherein Y' is N.

In one variation of formula I, m is 0, X^2 is H, p is 0, q is 0, r is 1, X is CH, Y' is N, R^1 is $S(=O)_2$, R^2 is $R^{2'}$, and $R^{2'}$ is methyl.

In certain embodiment of formula I, Y is OH.

The application provides the compounds of Formula I selected from the group consisting of:

N-{4-[4-(4-Piperazin-1-yl-indol-1-yl)-pyrimidin-2-ylamino]-cyclohexyl}-methanesulfonamide;

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

N-(4-{4-[4-(4-Methanesulfonyl-piperazin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-cyclohexyl)-methanesulfonamide;

N-(4-{4-[4-(4-Hydroxy-piperidin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-cyclohexyl)-methanesulfonamide;

N-(4-{4-[4-(4-Acetyl-piperazin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-cyclohexyl)-*N*-methyl-methanesulfonamide;

N-(4-{4-[4-(4-Methanesulfonyl-piperidin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-cyclohexyl)-methanesulfonamide;

4-{1-[2-(4-Methanesulfonylamino-cyclohexylamino)-pyrimidin-4-yl]-1*H*-indol-4-yl}-piperazine-1-carboxylic acid amide;

4-{1-[2-(4-Methanesulfonylamino-cyclohexylamino)-pyrimidin-4-yl]-1*H*-indol-4-yl}-piperazine-1-sulfonic acid amide;

N-[4-(4-{4-[4-(2-Cyano-acetyl)-piperazin-1-yl]-indol-1-yl}-pyrimidin-2-ylamino)-cyclohexyl]-methanesulfonamide;

Acetic acid 2-(4-{1-[2-(4-methanesulfonylamino-cyclohexylamino)-pyrimidin-4-yl]-1*H*-indol-4-yl}-piperazin-1-yl)-2-oxo-ethyl ester;

N-[4-(4-{4-[4-(2-Hydroxy-acetyl)-piperazin-1-yl]-indol-1-yl}-pyrimidin-2-ylamino)-cyclohexyl]-methanesulfonamide;

4-{4-[4-(4-Methanesulfonyl-piperidin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-cyclohexanol;

N-(4-{4-[4-(4-Methanesulfonyl-piperidin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-cyclohexyl)-acetamide;

2-(4-{4-[4-(4-Methanesulfonyl-piperidin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-cyclohexyl)-propan-2-ol;

[4-{4-[4-(4-Methanesulfonyl-piperidin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}- cyclohexyl] aminodimethylsulfonamide;

4-{4-[4-(4-Methanesulfonyl-piperidin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-1-methyl-cyclohexanol;

4-{4-[4-(4-Methanesulfonyl-piperidin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-1-methyl-cyclohexanol;

(4-Hydroxy-piperidin-1-yl)-(4-{4-[4-(4-methanesulfonyl-piperidin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-cyclohexyl)-methanone;

4-{4-[4-(4-Methanesulfonyl-piperidin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-cyclohexanecarboxylic acid ethylamide;

4-{4-[4-(4-Methanesulfonyl-piperidin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-cyclohexanecarboxylic acid ethyl ester;

1-[(R)-4-(1-{2-[4-(4-Hydroxy-piperidine-1-carbonyl)-cyclohexylamino]-pyrimidin-4-yl}-1*H*-indol-4-yl)-3-methyl-piperazin-1-yl]-ethanone;

[2-(4-{1-[2-(4-Methanesulfonylamino-cyclohexylamino)-pyrimidin-4-yl]-1*H*-indol-4-yl}-piperazin-1-yl)-2-oxo-ethyl]-carbamic acid *tert*-butyl ester;

N-[4-(4-{4-[4-(2-Dimethylamino-acetyl)-piperazin-1-yl]-indol-1-yl}-pyrimidin-2-ylamino)-cyclohexyl]-methanesulfonamide;

N-[4-(4-{4-[4-(2-Amino-acetyl)-piperazin-1-yl]-indol-1-yl}-pyrimidin-2-ylamino)-cyclohexyl]-methanesulfonamide;

3-[4-(1-{2-[4-((R)-3-Hydroxy-pyrrolidin-1-ylmethyl)-cyclohexylamino]-pyrimidin-4-yl}-1*H*-indol-4-yl)-piperazin-1-yl]-3-oxo-propionitrile;

N-[4-(4-{4-[4-(2-Cyano-acetyl)-piperazin-1-yl]-indol-1-yl}-pyrimidin-2-ylamino)-cyclohexyl]-*N*-(2-dimethylamino-ethyl)-methanesulfonamide;

3-(4-{1-[2-(4-Hydroxymethyl-cyclohexylamino)-pyrimidin-4-yl]-1*H*-indol-4-yl}-piperazin-1-yl)-3-oxo-propionitrile;

3-[4-(1-{2-[4-((S)-3-Hydroxy-pyrrolidin-1-ylmethyl)-cyclohexylamino]-pyrimidin-4-yl}-1*H*-indol-4-yl)-piperazin-1-yl]-3-oxo-propionitrile;

1-[4-(1-{2-[4-((R)-3-Hydroxy-pyrrolidin-1-ylmethyl)-cyclohexylamino]-pyrimidin-4-yl}-1*H*-indol-4-yl)-piperazin-1-yl]-ethanone;

(4-Ethoxy-piperidin-1-yl)-(4-{4-[4-(4-methanesulfonyl-piperidin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-cyclohexyl)-methanone;

((R)-3-Ethoxy-pyrrolidin-1-yl)-(4-{4-[4-(4-methanesulfonyl-piperidin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-cyclohexyl)-methanone;

((S)-3-Ethoxy-pyrrolidin-1-yl)-(4-{4-[4-(4-methanesulfonyl-piperidin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-cyclohexyl)-methanone;

Cyano-acetic acid (1R,3S)-3-(4-{4-[4-(2-cyano-acetyl)-piperazin-1-yl]-indol-1-yl}-pyrimidin-2-ylamino)-cyclohexyl ester;

3-(4-{1-[2-((1S,3S)-3-Hydroxy-cyclohexylamino)-pyrimidin-4-yl]-1*H*-indol-4-yl}-piperazin-1-yl)-3-oxo-propionitrile;

3-(4-{1-[2-((1S,3R)-3-Hydroxy-cyclohexylamino)-pyrimidin-4-yl]-1*H*-indol-4-yl}-piperazin-1-yl)-3-oxo-propionitrile;

Cyano-acetic acid (1S,3S)-3-(4-{4-[4-(2-cyano-acetyl)-piperazin-1-yl]-indol-1-yl}-pyrimidin-2-ylamino)-cyclohexyl ester;

1-{4-[1-(2-Cyclohexylamino-pyrimidin-4-yl)-1*H*-indol-4-yl]-piperazin-1-yl}-ethanone;

3-{4-[1-(2-Cyclohexylamino-pyrimidin-4-yl)-1*H*-indol-4-yl]-piperazin-1-yl}-3-oxo-propionitrile;

1-[4-(1-{2-[4-(2-Methoxy-ethoxy)-cyclohexylamino]-pyrimidin-4-yl}-1*H*-indol-4-yl)-piperazin-1-yl]-ethanone;

3-[4-(1-{2-[4-(2-Methoxy-ethoxy)-cyclohexylamino]-pyrimidin-4-yl}-1*H*-indol-4-yl)-piperazin-1-yl]-3-oxo-propionitrile;

1-(4-{1-[2-(4-Methanesulfonylmethyl-cyclohexylamino)-pyrimidin-4-yl]-1*H*-indol-4-yl}-piperazin-1-yl)-ethanone;

3-(4-{1-[2-(4-Methanesulfonylmethyl-cyclohexylamino)-pyrimidin-4-yl]-1*H*-indol-4-yl}-

piperazin-1-yl)-3-oxo-propionitrile;

1-[4-(1-{2-[4-(1-Hydroxy-1-methyl-ethyl)-cyclohexylamino]-pyrimidin-4-yl}-1*H*-indol-4-yl)-piperazin-1-yl]-ethanone;

N-[4-(4-{4-[4-(2-Cyano-acetyl)-piperazin-1-yl]-indol-1-yl}-pyrimidin-2-ylamino)-cyclohexyl]-*N*-(2-hydroxy-ethyl)-methanesulfonamide;

3-[4-(1-{2-[4-(1-Hydroxy-1-methyl-ethyl)-cyclohexylamino]-pyrimidin-4-yl}-1*H*-indol-4-yl)-piperazin-1-yl]-3-oxo-propionitrile;

(4-Ethyl-piperazin-1-yl)-(4-{4-[4-(4-methanesulfonyl-piperidin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-cyclohexyl)-methanone;

(4-Cyclopropyl-piperazin-1-yl)-(4-{4-[4-(4-methanesulfonyl-piperidin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-cyclohexyl)-methanone;

(4-*tert*-Butyl-piperazin-1-yl)-(4-{4-[4-(4-methanesulfonyl-piperidin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-cyclohexyl)-methanone;

(4-Cyclobutyl-piperazin-1-yl)-(4-{4-[4-(4-methanesulfonyl-piperidin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-cyclohexyl)-methanone;

(4-{4-[4-(4-Methanesulfonyl-piperidin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-cyclohexyl)-(octahydro-pyrido[1,2-*a*]pyrazin-2-yl)-methanone;

(4-{4-[4-(4-Methanesulfonyl-piperidin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-cyclohexyl)-(3-trifluoromethyl-5,6-dihydro-8*H*-[1,2,4]triazolo[4,3-*a*]pyrazin-7-yl)-methanone;

(Hexahydro-pyrrolo[1,2-*a*]pyrazin-2-yl)-(4-{4-[4-(4-methanesulfonyl-piperidin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-cyclohexyl)-methanone;

(5,6-Dihydro-8*H*-[1,2,4]triazolo[4,3-*a*]pyrazin-7-yl)-(4-{4-[4-(4-methanesulfonyl-piperidin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-cyclohexyl)-methanone;

(5,6-Dihydro-8*H*-imidazo[1,2-*a*]pyrazin-7-yl)-(4-{4-[4-(4-methanesulfonyl-piperidin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-cyclohexyl)-methanone;

3-(4-{1-[2-(4-Hydroxy-cyclohexylamino)-pyrimidin-4-yl]-1*H*-indol-4-yl}-piperazin-1-yl)-3-oxo-propionitrile;

3-[4-(1-{2-[4-(4-Ethyl-piperazine-1-carbonyl)-cyclohexylamino]-pyrimidin-4-yl}-1*H*-indol-4-yl)-piperazin-1-yl]-3-oxo-propionitrile;

3-(4-{1-[2-(4-Hydroxy-cyclohexylamino)-pyrimidin-4-yl]-1*H*-indol-4-yl}-piperazin-1-yl)-3-oxo-propionitrile;

3-(4-{1-[2-((1S,3R)-3-Hydroxy-cyclopentylamino)-pyrimidin-4-yl]-1*H*-indol-4-yl}-piperazin-1-yl)-3-oxo-propionitrile;

3-(4-{1-[2-((1R,3S)-3-Hydroxy-cyclopentylamino)-pyrimidin-4-yl]-1*H*-indol-4-yl}-piperazin-1-yl)-3-oxo-propionitrile;

3-(4-{1-[2-((1S,3S)-3-Hydroxy-cyclopentylamino)-pyrimidin-4-yl]-1*H*-indol-4-yl}-piperazin-1-yl)-3-oxo-propionitrile;

3-(4-{1-[2-((1R,3R)-3-Hydroxy-cyclopentylamino)-pyrimidin-4-yl]-1*H*-indol-4-yl}-piperazin-1-yl)-3-oxo-propionitrile;

4-{4-[4-(4-Methanesulfonyl-piperidin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-cyclohexanol;

4-(4-Acetyl-piperazin-1-yl)-1-[2-(4-hydroxy-cyclohexylamino)-pyrimidin-4-yl]-1*H*-indole-3-carboxylic acid amide;

4-(4-Acetyl-piperazin-1-yl)-1-[2-(4-methanesulfonylmethyl-cyclohexylamino)-pyrimidin-4-yl]-1*H*-indole-3-carboxylic acid amide;

4-{4-[4-(4-Methanesulfonyl-piperidin-1-yl)-indazol-1-yl]-pyrimidin-2-ylamino}-cyclohexanecarboxylic acid ethyl ester; and

4-{4-[4-(4-Methanesulfonyl-piperidin-1-yl)-indazol-1-yl]-pyrimidin-2-ylamino}-cyclohexanol.

In one aspect, the application provides a method of treating a JNK-mediated disorder in a subject having a JNK-mediated disorder, said method comprising administering to a subject in need thereof a therapeutically effective amount of any of the above compounds.

In certain embodiments of the method of treating a JNK-mediated disorder, the JNK-mediated disorder is characterized by cellular proliferation.

In certain embodiments of the method of treating a JNK-mediated disorder, the JNK-mediated disorder is arthritis.

In certain embodiments of the method of treating a JNK-mediated disorder, the arthritis is rheumatoid arthritis.

In certain embodiments of the method of treating a JNK-mediated disorder, the JNK-mediated disorder is asthma.

In certain embodiments of the method of treating a JNK-mediated disorder, the JNK-mediated disorder is diabetes.

In certain embodiments of the method of treating a JNK-mediated disorder, the JNK-mediated disorder is Alzheimer's disease.

In certain embodiments of the method of treating a JNK-mediated disorder, the JNK-mediated disorder is Parkinson's disease.

In certain embodiments of the method of treating a JNK-mediated disorder, the JNK-mediated disorder is ischemic stroke.

In certain embodiments of the method of treating a JNK-mediated disorder, the JNK-mediated disorder is cancer.

In certain embodiments of the method for treating a JNK-mediated disorder, wherein the JNK-mediated disorder is cancer, the cancer is brain cancer.

In certain embodiments of the method for treating a JNK-mediated disorder, wherein the JNK-mediated disorder is cancer, the cancer is leukemia.

In certain embodiments of the method of treating a JNK-mediated disorder, the JNK-mediated disorder is kidney disease.

In one aspect, the application provides a pharmaceutical composition comprising the compound of any one of the above embodiments, admixed with at least one pharmaceutically acceptable carrier, excipient or diluent.

A method for treating arthritis comprising co-administering to a patient in need thereof a therapeutically effective amount of an anti-inflammatory compound in combination with the compound of any of the above embodiments, variations, or aspects.

In a further apect, the application provides the use of any of the above compounds for the preparation of medicaments for the therapeutic and/or prophylactic treatment of a JNK mediated disorder.

In certain embodiments of the use of the above compound for the preparation of medicament wherein JNK mediated disorder is autoimmune disorder, inflammatory disorder, metabolic disorder, neurological disease, or cancer

In certain embodiments of the use of the above compound for the preparation of medicament wherein JNK mediated disorder is rheumatoid arthritis, asthma, type II diabetes, Alzheimer's disease, Parkinson's disease or stroke.

In a further apect, the application provides the compound of any of the above embodiments for use in the treatment of a JNK mediated disorder.

All publications cited in this disclosure are incorporated herein by reference in their entirety.

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. Thus, the phrase '"a" or "an" entity' as used herein refers to one or more of that entity; for example, a compound refers to one or more compounds or at least one compound. As such, the terms "a" (or "an"), "one or more", and "at least one" can be used interchangeably herein.

As used in this specification, whether in a transitional phrase or in the body of the claim, the terms "comprise(s)" and "comprising" are to be interpreted as having an open-ended meaning. That is, the terms are to be interpreted synonymously with the phrases "having at least" or "including at least". When used in the context of a process, the term "comprising" means that the process includes at least the recited steps, but may include additional steps. When used in the context of a compound or composition, the term "comprising" means that the compound

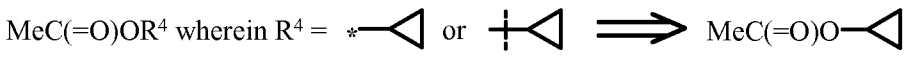
or composition includes at least the recited features or components, but may also include additional features or components.

As used herein, unless specifically indicated otherwise, the word "or" is used in the "inclusive" sense of "and/or" and not the "exclusive" sense of "either/or".

The term "independently" is used herein to indicate that a variable is applied in any one instance without regard to the presence or absence of a variable having that same or a different definition within the same compound. Thus, in a compound in which R" appears twice and is defined as "independently carbon or nitrogen", both R"s can be carbon, both R"s can be nitrogen, or one R" can be carbon and the other nitrogen.

When any variable (e.g., m, n, p, q, Q, r, R^1, R^2, R^3, R^4, X, X^1, X^2, X^3, X^4, X^5, Y^1, Y^2, Z^1, and Z^2) occurs more than one time in any moiety or formula depicting and describing compounds employed or claimed in the present invention, its definition on each occurrence is independent of its definition at every other occurrence. Also, combinations of substituents and/or variables are permissible only if such compounds result in stable compounds.

The symbols "*" at the end of a bond or " ------ " drawn through a bond each refer to the point of attachment of a functional group or other chemical moiety to the rest of the molecule of which it is a part. Thus, for example:



A bond drawn into ring system (as opposed to connected at a distinct vertex) indicates that the bond may be attached to any of the suitable ring atoms.

The term “optional” or “optionally” as used herein means that a 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. For example, “optionally substituted” means that the optionally substituted moiety may incorporate a hydrogen or a substituent.

The term "about" is used herein to mean approximately, in the region of, roughly, or around. When the term "about" is used in conjunction with a numerical range, it modifies that range

by extending the boundaries above and below the numerical values set forth. In general, the term "about" is used herein to modify a numerical value above and below the stated value by a variance of 20%.

Certain compounds of the invention may exhibit tautomerism. Tautomeric compounds can exist as two or more interconvertable species. Prototropic tautomers result from the migration of a covalently bonded hydrogen atom between two atoms. Tautomers generally exist in equilibrium and attempts to isolate an individual tautomers usually produce a mixture whose chemical and physical properties are consistent with a mixture of compounds. The position of the equilibrium is dependent on chemical features within the molecule. For example, in many aliphatic aldehydes and ketones, such as acetaldehyde, the keto form predominates while; in phenols, the enol form predominates. Common prototropic tautomers include keto/enol (-C(=O)-CH- ⇆ -C(-OH)=CH-), amide/imidic acid (-C(=O)-NH- ⇆ -C(-OH)=N-) and amidine (-C(=NR)-NH- ⇆ -C(-NHR)=N-) tautomers. The latter two are particularly common in heteroaryl and heterocyclic rings and the present invention encompasses all tautomeric forms of the compounds.

Technical and scientific terms used herein have the meaning commonly understood by one of skill in the art to which the present invention pertains, unless otherwise defined. Reference is made herein to various methodologies and materials known to those of skill in the art. Standard reference works setting forth the general principles of pharmacology include Goodman and Gilman's *The Pharmacological Basis of Therapeutics*, 10th Ed., McGraw Hill Companies Inc., New York (2001). Any suitable materials and/or methods known to those of skill can be utilized in carrying out the present invention. However, preferred materials and methods are described. Materials, reagents and the like to which reference are made in the following description and examples are obtainable from commercial sources, unless otherwise noted.

The definitions described herein may be appended to form chemically-relevant combinations, such as “heteroalkylaryl,” “haloalkylheteroaryl,” “arylalkylheterocyclyl,” “alkylcarbonyl,” “alkoxyalkyl,” and the like. When the term “alkyl” is used as a suffix following another term, as in “phenylalkyl,” or “hydroxyalkyl,” this is intended to refer to an alkyl group, as defined above, being substituted with one to two substituents selected from the other specifically-named group. Thus, for example, “phenylalkyl” refers to an alkyl group having one to two

phenyl substituents, and thus includes benzyl, phenylethyl, and biphenyl. An "alkylaminoalkyl" is an alkyl group having one to two alkylamino substituents. "Hydroxyalkyl" includes 2-hydroxyethyl, 2-hydroxypropyl, 1-(hydroxymethyl)-2-methylpropyl, 2-hydroxybutyl, 2,3-dihydroxybutyl, 2-(hydroxymethyl), 3-hydroxypropyl, and so forth. Accordingly, as used herein, the term "hydroxyalkyl" is used to define a subset of heteroalkyl groups defined below. The term -(ar)alkyl refers to either an unsubstituted alkyl or an aralkyl group. The term (hetero)aryl or (het)aryl refers to either an aryl or a heteroaryl group.

The term "acyl" as used herein denotes a group of formula -C(=O)R wherein R is hydrogen or lower alkyl as defined herein. The term or "alkylcarbonyl" as used herein denotes a group of formula C(=O)R wherein R is alkyl as defined herein. The term C_{1-6} acyl refers to a group -C(=O)R contain 6 carbon atoms. The term "arylcarbonyl" as used herein means a group of formula C(=O)R wherein R is an aryl group; the term "benzoyl" as used herein an "arylcarbonyl" group wherein R is phenyl.

The term "alkyl" as used herein denotes an unbranched or branched chain, saturated, monovalent hydrocarbon residue containing 1 to 10 carbon atoms. The term "lower alkyl" denotes a straight or branched chain hydrocarbon residue containing 1 to 6 carbon atoms. "C_{1-10} alkyl" as used herein refers to an alkyl composed of 1 to 10 carbons. Examples of alkyl groups include, but are not limited to, lower alkyl groups include methyl, ethyl, propyl, *i*-propyl, *n*-butyl, *i*-butyl, *t*-butyl or pentyl, isopentyl, neopentyl, hexyl, heptyl, and octyl.

When the term "alkyl" is used as a suffix following another term, as in "phenylalkyl," or "hydroxyalkyl," this is intended to refer to an alkyl group, as defined above, being substituted with one to two substituents selected from the other specifically-named group. Thus, for example, "phenylalkyl" denotes the radical R'R"-, wherein R' is a phenyl radical, and R" is an alkylene radical as defined herein with the understanding that the attachment point of the phenylalkyl moiety will be on the alkylene radical. Examples of arylalkyl radicals include, but are not limited to, benzyl, phenylethyl, 3-phenylpropyl. The terms "arylalkyl" or "aralkyl" are interpreted similarly except R' is an aryl radical. The terms "(het)arylalkyl" or "(het)aralkyl" are interpreted similarly except R' is optionally an aryl or a heteroaryl radical.

The term "alkylene" as used herein denotes a divalent saturated linear hydrocarbon radical of 1 to 10 carbon atoms (*e.g.*, $(CH_2)_n$)or a branched saturated divalent hydrocarbon radical of 2 to 10 carbon atoms (*e.g.*, -CHMe- or -$CH_2CH(i\text{-Pr})CH_2$-), unless otherwise indicated. Except in the case of methylene, the open valences of an alkylene group are not attached to the same atom. Examples of alkylene radicals include, but are not limited to, methylene, ethylene, propylene, 2-methyl-propylene, 1,1-dimethyl-ethylene, butylene, 2-ethylbutylene.

The term "alkoxy" as used herein means an -O-alkyl group, wherein alkyl is as defined above such as methoxy, ethoxy, *n*-propyloxy, *i*-propyloxy, *n*-butyloxy, *i*-butyloxy, *t*-butyloxy, pentyloxy, hexyloxy, including their isomers. "Lower alkoxy" as used herein denotes an alkoxy group with a "lower alkyl" group as previously defined. "C_{1-10} alkoxy" as used herein refers to an-O-alkyl wherein alkyl is C_{1-10}.

“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, and the like, including partially hydrogenated derivatives thereof.

The term "base" includes, but is not limited to, NaOH**,** KOH, LiOH and alkali metal carbonates such as potassium carbonate, sodium carbonate, lithium carbonate, sodium bicarbonate, cesium carbonate and the like.

“Cycloalkyl” or “carbocyclic ring” means a monovalent saturated carbocyclic moiety consisting of mono- or bicyclic rings. Cycloalkyl can optionally be substituted with one or more substituents, wherein each substituent 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, and the like, including partially unsaturated derivatives thereof.

"Heterocycloalkyl lower alkyl" mean a moiety of the formula $-R^a-R^b$, where R^a is lower alkylene and R^b is heterocycloalkyl as defined herein.

The term "heteroaryl" or "heteroaromatic" as used herein means a monocyclic or bicyclic radical of 5 to 12 ring atoms having at least one aromatic ring containing four to eight atoms per ring, incorporating one or more N, O, or S heteroatoms, the remaining ring atoms being carbon, with the understanding that the attachment point of the heteroaryl radical will be on an aromatic ring. As well known to those skilled in the art, heteroaryl rings have less aromatic character than their all-carbon counter parts. Thus, for the purposes of the invention, a heteroaryl group need only have some degree of aromatic character. Examples of heteroaryl moieties include monocyclic aromatic heterocycles having 5 to 6 ring atoms and 1 to 3 heteroatoms include, but is not limited to, pyridinyl, pyrimidinyl, pyrazinyl, pyrrolyl, pyrazolyl, imidazolyl, oxazol, isoxazole, thiazole, isothiazole, triazoline, thiadiazole and oxadiaxoline which can optionally be substituted with one or more, preferably one or two substituents selected from hydroxy, cyano, alkyl, alkoxy, thio, lower haloalkoxy, alkylthio, halo, haloalkyl, alkylsulfinyl, alkylsulfonyl, halogen, amino, alkylamino,dialkylamino, aminoalkyl, alkylaminoalkyl, and dialkylaminoalkyl, nitro, alkoxycarbonyl and carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, arylcarbamoyl, alkylcarbonylamino and arylcarbonylamino. Examples of bicyclic moieties include, but are not limited to, quinolinyl, isoquinolinyl, benzofuryl, benzothiophenyl, benzoxazole, benzisoxazole, benzothiazole and benzisothiazole. Bicyclic moieties can be optionally substituted on either ring; however the point of attachment is on a ring containing a heteroatom.

The term "hydroxyalkyl" as used herein denotes an alkyl radical as herein defined wherein one to three hydrogen atoms on different carbon atoms is/are replaced by hydroxyl groups.

Commonly used abbreviations include: acetyl (Ac), azo-*bis*-isobutyrylnitrile (AIBN), atmospheres (Atm), 9-borabicyclo[3.3.1]nonane (9-BBN or BBN), *tert*-butoxycarbonyl (Boc), di-*tert*-butyl pyrocarbonate or boc anhydride (BOC_2O), benzyl (Bn), butyl (Bu), Chemical Abstracts Registration Number (CASRN), benzyloxycarbonyl (CBZ or Z), carbonyl diimidazole (CDI), 1,4-diazabicyclo[2.2.2]octane (DABCO), diethylaminosulfur trifluoride (DAST), dibenzylideneacetone (dba), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), N,N'-dicyclohexylcarbodiimide (DCC), 1,2-dichloroethane (DCE), dichloromethane (DCM), diethyl azodicarboxylate (DEAD), di-*iso*-

propylazodicarboxylate (DIAD), di-*iso*-butylaluminumhydride (DIBAL or DIBAL-H), di-iso-propylethylamine (DIPEA), N,N-dimethyl acetamide (DMA), 4-N,N-dimethylaminopyridine (DMAP), N,N-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), 1,1'-*bis*-(diphenylphosphino)ethane (dppe), 1,1'-*bis*-(diphenylphosphino)ferrocene (dppf), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI), ethyl (Et), ethyl acetate (EtOAc), ethanol (EtOH), 2-ethoxy-2*H*-quinoline-1-carboxylic acid ethyl ester (EEDQ), diethyl ether (Et_2O), O-(7-azabenzotriazole-1-yl)-N, N,N'N'-tetramethyluronium hexafluorophosphate acetic acid (HATU), acetic acid (HOAc), 1-N-hydroxybenzotriazole (HOBt), high pressure liquid chromatography (HPLC), *iso*-propanol (IPA), lithium hexamethyl disilazane (LiHMDS), methanol (MeOH), melting point (mp), $MeSO_2$- (mesyl or Ms), , methyl (Me), acetonitrile (MeCN), *m*-chloroperbenzoic acid (MCPBA), mass spectrum (ms), methyl *t*-butyl ether (MTBE), N-bromosuccinimide (NBS), N-carboxyanhydride (NCA), N-chlorosuccinimide (NCS), N-methylmorpholine (NMM), N-methylpyrrolidone (NMP), pyridinium chlorochromate (PCC), pyridinium dichromate (PDC), phenyl (Ph), propyl (Pr), *iso*-propyl (*i*-Pr), pounds per square inch (psi), pyridine (pyr), room temperature (rt or RT), *tert*-butyldimethylsilyl or *t*-$BuMe_2Si$ (TBDMS), triethylamine (TEA or Et_3N), 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO), triflate or CF_3SO_2- (Tf), trifluoroacetic acid (TFA), 1,1'-*bis*-2,2,6,6-tetramethylheptane-2,6-dione (TMHD), O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium tetrafluoroborate (TBTU), thin layer chromatography (TLC), tetrahydrofuran (THF), trimethylsilyl or Me_3Si (TMS), *p*-toluenesulfonic acid monohydrate (TsOH or pTsOH), 4-Me-$C_6H_4SO_2$- or tosyl (Ts), N-urethane-N-carboxyanhydride (UNCA),. Conventional nomenclature including the prefixes *normal* (*n*), *iso* (*i*-), *secondary* (*sec*-), *tertiary* (*tert*-) and *neo* have their customary meaning when used with an alkyl moiety. (J. Rigaudy and D. P. Klesney, *Nomenclature in Organic Chemistry,* IUPAC 1979 Pergamon Press, Oxford.).

"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-hydroxymethylethyl, 3-hydroxybutyl, 2,3-dihydroxybutyl, 2-hydroxy-1-methylpropyl, 2-aminoethyl, 3-aminopropyl, 2-methylsulfonylethyl, aminosulfonylmethyl, aminosulfonylethyl, aminosulfonylpropyl, methylaminosulfonylmethyl, methylaminosulfonylethyl, methylaminosulfonylpropyl, and the like.

"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 and the like, including partially hydrogenated derivatives thereof.

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

"Haloalkyl" means alkyl as defined herein in which one or more hydrogen has been replaced with same or different halogen. The term "lower haloalkyl" denotes a straight or branched chain hydrocarbon residue containing 1 to 6 carbon atoms substituted with one or more halogen atom. Exemplary haloalkyls include $-CH_2Cl$, $-CH_2CF_3$, $-CH_2CCl_3$, $-CF_2CF_3$, $-CF_3$, and the like.

"Heterocyclyl", "heterocycle", or "heterocycloalkyl" means a monovalent saturated moiety, consisting of one to two rings, incorporating one, two, or three or four heteroatoms (chosen

from nitrogen, oxygen or sulfur). The heterocyclyl ring may be optionally fuse to a heteroaryl group as defined herein. 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, octahydro-pyrrolo[1,2-a]pyrazine, octahydro-pyrido[1,2-a]pyrazine, 5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine, 5,6,7,8-tetrahydro-imidazo[1,2-a]pyrazine, dihydro-8*H*-[1,2,4]triazolo[4,3-*a*]pyrazine, hexahydro-pyrrolo[1,2-*a*]pyrazine, 5,6-Dihydro-8*H*-[1,2,4]triazolo[4,3-*a*]pyrazine, 5,6-Dihydro-8*H*-imidazo[1,2-*a*]pyrazine and the like.

"Optionally substituted" means a substituent which is substituted independently with zero to three substituents selected from lower alkyl, halo, OH, cyano, amino, nitro, lower alkoxy, or halo-lower alkyl.

Preferred radicals for the chemical groups whose definitions are given above are those specifically exemplified in Examples.

Preferred "oxidizing agents" include peracids like in-chloroperbenzoic acid (MCPBA) and peracetic acid, but other oxidizing agents like hydrogen peroxide, permanganate salts, or persulfate salts can be used to oxidize a thioether to a sulfone.

"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, benzene-sulfonyloxy, tosyloxy, and thienyloxy, dihalophosphinoyloxy, optionally substituted benzyloxy, isopropyloxy, acyloxy, and the like.

"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.

"Agonist" refers to a compound that enhances the activity of another compound or receptor site.

"Antagonist" refers to a compound that diminishes or prevents the action of another compound or receptor site.

The term "drug candidate" refers to a compound or preparation which is to be tested for possible effect in the treatment of a disease state in an animal, regardless of whether said drug candidate has any known biological activity.

The term "homologous" as used herein refers to a protein that performs substantially the same function in another subject species and shares substantial sequence identity, to the extent that they are recognized in the art as being different versions of the same protein, differing primarily in the species in which they are found. Thus, for example, human ERG, mouse ERG, and rat ERG are all considered homologous to each other.

"Modulator" means a molecule that interacts with a target. The interactions include, but are not limited to, agonist, antagonist, and the like, as defined herein.

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

The term "cell line" refers to a clone of immortalized mammalian cells. A "stable" cell line is a cell line that exhibits substantially consistent characteristics over time (e.g., with each doubling). A stable cell line within the scope of this invention provides a substantial proportion of cells that are capable of providing a seal resistance of greater than about 50 MOhm, a current amplitude of greater than about 200 pA, and provide a current amplitude that does not vary by more than approximately 20% over one hour under control conditions.

"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:

(1) acid addition salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; 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, and the like; or

(2) 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, and the like. Acceptable inorganic bases include aluminum hydroxide, calcium hydroxide, potassium hydroxide, sodium carbonate and sodium hydroxide.

It should be understood that all references to pharmaceutically acceptable salts include solvent addition forms (solvates) or crystal forms (polymorphs) as defined herein, of the same acid addition salt.

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

"Solvates" means solvent additions forms that contain either stoichiometric or non stoichiometric amounts of solvent. Some compounds have a tendency to trap a fixed molar ratio of solvent molecules in the crystalline solid state, thus forming a solvate. If the solvent is water the solvate formed is a hydrate, when the solvent is alcohol, the solvate formed is an alcoholate. Hydrates are formed by the combination of one or more molecules of water with one of the substances in which the water retains its molecular state as H_2O, such combination being able to form one or more hydrate.

"Subject" includes mammals and birds. "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; and the like. 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 judgement of the attending medical or veterinary practitioner, and other factors.

"Pharmacological effect" as used herein encompasses effects produced in the subject that achieve the intended purpose of a therapy. For example, a pharmacological effect would be one that results in the prevention, alleviation or reduction of urinary incontinence in a treated subject.

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

“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.

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

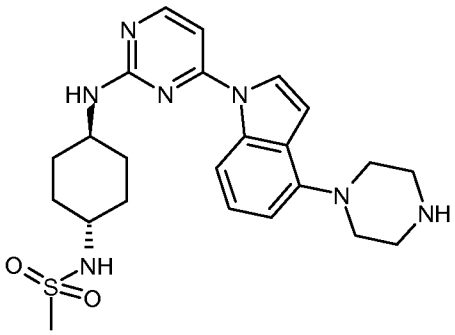
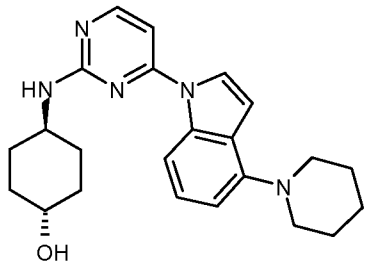
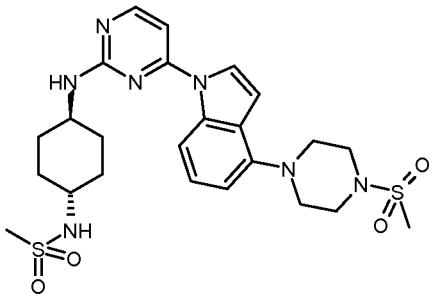
The compounds described below are JNK inhibitors useful for inhibiting JNK and treating JNK-mediated disorders, and the like. Examples of representative compounds encompassed by the present invention and within the scope of the invention are provided in Table X as compounds.

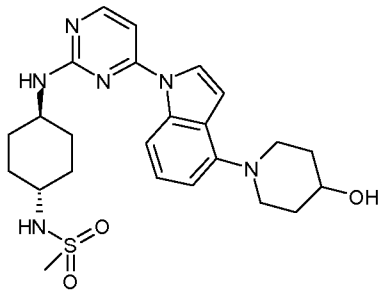
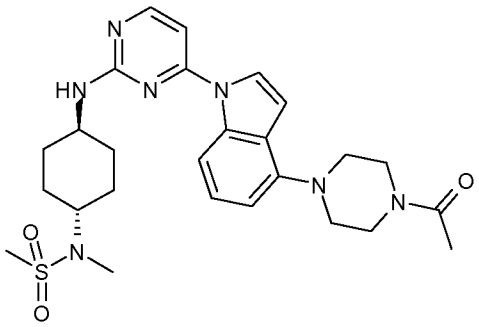
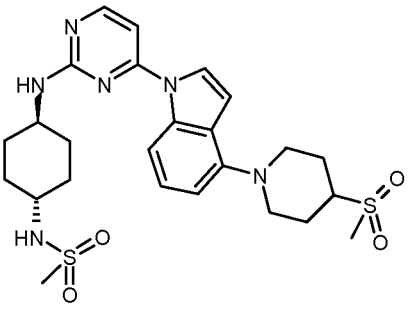
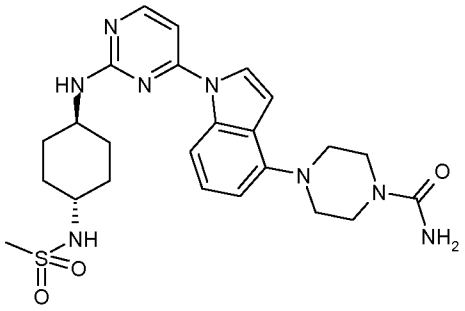
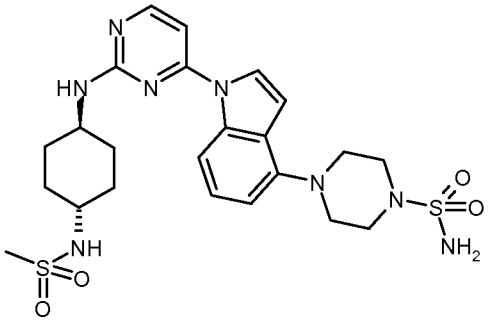
These examples and preparations which follow are provided to enable those skilled in the art to more clearly understand and to practice the present invention. They should not be

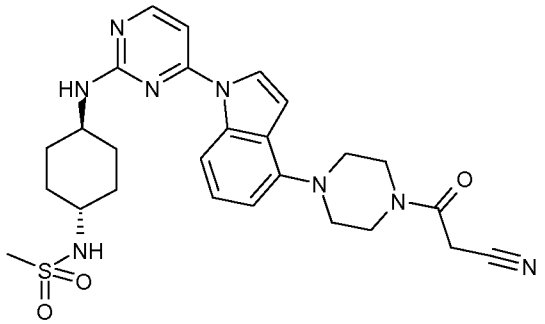
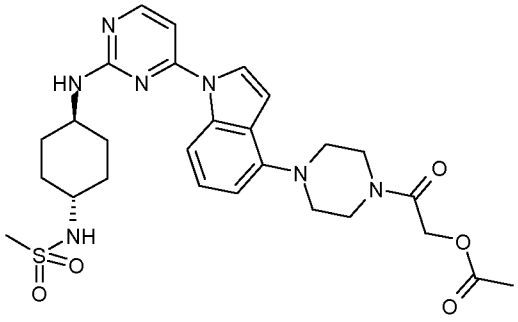
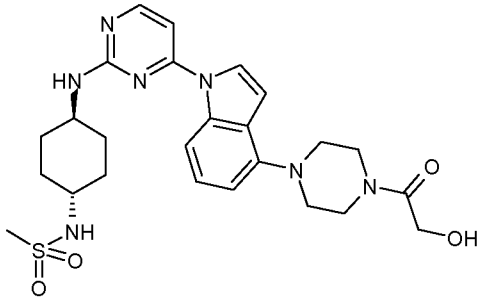
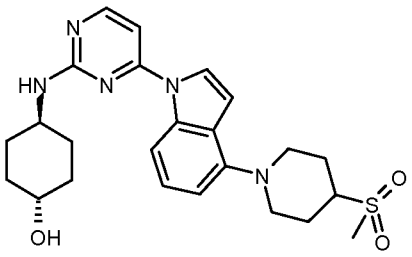
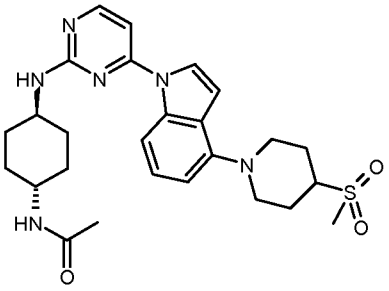
considered as limiting the scope of the invention, but merely as being illustrative and representative thereof.

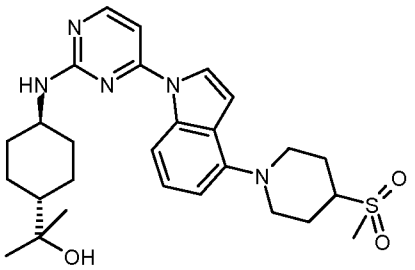
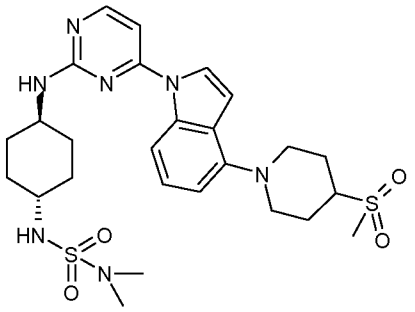
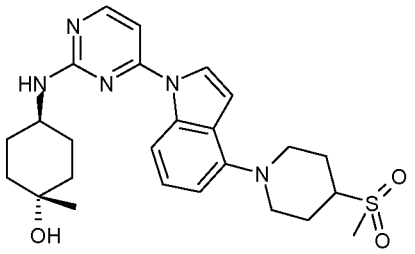
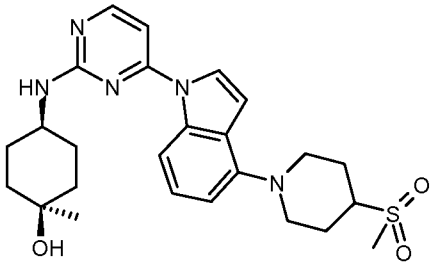
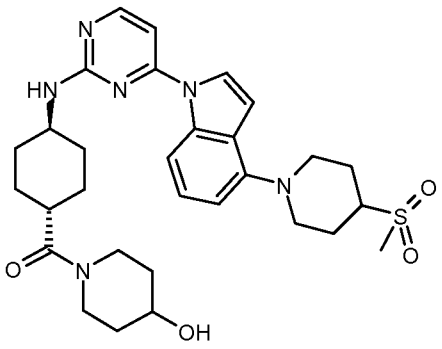
In general, the nomenclature used in this Application is based on AUTONOMTM v.4.0, a Beilstein Institute computerized system for the generation of IUPAC systematic nomenclature. If there is a discrepancy between a depicted structure and a name given that structure, the depicted structure is to be accorded more weight. In addition, if the stereochemistry of a structure or a portion of a structure is not indicated with, for example, bold or dashed lines, the structure or portion of the structure is to be interpreted as encompassing all stereoisomers of it.

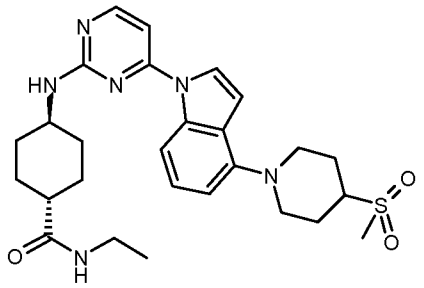
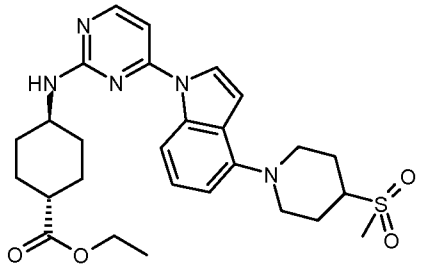
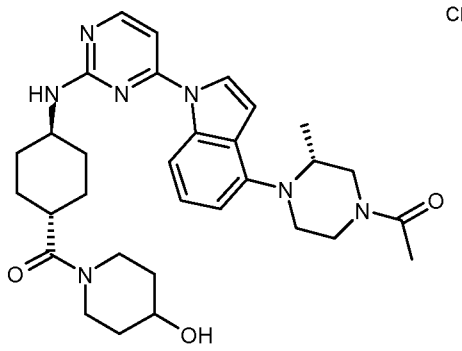
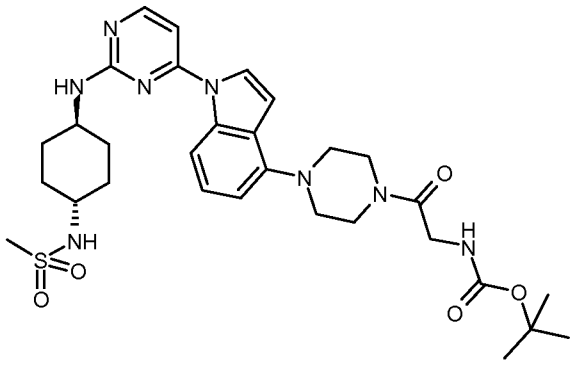
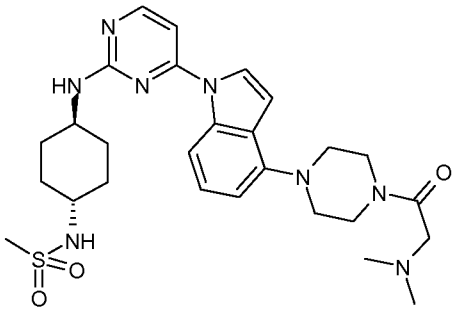
TABLE X.

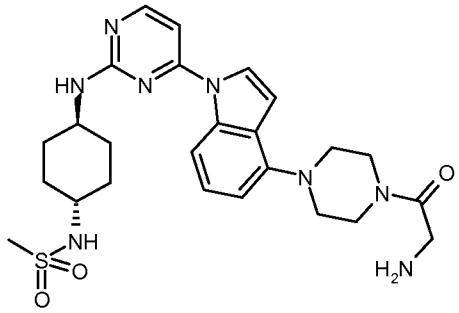
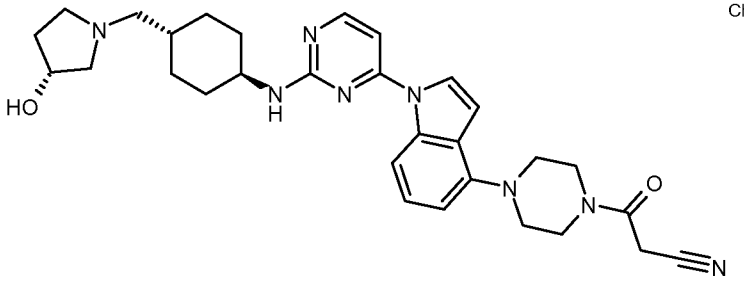
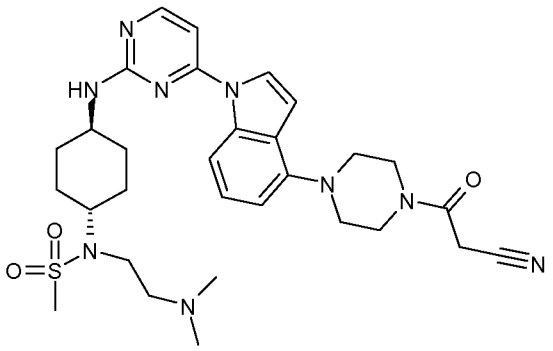
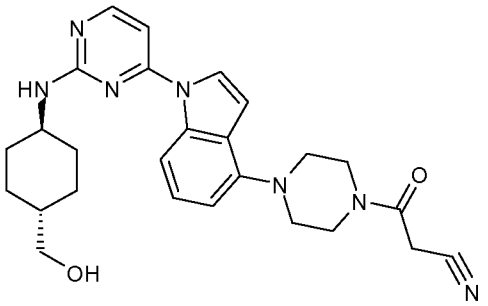
	Structure	Nomenclature
I-1		*N*-{4-[4-(4-Piperazin-1-yl-indol-1-yl)-pyrimidin-2-ylamino]-cyclohexyl}-methanesulfonamide
I-2		4-[4-(4-Piperidin-1-yl-indol-1-yl)-pyrimidin-2-ylamino]-cyclohexanol
I-3		*N*-(4-{4-[4-(4-Methanesulfonyl-piperazin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-cyclohexyl)-methanesulfonamide

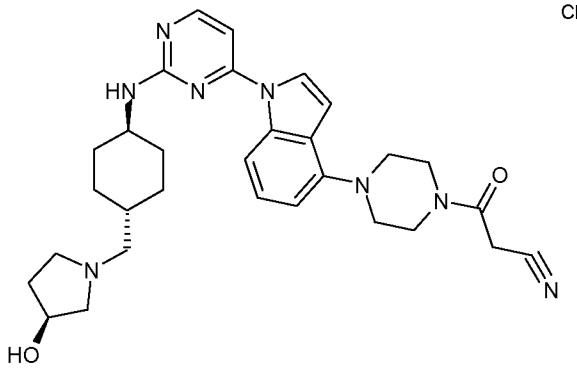
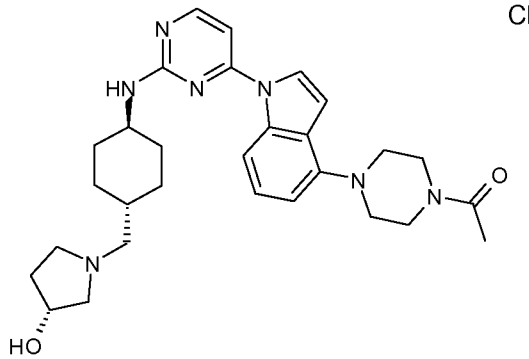
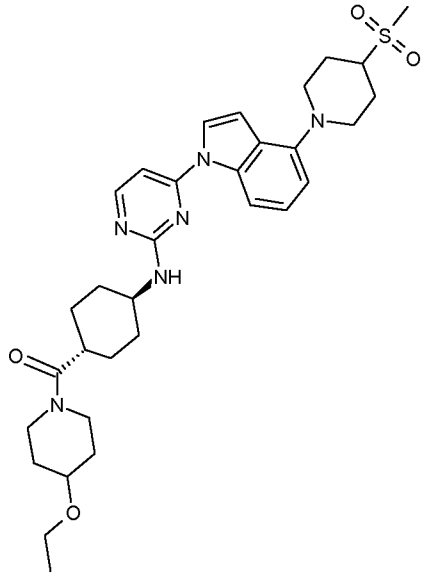
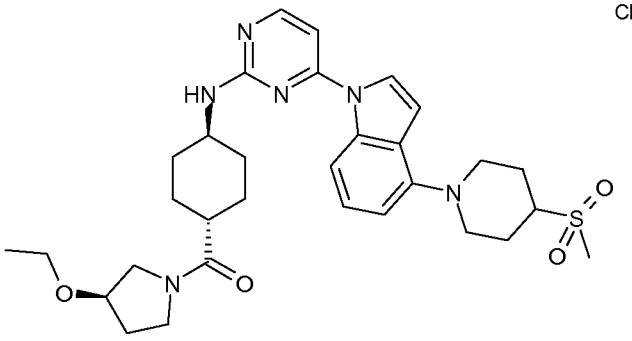
I-4		*N*-(4-{4-[4-(4-Hydroxy-piperidin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-cyclohexyl)-methanesulfonamide
I-5		*N*-(4-{4-[4-(4-Acetyl-piperazin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-cyclohexyl)-*N*-methyl-methanesulfonamide
I-6		*N*-(4-{4-[4-(4-Methanesulfonyl-piperidin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-cyclohexyl)-methanesulfonamide
I-7		4-{1-[2-(4-Methanesulfonylamino-cyclohexylamino)-pyrimidin-4-yl]-1*H*-indol-4-yl}-piperazine-1-carboxylic acid amide
I-8		4-{1-[2-(4-Methanesulfonylamino-cyclohexylamino)-pyrimidin-4-yl]-1*H*-indol-4-yl}-piperazine-1-sulfonic acid amide

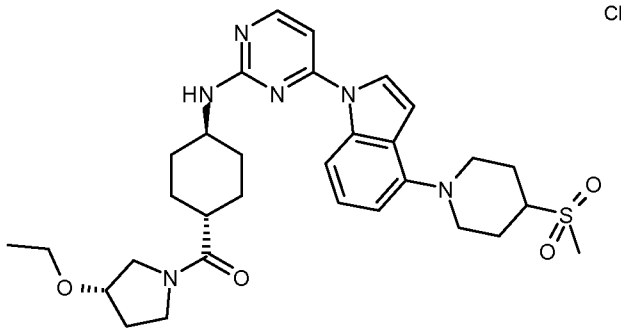
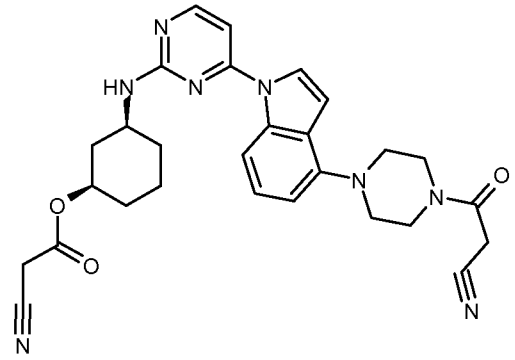
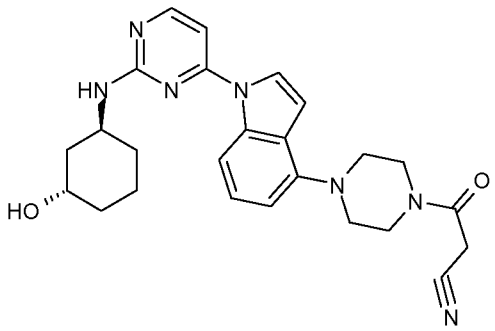
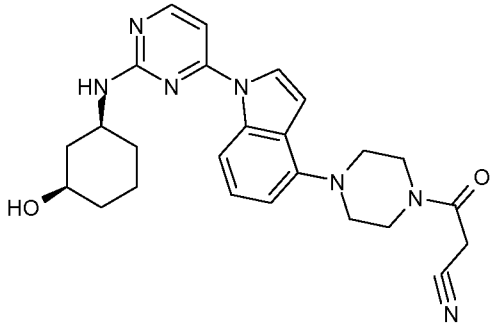
I-9		*N*-[4-(4-{4-[4-(2-Cyano-acetyl)-piperazin-1-yl]-indol-1-yl}-pyrimidin-2-ylamino)-cyclohexyl]-methanesulfonamide
I-10		Acetic acid 2-(4-{1-[2-(4-methanesulfonylamino-cyclohexylamino)-pyrimidin-4-yl]-1*H*-indol-4-yl}-piperazin-1-yl)-2-oxo-ethyl ester
I-11		*N*-[4-(4-{4-[4-(2-Hydroxy-acetyl)-piperazin-1-yl]-indol-1-yl}-pyrimidin-2-ylamino)-cyclohexyl]-methanesulfonamide
I-12		4-{4-[4-(4-Methanesulfonyl-piperidin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-cyclohexanol
I-13		*N*-(4-{4-[4-(4-Methanesulfonyl-piperidin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-cyclohexyl)-acetamide

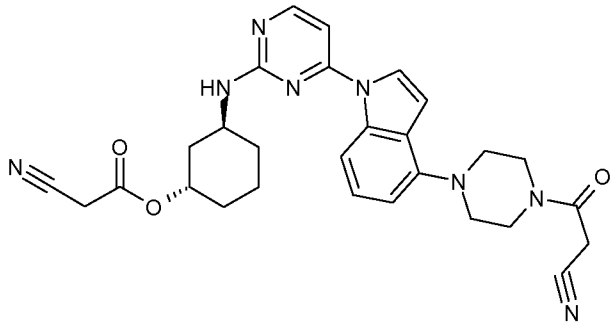
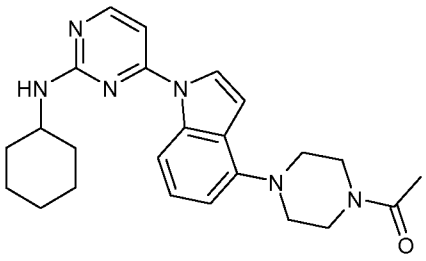
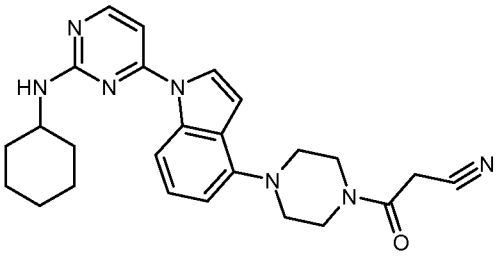
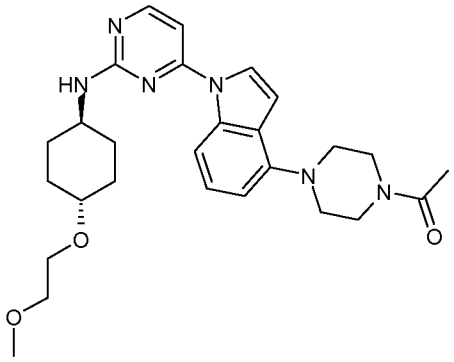
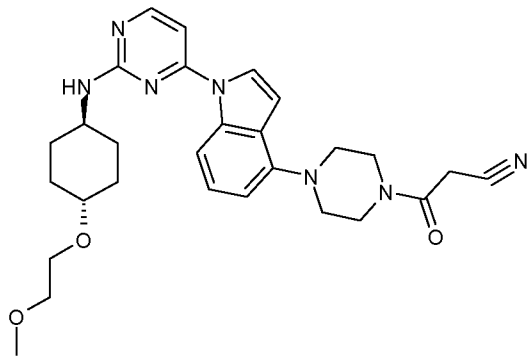
I-14		2-(4-{4-[4-(4-Methanesulfonyl-piperidin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-cyclohexyl)-propan-2-ol
I-15		[4-{4-[4-(4-Methanesulfonyl-piperidin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-cyclohexyl] aminodimethylsulfonamide
I-16		4-{4-[4-(4-Methanesulfonyl-piperidin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-1-methyl-cyclohexanol
I-17		4-{4-[4-(4-Methanesulfonyl-piperidin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-1-methyl-cyclohexanol
I-18		(4-Hydroxy-piperidin-1-yl)-(4-{4-[4-(4-methanesulfonyl-piperidin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-cyclohexyl)-methanone

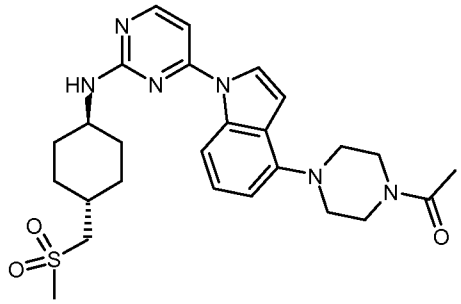
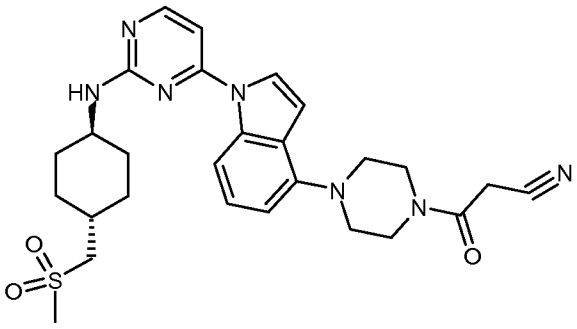
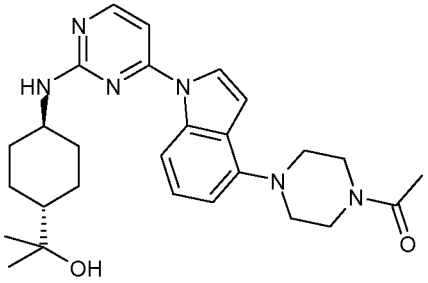
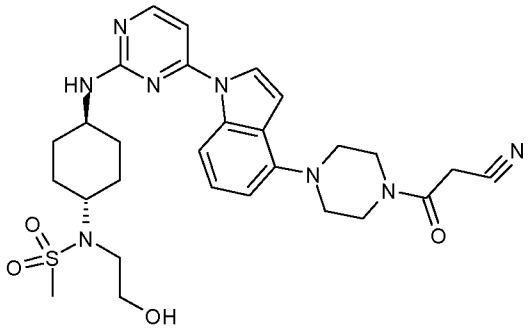
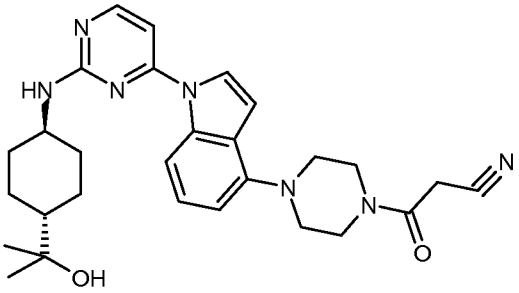
I-19		4-{4-[4-(4-Methanesulfonyl-piperidin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-cyclohexanecarboxylic acid ethylamide
I-20		4-{4-[4-(4-Methanesulfonyl-piperidin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-cyclohexanecarboxylic acid ethyl ester
I-21	 Chiral	1-[(R)-4-(1-{2-[4-(4-Hydroxy-piperidine-1-carbonyl)-cyclohexylamino]-pyrimidin-4-yl}-1*H*-indol-4-yl)-3-methyl-piperazin-1-yl]-ethanone
I-22		[2-(4-{1-[2-(4-Methanesulfonylamino-cyclohexylamino)-pyrimidin-4-yl]-1*H*-indol-4-yl}-piperazin-1-yl)-2-oxo-ethyl]-carbamic acid *tert*-butyl ester
I-23		*N*-[4-(4-{4-[4-(2-Dimethylamino-acetyl)-piperazin-1-yl]-indol-1-yl}-pyrimidin-2-ylamino)-cyclohexyl]-methanesulfonamide

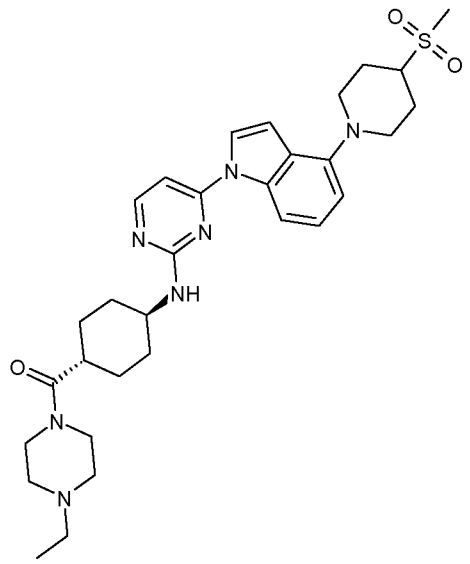
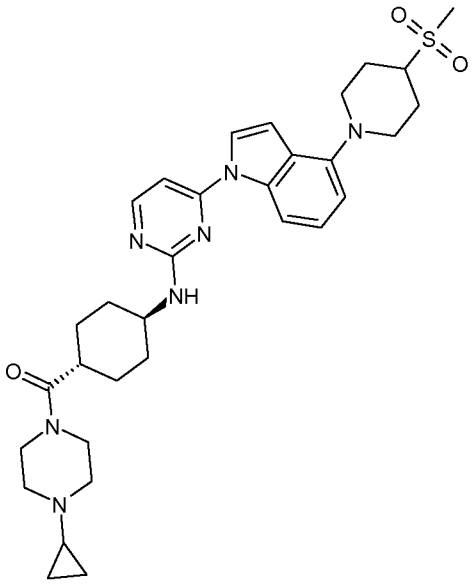
I-24		*N*-[4-(4-{4-[4-(2-Amino-acetyl)-piperazin-1-yl]-indol-1-yl}-pyrimidin-2-ylamino)-cyclohexyl]-methanesulfonamide
I-25	 Chiral	3-[4-(1-{2-[4-((R)-3-Hydroxy-pyrrolidin-1-ylmethyl)-cyclohexylamino]-pyrimidin-4-yl}-1*H*-indol-4-yl)-piperazin-1-yl]-3-oxo-propionitrile
I-26		*N*-[4-(4-{4-[4-(2-Cyano-acetyl)-piperazin-1-yl]-indol-1-yl}-pyrimidin-2-ylamino)-cyclohexyl]-*N*-(2-dimethylamino-ethyl)-methanesulfonamide
I-27		3-(4-{1-[2-(4-Hydroxymethyl-cyclohexylamino)-pyrimidin-4-yl]-1*H*-indol-4-yl}-piperazin-1-yl)-3-oxo-propionitrile

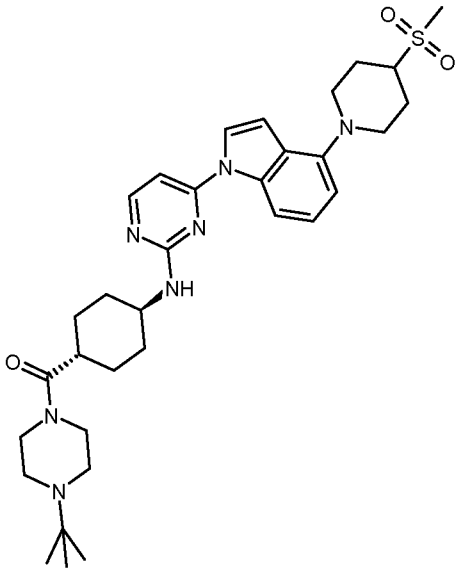
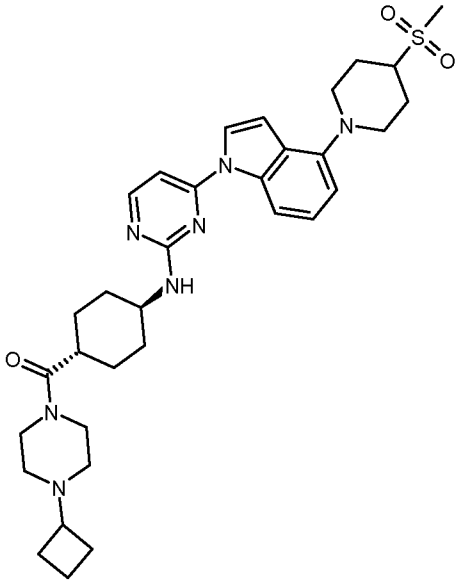
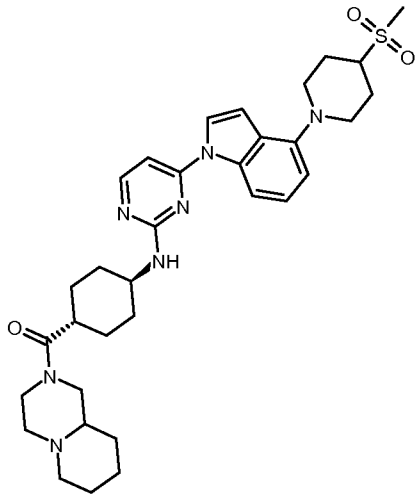
I-28	 Chiral	3-[4-(1-{2-[4-((S)-3-Hydroxy-pyrrolidin-1-ylmethyl)-cyclohexylamino]-pyrimidin-4-yl}-1*H*-indol-4-yl)-piperazin-1-yl]-3-oxo-propionitrile
I-29	 Chiral	1-[4-(1-{2-[4-((R)-3-Hydroxy-pyrrolidin-1-ylmethyl)-cyclohexylamino]-pyrimidin-4-yl}-1*H*-indol-4-yl)-piperazin-1-yl]-ethanone
I-30		(4-Ethoxy-piperidin-1-yl)-(4-{4-[4-(4-methanesulfonyl-piperidin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-cyclohexyl)-methanone
I-31	 Chiral	((R)-3-Ethoxy-pyrrolidin-1-yl)-(4-{4-[4-(4-methanesulfonyl-piperidin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-cyclohexyl)-methanone

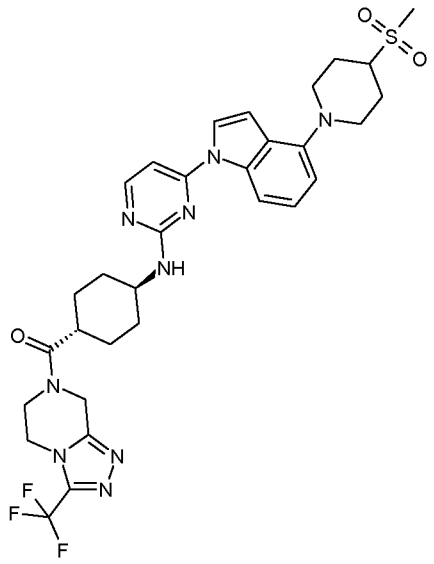
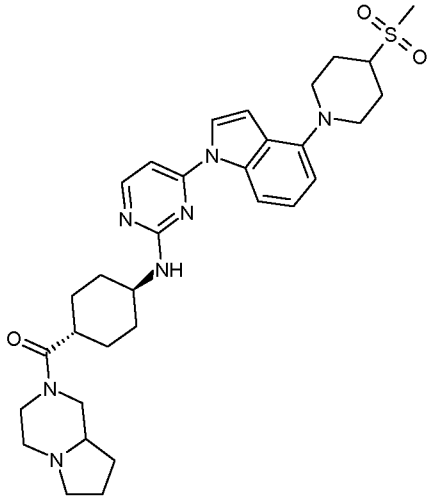
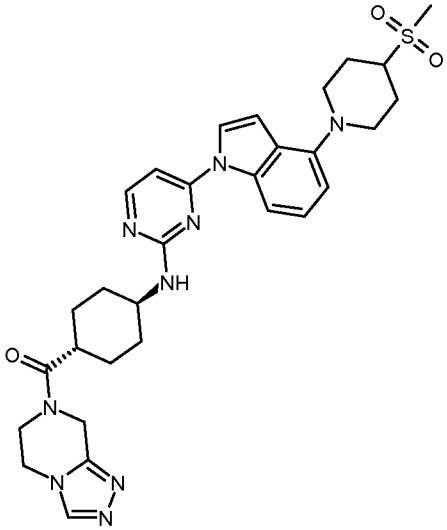
I-32	 Chiral	((S)-3-Ethoxy-pyrrolidin-1-yl)-(4-{4-[4-(4-methanesulfonyl-piperidin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-cyclohexyl)-methanone
I-33		Cyano-acetic acid (1R,3S)-3-(4-{4-[4-(2-cyano-acetyl)-piperazin-1-yl]-indol-1-yl}-pyrimidin-2-ylamino)-cyclohexyl ester
I-34		3-(4-{1-[2-((1S,3S)-3-Hydroxy-cyclohexylamino)-pyrimidin-4-yl]-1*H*-indol-4-yl}-piperazin-1-yl)-3-oxo-propionitrile
I-35		3-(4-{1-[2-((1S,3R)-3-Hydroxy-cyclohexylamino)-pyrimidin-4-yl]-1*H*-indol-4-yl}-piperazin-1-yl)-3-oxo-propionitrile

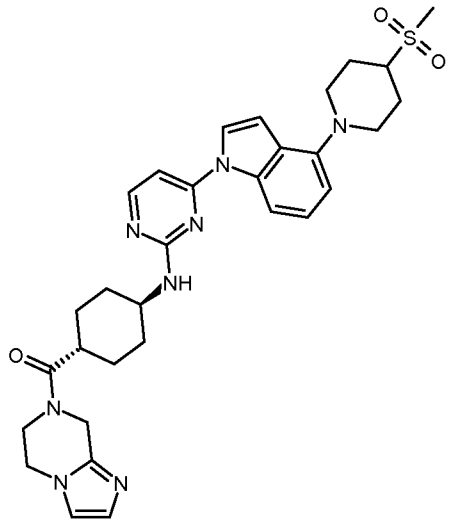
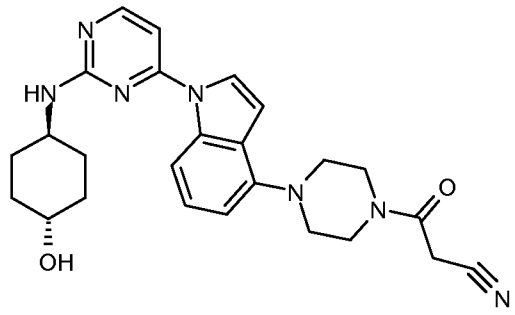
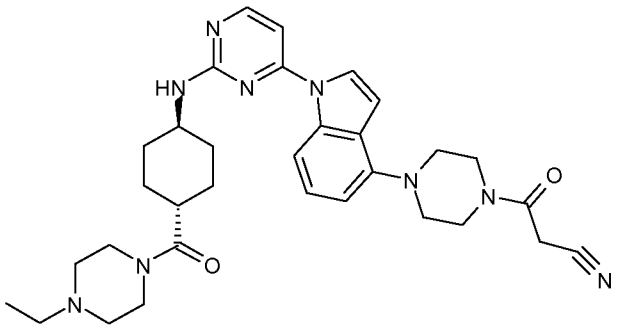
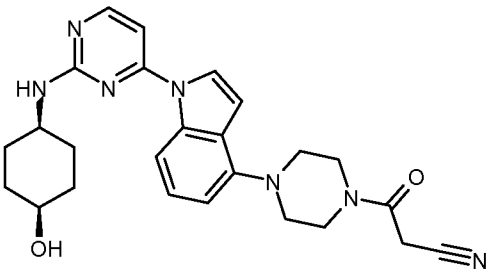
I-36		Cyano-acetic acid (1S,3S)-3-(4-{4-[4-(2-cyano-acetyl)-piperazin-1-yl]-indol-1-yl}-pyrimidin-2-ylamino)-cyclohexyl ester
I-37		1-{4-[1-(2-Cyclohexylamino-pyrimidin-4-yl)-1*H*-indol-4-yl]-piperazin-1-yl}-ethanone
I-38		3-{4-[1-(2-Cyclohexylamino-pyrimidin-4-yl)-1*H*-indol-4-yl]-piperazin-1-yl}-3-oxo-propionitrile
I-39		1-[4-(1-{2-[4-(2-Methoxy-ethoxy)-cyclohexylamino]-pyrimidin-4-yl}-1*H*-indol-4-yl)-piperazin-1-yl]-ethanone
I-40		3-[4-(1-{2-[4-(2-Methoxy-ethoxy)-cyclohexylamino]-pyrimidin-4-yl}-1*H*-indol-4-yl)-piperazin-1-yl]-3-oxo-propionitrile

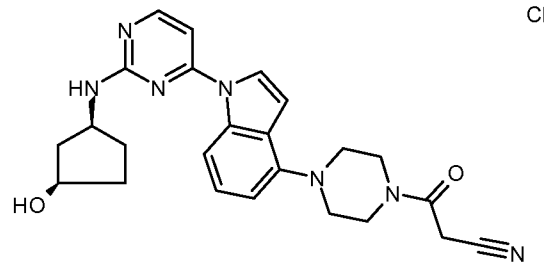
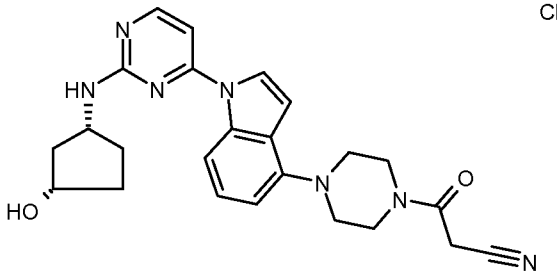
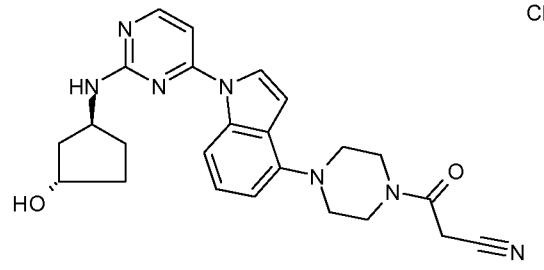
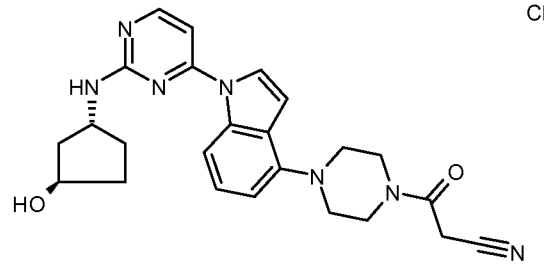
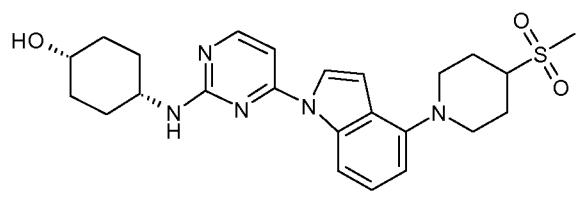
I-41		1-(4-{1-[2-(4-Methanesulfonylmethyl-cyclohexylamino)-pyrimidin-4-yl]-1*H*-indol-4-yl}-piperazin-1-yl)-ethanone
I-42		3-(4-{1-[2-(4-Methanesulfonylmethyl-cyclohexylamino)-pyrimidin-4-yl]-1*H*-indol-4-yl}-piperazin-1-yl)-3-oxo-propionitrile
I-43		1-[4-(1-{2-[4-(1-Hydroxy-1-methyl-ethyl)-cyclohexylamino]-pyrimidin-4-yl}-1*H*-indol-4-yl)-piperazin-1-yl]-ethanone
I-44		*N*-[4-(4-{4-[4-(2-Cyano-acetyl)-piperazin-1-yl]-indol-1-yl}-pyrimidin-2-ylamino)-cyclohexyl]-*N*-(2-hydroxy-ethyl)-methanesulfonamide
I-45		3-[4-(1-{2-[4-(1-Hydroxy-1-methyl-ethyl)-cyclohexylamino]-pyrimidin-4-yl}-1*H*-indol-4-yl)-piperazin-1-yl]-3-oxo-propionitrile

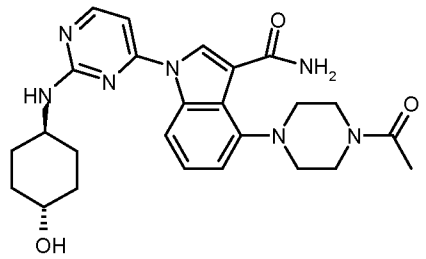
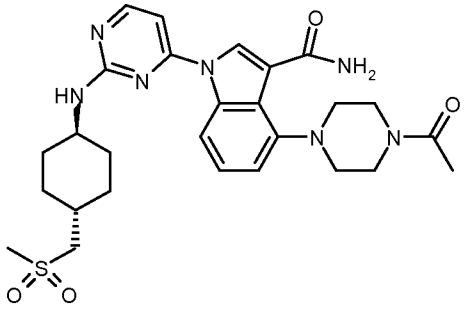
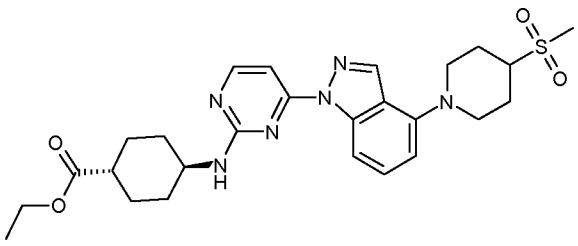
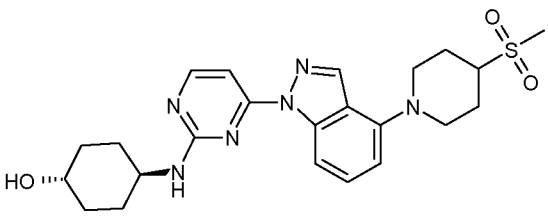
I-46		(4-Ethyl-piperazin-1-yl)-(4-{4-[4-(4-methanesulfonyl-piperidin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-cyclohexyl)-methanone
I-47		(4-Cyclopropyl-piperazin-1-yl)-(4-{4-[4-(4-methanesulfonyl-piperidin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-cyclohexyl)-methanone

I-48		(4-*tert*-Butyl-piperazin-1-yl)-(4-{4-[4-(4-methanesulfonyl-piperidin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-cyclohexyl)-methanone
I-49		(4-Cyclobutyl-piperazin-1-yl)-(4-{4-[4-(4-methanesulfonyl-piperidin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-cyclohexyl)-methanone
I-50		(4-{4-[4-(4-Methanesulfonyl-piperidin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-cyclohexyl)-(octahydro-pyrido[1,2-*a*]pyrazin-2-yl)-methanone

I-51		(4-{4-[4-(4-Methanesulfonyl-piperidin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-cyclohexyl)-(3-trifluoromethyl-5,6-dihydro-8*H*-[1,2,4]triazolo[4,3-*a*]pyrazin-7-yl)-methanone
I-52		(Hexahydro-pyrrolo[1,2-*a*]pyrazin-2-yl)-(4-{4-[4-(4-methanesulfonyl-piperidin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-cyclohexyl)-methanone
I-53		(5,6-Dihydro-8*H*-[1,2,4]triazolo[4,3-*a*]pyrazin-7-yl)-(4-{4-[4-(4-methanesulfonyl-piperidin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-cyclohexyl)-methanone

I-54		(5,6-Dihydro-8*H*-imidazo[1,2-*a*]pyrazin-7-yl)-(4-{4-[4-(4-methanesulfonyl-piperidin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-cyclohexyl)-methanone
I-55		3-(4-{1-[2-(4-Hydroxy-cyclohexylamino)-pyrimidin-4-yl]-1*H*-indol-4-yl}-piperazin-1-yl)-3-oxo-propionitrile
I-56		3-[4-(1-{2-[4-(4-Ethyl-piperazine-1-carbonyl)-cyclohexylamino]-pyrimidin-4-yl}-1*H*-indol-4-yl)-piperazin-1-yl]-3-oxo-propionitrile
I-57		3-(4-{1-[2-(4-Hydroxy-cyclohexylamino)-pyrimidin-4-yl]-1*H*-indol-4-yl}-piperazin-1-yl)-3-oxo-propionitrile

I-58	 Chiral	3-(4-{1-[2-((1S,3R)-3-Hydroxy-cyclopentylamino)-pyrimidin-4-yl]-1*H*-indol-4-yl}-piperazin-1-yl)-3-oxo-propionitrile
I-59	 Chiral	3-(4-{1-[2-((1R,3S)-3-Hydroxy-cyclopentylamino)-pyrimidin-4-yl]-1*H*-indol-4-yl}-piperazin-1-yl)-3-oxo-propionitrile
I-60	 Chiral	3-(4-{1-[2-((1S,3S)-3-Hydroxy-cyclopentylamino)-pyrimidin-4-yl]-1*H*-indol-4-yl}-piperazin-1-yl)-3-oxo-propionitrile
I-61	 Chiral	3-(4-{1-[2-((1R,3R)-3-Hydroxy-cyclopentylamino)-pyrimidin-4-yl]-1*H*-indol-4-yl}-piperazin-1-yl)-3-oxo-propionitrile
I-62		4-{4-[4-(4-Methanesulfonyl-piperidin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-cyclohexanol

I-63		4-(4-Acetyl-piperazin-1-yl)-1-[2-(4-hydroxy-cyclohexylamino)-pyrimidin-4-yl]-1*H*-indole-3-carboxylic acid amide
I-64		4-(4-Acetyl-piperazin-1-yl)-1-[2-(4-methanesulfonylmethyl-cyclohexylamino)-pyrimidin-4-yl]-1*H*-indole-3-carboxylic acid amide
I-65		4-{4-[4-(4-Methanesulfonyl-piperidin-1-yl)-indazol-1-yl]-pyrimidin-2-ylamino}-cyclohexanecarboxylic acid ethyl ester
I-66		4-{4-[4-(4-Methanesulfonyl-piperidin-1-yl)-indazol-1-yl]-pyrimidin-2-ylamino}-cyclohexanol

UTILITY

The compounds of this invention are JNK inhibitors 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 disorders, inflammatory disorders, metabolic disorders, 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 Compositions

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, and the like. 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, and the like.

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 also 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 chloro-fluorocarbon (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 subdermal 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.

LIST OF ABBREVIATIONS

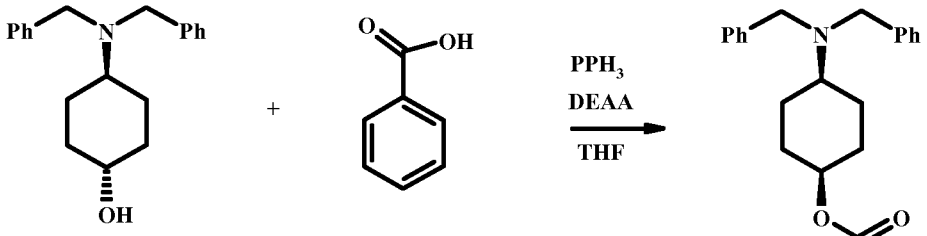
Ac_2O	Acetic anhydride
AcOH	Acetic acid
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-Dichloroethane
DCM	Dichloromethane/Methylene chloride
DIPEA	Diisopropylethylamine
DMF	*N*,*N*-dimethylformamide
DMSO	Dimethyl sulfoxide
EDCI	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
Et_2O	Diethyl ether
EtOH	Ethanol/Ethyl alcohol
EtOAc	Ethyl acetate
HOBt	1-Hydroxybenzotriazole
LDA	Lithium diisopropylamide
LiHMDS	Lithium bis(trimethylsilyl)amide
m-CPBA	3-Chloroperoxybenzoic acid

MeOH	Methanol/Methyl alcohol
MW	Microwaves
NMP	1-Methyl-2-pyrrolidinone
PMB	4-Methoxy benzyl
RT	Room temperature
TBME	*tert*-Butyl methyl ether
TFA	Trifluoroacetic acid
Tf_2O	Trifluoromethanesulfonic anhydride
THF	Tetrahydrofuran
TLC	Thin layer chromatography

EXAMPLES

The following preparations and examples are given to enable those skilled in the art to more clearly understand and to practice the present invention. They should not be considered as limiting the scope of the invention, but merely as being illustrative and representative thereof.

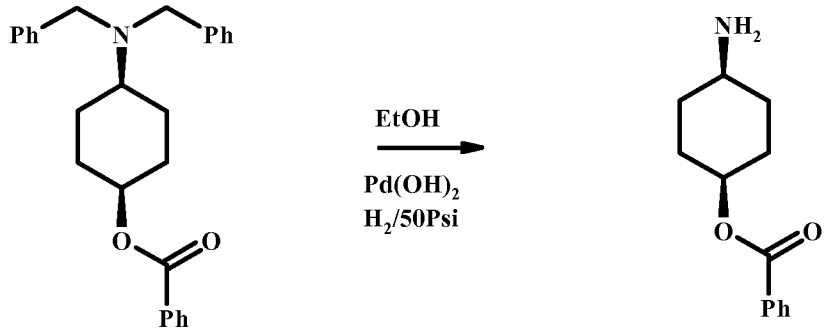
Example 1.



I **II** **III**

5.23g of **I** in 100mL THF was treated with 2.6g of **II**, 4.65g PPH_3, and 8.4mL DEAA. The mixture was then diluted with EtOAc, washed with water, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was triturated with hexane and the resultant solid filtered off and the filtrate was concentrated *in vacuo* and purified on a column using 100% hexane to 15:1 EtOAc: hexane to yield product **III**.

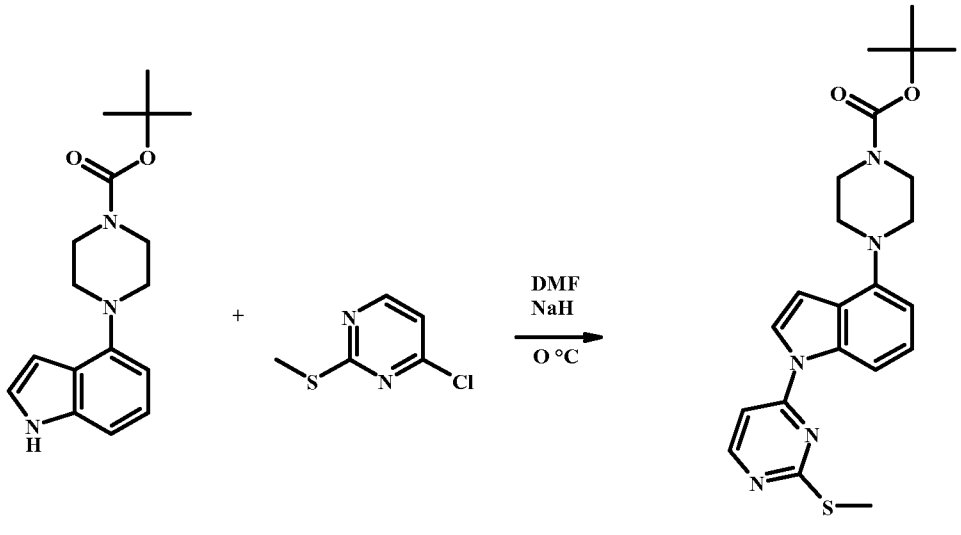
Example 2.



I II

0.75g of **I** in 100mL EtOH was treated with 0.15g $Pd(OH)_2$, purged with N_2, and then treated with H_2 at 50 psi for 2 days. The mixture was then filtered, dried *in vacuo* to yield 0.39g of **II**.

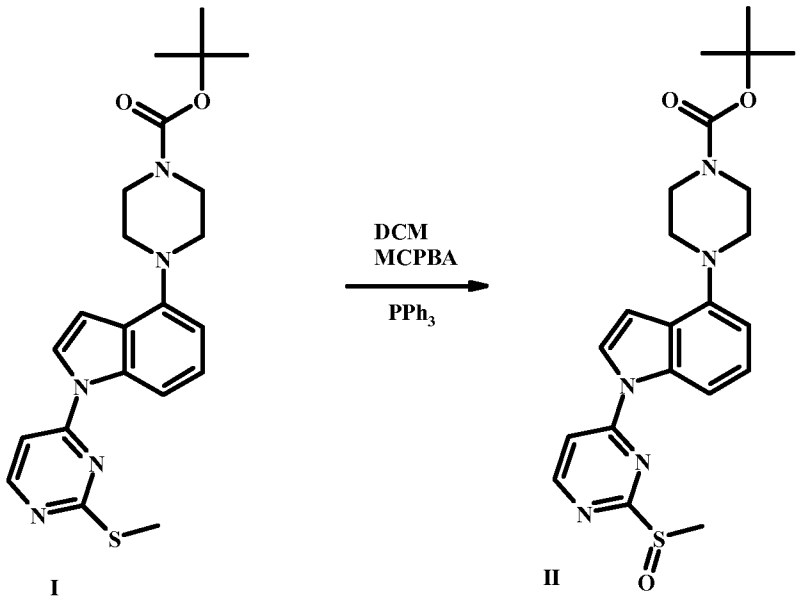
Example 3.



I II III

10.53g of **I** in 100mL DMF and cooled to 0 °C was gradually treated with 1.54g NaH and stirred at 0 °C for 1 h followed by the dropwise addition of 4.4mL of **II** and stirred for 4 h at 0 °C. The mixture was diluted with water and the solid separated and was filtered, washed with water, and dried. The solid was then triturated with EtOAc/hexane and filtered and dried to yield 14g of **III**.

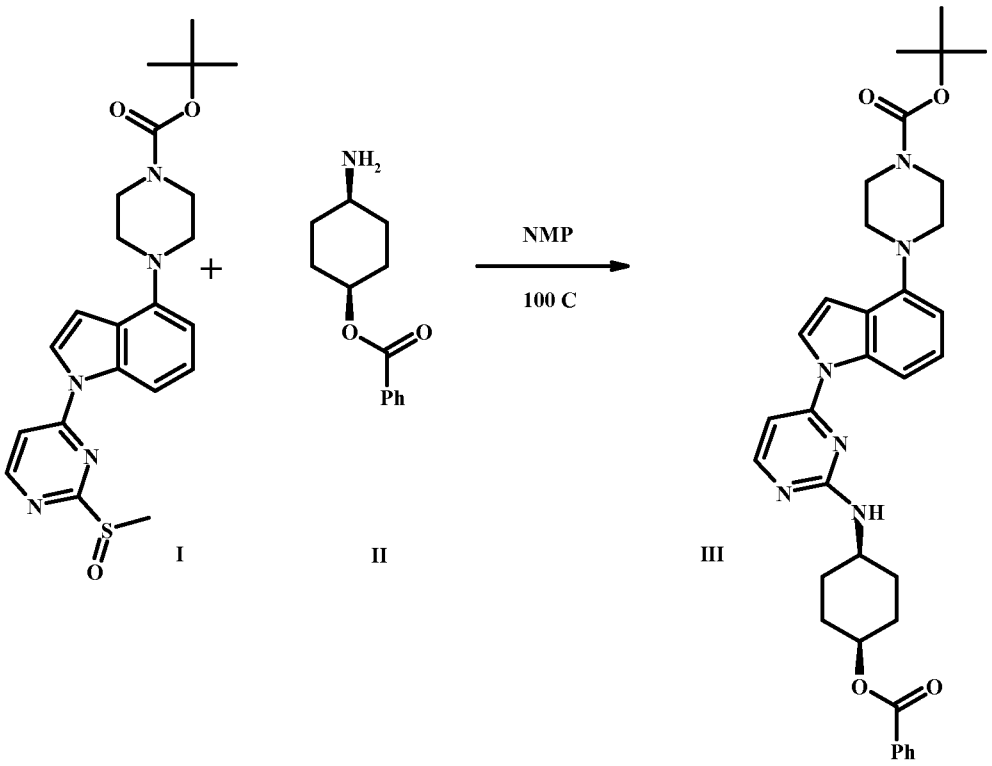
Example 4.



I II

14g of **I** in 500mL DCM cooled to 0 °C was treated with 14.72g of MCPBA and allowed to stir at 0 °C for 2 h. 25.8g PPh_3 was then added and stirred at rt overnight. The mixture was then washed with saturated $NaHCO_3$ solution and the organic layer was separated and dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was then triturated with hot EtOAc and the solid was filtered, dried at 50 °C *in vacuo* to yield 11g of **II**.

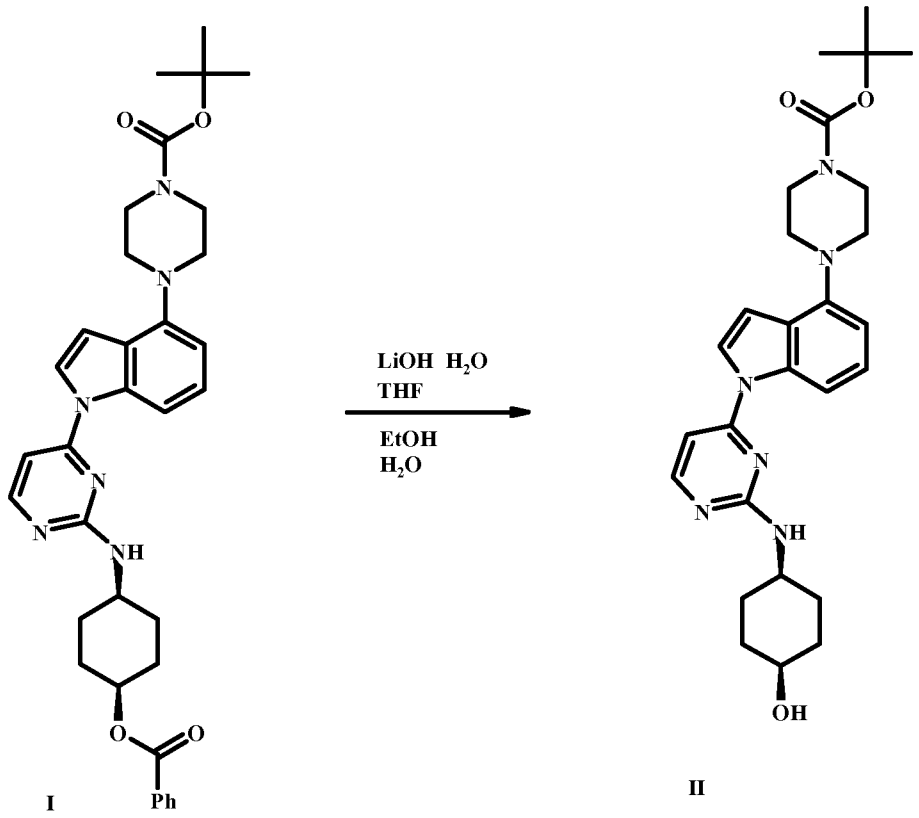
Example 5.



I II III

0.26g of **I** in 2mL NMP was treated with 0.39g of **II** and allowed to stir at 100 °C for 5 h, cooled to r.t., diluted with water, the solid separated, filtered and dried. The solid was purified by silica column using 100% DCM to 5% MeOH/DCM. The fractions containing the product were concentrated *in vacuo* and triturated with EtOAc. The solid was filtered and dried to yield 0.225g of **III**.

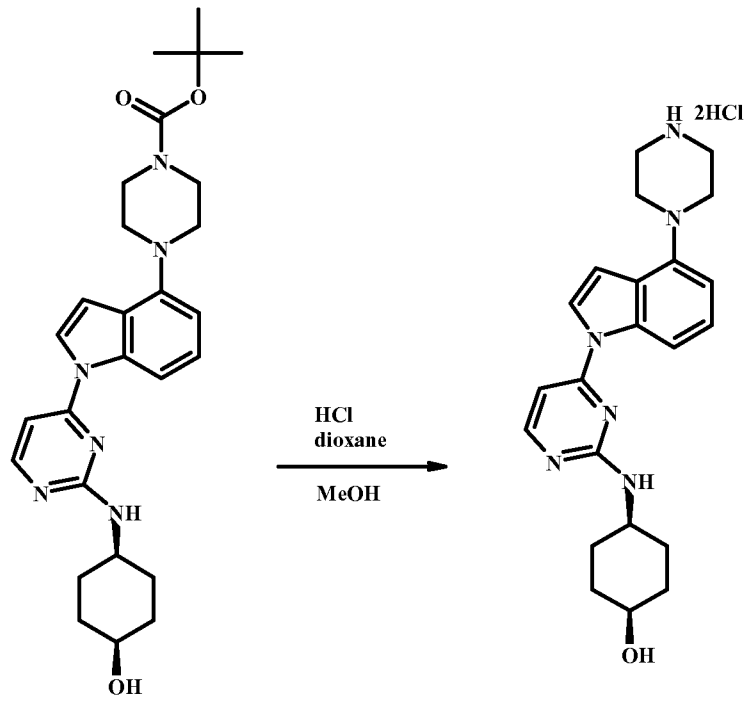
Example 6.



I II

0.225g of **I** in 25mL THF, 5mL EtOH, and 5mL H_2O was treated with 80mg of $LiOH^{\bullet}H_2O$ and was allowed to stir a r.t. for 2 days. The reaction was then concentrated and allowed to stir until reaction completion. The mixture was then diluted with 1N NaOH, extracted with EtOAc, the organic layer separated and dried over Na_2SO_4, filtered and concentrated *in vacuo* to yield 0.165g **II**.

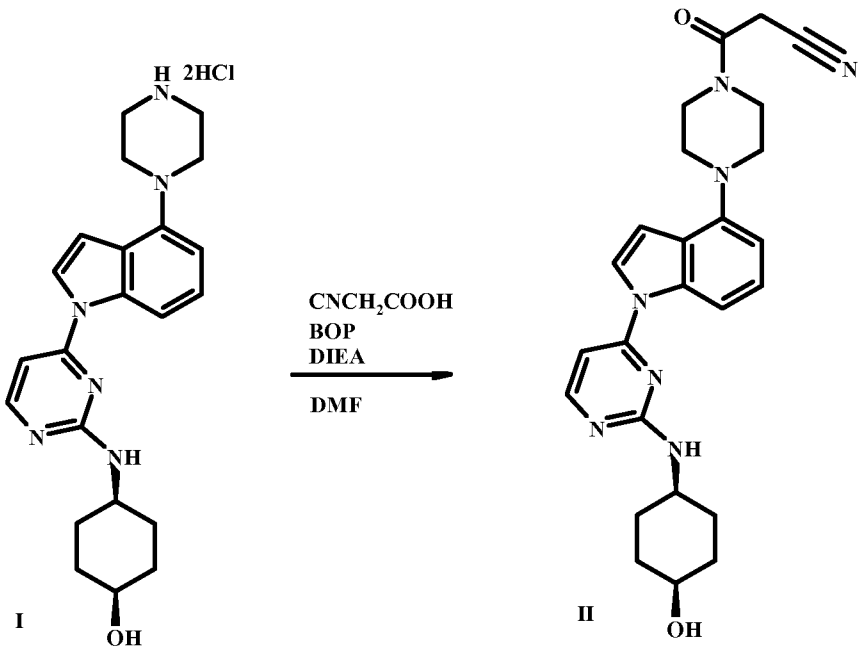
Example 7.



I II

0.165g of *I* in 5mL MeOH was treated with 25mL 4.0M HCl in dioxane and allowed to stir at r.t. for 4 h and then concentrated *in vacuo*. The resulting solid was then separated, filtered, and dried *in vacuo* overnight to yield 0.17g of **II**.

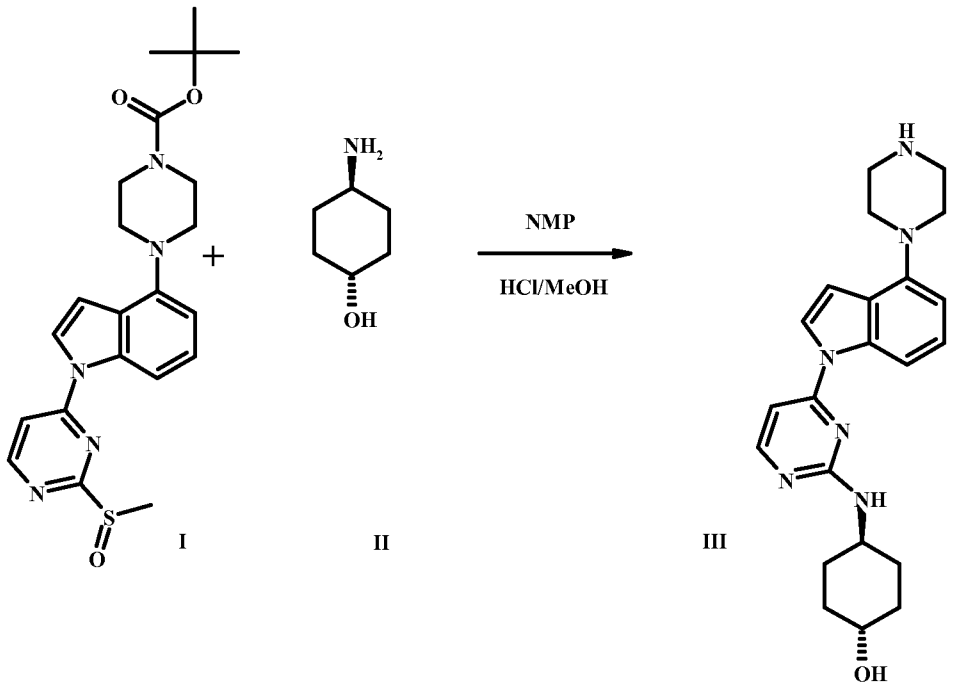
Example 8.



I II

0.1g of **I** in 3mL DMF was treated with 22mg of $CNCH_2COOH$, 0.12g BOP, and 0.2mL DIEA and allowed to stir at r.t. overnight. The mixture was then diluted with water, extracted with DCM, purified on a silica gel column using 100% DCM to 10:1 MeOH:DCM. The fractions containing the product were concentrated *in vacuo*, the residue triturated with EtOAc, the solid separated, filtered, and dried at 50 °C *in vacuo* overnight to yield 27.7mg of **II**.

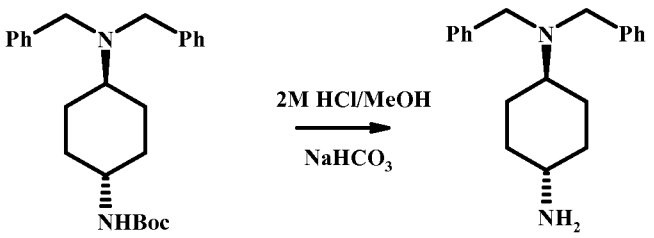
Example 9.



I II III

0.3g of **I** was treated with 0.235g of **II** in 2mL NMP and stirred at 100 °C for 7 h, cooled to r.t. and diluted with water, the solid separated, filtered, and dried. The solid was then purified by silica gel column using 100% DCM to 10% MeOH/DCM. The fractions containing the product was then concentrated *in vacuo* overnight, the residue then dissolved in 50mL HCl/MEOH and stirred at r.t. overnight, then concentrated *in vacuo* overnight to yield 0.3g **III**.

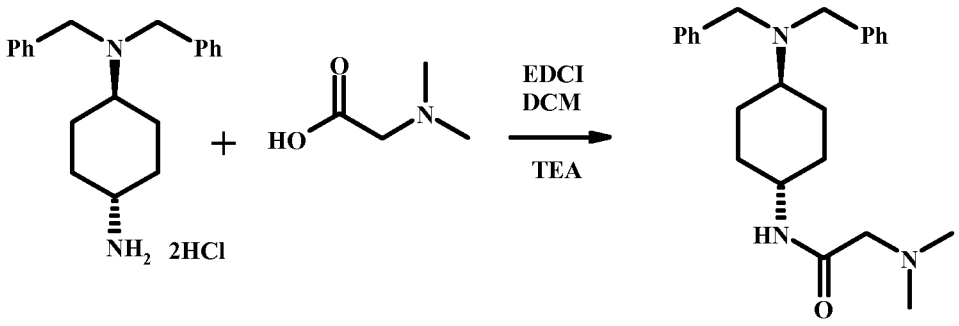
Example 10.



I II

12g of **I** in 100mL 2M HCl/MeOH was allowed to stir at r.t., the mixture concentrated *in vacuo*, then diluted with water and neutralized with saturated $NaHCO_3$. the solid was then separated, filtered, and washed with water and dried *in vacuo* to yield 7g of **II**.

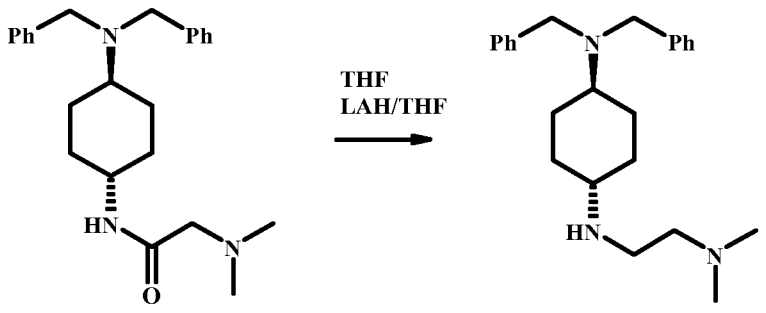
Example 11.



I II III

0.776g of Ii in 100mL DCM was treated with 1.44g EDCI, and 2.8mL TEA and then treated with 1.84g of **I** and stirred at r.t. for 4 h. the reaction mixture was then concentrated in vacuo and diluted with water, extracted with DCM, washed with saturated $NaHCO_3$ and brine, the purified on a silica gel column using 100% DCM to 10% MeOH/DCM. The fractions containing the product were then combined and dried in vacuo to yield 0.61g of **III**.

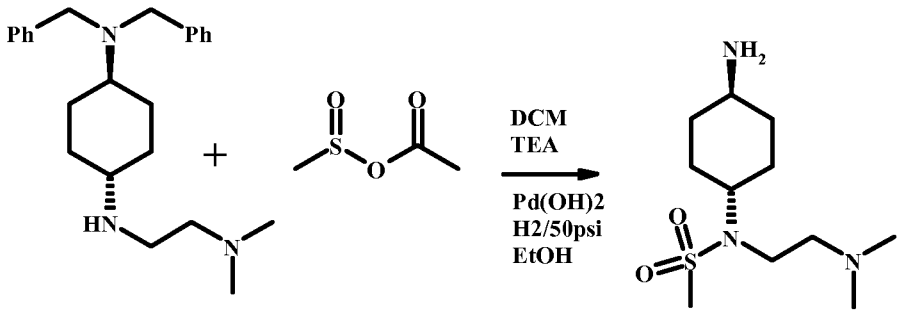
Example 12.



I II

2.2g of **I** in 100mL THF was treated with LAH in THF dropwise at r.t. and refluxed overnight and then cooled to r.t. and quenched with 10% aqueous salt solution, extracted with EtOAc, dried over Na_2SO_4, filtered, and concentrated *in vacuo* overnight to yield 2.2g of **II**.

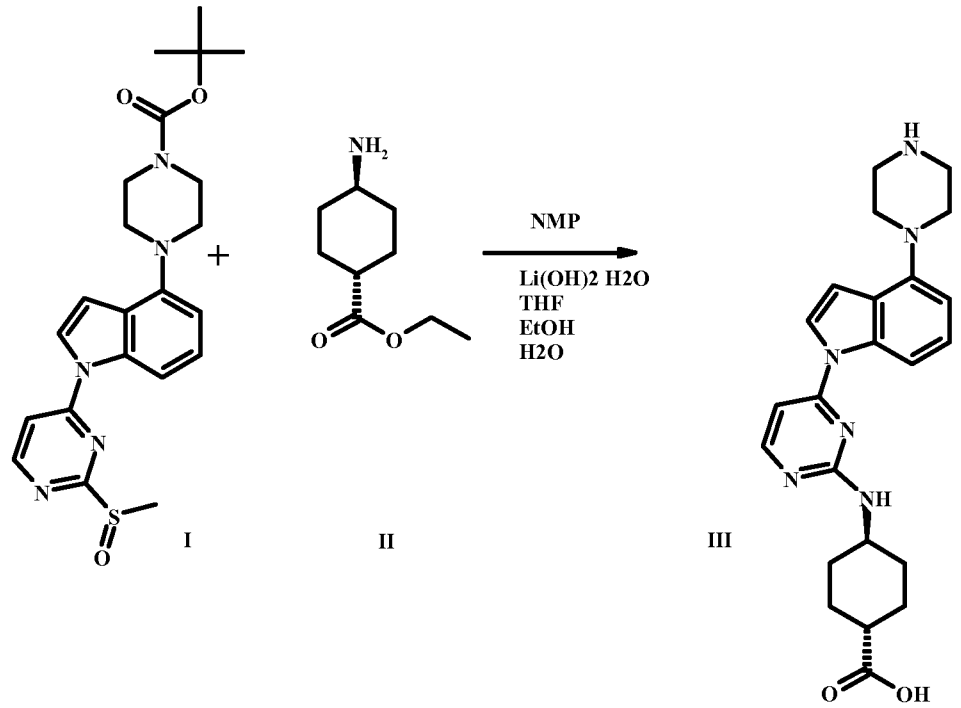
Example 13.



I II

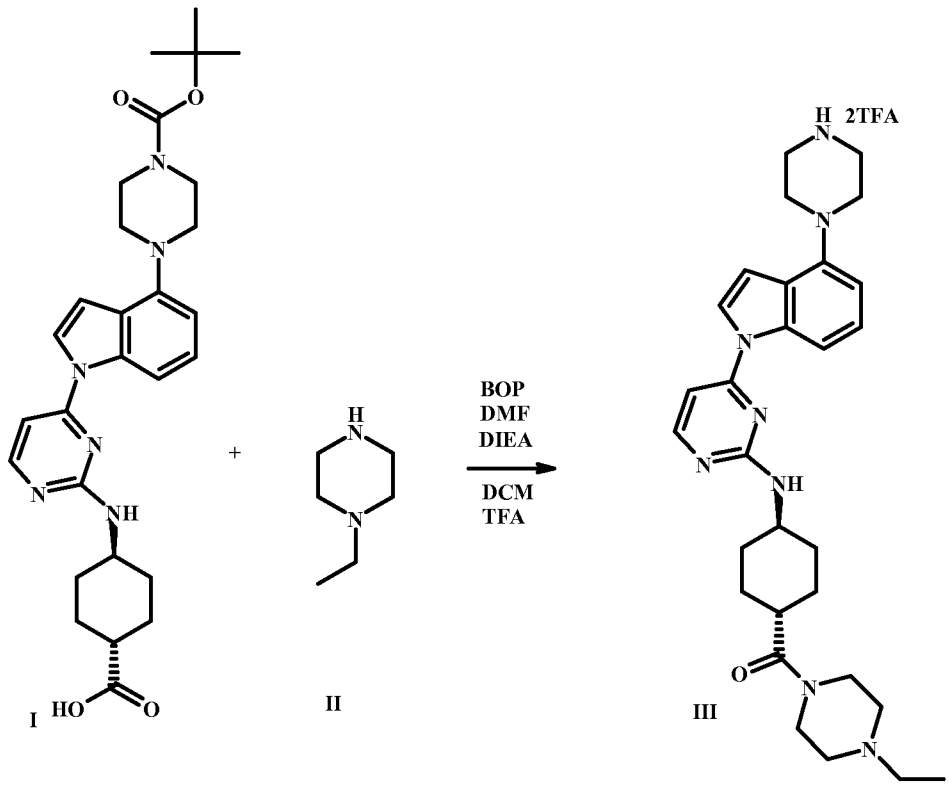
2.2g of **I** was treated with 1.15g of **II** in 100mL DCM and treated with 1.7mL TEA. The product of this reaction was then treated with 0.6g $Pd(OH)_2$ and H_2 at 50psi in 100mL EtOH to yield 1g of **III**.

Example 14.



0.4g of **I** was treated with 0.465g of **II** in 3mL NMP and stirred at 100 °C for 5 h, cooled to r.t. and diluted with water, the solid separated, filtered, and dried. The solid was then purified by silica gel column using 100% DCM to 5% MeOH/DCM. The fractions containing the product was then concentrated *in vacuo* overnight, the residue triturated with EtOAc, and the solid separated, filtered, and dried *in vacuo*. The solid, 028g, was then dissolved in 20mL THF and 5mL EtOH and 0.11g of $Li(OH)_2 \cdot H_2O$ was then added followed by the addition of 5mL water. The mixture was allowed to stir at r.t. overnight, then concentrated *in vacuo* then neutralized with HCl and the solid separated, filtered and dried *in vacuo* overnight at 50 °C to yield 0.244g **III**.

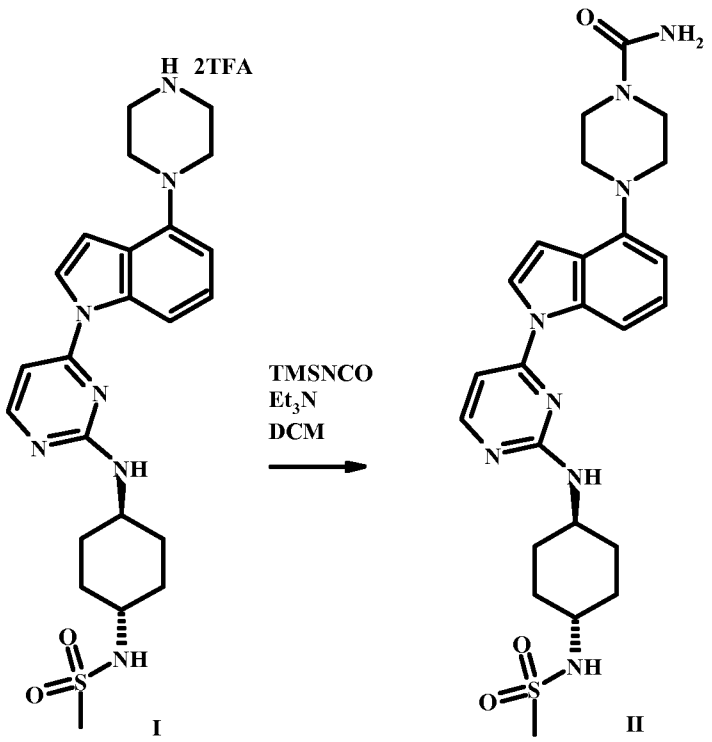
Example 15.



I II III

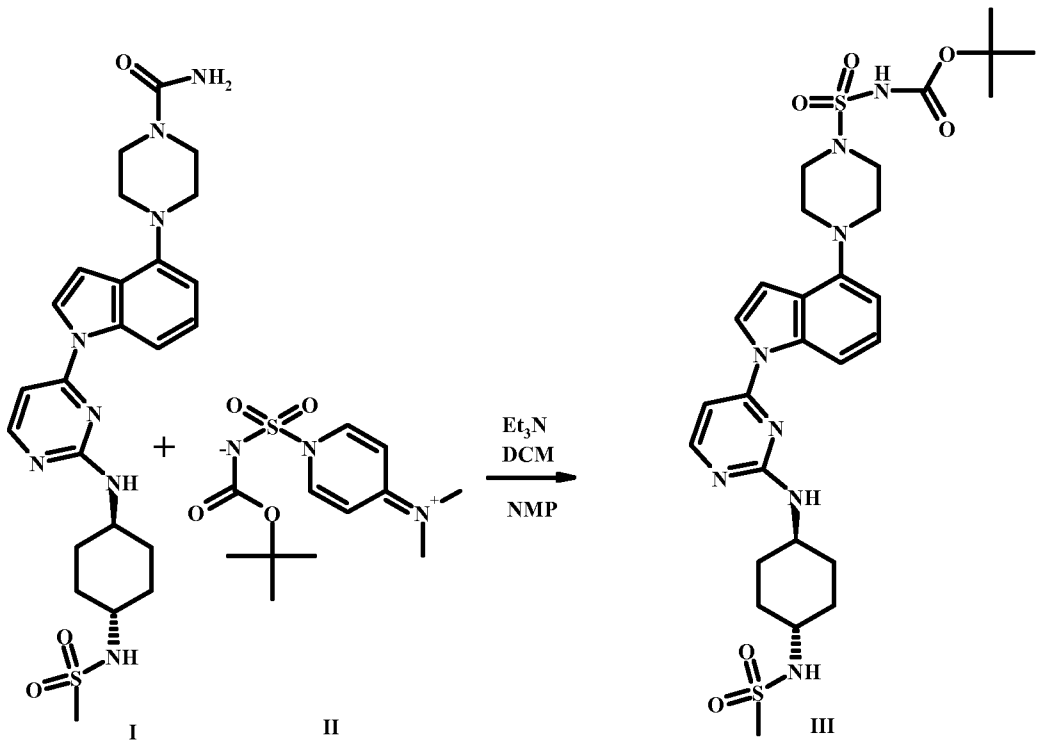
0.224g of **I** in 2mL DMF was treated with 0.311g of BOP, 0.33mL DIEA, anmd 80mg of **II** and allowed to stir at r.t. overnight, diluted with water, the solid separated, filtered, and then dried *in vacuo* and purified by silica gel column using 100% DCM to 20% MeOH/DCM and the fractions concentrated *in vacuo*. The product of this reaction, 0.28g, was then treated with 3mL TFA in 30mL DCM and allowed to stir at r.t. overnight and the solid separated, filtered, dried *in vacuo* to yield 0.4g **III**.

Example 16.



0.5g of **I** in 3mL DCM and 3mL NMP was treated with 0.27mL Et_3N and stirred for 10 min then cooled to 4 C and 0.10mL TMSNCO then added dropwise and the mixture allowed to warm to r.t. and stirred at r.t. for 18 h and an additional 0.05mL of TMSNCO added and the mixture allowed to reflux for 2 h and stir at r.t. for 18 h. The mixture was then concentrated *in vacuo*, water added to precipitate, the solid filtered and purified on a silica gel column using 0% to 5% MeOH/DCM and the fractions dried *in vacuo* to yield 0.053g (11%) of product **II**.

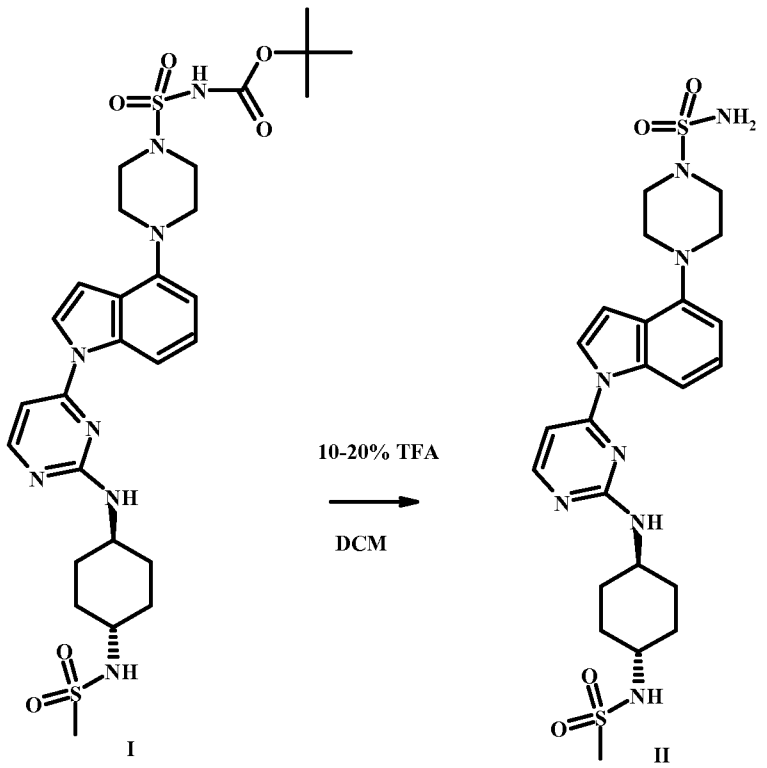
Example 17.



I II III

0.5g of **I** in 3mL DCM was treated with 0.27mL Et3N in 1-3mL NMP and stirred at r.t. for 10 min and 0.323g of **II** then added and the reaction allowed to stir at r.t. for 16 h. The reaction mixture was then diluted with 100mL EtOAc, washed with water, extracted with EtOAc, the organics combined and washed with water and brine (2x), and dried over Na_2SO_4, filtered, and the filtrate concentrated *in vacuo*, the solid triturated with DCM and pet. Ether, the solid filtered off, and dried in vacuo to yield 0.388g of **III**.

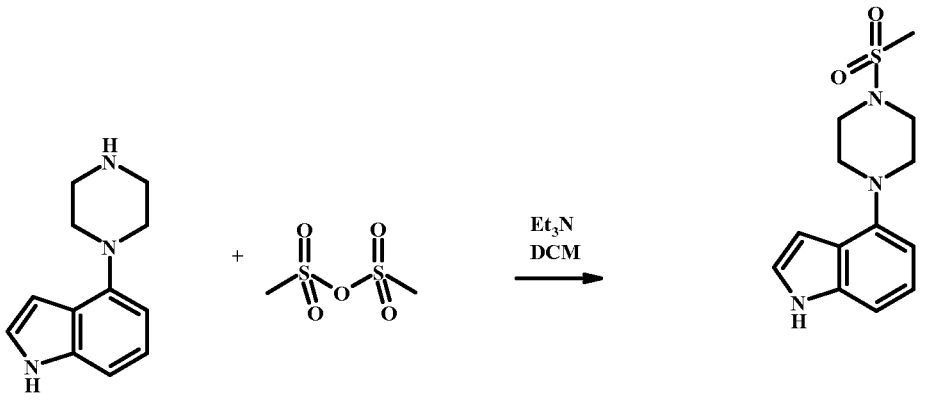
Example 18.



I II

0.388g of **I** in 20mL DCM was cooled to 4 °C and treated with 2mL TFA in 10mL DCM (20%) and the mixture was allowed to stir at r.t. for 24 h. The reaction mixture was then concentrated *in vacuo*, extracted with EtOAc, washed with sat'd $NaHCO_3$, the organics dried over Na_2SO_4, concentrated and purified on a silica gel column usin 0% to 10% MeOH/DCM, and the product triturated with EtOAc and dried *in vacuo* to yield 0.017g of **II**.

Example 19.

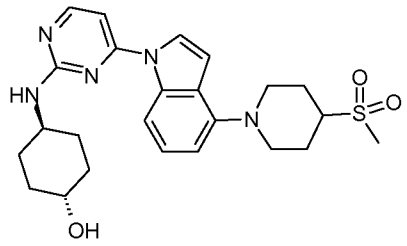


I II III

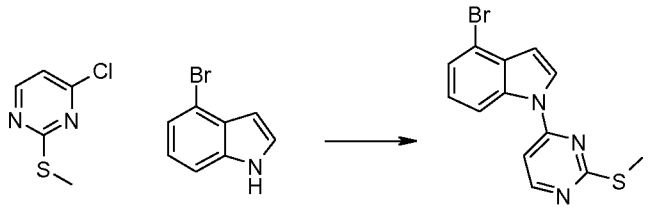
1.0mL of Et_3N and 0.667g of **II** were added to a suspension of **I** (1.00g) in 15mL DCM under N_2. The suspension was cooled on an ice bath to 4 °C and 0.53mL of Et_3N was added slowly

and the reaction allowed to reach r.t., water added, the mixture extracted with DCM and washed with water. The organic layer was dried with Na_2SO_4, concentrated in vacuo to yield the product **III** (0.950g, 95%)

Example 20: *Trans*-4-{4-[4-(4-Methanesulfonyl-piperidin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-cyclohexanol

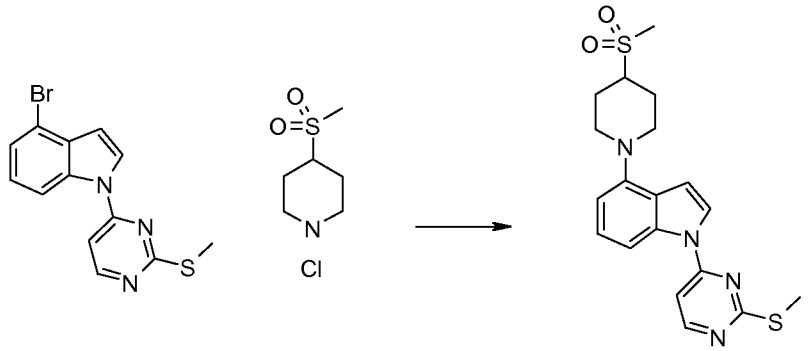


Step 1: Preparation of 4-bromo-1-(2-methylsulfanyl-pyrimidin-4-yl)-1H-indole



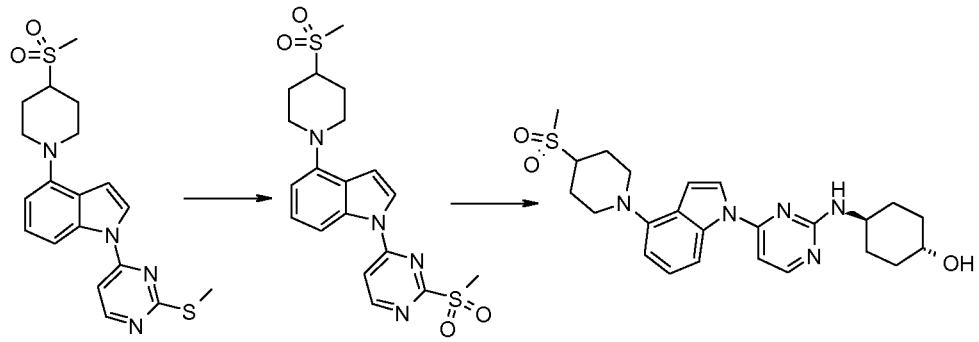
4-Bromoindole (20g, 102 mmol) was dissolved in 70 mL of NMP and the solution was stirred under ice bath. Sodium hydride (6g, 60% in mineral oil, 150 mmol) was added in small portions over 30 minutes. The mixture was stirred at room temperature for 40 minutes and then cooled under ice bath. A solution of 4-chloro-2-methylsulfanylpyridine (19.7g, 122 mmol) in 10 mL of NMP was added through a dropping funnel over 10 minutes. The mixture was stirred at room temperature overnight. Water (150 mL) was added with stirring. The solid material was filtered and washed with water, air dried. This material was suspended in hot ethyl acetate (200 mL) and dichloromethane (200 mL) was added to give a clear solution. Charcoal (5g) was added and the mixture was stirred for 10 minutes, filtered through Celite. The resulting solution was gently evaporated to remove dichloromethane until crystalline material appeared. The mixture was kept at room temperature for 2hrs and crystals were filtered, rinsed with cold ethyl acetate (90 mL), air dried, to give 4-bromo-1-(2-methylsulfanyl-pyrimidin-4-yl)-1H-indole as an off white solid (21.5g, 65%). LC-MS calcd for $C_{13}H_{10}BrN_3S$ (m/e) 318.98, obsd 320.0 (M+H).

Step 2: Preparation of 4-(4-methanesulfonyl-piperidin-1-yl)-1-(2-methylsulfanyl-pyrimidin-4-yl)-1*H*-indole



4-Methylsulfonyl-piperidine hydrochloride (6.89g, 34.5 mmol) was grinded into fine powder and mixed with fine powder of sodium tert-butoxide (7.65g, 79.6 mmol) in dry dioxane (180 mL). After 30 minutes of stirring, 4-bromo-1-(2-(methylthio)pyrimidin-4-yl)-1H-indole (8.5g, 26.5 mmol) was added followed by dry dioxane (10 mL) and the mixture was bubbled with argon for 10 minutes. Bis(tri-tert-butylphosphine)palladium (1.02g, 2.0 mmol) was added followed by dry dioxane (10 mL). The mixture was bubbled with argon for 5 minutes and then sealed. The sealed thick wall bottle was put into oil bath at 65 °C and heated to 120 °C. The mixture was stirred at 120 °C for 1.5 hr. The resulting mixture was cooled to 50°C and filtered through a thin layer of Celite, rinsed with dioxane (100 mL). The filtrate was concentrated and extracted with dichloromethane and saturated ammonium chloride solution. The organic layer was dried and concentrated to a volume about 25 mL. The mixture was treated with ethyl acetate (150 mL) and the yellow solid was filtered to give the desired compound (4.65g). The filtrate was concentrated and dissolved in dichloromethane and purified through ISCO flash column chromatography (200g silica gel, 20% to 100% ethyl acetate in hexanes) to give second batch of desired product as a yellow solid (1.67g, combined total 6.32g, yield 59.1%). LC-MS calcd for $C_{19}H_{22}N_4O_2S_2$ (m/e) 402.12, obsd 402.9 (M+H).

Step 3: Preparation of *trans*-4-{4-[4-(4-methanesulfonyl-piperidin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-cyclohexanol

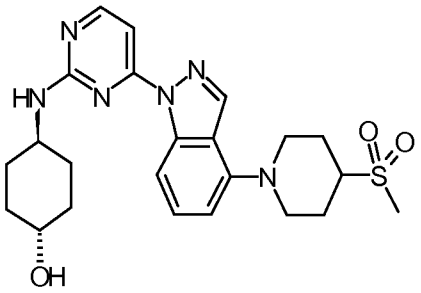


4-(4-(Methylsulfonyl)piperidin-1-yl)-1-(2-(methylthio)pyrimidin-4-yl)-1H-indole (8.02g, 19.9 mmol) was dissolved in 900 mL of dichloromethane. The solution was cooled under ice bath and MCPBA (15.1g, max purity 77%, 67 mmol) was added in small portions over 20 minutes with stirring. The mixture was stirred in ice bath for 1 hr and at room temperature for 2 hrs. Stirring bar was removed and the solution was cooled in ice bath. Polymer bound triphenylphosphine (32g, 3 mmol/g loading, about 96 mmol) was added and the mixture was put on an Orbital Shaker for 12 hrs. The mixture was filtered and rinsed with dichloromethane (400 mL). The filtrate was extracted with 0.2N sodium hydroxide solution (800 mL) and dichloromethane. The organic layer was washed with sodium chloride solution, dried over sodium sulfate and filtered. Solvents were evaporated to give a dark foam material (8.5g). This material was dissolved in dichloromethane (100 mL) and treated with charcoal (3g). The resulting mixture was filtered through Celite. The filtrate was treated with hot ethyl acetate (200 mL) and the mixture was gently evaporated to remove dichloromethane. The crystalline material was filtered to give a mixture of sulfone and sulfoxide (1:1 ratio, 4.30g, 49.7% yield). LC-MS for the sulfone calcd for $C_{19}H_{22}N_4O_4S_2$ (m/e) 434.11, obsd 434.9 (M+H); for the sulfoxide calcd for $C_{19}H_{22}N_4O_3S_2$ (m/e) 418.11, obsd 418.9 (M+H).

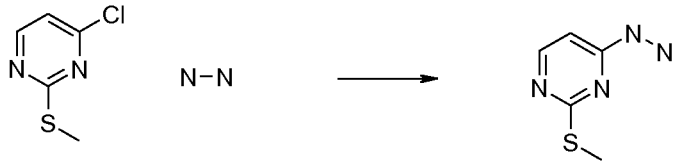
The mixed sulfone and sulfoxide from above (4.30g, 9.9 mmol) and *trans*-4-aminocyclohexanol (3.42g, 29.7 mmol) were suspended in 150 mL of dioxane in a sealed tube and stirred at 150 °C for 2 hrs. The mixture was cooled to 40 °C with stirring. The top clear solution was decanted and the dark tar was rinsed with dioxane (60 mL). The combined dioxane solution was evaporated and the residue was extracted with a mixture of ethyl acetate and THF and ammonium chloride solution. The organic layer was washed with concentrated ammonium chloride solution and dried over sodium sulfate. Solvents were evaporated and the residue was dissolved in methanol (200 mL). The clear solution was gently evaporated until crystalline material appeared (less than 20 mL methanol was evaporated). The

crystalline mixture was kept at room temperature for 2 hrs and then filtered, rinsed with methanol followed by ether, to give the desired off white crystalline solid as *trans*-4-{4-[4-(4-methanesulfonyl-piperidin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-cyclohexanol (3.27g, 70.4% yield).

Example 21: *Trans*-4-{4-[4-(4-Methanesulfonyl-piperidin-1-yl)-indazol-1-yl]-pyrimidin-2-ylamino}-cyclohexanol

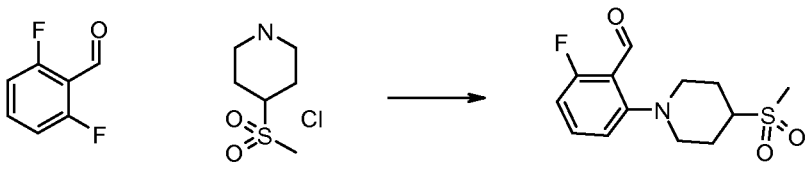


Step1: Preparation of N-(2-methylsulfanyl-pyrimidin-4-yl)-hydrazine



In a 250 mL round bottom flask, 4-chloro-2-methylsulfanyl-pyrimidine (5g, 31.1 mmol), hydrazine (4.5g, 140 mmol) and potassium carbonate (6.45g, 46.7 mmol) were combined with ethanol (50 mL). The mixture was refluxed for 3hrs and filtered. The filtered solid was rinsed with ethanol (30 mL). The combined ethanol solution was evaporated to give a crude oily mixture which was purified by ISCO flash column chromatography (30% to 100% ethyl acetate in hexanes) to give N-(2-methylsulfanyl-pyrimidin-4-yl)-hydrazine as a white solid (2.8g, 57.6% yield).

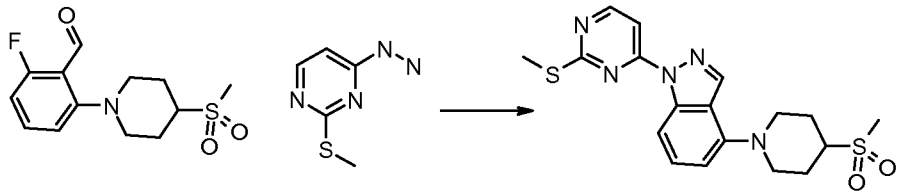
Step 2: Preparation of 2-fluoro-6-(4-methanesulfonylpiperidine-1-yl)benzaldehyde



In a 250 mL round bottom flask, 2,6-difluorobenzaldehyde (7.12g, 5.4 mL, 50.1 mmol), 4-methanesulfonylpiperidine hydrochloride (10g, 50.1 mmol) and DIPEA (7.77g, 60.1 mmol) were combined with acetonitrile (75 mL). The mixture was stirred and heated at 80 °C

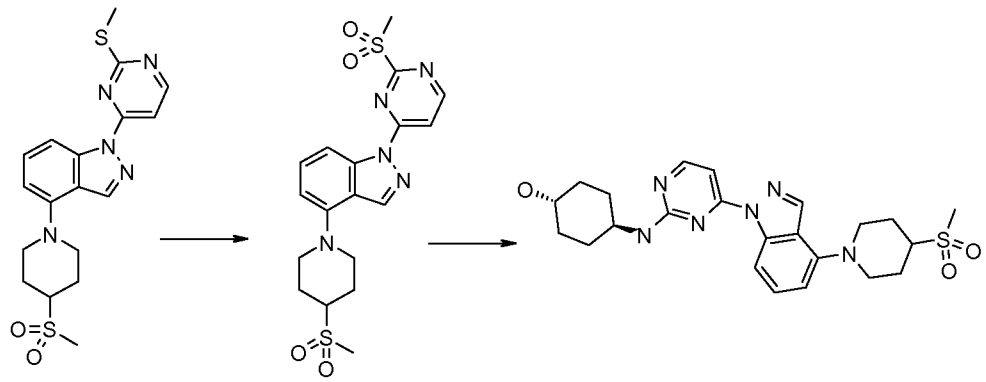
overnight. The mixture was evaporated and extracted with dichloromethane and citric acid solution. The organic layer was washed with brine, dried over sodium sulfate, and evaporated. The crude solid was triturated with cold ethyl acetate to afford 2-fluoro-6-(4-methanesulfonylpiperidine-1-yl)benzaldehyde (12g, 84% yield). LC-MS calcd for $C_{13}H_{16}FNO_3S$ (m/e) 285.08, obsd 286.0 (M+H).

Step 3: Preparation of 4-(4-methanesulfonyl-piperidin-1-yl)-1-(2-methylsulfanyl-pyrimidin-4-yl)-1H-indazole



In a 50 mL round bottom flask, 2-fluoro-6-(4-methanesulfonylpiperidine-1-yl)benzaldehyde (1.37g, 4.8 mmol), N-(2-methylsulfanyl-pyrimidin-4-yl)-hydrazine (0.75g, 4.8 mmol) and DBU (2.19g, 14.4 mmol) were combined with DMSO (17 mL). The mixture was stirred at 180 °C for 1.5 hr in a microwave. The brown solution was blown to dryness and the residue was purified through ISCO flash column chromatography (30% to 100% ethyl acetate in hexanes) to provide 4-(4-methanesulfonyl-piperidin-1-yl)-1-(2-methylsulfanyl-pyrimidin-4-yl)-1H-indazole as a pale orange solid (750mg, 38.7% yield). LC-MS calcd for $C_{18}H_{21}N_5O_2S_2$ (m/e) 403.11, obsd 404.0 (M+H).

Step 4: Preparation of *trans*-4-{4-[4-(4-methanesulfonyl-piperidin-1-yl)-indazol-1-yl]-pyrimidin-2-ylamino}-cyclohexanol



To a 250 mL round bottom flask was added 4-(4-methanesulfonyl-piperidin-1-yl)-1-(2-methylsulfanyl-pyrimidin-4-yl)-1H-indazole (1.1g, 2.72 mmol) in dichloromethane (75 mL).

The solution was stirred under ice bath and MCPBA (1.85g, 77% maximum, 8.25 mmol) was added in portions. The mixture was stirred under ice bath for 1 hr and then at room temperature for 1.5 hr. The resulting mixture was cooled under ice bath and polymer bound triphenylphosphine (5.0g, 3mmol/g loading) was added. The mixture was put on an Orbital Shaker for 12 hrs and then filtered, rinsed with dichloromethane (75 mL). The filtrate was extracted with 0.2N sodium hydroxide solution and dichloromethane. The organic layer was washed with sodium chloride solution, dried over sodium sulfate and filtered. Solvents were evaporated to give a yellow solid material (1.36g). LC-MS indicated 70% sulfone and 30% sulfoxide. LC-MS for the sulfoxide calcd for $C_{18}H_{21}N_5O_3S_2$ (m/e) 419.11, obsd 420.0 (M+H); LC-MS for the sulfone calcd for $C_{18}H_{21}N_5O_4S_2$ (m/e) 435.10, obsd 436.0 (M+H).

The above yellow solid compound (1.36g) was mixed with *trans*-4-aminocyclohexanol (950 mg, 8.25 mmol) in a sealed thick wall bottle containing dioxane (100 mL). The mixture was stirred in an oil bath heated to 120 °C. After 7 hrs of heating, the mixture was cooled down and extracted with a mixture of THF (20 mL), ethyl acetate (60 mL) and saturated ammonium chloride solution (50 mL). The aqueous phase was further extracted with ethyl acetate (100 mL). The combined organic layer was dried over sodium sulfate and filtered. Solvents were evaporated and the residue was purified through ISCO flash column chromatography (40g silica gel, 5% to 10% acetic acid in ethyl acetate) to provide *trans*-4-{4-[4-(4-methanesulfonyl-piperidin-1-yl)-indazol-1-yl]-pyrimidin-2-ylamino}-cyclohexanol as a pale yellow solid (490 mg, 38.2% yield, two steps). LC-MS calcd for $C_{23}H_{30}N_6O_3S$ (m/e) 470.21, obsd 471.0 (M+H).

Biological Assays

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, 20 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 30ºC 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. Representative results are shown in Table 1 below:

Table 1: Representative Compound IC_{50}'s for JNK1 and JNK2

Compound	JNK1 (μM)	JNK2 (μM)
I-1	0.2110	1.4296
I-2	0.0939	0.6544
I-3	0.0293	0.182
I-4	0.0429	0.2920
I-5	0.0103	0.1054
I-6	0.0030	0.0235
I-7	0.0191	0.0861
I-8	0.0140	0.0823
I-9	0.0054	0.0362
I-10	0.0104	0.0749
I-11	0.0100	0.0681
I-12	0.0031	0.0179
I-13	0.0066	0.0493
I-14	0.003	0.0192
I-15	0.0036	0.0208
I-16	0.0117	0.0660
I-17	0.0085	0.0477
I-18	0.0083	0.0332
I-19	0.0061	0.0328
I-20	0.0068	0.0401

I-21	0.0312	0.1376
I-22	0.0036	0.0264
I-23	0.3775	1.6251
I-24	0.0777	0.4770
I-25	0.0042	0.0256
I-25	0.0042	0.0256
I-26	0.0037	0.0246
I-27	0.0020	0.0128
I-31	0.0096	0.0548
I-32	0.0124	0.0856
I-37	0.0484	4.0260
I-38	0.0049	0.0428
I-41	0.0250	0.1638
I-42	0.0024	0.0136
I-44		0.0192
I-45		0.0334
I-46		0.0360
I-47		0.0296
I-48		0.0545
I-49		0.0598
I-50		0.0156
I-51	0.0036	0.0062
I-52		0.0218
I-53		0.0117
I-54		0.0152
I-55	0.0044	0.0231
I-56	0.0092	0.0187
I-57	0.0159	0.0884
I-58		0.8060
I-59		0.5702
I-60		0.1497
I-61		0.1054
I-62	0.0321	0.1452
I-63	0.0124	0.0257
I-66	0.0058	0.0167

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

Female Wistar-Han rats procured from Charles River Laboratories are allowed to acclimate for one week prior to use and achieve an approximate body weight of 101-130 g . Rats are administered test compound (N = 8 per compound) via oral gavage 30 min prior to an intraperitoneal challenge of 0.5 μg recombinant rat TNF-α (Biosource). Blood is collected via cardiocentesis 90 min after TNF-α challenge. Plasma is prepared using lithium heparin separation tubes (BD microtainer) and frozen at -80°C until analyzed. IL-6 levels are 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) are determined.

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

Female Wistar-Han rats procured from Charles River Laboratories are allowed to acclimate for one week prior to use and achieve an approximate body weight of 114-132 g . Rats are administered compound 18 (N = 8 per dose) subcutaneously 30 min prior to an intra-peritoneal challenge of 0.5 μg recombinant rat TNF-α (Biosource). Blood is collected via cardiocentesis 90 min after TNF-α challenge. Plasma is prepared using lithium heparin separation tubes (BD microtainer) and frozen at -80°C until analyzed. IL-6 levels are 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) are determined.

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.

2= swelling 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.

Rat Pharmacokinetic Study:

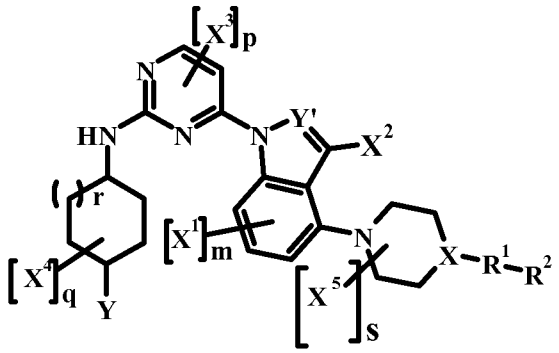
Female Wistar/Han (CRL: WI) Rats (Charles River, Hollister, CA) weighing between 180 and 220g are used. Animals are allowed free access to a standard laboratory chow and tap water and are housed in a constant temperature-humidity environment. Three rats per dose regime are administered either single 10 mg/kg IV bolus doses (50% cyclodextran/water) or single 10 mg/kg oral suspension doses prepared in aqueous vehicle containing 0.9% NaCl, 0.5% sodium carboxymethyl cellulose, 0.4% polysorbate 80 and 0.9% benzyl alcohol. Blood

is collected from each rat anesthetized with CO_2:O_2 (60:40) via the orbital sinus or cardiac puncture at 1, 3, 6, 8, and 24 h after dosing. Plasma levels of test compounds are assayed by a LC/MS method. In this method, an aliquot of plasma is treated by mixing with acetonitrile to precipitate protein, centrifuged to clarify the supernatant, then further diluted with formate buffer (50mM), and injected onto an HPLC. Test compounds are separated from endogenous interfering substances and subsequently eluted from the HPLC column for mass spectrometric quantification.

While the present invention has been described with reference to the specific embodiments thereof, it should be understood by those skilled in the art that various changes may be made and equivalents may be substituted without departing from the true spirit and scope of the invention. In addition, many modifications may be made to adapt a particular situation, material, composition of matter, process, process step or steps, to the objective spirit and scope of the present invention. All such modifications are intended to be within the scope of the claims appended hereto.

Claims:

1. A compound of formula **I**



I

or a pharmaceutically acceptable salt thereof,

wherein:

Y' is CH or N;

X is CH or N;

each X^1 is independently halogen, lower alkyl, lower alkoxy, lower haloalkyl, or hydroxy;

m is 0, 1, or 2;

X^2 is H, lower alkyl, lower alkoxy, amido, lower haloalkyl, or lower haloalkoxy;

X^3 is lower alkyl, lower alkoxy, or lower haloalkyl;

p is 0 or 1;

each X^4 is independently lower alkyl, lower alkoxy, lower haloalkyl, hydroxy, lower hydroxylalkyl, $OC(=O)Z^2$, or halogen;

q is 0, 1, or 2;

X^5 is lower alkyl;

s is 0, 1 or2;

r is 0 or 1;

Y is H, OH, $C(=O)Z^2$, $C(=O)OZ^2$, OZ^2, $OC(=O)Z^2$, $N(Z^1)C(=O)(Z^2)$, $C(Z^1)_2S(O)_2Z^2$, $N(Z^1)S(O)_2Z^2$, $N(Z^1)S(O)_2N(Z^1)(Z^2)$, $C(Z^1)_2(Z^2)$, or $(C=O)N(Z^1)(Z^2)$;

Z^1 is H or $Z^{1'}$;

$Z^{1'}$ is lower alkyl, optionally substituted with one or more $Z^{1''}$;

each $Z^{1''}$ is independently halogen, hydroxy, lower haloalkyl, dialkylamino or amino;

Z^2 is H or $Z^{2'}$;

$Z^{2'}$ is hydroxy, lower alkyl, lower alkoxy, lower hydroxyalkyl, lower haloalkyl, cycloalkyl, cycloalkyl lower alkyl, heterocycloalkyl, heterocycloalkyl lower alkyl, optionally substituted with one or more $Z^{2''}$;

each $Z^{2''}$ is independently halogen, hydroxy, lower alkyl, cycloalkyl, cyano, lower haloalkyl, amino, carboxylic acid, ester, or lower alkoxy;

R^1 is a bond, C(=O), C(=O)O, $C(=O)CH_2OC(=O)$, $C(=O)CH_2NHC(=O)O$, or $S(=O)_2$;

R^2 is H or $R^{2'}$;

$R^{2'}$ is hydroxy, lower alkyl, $N(R^3)_2$, lower hydroxyalkyl, or lower haloalkyl, optionally substituted with one or more $R^{2''}$;

each $R^{2''}$ is independently cyano, amino, dialkylamino, hydroxy, lower hydroxyalkyl, or lower alkoxy; and

each R^3 is independently H, lower alkyl, lower cycloalkyl, phenyl, lower heterocycloalkyl, or both R^3 together form a heterocyclic ring;

with the proviso that when X is N, X^2 is H, Y' is CH, R^1 is C(=O), R^2 is methyl, r is 1, m is 0, p is 0, q is 0, Y is $N(Z^1)S(O)_2Z^2$, and Z^2 is methyl, then Z^1 is not H or hydroxyethyl.

2. The compound according to claim 1

wherein:

Y' is CH or N;

X is CH or N;

each X^1 is independently halogen, lower alkyl, lower alkoxy, lower haloalkyl, or hydroxy;

m is 0, 1, or 2;

X^2 is H, lower alkyl, lower alkoxy, amido, lower haloalkyl, or lower haloalkoxy;

X^3 is lower alkyl, lower alkoxy, or lower haloalkyl;

p is 0 or 1;

each X^4 is independently lower alkyl, lower alkoxy, lower haloalkyl, hydroxy, lower hydroxylalkyl, $OC(=O)Z^2$, or halogen;

q is 0, 1, or 2;

s is 0;

r is 0 or 1;

Y is H, OH, $C(=O)Z^2$, $C(=O)OZ^2$, OZ^2, $OC(=O)Z^2$, $N(Z^1)C(=O)(Z^2)$, $C(Z^1)_2S(O)_2Z^2$, $N(Z^1)S(O)_2Z^2$, $N(Z^1)S(O)_2N(Z^1)(Z^2)$, $C(Z^1)_2(Z^2)$, or $(C=O)N(Z^1)(Z^2)$;

Z^1 is H or $Z^{1'}$;

$Z^{1'}$ is lower alkyl, optionally substituted with one or more $Z^{1''}$;

each $Z^{1''}$ is independently halogen, hydroxy, lower haloalkyl, or amino;

Z^2 is H or $Z^{2'}$;

$Z^{2'}$ is lower alkyl, lower alkoxy, lower hydroxyalkyl, lower haloalkyl, cycloalkyl, cycloalkyl lower alkyl, heterocycloalkyl, heterocycloalkyl lower alkyl, optionally substituted with one or more $Z^{2''}$;

each $Z^{2''}$ is independently halogen, hydroxy, lower alkyl, cyano, lower haloalkyl, amino, carboxylic acid, ester, or lower alkoxy;

R^1 is C(=O), C(=O)O, $C(=O)CH_2OC(=O)$, $C(=O)CH_2NHC(=O)O$, or $S(=O)_2$;

R^2 is H or $R^{2'}$;

$R^{2'}$ is lower alkyl, $N(R^3)_2$, lower hydroxyalkyl, or lower haloalkyl, optionally substituted with one or more $R^{2''}$;

each $R^{2''}$ is independently cyano, amino, hydroxy, lower hydroxyalkyl, or lower alkoxy; and

each R^3 is independently H, lower alkyl, lower cycloalkyl, phenyl, lower heterocycloalkyl, or both R^3 together form a heterocyclic ring;

with the proviso that when X is N, X^2 is H, Y' is CH, R^1 is C(=O), R^2 is methyl, r is 1, m is 0, p is 0, q is 0, Y is $N(Z^1)S(O)_2Z^2$, and Z^2 is methyl, then Z^1 is not H or hydroxyethyl.

3. The compound according to either claim 1 or 2 wherein:

Y' is CH or N;

X is CH or N;

m is 0;

X^2 is H or amido;

p is 0

each X^4 is independently lower alkyl, hydroxy, $OC(=O)Z^2$;

q is 0 or 1;

s is 0 ;

r is 0 or 1;

Y is H, OH, $C(=O)Z^2$, $C(=O)OZ^2$, OZ^2, $N(Z^1)C(=O)(Z^2)$, $C(Z^1)_2S(O)_2Z^2$, $N(Z^1)S(O)_2Z^2$, $N(Z^1)S(O)_2N(Z^1)(Z^2)$, $C(Z^1)_2(Z^2)$, or $(C=O)N(Z^1)(Z^2)$;

Z^1 is H or $Z^{1'}$;

$Z^{1'}$ is lower alkyl, optionally substituted with one or more $Z^{1''}$;

each $Z^{1''}$ is dialkylamino;

Z^2 is H or $Z^{2'}$;

$Z^{2'}$ is hydroxy, lower alkyl or heterocycloalkyl, optionally substituted with one or more $Z^{2''}$;

each $Z^{2''}$ is independently hydroxy, lower alkyl, cycloalkyl, cyano, or lower alkoxy;

R^1 is a bond, C(=O), $C(=O)CH_2OC(=O)$, $C(=O)CH_2NHC(=O)O$, or $S(=O)_2$;

R^2 is H or $R^{2'}$;

$R^{2'}$ is hydroxy, lower alkyl, $N(R^3)_2$, lower hydroxyalkyl, optionally substituted with one or more $R^{2''}$;

each $R^{2''}$ is independently cyano, amino or dialkylamino; and

each R^3 is H ;

with the proviso that when X is N, X^2 is H, Y' is CH, R^1 is C(=O), R^2 is methyl, r is 1, m is 0, p is 0, q is 0, Y is $N(Z^1)S(O)_2Z^2$, and Z^2 is methyl, then Z^1 is not H.

4. The compound according to any one of claims 1 to 3, wherein m is 0, X^2 is H, p is 0, q is 0, r is 0, X is N, Y' is CH, R^1 is C(=O), R^2 is $R^{2'}$, $R^{2'}$ is methylene, and $R^{2''}$ is cyano.

5. The compound according to any one of claims 1 to 4, wherein m is 0, p is 0, q is 0, r is 1, X is N, Y' is CH, R^1 is C(=O), R^2 is $R^{2'}$, $R^{2'}$ is methylene, and $R^{2''}$ is cyano.

6. The compound according to any one of claims 1 to 5, wherein m is 0, X^2 is H, p is 0, q is 0, r is 1, X is N, Y' is CH, R^1 is C(=O), R^2 is $R^{2'}$, and $R^{2'}$ is methyl.

7. The compound according to any one of claims 1 to 6, wherein m is 0, p is 0, q is 0, r is 1, X is CH, Y' is CH, R^1 is $S(=O)_2$, R^2 is $R^{2'}$, and $R^{2'}$ is methyl.

8. The compound according to any one of claims 1 to 7, wherein R^1 is C(=O), R^2 is $R^{2'}$, $R^{2'}$ is methylene, and $R^{2''}$ is cyano.

9. The compound according to any one of claims1 to 8, wherein R^1 is $S(=O)_2$, R^2 is $R^{2'}$, and $R^{2'}$ is methyl.

10. The compound according to any one of claims 1 to 3, wherein Y' is N.

11. The compound according to any one of claims 1 to 3, m is 0, X^2 is H, p is 0, q is 0, r is 1, X is CH, Y' is N, R^1 is $S(=O)_2$, R^2 is $R^{2'}$, and $R^{2'}$ is methyl.

12. The compound according to any one of claims 1 to 11, wherein s is 0.

13. A compound selected from the group consisting of:

N-{4-[4-(4-Piperazin-1-yl-indol-1-yl)-pyrimidin-2-ylamino]-cyclohexyl}-methanesulfonamide;

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

N-(4-{4-[4-(4-Methanesulfonyl-piperazin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-cyclohexyl)-methanesulfonamide;

N-(4-{4-[4-(4-Hydroxy-piperidin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-cyclohexyl)-methanesulfonamide;

N-(4-{4-[4-(4-Acetyl-piperazin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-cyclohexyl)-*N*-methyl-methanesulfonamide;

N-(4-{4-[4-(4-Methanesulfonyl-piperidin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-cyclohexyl)-methanesulfonamide;

4-{1-[2-(4-Methanesulfonylamino-cyclohexylamino)-pyrimidin-4-yl]-1*H*-indol-4-yl}-piperazine-1-carboxylic acid amide;

4-{1-[2-(4-Methanesulfonylamino-cyclohexylamino)-pyrimidin-4-yl]-1*H*-indol-4-yl}-piperazine-1-sulfonic acid amide;

N-[4-(4-{4-[4-(2-Cyano-acetyl)-piperazin-1-yl]-indol-1-yl}-pyrimidin-2-ylamino)-cyclohexyl]-methanesulfonamide;

Acetic acid 2-(4-{1-[2-(4-methanesulfonylamino-cyclohexylamino)-pyrimidin-4-yl]-1*H*-indol-4-yl}-piperazin-1-yl)-2-oxo-ethyl ester;

N-[4-(4-{4-[4-(2-Hydroxy-acetyl)-piperazin-1-yl]-indol-1-yl}-pyrimidin-2-ylamino)-cyclohexyl]-methanesulfonamide;

4-{4-[4-(4-Methanesulfonyl-piperidin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-cyclohexanol;

N-(4-{4-[4-(4-Methanesulfonyl-piperidin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-cyclohexyl)-acetamide;

2-(4-{4-[4-(4-Methanesulfonyl-piperidin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-cyclohexyl)-propan-2-ol;

[4-{4-[4-(4-Methanesulfonyl-piperidin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-cyclohexyl] aminodimethylsulfonamide;

4-{4-[4-(4-Methanesulfonyl-piperidin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-1-methyl-cyclohexanol;

4-{4-[4-(4-Methanesulfonyl-piperidin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-1-methyl-cyclohexanol;

(4-Hydroxy-piperidin-1-yl)-(4-{4-[4-(4-methanesulfonyl-piperidin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-cyclohexyl)-methanone;

4-{4-[4-(4-Methanesulfonyl-piperidin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-cyclohexanecarboxylic acid ethylamide;

4-{4-[4-(4-Methanesulfonyl-piperidin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-cyclohexanecarboxylic acid ethyl ester;

1-[(R)-4-(1-{2-[4-(4-Hydroxy-piperidine-1-carbonyl)-cyclohexylamino]-pyrimidin-4-yl}-1*H*-indol-4-yl)-3-methyl-piperazin-1-yl]-ethanone;

[2-(4-{1-[2-(4-Methanesulfonylamino-cyclohexylamino)-pyrimidin-4-yl]-1*H*-indol-4-yl}-piperazin-1-yl)-2-oxo-ethyl]-carbamic acid *tert*-butyl ester;

N-[4-(4-{4-[4-(2-Dimethylamino-acetyl)-piperazin-1-yl]-indol-1-yl}-pyrimidin-2-ylamino)-cyclohexyl]-methanesulfonamide;

N-[4-(4-{4-[4-(2-Amino-acetyl)-piperazin-1-yl]-indol-1-yl}-pyrimidin-2-ylamino)-cyclohexyl]-methanesulfonamide;

3-[4-(1-{2-[4-((R)-3-Hydroxy-pyrrolidin-1-ylmethyl)-cyclohexylamino]-pyrimidin-4-yl}-1*H*-indol-4-yl)-piperazin-1-yl]-3-oxo-propionitrile;

N-[4-(4-{4-[4-(2-Cyano-acetyl)-piperazin-1-yl]-indol-1-yl}-pyrimidin-2-ylamino)-cyclohexyl]-*N*-(2-dimethylamino-ethyl)-methanesulfonamide;

3-(4-{1-[2-(4-Hydroxymethyl-cyclohexylamino)-pyrimidin-4-yl]-1*H*-indol-4-yl}-piperazin-1-yl)-3-oxo-propionitrile;

3-[4-(1-{2-[4-((S)-3-Hydroxy-pyrrolidin-1-ylmethyl)-cyclohexylamino]-pyrimidin-4-yl}-1*H*-indol-4-yl)-piperazin-1-yl]-3-oxo-propionitrile;

1-[4-(1-{2-[4-((R)-3-Hydroxy-pyrrolidin-1-ylmethyl)-cyclohexylamino]-pyrimidin-4-yl}-1*H*-indol-4-yl)-piperazin-1-yl]-ethanone;

(4-Ethoxy-piperidin-1-yl)-(4-{4-[4-(4-methanesulfonyl-piperidin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-cyclohexyl)-methanone;

((R)-3-Ethoxy-pyrrolidin-1-yl)-(4-{4-[4-(4-methanesulfonyl-piperidin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-cyclohexyl)-methanone;

((S)-3-Ethoxy-pyrrolidin-1-yl)-(4-{4-[4-(4-methanesulfonyl-piperidin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-cyclohexyl)-methanone;

Cyano-acetic acid (1R,3S)-3-(4-{4-[4-(2-cyano-acetyl)-piperazin-1-yl]-indol-1-yl}-pyrimidin-2-ylamino)-cyclohexyl ester;

3-(4-{1-[2-((1S,3S)-3-Hydroxy-cyclohexylamino)-pyrimidin-4-yl]-1*H*-indol-4-yl}-piperazin-1-yl)-3-oxo-propionitrile;

3-(4-{1-[2-((1S,3R)-3-Hydroxy-cyclohexylamino)-pyrimidin-4-yl]-1*H*-indol-4-yl}-piperazin-1-yl)-3-oxo-propionitrile;

Cyano-acetic acid (1S,3S)-3-(4-{4-[4-(2-cyano-acetyl)-piperazin-1-yl]-indol-1-yl}-pyrimidin-2-ylamino)-cyclohexyl ester;

1-{4-[1-(2-Cyclohexylamino-pyrimidin-4-yl)-1*H*-indol-4-yl]-piperazin-1-yl}-ethanone;

3-{4-[1-(2-Cyclohexylamino-pyrimidin-4-yl)-1*H*-indol-4-yl]-piperazin-1-yl}-3-oxo-propionitrile;

1-[4-(1-{2-[4-(2-Methoxy-ethoxy)-cyclohexylamino]-pyrimidin-4-yl}-1*H*-indol-4-yl)-piperazin-1-yl]-ethanone;

3-[4-(1-{2-[4-(2-Methoxy-ethoxy)-cyclohexylamino]-pyrimidin-4-yl}-1*H*-indol-4-yl)-piperazin-1-yl]-3-oxo-propionitrile;

1-(4-{1-[2-(4-Methanesulfonylmethyl-cyclohexylamino)-pyrimidin-4-yl]-1*H*-indol-4-yl}-piperazin-1-yl)-ethanone;

3-(4-{1-[2-(4-Methanesulfonylmethyl-cyclohexylamino)-pyrimidin-4-yl]-1*H*-indol-4-yl}-piperazin-1-yl)-3-oxo-propionitrile;

1-[4-(1-{2-[4-(1-Hydroxy-1-methyl-ethyl)-cyclohexylamino]-pyrimidin-4-yl}-1*H*-indol-4-yl)-piperazin-1-yl]-ethanone;

N-[4-(4-{4-[4-(2-Cyano-acetyl)-piperazin-1-yl]-indol-1-yl}-pyrimidin-2-ylamino)-cyclohexyl]-*N*-(2-hydroxy-ethyl)-methanesulfonamide;

3-[4-(1-{2-[4-(1-Hydroxy-1-methyl-ethyl)-cyclohexylamino]-pyrimidin-4-yl}-1*H*-indol-4-

yl)-piperazin-1-yl]-3-oxo-propionitrile;

(4-Ethyl-piperazin-1-yl)-(4-{4-[4-(4-methanesulfonyl-piperidin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-cyclohexyl)-methanone;

(4-Cyclopropyl-piperazin-1-yl)-(4-{4-[4-(4-methanesulfonyl-piperidin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-cyclohexyl)-methanone;

(4-*tert*-Butyl-piperazin-1-yl)-(4-{4-[4-(4-methanesulfonyl-piperidin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-cyclohexyl)-methanone;

(4-Cyclobutyl-piperazin-1-yl)-(4-{4-[4-(4-methanesulfonyl-piperidin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-cyclohexyl)-methanone;

(4-{4-[4-(4-Methanesulfonyl-piperidin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-cyclohexyl)-(octahydro-pyrido[1,2-*a*]pyrazin-2-yl)-methanone;

(4-{4-[4-(4-Methanesulfonyl-piperidin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-cyclohexyl)-(3-trifluoromethyl-5,6-dihydro-8*H*-[1,2,4]triazolo[4,3-*a*]pyrazin-7-yl)-methanone;

(Hexahydro-pyrrolo[1,2-*a*]pyrazin-2-yl)-(4-{4-[4-(4-methanesulfonyl-piperidin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-cyclohexyl)-methanone;

(5,6-Dihydro-8*H*-[1,2,4]triazolo[4,3-*a*]pyrazin-7-yl)-(4-{4-[4-(4-methanesulfonyl-piperidin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-cyclohexyl)-methanone;

(5,6-Dihydro-8*H*-imidazo[1,2-*a*]pyrazin-7-yl)-(4-{4-[4-(4-methanesulfonyl-piperidin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-cyclohexyl)-methanone;

3-(4-{1-[2-(4-Hydroxy-cyclohexylamino)-pyrimidin-4-yl]-1*H*-indol-4-yl}-piperazin-1-yl)-3-oxo-propionitrile;

3-[4-(1-{2-[4-(4-Ethyl-piperazine-1-carbonyl)-cyclohexylamino]-pyrimidin-4-yl}-1*H*-indol-4-yl)-piperazin-1-yl]-3-oxo-propionitrile;

3-(4-{1-[2-(4-Hydroxy-cyclohexylamino)-pyrimidin-4-yl]-1*H*-indol-4-yl}-piperazin-1-yl)-3-oxo-propionitrile;

3-(4-{1-[2-((1S,3R)-3-Hydroxy-cyclopentylamino)-pyrimidin-4-yl]-1*H*-indol-4-yl}-piperazin-1-yl)-3-oxo-propionitrile;

3-(4-{1-[2-((1R,3S)-3-Hydroxy-cyclopentylamino)-pyrimidin-4-yl]-1*H*-indol-4-yl}-piperazin-1-yl)-3-oxo-propionitrile;

3-(4-{1-[2-((1S,3S)-3-Hydroxy-cyclopentylamino)-pyrimidin-4-yl]-1*H*-indol-4-yl}-piperazin-1-yl)-3-oxo-propionitrile;

3-(4-{1-[2-((1R,3R)-3-Hydroxy-cyclopentylamino)-pyrimidin-4-yl]-1*H*-indol-4-yl}-piperazin-1-yl)-3-oxo-propionitrile;

4-{4-[4-(4-Methanesulfonyl-piperidin-1-yl)-indol-1-yl]-pyrimidin-2-ylamino}-cyclohexanol;

4-(4-Acetyl-piperazin-1-yl)-1-[2-(4-hydroxy-cyclohexylamino)-pyrimidin-4-yl]-1*H*-indole-3-carboxylic acid amide;

4-(4-Acetyl-piperazin-1-yl)-1-[2-(4-methanesulfonylmethyl-cyclohexylamino)-pyrimidin-4-yl]-1*H*-indole-3-carboxylic acid amide;

4-{4-[4-(4-Methanesulfonyl-piperidin-1-yl)-indazol-1-yl]-pyrimidin-2-ylamino}-cyclohexanecarboxylic acid ethyl ester; and

4-{4-[4-(4-Methanesulfonyl-piperidin-1-yl)-indazol-1-yl]-pyrimidin-2-ylamino}-cyclohexanol.

14. A method of treating a JNK-mediated disorder in a subject having a JNK-mediated disorder, said method comprising administering to a subject in need thereof a therapeutically effective amount of the compound of any one of claims 1-13.

15. The method of claim 14, wherein the JNK-mediated disorder is characterized by cellular proliferation.

16. The method of claim 14, wherein the JNK-mediated disorder is arthritis.

17. The method of claim 14, wherein the arthritis is rheumatoid arthritis.

18. The method of claim 14, wherein the JNK-mediated disorder is asthma.

19. The method of claim 14, wherein the JNK-mediated disorder is diabetes.

20. The method of claim 14, wherein the JNK-mediated disorder is Alzheimer's disease.

21. The method of claim 14, wherein the JNK-mediated disorder is Parkinson's disease.

22. The method of claim 14, wherein the JNK-mediated disorder is ischemic stroke.

23. The method of claim 14, wherein the JNK-mediated disorder is cancer.

24. The method of claim 14, wherein the cancer is brain cancer.

25. The method of claim 14, wherein the cancer is leukemia.

26. The method of claim 14, wherein the JNK-mediated disorder is kidney disease.

27. A pharmaceutical composition comprising the compound of any one of claims 1-13, admixed with at least one pharmaceutically acceptable carrier, excipient or diluent.

28. A method for treating arthritis comprising co-administering to a patient in need thereof a therapeutically effective amount of an anti-inflammatory compound in combination with the compound of any one of claims 1-13.

29. Use of the compound of any one of claims 1 to 13 in the manufacture of a medicament for the treatment of an inflammatory disorder.

30. Compound according to any one of the claims 1 to 13 for use in the treatment of an inflammatory disorder.

31. The invention as described herein above.

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