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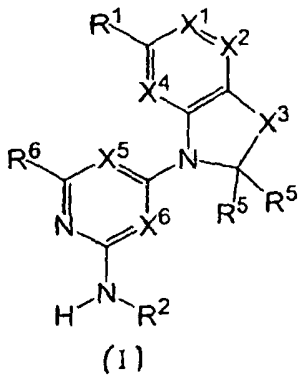
(54) Title: SUBSTITUTED HETEROCYCLIC COMPOUNDS AND METHODS OF USE



(I)

(57) Abstract: The present invention relates to nitrogen-containing compounds according to formula (I) and pharmaceutically acceptable salts thereof. Also included is a method of treatment of inflammation, rheumatoid arthritis, Pagets disease, osteoporosis, multiple myeloma, uveitis, acute or chronic myelogenous leukemia, pancreatic ß cell destruction, osteoarthritis, rheumatoid spondylitis, gouty arthritis, inflammatory bowel disease, adult respiratory distress syndrome (ARDS), psoriasis, Crohn's disease, allergic rhinitis, ulcerative colitis, anaphylaxis, contact dermatitis, asthma, muscle degeneration, cachexia, Reiter's syndrome, type I diabetes, type II diabetes, bone resorption diseases, graft vs. host reaction, Alzheimer's disease, stroke, myocardial infarction, ischemia reperfusion injury, atherosclerosis, brain trauma, multiple sclerosis, cerebral malaria, sepsis, septic shock, toxic shock syndrome, fever, myalgias due to HIV-1, HIV-2, HIV-3, cytomegalovirus (CMV), influenza, adenovirus, the herpes viruses or herpes zoster infection in a mammal comprising administering an effective amount a compound as described above.

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SUBSTITUTED HETEROCYCLIC COMPOUNDS AND METHODS OF USE

BACKGROUND OF THE INVENTION

The present invention comprises a new class of compounds useful in treating diseases, such as TNF-α, IL-1β, IL-6 and/or IL-8 mediated diseases and other maladies, such as pain and diabetes. In particular, the compounds of the invention are useful for the prophylaxis and treatment of diseases or conditions involving inflammation. This invention also relates to intermediates and processes useful in the preparation of such compounds.

Interleukin-1 (IL-1) and Tumor Necrosis Factor α (TNF-α) are pro-inflammatory cytokines secreted by a variety of cells, including monocytes and macrophages, in response to many inflammatory stimuli (*e.g.*, lipopolysaccharide - LPS) or external cellular stress (*e.g.*, osmotic shock and peroxide).

Elevated levels of TNF-α and/or IL-1 over basal levels have been implicated in mediating or exacerbating a number of disease states including rheumatoid arthritis; Pagets disease; osteoporosis; multiple myeloma; uveititis; acute and chronic myelogenous leukemia; pancreatic β cell destruction; osteoarthritis; rheumatoid spondylitis; gouty arthritis; inflammatory bowel disease; adult respiratory distress syndrome (ARDS); psoriasis; Crohn's disease; allergic rhinitis; ulcerative colitis; anaphylaxis; contact dermatitis; asthma; muscle degeneration; cachexia; Reiter's syndrome; type I and type II diabetes; bone resorption diseases; graft vs. host reaction; ischemia reperfusion injury; atherosclerosis; brain trauma; multiple sclerosis; cerebral malaria; sepsis; septic shock; toxic shock syndrome; fever, and myalgias due to infection. HIV-1, HIV-2, HIV-3, cytomegalovirus (CMV), influenza, adenovirus, the herpes viruses (including HSV-1, HSV-2), and herpes zoster are also exacerbated by TNF-α.

It has been reported that TNF-α plays a role in head trauma, stroke, and ischemia. For instance, in animal models of head trauma (rat), TNF-α levels increased in the contused hemisphere (Shohami et al., J. Cereb. Blood Flow Metab., 14:615 (1994)). In a rat model of ischemia wherein the middle cerebral artery was occluded, the levels of TNF-α mRNA of TNF-α increased (Feurstein et al., Neurosci. Lett., 164:125 (1993)). Administration of TNF-α into the rat cortex has been reported to result in significant neutrophil accumulation in capillaries and adherence in small blood vessels. TNF-α

promotes the infiltration of other cytokines (IL-1β, IL-6) and also chemokines, which promote neutrophil infiltration into the infarct area (Feurstein, Stroke 25:1481 (1994)). TNF-α has also been implicated to play a role in type II diabetes (Endocrinol., 130:43-52, 1994; and Endocrinol., 136:1474-1481, 1995).

TNF-α appears to play a role in promoting certain viral life cycles and disease states associated with them. For instance, TNF-α secreted by monocytes induced elevated levels of HIV expression in a chronically infected T cell clone (Clouse et al., J. Immunol., 142:431 (1989)). Lahdevirta et al., (Am. J. Med., 85:289 (1988)) discussed the role of TNF-α in the HIV associated states of cachexia and muscle degradation.

TNF-α is upstream in the cytokine cascade of inflammation. As a result, elevated levels of TNF-α may lead to elevated levels of other inflammatory and proinflammatory cytokines, such as IL-1, IL-6, and IL-8.

Elevated levels of IL-1 over basal levels have been implicated in mediating or exacerbating a number of disease states including rheumatoid arthritis; osteoarthritis; rheumatoid spondylitis; gouty arthritis; inflammatory bowel disease; adult respiratory distress syndrome (ARDS); psoriasis; Crohn's disease; ulcerative colitis; anaphylaxis; muscle degeneration; cachexia; Reiter's syndrome; type I and type II diabetes; bone resorption diseases; ischemia reperfusion injury; atherosclerosis; brain trauma; multiple sclerosis; sepsis; septic shock; and toxic shock syndrome. Viruses sensitive to TNF-α inhibition, *e.g.*, HIV-1, HIV-2, HIV-3, are also affected by IL-1.

TNF-α and IL-1 appear to play a role in pancreatic β cell destruction and diabetes. Pancreatic β cells produce insulin which helps mediate blood glucose homeostasis. Deterioration of pancreatic β cells often accompanies type I diabetes. Pancreatic β cell functional abnormalities may occur in patients with type II diabetes. Type II diabetes is characterized by a functional resistance to insulin. Further, type II diabetes is also often accompanied by elevated levels of plasma glucagon and increased rates of hepatic glucose production. Glucagon is a regulatory hormone that attenuates liver gluconeogenesis inhibition by insulin. Glucagon receptors have been found in the liver, kidney and adipose tissue. Thus glucagon antagonists are useful for attenuating plasma glucose levels (WO 97/16442, incorporated herein by reference in its entirety). By antagonizing the glucagon receptors, it is thought that insulin responsiveness in the

liver will improve, thereby decreasing gluconeogenesis and lowering the rate of hepatic glucose production.

In rheumatoid arthritis models in animals, multiple intra-articular injections of IL-1 have led to an acute and destructive form of arthritis (Chandrasekhar et al., Clinical Immunol. Immunopathol., 55:382 (1990)). In studies using cultured rheumatoid synovial cells, IL-1 is a more potent inducer of stromelysin than is TNF-α (Firestein, Am. J. Pathol., 140:1309 (1992)). At sites of local injection, neutrophil, lymphocyte, and monocyte emigration has been observed. The emigration is attributed to the induction of chemokines (*e.g.*, IL-8), and the up-regulation of adhesion molecules (Dinarello, Eur. Cytokine Netw., 5:517-531 (1994)).

IL-1 also appears to play a role in promoting certain viral life cycles. For example, cytokine-induced increase of HIV expression in a chronically infected macrophage line has been associated with a concomitant and selective increase in IL-1 production (Folks et al., J. Immunol., 136:40 (1986)). Beutler et al. (J. Immunol., 135:3969 (1985)) discussed the role of IL-1 in cachexia. Baracos et al. (New Eng. J. Med., 308:553 (1983)) discussed the role of IL-1 in muscle degeneration.

In rheumatoid arthritis, both IL-1 and TNF-α induce synoviocytes and chondrocytes to produce collagenase and neutral proteases, which leads to tissue destruction within the arthritic joints. In a model of arthritis (collagen-induced arthritis (CIA) in rats and mice), intra-articular administration of TNF-α either prior to or after the induction of CIA led to an accelerated onset of arthritis and a more severe course of the disease (Brahn et al., Lymphokine Cytokine Res., 11:253 (1992); and Cooper, Clin. Exp. Immunol., 898:244 (1992)).

IL-8 has been implicated in exacerbating and/or causing many disease states in which massive neutrophil infiltration into sites of inflammation or injury (*e.g.*, ischemia) is mediated by the chemotactic nature of IL-8, including, but not limited to, the following: asthma, inflammatory bowel disease, psoriasis, adult respiratory distress syndrome, cardiac and renal reperfusion injury, thrombosis and glomerulonephritis. In addition to the chemotaxis effect on neutrophils, IL-8 also has the ability to activate neutrophils. Thus, reduction in IL-8 levels may lead to diminished neutrophil infiltration.

Several approaches have been taken to block the effect of TNF-α. One approach involves using soluble receptors for TNF-α (*e.g.*, TNFR-55 or TNFR-75), which have demonstrated efficacy in animal models of TNF-α-mediated disease states. A second

approach to neutralizing TNF-α using a monoclonal antibody specific to TNF-α, cA2, has demonstrated improvement in swollen joint count in a Phase II human trial of rheumatoid arthritis (Feldmann et al., Immunological Reviews, 195-223 (1995)). These approaches block the effects of TNF-α and IL-1 by either protein sequestration or receptor antagonism.

US 5,100,897, incorporated herein by reference in its entirety, describes pyrimidinone compounds useful as angiotensin II antagonists wherein one of the pyrimidinone ring nitrogen atoms is substituted with a substituted phenylmethyl or phenethyl radical.

US 5,162,325, incorporated herein by reference in its entirety, describes pyrimidinone compounds useful as angiotensin II antagonists wherein one of the pyrimidinone ring nitrogen atoms is substituted with a substituted phenylmethyl radical.

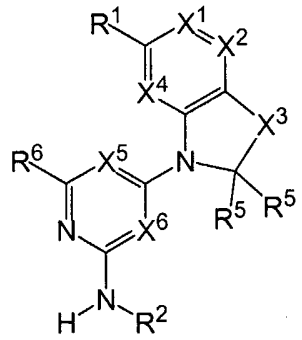
EP 481448, incorporated herein by reference in its entirety, describes pyrimidinone compounds useful as angiotensin II antagonists wherein one of the pyrimidinone ring nitrogen atoms is substituted with a substituted phenyl, phenylmethyl or phenethyl radical.

CA 2,020,370, incorporated herein by reference in its entirety, describes pyrimidinone compounds useful as angiotensin II antagonists wherein one of the pyrimidinone ring nitrogen atoms is substituted with a substituted biphenylaliphatic hydrocarbon radical.

BRIEF DESCRIPTION OF THE INVENTION

The present invention comprises a new class of compounds useful in the prophylaxis and treatment of diseases, such as TNF-α, IL-1β, IL-6 and/or IL-8 mediated diseases and other maladies, such as pain and diabetes. In particular, the compounds of the invention are useful for the prophylaxis and treatment of diseases or conditions involving inflammation. Accordingly, the invention also comprises pharmaceutical compositions and medicments comprising the compounds; methods for the prophylaxis and treatment of TNF-α, IL-1β, IL-6 and/or IL-8 mediated diseases, such as inflammatory, pain and diabetes diseases, using the compounds, compositions and medicaments of the invention, and intermediates and processes useful for the preparation of the compounds of the invention.

The compounds of the invention are represented by the following general structure:

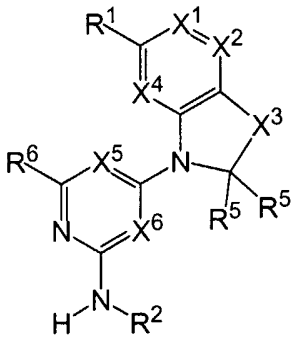


wherein R^1, R^2, R^5, R^6, X^1, X^2, X^3, X^4, X^5 and X^6 are defined herein.

The foregoing merely summarizes certain aspects of the invention and is not intended, nor should it be construed, as limiting the invention in any way. All patents and other publications recited herein are hereby incorporated by reference in their entirety.

DETAILED DESCRIPTION OF THE INVENTION

In accordance with the present invention, there is provided compounds of the formula I:



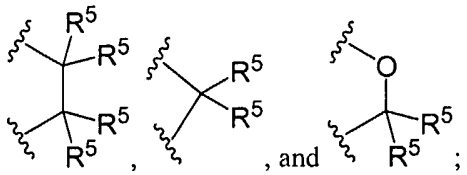
I

or a pharmaceutically acceptable salt or hydrate thereof, wherein

X^1 is N or CR^3;

X^2 is N or CR^4;

X^3 is selected from



X^4 is N or CR^4;

X^5 is N or CR^6;

X^6 is N or CR^6;

R^1 is a saturated, partially saturated or unsaturated 5-, 6- or 7-membered, ring containing 0, 1, 2 or 3 atoms selected from N, O and S, wherein the ring is substituted by 0, 1, 2 or 3 substituents selected from C_{1-8}alkyl, C_{1-4}haloalkyl, halo, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^b$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}$alkylNR^aR^a, $-OC_{2-6}$alkylOR^a, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}$alkylNR^aR^a and $-NR^aC_{2-6}$alkylOR^a;

R^2 is C_{1-8}alkyl substituted by 0, 1, 2 or 3 substituents selected from C_{1-2}haloalkyl, halo, oxo, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}$alkylNR^aR^a, $-OC_{2-6}$alkylOR^a, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}$alkylNR^aR^a, $-NR^aC_{2-6}$alkylOR^a, $-C(=O)R^g$, $-C(=O)OR^g$, $-C(=O)NR^aR^g$, $-C(=NR^a)NR^aR^g$, $-OR^g$, $-OC(=O)R^g$, $-OC(=O)NR^aR^g$, $-OC(=O)N(R^a)S(=O)_2R^g$, $-OC_{2-6}$alkylNR^aR^g, $-OC_{2-6}$alkylOR^g, $-SR^g$, $-S(=O)R^g$, $-S(=O)_2R^g$, $-S(=O)_2NR^aR^g$, $-NR^aR^g$, $-N(R^a)C(=O)R^g$, $-N(R^a)C(=O)OR^g$, $-N(R^a)C(=O)NR^aR^g$, $-C(=O)R^e$, $-C(=O)OR^e$, $-C(=O)NR^aR^e$, $-C(=NR^a)NR^aR^e$, $-OR^e$, $-OC(=O)R^e$, $-OC(=O)NR^aR^e$, $-OC(=O)N(R^a)S(=O)_2R^e$, $-OC_{2-6}$alkylNR^aR^e, $-OC_{2-6}$alkylOR^e, $-SR^e$, $-S(=O)R^e$, $-S(=O)_2R^e$, $-S(=O)_2NR^aR^e$, $-NR^aR^e$, $-N(R^a)C(=O)R^e$, $-N(R^a)C(=O)OR^e$ and $-N(R^a)C(=O)NR^aR^e$, and additionally substituted by 0, 1 or 2 saturated, partially saturated or unsaturated 5-, 6- or 7-membered monocyclic or 6-, 7-, 8-, 9-, 10- or 11-membered bicyclic rings containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, wherein the carbon atoms of the rings are substituted by 0, 1 or 2 oxo groups and the rings is substituted by 0, 1, 2 or 3 substituents selected from R^e, R^g, C_{1-8}alkyl, C_{1-4}haloalkyl, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}$alkylNR^aR^a, $-OC_{2-6}$alkylOR^a, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$,

$-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ and $-NR^aC_{2-6}alkylOR^a$; or

R^2 is a saturated, partially saturated or unsaturated 5-, 6- or 7-membered monocyclic or 6-, 7-, 8-, 9-, 10- or 11-membered bicyclic rings containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, wherein the carbon atoms of the rings are substituted by 0, 1 or 2 oxo groups and the rings is substituted by 0, 1, 2 or 3 substituents selected from R^e, R^g, $C_{1-8}alkyl$, $C_{1-4}haloalkyl$, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ and $-NR^aC_{2-6}alkylOR^a$, and additionally substituted by 0, 1 or 2 $C_{1-8}alkyl$ groups, each being substituted by 0, 1, 2 or 3 substituents selected from $C_{1-2}haloalkyl$, halo, oxo, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$, $-NR^aC_{2-6}alkylOR^a$, $-C(=O)R^g$, $-C(=O)OR^g$, $-C(=O)NR^aR^g$, $-C(=NR^a)NR^aR^g$, $-OR^g$, $-OC(=O)R^g$, $-OC(=O)NR^aR^g$, $-OC(=O)N(R^a)S(=O)_2R^g$, $-OC_{2-6}alkylNR^aR^g$, $-OC_{2-6}alkylOR^g$, $-SR^g$, $-S(=O)R^g$, $-S(=O)_2R^g$, $-S(=O)_2NR^aR^g$, $-NR^aR^g$, $-N(R^a)C(=O)R^g$, $-N(R^a)C(=O)OR^g$, $-N(R^a)C(=O)NR^aR^g$, $-C(=O)R^e$, $-C(=O)OR^e$, $-C(=O)NR^aR^e$, $-C(=NR^a)NR^aR^e$, $-OR^e$, $-OC(=O)R^e$, $-OC(=O)NR^aR^e$, $-OC(=O)N(R^a)S(=O)_2R^e$, $-OC_{2-6}alkylNR^aR^e$, $-OC_{2-6}alkylOR^e$, $-SR^e$, $-S(=O)R^e$, $-S(=O)_2R^e$, $-S(=O)_2NR^aR^e$, $-NR^aR^e$, $-N(R^a)C(=O)R^e$, $-N(R^a)C(=O)OR^e$ and $-N(R^a)C(=O)NR^aR^e$, and additionally substituted by 0, 1 or 2 saturated, partially saturated or unsaturated 5-, 6- or 7-membered monocyclic or 6-, 7-, 8-, 9-, 10- or 11-membered bicyclic rings containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, wherein the carbon atoms of the rings are substituted by 0, 1 or 2 oxo groups and the rings is substituted by 0, 1, 2 or 3 substituents selected from R^e, R^g, $C_{1-8}alkyl$, $C_{1-4}haloalkyl$, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$,

$-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ and $-NR^aC_{2-6}alkylOR^a$; wherein any part of R^2 is additionally substituted by 0, 1, 2, 3, 4, 5 or 6 atoms selected from Br, Cl, F and I;

R^3 is independently, in each instance, selected from H, R^e, C_{1-4}haloalkyl, halo, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^b$, $-OR^e$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-NR^aR^c$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ and $-NR^aC_{2-6}alkylOR^a$;

R^4 is independently in each instance H, R^e, C_{1-4}haloalkyl, halo, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^b$, $-OR^e$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-NR^aR^e$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ or $-NR^aC_{2-6}alkylOR^a$;

R^5 is independently in each instance H, R^e, C_{1-4}haloalkyl, halo, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^b$, $-OR^e$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-NR^aR^e$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ or $-NR^aC_{2-6}alkylOR^a$;

R^6 is independently in each instance H, C_{1-8}alkyl, C_{1-4}haloalkyl, $-NR^aR^a$, $-OR^a$, or halo;

R^a is independently, at each instance, H or R^b;

R^b is independently, at each instance, phenyl, benzyl or C_{1-6}alkyl, the phenyl, benzyl and C_{1-6}alkyl being substituted by 0, 1, 2 or 3 substituents selected from halo, C_{1-4}alkyl, C_{1-3}haloalkyl, $-OC_{1-4}$alkyl, $-NH_2$, $-NHC_{1-4}$alkyl, $-N(C_{1-4}alkyl)C_{1-4}$alkyl;

R^d is independently at each instance C_{1-8}alkyl, C_{1-4}haloalkyl, halo, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}$alkylNR$^aR^a$, $-OC_{2-6}$alkylOR^a, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}$alkylNR$^aR^a$ or $-NR^aC_{2-6}$alkylOR^a;

R^e is independently at each instance C_{1-6}alkyl substituted by 0, 1, 2 or 3 substituents independently selected from R^d and additionally substituted by 0 or 1 substituents selected from R^g; and

R^g is independently at each instance a saturated, partially saturated or unsaturated 5-, 6- or 7-membered monocyclic or 6-, 7-, 8-, 9-, 10- or 11-membered bicyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, wherein the carbon atoms of the ring are substituted by 0, 1 or 2 oxo groups and the ring is substituted by 0, 1, 2 or 3 substituents selected from R^b, C_{1-4}haloalkyl, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}$alkylNR$^aR^a$, $-OC_{2-6}$alkylOR^a, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}$alkylNR$^aR^a$ and $-NR^aC_{2-6}$alkylOR^a, and additionally substituted by 0, 1, 2, 3, 4, 5 or 6 atoms selected from Br, Cl, F and I.

In another embodiment, in conjunction with the above and below embodiments,

R^1 is a saturated or unsaturated 5- or 6-membered, ring containing 0, 1, 2 or 3 atoms selected from N, O and S, wherein the ring is substituted by 1, 2 or 3 substituents selected from C_{1-4}alkyl, C_{1-4}haloalkyl, halo, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}$alkylNR$^aR^a$, $-OC_{2-6}$alkylOR^a, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}$alkylNR$^aR^a$ and $-NR^aC_{2-6}$alkylOR^a.

In another embodiment, in conjunction with the above and below embodiments, R^1 is a saturated or unsaturated 5- or 6-membered, ring containing 0, 1, 2 or 3 atoms selected from N, O and S, wherein the ring is substituted by 1, 2 or 3 substituents selected from C_{1-4}alkyl, C_{1-4}haloalkyl, halo, cyano, nitro, $-OR^a$, $-OC(=O)R^b$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-NR^aR^a$ and $-N(R^a)C(=O)R^b$.

In another embodiment, in conjunction with the above and below embodiments, R^1 is a saturated or unsaturated 5- or 6-membered, ring containing 0, 1, 2 or 3 atoms selected from N, O and S, wherein the ring is substituted by 0, 1, 2 or 3 substituents selected from C_{1-4}alkyl, C_{1-4}haloalkyl and halo.

In another embodiment, in conjunction with the above and below embodiments, R^1 is a saturated or unsaturated 6-membered, ring containing 0, 1, 2 or 3 atoms selected from N, O and S, wherein the ring is substituted by 0, 1, 2 or 3 substituents selected from C_{1-4}alkyl, C_{1-4}haloalkyl and halo.

In another embodiment, in conjunction with the above and below embodiments, R^1 is phenyl substituted by 0, 1, 2 or 3 substituents selected from C_{1-4}alkyl, C_{1-4}haloalkyl and halo.

In another embodiment, in conjunction with the above and below embodiments, R^1 is phenyl.

In another embodiment, in conjunction with the above and below embodiments, R^1 is phenyl substituted by 1, 2 or 3 substituents selected from C_{1-4}alkyl, C_{1-4}haloalkyl and halo.

In another embodiment, in conjunction with the above and below embodiments, R^1 is pyridinyl substituted by 0, 1, 2 or 3 substituents selected from C_{1-4}alkyl, C_{1-4}haloalkyl and halo.

In another embodiment, in conjunction with the above and below embodiments, R^1 is pyrimidinyl substituted by 0, 1, 2 or 3 substituents selected from C_{1-4}alkyl, C_{1-4}haloalkyl and halo.

In another embodiment, in conjunction with the above and below embodiments, R^1 is a saturated or unsaturated 5-membered, ring containing 1 or 2 atoms selected from N, O and S, wherein the ring is substituted by 0, 1, 2 or 3 substituents selected from C_{1-4}alkyl, C_{1-4}haloalkyl and halo.

In another embodiment, in conjunction with the above and below embodiments, R^2 is C_{1-8}alkyl substituted by 0, 1, 2 or 3 substituents selected from C_{1-2}haloalkyl,

halo, oxo, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$, $-NR^aC_{2-6}alkylOR^a$, $-C(=O)R^g$, $-C(=O)OR^g$, $-C(=O)NR^aR^g$, $-C(=NR^a)NR^aR^g$, $-OR^g$, $-OC(=O)R^g$, $-OC(=O)NR^aR^g$, $-OC(=O)N(R^a)S(=O)_2R^g$, $-OC_{2-6}alkylNR^aR^g$, $-OC_{2-6}alkylOR^g$, $-SR^g$, $-S(=O)R^g$, $-S(=O)_2R^g$, $-S(=O)_2NR^aR^g$, $-NR^aR^g$, $-N(R^a)C(=O)R^g$, $-N(R^a)C(=O)OR^g$, $-N(R^a)C(=O)NR^aR^g$, $-C(=O)R^e$, $-C(=O)OR^e$, $-C(=O)NR^aR^e$, $-C(=NR^a)NR^aR^e$, $-OR^e$, $-OC(=O)R^e$, $-OC(=O)NR^aR^e$, $-OC(=O)N(R^a)S(=O)_2R^e$, $-OC_{2-6}alkylNR^aR^e$, $-OC_{2-6}alkylOR^e$, $-SR^e$, $-S(=O)R^e$, $-S(=O)_2R^e$, $-S(=O)_2NR^aR^e$, $-NR^aR^e$, $-N(R^a)C(=O)R^e$, $-N(R^a)C(=O)OR^e$ and $-N(R^a)C(=O)NR^aR^e$, and additionally substituted by 0, 1 or 2 saturated, partially saturated or unsaturated 5-, 6- or 7-membered monocyclic or 6-, 7-, 8-, 9-, 10- or 11-membered bicyclic rings containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, wherein the carbon atoms of the rings are substituted by 0, 1 or 2 oxo groups and the rings is substituted by 0, 1, 2 or 3 substituents selected from R^e, R^g, $C_{1-8}alkyl$, $C_{1-4}haloalkyl$, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ and $-NR^aC_{2-6}alkylOR^a$.

In another embodiment, in conjunction with the above and below embodiments, R^2 is $C_{1-8}alkyl$.

In another embodiment, in conjunction with the above and below embodiments, R^2 is $C_{1-8}alkyl$ substituted by 1, 2 or 3 substituents selected from $C_{1-2}haloalkyl$, halo, oxo, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$, $-NR^aC_{2-6}alkylOR^a$, $-C(=O)R^g$, $-C(=O)OR^g$,

-C(=O)NR^aR^g, -C(=NR^a)NR^aR^g, -OR^g, -OC(=O)R^g, -OC(=O)NR^aR^g, -OC(=O)N(R^a)S(=O)$_2R^g$, -OC_{2-6}alkylNR^aR^g, -OC_{2-6}alkylOR^g, -SR^g, -S(=O)R^g, -S(=O)$_2R^g$, -S(=O)$_2NR^aR^g$, -NR^aR^g, -N(R^a)C(=O)R^g, -N(R^a)C(=O)OR^g, -N(R^a)C(=O)NR^aR^g, -C(=O)R^e, -C(=O)OR^e, -C(=O)NR^aR^e, -C(=NR^a)NR^aR^e, -OR^e, -OC(=O)R^e, -OC(=O)NR^aR^e, -OC(=O)N(R^a)S(=O)$_2R^e$, -OC_{2-6}alkylNR^aR^e, -OC_{2-6}alkylOR^e, -SR^e, -S(=O)R^e, -S(=O)$_2R^e$, -S(=O)$_2NR^aR^e$, -NR^aR^e, -N(R^a)C(=O)R^e, -N(R^a)C(=O)OR^e and -N(R^a)C(=O)NR^aR^e, and additionally substituted by 0, 1 or 2 saturated, partially saturated or unsaturated 5-, 6- or 7-membered monocyclic or 6-, 7-, 8-, 9-, 10- or 11-membered bicyclic rings containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, wherein the carbon atoms of the rings are substituted by 0, 1 or 2 oxo groups and the rings is substituted by 0, 1, 2 or 3 substituents selected from R^e, R^g, C_{1-8}alkyl, C_{1-4}haloalkyl, cyano, nitro, -C(=O)R^b, -C(=O)OR^b, -C(=O)NR^aR^a, -C(=NR^a)NR^aR^a, -OR^a, -OC(=O)R^b, -OC(=O)NR^aR^a, -OC(=O)N(R^a)S(=O)$_2R^b$, -OC_{2-6}alkylNR^aR^a, -OC_{2-6}alkylOR^a, -SR^a, -S(=O)R^b, -S(=O)$_2R^b$, -S(=O)$_2NR^aR^a$, -S(=O)$_2$N(R^a)C(=O)R^b, -S(=O)$_2$N(R^a)C(=O)OR^b, -S(=O)$_2$N(R^a)C(=O)NR^aR^a, -NR^aR^a, -N(R^a)C(=O)R^b, -N(R^a)C(=O)OR^b, -N(R^a)C(=O)NR^aR^a, -N(R^a)C(=NR^a)NR^aR^a, -N(R^a)S(=O)$_2R^b$, -N(R^a)S(=O)$_2NR^aR^a$, -NR^aC_{2-6}alkylNR^aR^a and -NR^aC_{2-6}alkylOR^a.

In another embodiment, in conjunction with the above and below embodiments, R^2 is C_{1-8}alkyl substituted by 0, 1, 2 or 3 substituents selected from C_{1-2}haloalkyl, halo, oxo, cyano, nitro, -C(=O)R^b, -C(=O)OR^b, -C(=O)NR^aR^a, -C(=NR^a)NR^aR^a, -OR^a, -OC(=O)R^b, -OC(=O)NR^aR^a, -OC(=O)N(R^a)S(=O)$_2R^b$, -OC_{2-6}alkylNR^aR^a, -OC_{2-6}alkylOR^a, -SR^a, -S(=O)R^b, -S(=O)$_2R^b$, -S(=O)$_2NR^aR^a$, -S(=O)$_2$N(R^a)C(=O)R^b, -S(=O)$_2$N(R^a)C(=O)OR^b, -S(=O)$_2$N(R^a)C(=O)NR^aR^a, -NR^aR^a, -N(R^a)C(=O)R^b, -N(R^a)C(=O)OR^b, -N(R^a)C(=O)NR^aR^a, -N(R^a)C(=NR^a)NR^aR^a, -N(R^a)S(=O)$_2R^b$, -N(R^a)S(=O)$_2NR^aR^a$, -NR^aC_{2-6}alkylNR^aR^a, -NR^aC_{2-6}alkylOR^a, -C(=O)R^g, -C(=O)OR^g, -C(=O)NR^aR^g, -C(=NR^a)NR^aR^g, -OR^g, -OC(=O)R^g, -OC(=O)NR^aR^g, -OC(=O)N(R^a)S(=O)$_2R^g$, -OC_{2-6}alkylNR^aR^g, -OC_{2-6}alkylOR^g, -SR^g, -S(=O)R^g, -S(=O)$_2R^g$, -S(=O)$_2NR^aR^g$, -NR^aR^g, -N(R^a)C(=O)R^g, -N(R^a)C(=O)OR^g, -N(R^a)C(=O)NR^aR^g, -C(=O)R^e, -C(=O)OR^e, -C(=O)NR^aR^e, -C(=NR^a)NR^aR^e, -OR^e, -OC(=O)R^e, -OC(=O)NR^aR^e, -OC(=O)N(R^a)S(=O)$_2R^e$, -OC_{2-6}alkylNR^aR^e, -OC_{2-6}alkylOR^e, -SR^e, -S(=O)R^e, -S(=O)$_2R^e$, -S(=O)$_2NR^aR^e$, -NR^aR^e, -N(R^a)C(=O)R^e, -N(R^a)C(=O)OR^e and -N(R^a)C(=O)NR^aR^e, and additionally substituted by 1 or 2 saturated, partially saturated or unsaturated 5-, 6- or 7-membered monocyclic or 6-, 7-, 8-, 9-, 10- or 11-membered

bicyclic rings containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, wherein the carbon atoms of the rings are substituted by 0, 1 or 2 oxo groups and the rings is substituted by 0, 1, 2 or 3 substituents selected from R^e, R^g, C_{1-8}alkyl, C_{1-4}haloalkyl, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}$alkylNR^aR^a, $-OC_{2-6}$alkylOR^a, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}$alkylNR^aR^a and $-NR^aC_{2-6}$alkylOR^a.

In another embodiment, in conjunction with the above and below embodiments, R^2 is C_{2-8}alkyl substituted by 0, 1, 2 or 3 substituents selected from C_{1-2}haloalkyl, halo, oxo, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}$alkylNR^aR^a, $-OC_{2-6}$alkylOR^a, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}$alkylNR^aR^a, $-NR^aC_{2-6}$alkylOR^a, $-C(=O)R^g$, $-C(=O)OR^g$, $-C(=O)NR^aR^g$, $-C(=NR^a)NR^aR^g$, $-OR^g$, $-OC(=O)R^g$, $-OC(=O)NR^aR^g$, $-OC(=O)N(R^a)S(=O)_2R^g$, $-OC_{2-6}$alkylNR^aR^g, $-OC_{2-6}$alkylOR^g, $-SR^g$, $-S(=O)R^g$, $-S(=O)_2R^g$, $-S(=O)_2NR^aR^g$, $-NR^aR^g$, $-N(R^a)C(=O)R^g$, $-N(R^a)C(=O)OR^g$, $-N(R^a)C(=O)NR^aR^g$, $-C(=O)R^e$, $-C(=O)OR^e$, $-C(=O)NR^aR^e$, $-C(=NR^a)NR^aR^e$, $-OR^e$, $-OC(=O)R^e$, $-OC(=O)NR^aR^e$, $-OC(=O)N(R^a)S(=O)_2R^e$, $-OC_{2-6}$alkylNR^aR^e, $-OC_{2-6}$alkylOR^e, $-SR^e$, $-S(=O)R^e$, $-S(=O)_2R^e$, $-S(=O)_2NR^aR^e$, $-NR^aR^e$, $-N(R^a)C(=O)R^e$, $-N(R^a)C(=O)OR^e$ and $-N(R^a)C(=O)NR^aR^e$, and additionally substituted by 1 or 2 saturated, partially saturated or unsaturated 5-, 6- or 7-membered monocyclic or 6-, 7-, 8-, 9-, 10- or 11-membered bicyclic rings containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, wherein the carbon atoms of the rings are substituted by 0, 1 or 2 oxo groups and the rings is substituted by 0, 1, 2 or 3 substituents selected from R^e, R^g, C_{1-8}alkyl, C_{1-4}haloalkyl, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}$alkylNR^aR^a, $-OC_{2-6}$alkylOR^a, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$,

$-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ and $-NR^aC_{2-6}alkylOR^a$.

In another embodiment, in conjunction with the above and below embodiments, R^2 is a saturated, partially saturated or unsaturated 5-, 6- or 7-membered monocyclic or 6-, 7-, 8-, 9-, 10- or 11-membered bicyclic rings containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, wherein the carbon atoms of the rings are substituted by 0, 1 or 2 oxo groups and the rings is substituted by 0, 1, 2 or 3 substituents selected from R^e, R^g, $C_{1-8}alkyl$, $C_{1-4}haloalkyl$, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ and $-NR^aC_{2-6}alkylOR^a$, and additionally substituted by 0, 1 or 2 $C_{1-8}alkyl$ groups, each being substituted by 0, 1, 2 or 3 substituents selected from $C_{1-2}haloalkyl$, halo, oxo, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$, $-NR^aC_{2-6}alkylOR^a$, $-C(=O)R^g$, $-C(=O)OR^g$, $-C(=O)NR^aR^g$, $-C(=NR^a)NR^aR^g$, $-OR^g$, $-OC(=O)R^g$, $-OC(=O)NR^aR^g$, $-OC(=O)N(R^a)S(=O)_2R^g$, $-OC_{2-6}alkylNR^aR^g$, $-OC_{2-6}alkylOR^g$, $-SR^g$, $-S(=O)R^g$, $-S(=O)_2R^g$, $-S(=O)_2NR^aR^g$, $-NR^aR^g$, $-N(R^a)C(=O)R^g$, $-N(R^a)C(=O)OR^g$, $-N(R^a)C(=O)NR^aR^g$, $-C(=O)R^e$, $-C(=O)OR^e$, $-C(=O)NR^aR^e$, $-C(=NR^a)NR^aR^e$, $-OR^e$, $-OC(=O)R^e$, $-OC(=O)NR^aR^e$, $-OC(=O)N(R^a)S(=O)_2R^e$, $-OC_{2-6}alkylNR^aR^e$, $-OC_{2-6}alkylOR^e$, $-SR^e$, $-S(=O)R^e$, $-S(=O)_2R^e$, $-S(=O)_2NR^aR^e$, $-NR^aR^e$, $-N(R^a)C(=O)R^e$, $-N(R^a)C(=O)OR^e$ and $-N(R^a)C(=O)NR^aR^e$, and additionally substituted by 0, 1 or 2 saturated, partially saturated or unsaturated 5-, 6- or 7-membered monocyclic or 6-, 7-, 8-, 9-, 10- or 11-membered bicyclic rings containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, wherein the carbon atoms of the rings are substituted by 0, 1 or 2 oxo groups and the rings is substituted by 0, 1, 2 or 3 substituents selected from R^e, R^g, $C_{1-8}alkyl$, $C_{1-4}haloalkyl$, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$,

$-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ and $-NR^aC_{2-6}alkylOR^a$; wherein any part of R^2 is additionally substituted by 0, 1, 2, 3, 4, 5 or 6 atoms selected from Br, Cl, F and I.

In another embodiment, in conjunction with the above and below embodiments, R^2 is a saturated, partially saturated or unsaturated 5-, 6- or 7-membered monocyclic ring containing 1, 2 or 3 atoms selected from N, O and S, wherein the carbon atoms of the rings are substituted by 0, 1 or 2 oxo groups and the rings is substituted by 0, 1, 2 or 3 substituents selected from R^e, R^g, $C_{1-8}alkyl$, $C_{1-4}haloalkyl$, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ and $-NR^aC_{2-6}alkylOR^a$, and additionally substituted by 0, 1 or 2 $C_{1-8}alkyl$ groups, each being substituted by 0, 1, 2 or 3 substituents selected from $C_{1-2}haloalkyl$, halo, oxo, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$, $-NR^aC_{2-6}alkylOR^a$, $-C(=O)R^g$, $-C(=O)OR^g$, $-C(=O)NR^aR^g$, $-C(=NR^a)NR^aR^g$, $-OR^g$, $-OC(=O)R^g$, $-OC(=O)NR^aR^g$, $-OC(=O)N(R^a)S(=O)_2R^g$, $-OC_{2-6}alkylNR^aR^g$, $-OC_{2-6}alkylOR^g$, $-SR^g$, $-S(=O)R^g$, $-S(=O)_2R^g$, $-S(=O)_2NR^aR^g$, $-NR^aR^g$, $-N(R^a)C(=O)R^g$, $-N(R^a)C(=O)OR^g$, $-N(R^a)C(=O)NR^aR^g$, $-C(=O)R^e$, $-C(=O)OR^e$, $-C(=O)NR^aR^e$, $-C(=NR^a)NR^aR^e$, $-OR^e$, $-OC(=O)R^e$, $-OC(=O)NR^aR^e$, $-OC(=O)N(R^a)S(=O)_2R^e$, $-OC_{2-6}alkylNR^aR^e$, $-OC_{2-6}alkylOR^e$, $-SR^e$, $-S(=O)R^e$, $-S(=O)_2R^e$, $-S(=O)_2NR^aR^e$, $-NR^aR^e$, $-N(R^a)C(=O)R^e$, $-N(R^a)C(=O)OR^e$ and $-N(R^a)C(=O)NR^aR^e$, and additionally substituted by 0, 1 or 2 saturated, partially saturated or unsaturated 5-, 6- or 7-membered monocyclic or 6-, 7-, 8-, 9-, 10- or 11-membered bicyclic rings containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, wherein the

carbon atoms of the rings are substituted by 0, 1 or 2 oxo groups and the rings is substituted by 0, 1, 2 or 3 substituents selected from R^e, R^g, C_{1-8}alkyl, C_{1-4}haloalkyl, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}$alkylNR^aR^a, $-OC_{2-6}$alkylOR^a, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}$alkylNR^aR^a and $-NR^aC_{2-6}$alkylOR^a; wherein any part of R^2 is additionally substituted by 0, 1, 2, 3, 4, 5 or 6 atoms selected from Br, Cl, F and I.

In another embodiment, in conjunction with the above and below embodiments, R^2 is a saturated or partially saturated 5-, 6- or 7-membered monocyclic ring containing 1, 2 or 3 atoms selected from N, O and S, wherein the carbon atoms of the rings are substituted by 0, 1 or 2 oxo groups and the rings is substituted by 0, 1, 2 or 3 substituents selected from R^e, R^g, C_{1-8}alkyl, C_{1-4}haloalkyl, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}$alkylNR^aR^a, $-OC_{2-6}$alkylOR^a, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}$alkylNR^aR^a and $-NR^aC_{2-6}$alkylOR^a, and additionally substituted by 0, 1 or 2 C_{1-8}alkyl groups, each being substituted by 0, 1, 2 or 3 substituents selected from C_{1-2}haloalkyl, halo, oxo, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}$alkylNR^aR^a, $-OC_{2-6}$alkylOR^a, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}$alkylNR^aR^a, $-NR^aC_{2-6}$alkylOR^a, $-C(=O)R^g$, $-C(=O)OR^g$, $-C(=O)NR^aR^g$, $-C(=NR^a)NR^aR^g$, $-OR^g$, $-OC(=O)R^g$, $-OC(=O)NR^aR^g$, $-OC(=O)N(R^a)S(=O)_2R^g$, $-OC_{2-6}$alkylNR^aR^g, $-OC_{2-6}$alkylOR^g, $-SR^g$, $-S(=O)R^g$, $-S(=O)_2R^g$, $-S(=O)_2NR^aR^g$, $-NR^aR^g$, $-N(R^a)C(=O)R^g$, $-N(R^a)C(=O)OR^g$, $-N(R^a)C(=O)NR^aR^g$, $-C(=O)R^e$, $-C(=O)OR^e$, $-C(=O)NR^aR^e$, $-C(=NR^a)NR^aR^e$, $-OR^e$, $-OC(=O)R^e$, $-OC(=O)NR^aR^e$, $-OC(=O)N(R^a)S(=O)_2R^e$, $-OC_{2-6}$alkylNR^aR^e, $-OC_{2-6}$alkylOR^e, $-SR^e$, $-S(=O)R^e$, $-S(=O)_2R^e$, $-S(=O)_2NR^aR^e$, $-NR^aR^e$, $-N(R^a)C(=O)R^e$, $-N(R^a)C(=O)OR^e$ and

$-N(R^a)C(=O)NR^aR^e$, and additionally substituted by 0, 1 or 2 saturated, partially saturated or unsaturated 5-, 6- or 7-membered monocyclic or 6-, 7-, 8-, 9-, 10- or 11-membered bicyclic rings containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, wherein the carbon atoms of the rings are substituted by 0, 1 or 2 oxo groups and the rings is substituted by 0, 1, 2 or 3 substituents selected from R^e, R^g, C_{1-8}alkyl, C_{1-4}haloalkyl, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}$alkylNR$^aR^a$, $-OC_{2-6}$alkylOR^a, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}$alkylNR$^aR^a$ and $-NR^aC_{2-6}$alkylOR^a; wherein any part of R^2 is additionally substituted by 0, 1, 2, 3, 4, 5 or 6 atoms selected from Br, Cl, F and I.

In another embodiment, in conjunction with the above and below embodiments, R^2 is a saturated or partially saturated 5-, 6- or 7-membered monocyclic ring containing 1, 2 or 3 atoms selected from N, O and S, wherein the carbon atoms of the rings are substituted by 0, 1 or 2 oxo groups and the rings is substituted by 1, 2 or 3 substituents selected from R^e, R^g, C_{1-8}alkyl, C_{1-4}haloalkyl, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}$alkylNR$^aR^a$, $-OC_{2-6}$alkylOR^a, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}$alkylNR$^aR^a$ and $-NR^aC_{2-6}$alkylOR^a, and additionally substituted by 0, 1 or 2 C_{1-8}alkyl groups, each being substituted by 0, 1, 2 or 3 substituents selected from C_{1-2}haloalkyl, halo, oxo, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}$alkylNR$^aR^a$, $-OC_{2-6}$alkylOR^a, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}$alkylNR$^aR^a$, $-NR^aC_{2-6}$alkylOR^a, $-C(=O)R^g$, $-C(=O)OR^g$, $-C(=O)NR^aR^g$, $-C(=NR^a)NR^aR^g$, $-OR^g$, $-OC(=O)R^g$, $-OC(=O)NR^aR^g$, $-OC(=O)N(R^a)S(=O)_2R^g$, $-OC_{2-6}$alkylNR$^aR^g$, $-OC_{2-6}$alkylOR^g, $-SR^g$, $-S(=O)R^g$, $-S(=O)_2R^g$, $-S(=O)_2NR^aR^g$, $-NR^aR^g$, $-N(R^a)C(=O)R^g$, $-N(R^a)C(=O)OR^g$, $-N(R^a)C(=O)NR^aR^g$,

$-C(=O)R^e$, $-C(=O)OR^e$, $-C(=O)NR^aR^e$, $-C(=NR^a)NR^aR^e$, $-OR^e$, $-OC(=O)R^e$, $-OC(=O)NR^aR^e$, $-OC(=O)N(R^a)S(=O)_2R^e$, $-OC_{2-6}alkylNR^aR^e$, $-OC_{2-6}alkylOR^e$, $-SR^e$, $-S(=O)R^e$, $-S(=O)_2R^e$, $-S(=O)_2NR^aR^e$, $-NR^aR^e$, $-N(R^a)C(=O)R^e$, $-N(R^a)C(=O)OR^e$ and $-N(R^a)C(=O)NR^aR^e$, and additionally substituted by 0, 1 or 2 saturated, partially saturated or unsaturated 5-, 6- or 7-membered monocyclic or 6-, 7-, 8-, 9-, 10- or 11-membered bicyclic rings containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, wherein the carbon atoms of the rings are substituted by 0, 1 or 2 oxo groups and the rings is substituted by 0, 1, 2 or 3 substituents selected from R^e, R^g, $C_{1-8}alkyl$, $C_{1-4}haloalkyl$, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ and $-NR^aC_{2-6}alkylOR^a$; wherein any part of R^2 is additionally substituted by 0, 1, 2, 3, 4, 5 or 6 atoms selected from Br, Cl, F and I.

In another embodiment, in conjunction with the above and below embodiments, R^2 is a saturated or partially saturated 5-, 6- or 7-membered monocyclic ring containing 1, 2 or 3 atoms selected from N, O and S, wherein the carbon atoms of the rings are substituted by 0, 1 or 2 oxo groups and the rings is substituted by 0, 1, 2 or 3 substituents selected from R^e, R^g, $C_{1-8}alkyl$, $C_{1-4}haloalkyl$, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ and $-NR^aC_{2-6}alkylOR^a$, and additionally substituted by 1 or 2 $C_{1-8}alkyl$ groups, each being substituted by 1, 2 or 3 substituents selected from $C_{1-2}haloalkyl$, halo, oxo, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$, $-NR^aC_{2-6}alkylOR^a$, $-C(=O)R^g$,

$-C(=O)OR^g$, $-C(=O)NR^aR^g$, $-C(=NR^a)NR^aR^g$, $-OR^g$, $-OC(=O)R^g$, $-OC(=O)NR^aR^g$, $-OC(=O)N(R^a)S(=O)_2R^g$, $-OC_{2-6}alkylNR^aR^g$, $-OC_{2-6}alkylOR^g$, $-SR^g$, $-S(=O)R^g$, $-S(=O)_2R^g$, $-S(=O)_2NR^aR^g$, $-NR^aR^g$, $-N(R^a)C(=O)R^g$, $-N(R^a)C(=O)OR^g$, $-N(R^a)C(=O)NR^aR^g$, $-C(=O)R^e$, $-C(=O)OR^e$, $-C(=O)NR^aR^e$, $-C(=NR^a)NR^aR^e$, $-OR^e$, $-OC(=O)R^e$, $-OC(=O)NR^aR^e$, $-OC(=O)N(R^a)S(=O)_2R^e$, $-OC_{2-6}alkylNR^aR^e$, $-OC_{2-6}alkylOR^e$, $-SR^e$, $-S(=O)R^e$, $-S(=O)_2R^e$, $-S(=O)_2NR^aR^e$, $-NR^aR^e$, $-N(R^a)C(=O)R^e$, $-N(R^a)C(=O)OR^e$ and $-N(R^a)C(=O)NR^aR^e$, and additionally substituted by 0, 1 or 2 saturated, partially saturated or unsaturated 5-, 6- or 7-membered monocyclic or 6-, 7-, 8-, 9-, 10- or 11-membered bicyclic rings containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, wherein the carbon atoms of the rings are substituted by 0, 1 or 2 oxo groups and the rings is substituted by 0, 1, 2 or 3 substituents selected from R^e, R^g, $C_{1-8}alkyl$, $C_{1-4}haloalkyl$, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ and $-NR^aC_{2-6}alkylOR^a$; wherein any part of R^2 is additionally substituted by 0, 1, 2, 3, 4, 5 or 6 atoms selected from Br, Cl, F and I.

In another embodiment, in conjunction with the above and below embodiments, R^2 is a saturated or partially saturated 5-, 6- or 7-membered monocyclic ring containing 1 or 2 N atoms, wherein the carbon atoms of the rings are substituted by 0, 1 or 2 oxo groups and the rings is substituted by 1, 2 or 3 substituents selected from R^e, R^g, $C_{1-8}alkyl$, $C_{1-4}haloalkyl$, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ and $-NR^aC_{2-6}alkylOR^a$, and additionally substituted by 0, 1 or 2 $C_{1-8}alkyl$ groups, each being substituted by 0, 1, 2 or 3 substituents selected from $C_{1-2}haloalkyl$, halo, oxo, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$,

$-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$, $-NR^aC_{2-6}alkylOR^a$, $-C(=O)R^g$, $-C(=O)OR^g$, $-C(=O)NR^aR^g$, $-C(=NR^a)NR^aR^g$, $-OR^g$, $-OC(=O)R^g$, $-OC(=O)NR^aR^g$, $-OC(=O)N(R^a)S(=O)_2R^g$, $-OC_{2-6}alkylNR^aR^g$, $-OC_{2-6}alkylOR^g$, $-SR^g$, $-S(=O)R^g$, $-S(=O)_2R^g$, $-S(=O)_2NR^aR^g$, $-NR^aR^g$, $-N(R^a)C(=O)R^g$, $-N(R^a)C(=O)OR^g$, $-N(R^a)C(=O)NR^aR^g$, $-C(=O)R^e$, $-C(=O)OR^e$, $-C(=O)NR^aR^e$, $-C(=NR^a)NR^aR^e$, $-OR^e$, $-OC(=O)R^e$, $-OC(=O)NR^aR^e$, $-OC(=O)N(R^a)S(=O)_2R^e$, $-OC_{2-6}alkylNR^aR^e$, $-OC_{2-6}alkylOR^e$, $-SR^e$, $-S(=O)R^e$, $-S(=O)_2R^e$, $-S(=O)_2NR^aR^e$, $-NR^aR^e$, $-N(R^a)C(=O)R^e$, $-N(R^a)C(=O)OR^e$ and $-N(R^a)C(=O)NR^aR^e$, and additionally substituted by 0, 1 or 2 saturated, partially saturated or unsaturated 5-, 6- or 7-membered monocyclic or 6-, 7-, 8-, 9-, 10- or 11-membered bicyclic rings containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, wherein the carbon atoms of the rings are substituted by 0, 1 or 2 oxo groups and the rings is substituted by 0, 1, 2 or 3 substituents selected from R^e, R^g, C_{1-8}alkyl, C_{1-4}haloalkyl, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ and $-NR^aC_{2-6}alkylOR^a$; wherein any part of R^2 is additionally substituted by 0, 1, 2, 3, 4, 5 or 6 atoms selected from Br, Cl, F and I.

In another embodiment, in conjunction with the above and below embodiments, R^3 is independently, in each instance, selected from H, R^e, C_{1-4}haloalkyl, halo, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^b$, $-OR^e$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-NR^aR^e$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ and $-NR^aC_{2-6}alkylOR^a$.

In another embodiment, in conjunction with the above and below embodiments, R^3 is H.

In another embodiment, in conjunction with the above and below embodiments, R^3 is independently, in each instance, selected from H, C_{1-6}alkyl, C_{1-4}haloalkyl and halo.

In another embodiment, in conjunction with the above and below embodiments, R^3 is independently, in each instance, selected from R^e, C_{1-4}haloalkyl, halo, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^b$, $-OR^e$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}$alkylNR^{a}R^a, $-OC_{2-6}$alkylOR^a, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-NR^aR^e$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}$alkylNR^{a}R^a and $-NR^aC_{2-6}$alkylOR^a.

In another embodiment, in conjunction with any of the above and below embodiments, R^4 is independently in each instance R^e, C_{1-4}haloalkyl, halo, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^b$, $-OR^e$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}$alkylNR^{a}R^a, $-OC_{2-6}$alkylOR^a, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-NR^aR^e$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}$alkylNR^{a}R^a or $-NR^aC_{2-6}$alkylOR^a.

In another embodiment, in conjunction with any of the above and below embodiments, R^4 is H.

In another embodiment, in conjunction with any of the above and below embodiments, R^5 is independently in each instance R^e, C_{1-4}haloalkyl, halo, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^b$, $-OR^e$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}$alkylNR^{a}R^a, $-OC_{2-6}$alkylOR^a, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-NR^aR^e$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}$alkylNR^{a}R^a or $-NR^aC_{2-6}$alkylOR^a.

In another embodiment, in conjunction with any of the above and below embodiments, R^5 is H.

In another embodiment, in conjunction with any of the above and below embodiments, R^6 is H.

In another embodiment, in conjunction with any of the above and below embodiments, R^6 is independently in each instance C_{1-8}alkyl, C_{1-4}haloalkyl, $-NR^aR^a$, $-OR^a$, or halo.

In another embodiment, in conjunction with any of the above and below embodiments, X^1 is CR^3 and X^2 is N.

In another embodiment, in conjunction with any of the above and below embodiments, X^1 is N and X^2 is CR^4.

In another embodiment, in conjunction with any of the above and below embodiments, X^1 is CR^3 and X^2 is CR^4.

In another embodiment, in conjunction with any of the above and below embodiments, X^4 is CR^4.

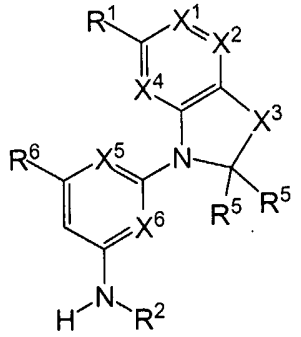
In another embodiment, in conjunction with any of the above and below embodiments, X^4 is N.

In another embodiment, in conjunction with any of the above and below embodiments, X^5 is N and X^6 is CR^6.

In another embodiment, in conjunction with any of the above and below embodiments, X^5 is CR^6 and X^6 is N.

In another embodiment, in conjunction with any of the above and below embodiments, X^5 is CR^6 and X^6 is CR^6.

In accordance with another embodiment of the present invention, there is provided compounds of the Formula II:



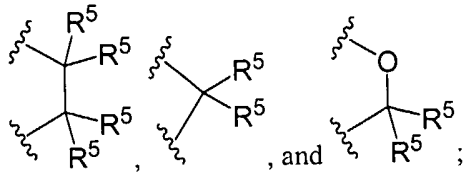
II

or a pharmaceutically acceptable salt or hydrate thereof, wherein

X^1 is N or CR^3;

X^2 is N or CR^4;

X^3 is selected from



X^4 is N or CR^4;

X^5 is N or CR^6;

X^6 is N or CR^6, provided that at least one of X^5 and X^6 is N; and wherein

R^{1-6} and R^{a-g} are as defined in compounds of formula I .

In yet a further embodiment, it is comtemplated that compounds of formula II may be in conjunction with any of the other above or below embodiments herein.

Another aspect of the invention relates to a pharmaceutical composition comprising a compound according to any one of the above embodiments and a pharmaceutically acceptable carrier.

Another aspect of the invention relates to a method of prophylaxis or treatment of inflammation comprising administering an effective amount of a compound according to any one of the above embodiments.

Another aspect of the invention relates to a method of prophylaxis or treatment of rheumatoid arthritis, Pagets disease, osteoporosis, multiple myeloma, uveititis, acute or chronic myelogenous leukemia, pancreatic β cell destruction, osteoarthritis, rheumatoid spondylitis, gouty arthritis, inflammatory bowel disease, adult respiratory distress syndrome (ARDS), psoriasis, Crohn's disease, allergic rhinitis, ulcerative colitis, anaphylaxis, contact dermatitis, asthma, muscle degeneration, cachexia, Reiter's syndrome, type I diabetes, type II diabetes, bone resorption diseases, graft vs. host reaction, Alzheimer's disease, stroke, myocardial infarction, ischemia reperfusion injury, atherosclerosis, brain trauma, multiple sclerosis, cerebral malaria, sepsis, septic shock, toxic shock syndrome, fever, myalgias due to HIV-1, HIV-2, HIV-3, cytomegalovirus (CMV), influenza, adenovirus, the herpes viruses or herpes zoster infection in a mammal comprising administering an effective amount of a compound according to any one of the above embodiments.

Another aspect of the invention relates to a method of lowering plasma concentrations of either or both TNF-a and IL-1 comprising administering an effective amount of a compound according to any one of the above embodiments.

Another aspect of the invention relates to a method of lowering plasma concentrations of either or both IL-6 and IL-8 comprising administering an effective amount of a compound according to any one of the above embodiments.

Another aspect of the invention relates to a method of prophylaxis or treatment of diabetes disease in a mammal comprising administering an effective amount of a compound according to any one of the above embodiments to produce a glucagon antagonist effect.

Another aspect of the invention relates to a method of prophylaxis or treatment of a pain disorder in a mammal comprising administering an effective amount of a compound according to any one of the above embodiments.

Another aspect of the invention relates to a method of decreasing prostaglandins production in a mammal comprising administering an effective amount of a compound according to any one of the above embodiments.

Another aspect of the invention relates to a method of decreasing cyclooxygenase enzyme activity in a mammal comprising administering an effective amount of a compound according to any one of the above embodiments. In another embodiment, the cyclooxygenase enzyme is COX-2.

Another aspect of the invention relates to a method of decreasing cyclooxygenase enzyme activity in a mammal comprising administering an effective amount of the above pharmaceutical composition. In another embodiment the cyclooxygenase enzyme is COX-2.

Another aspect of the invention relates to the manufacture of a medicament comprising a compound according to any one of the above embodiments.

Another aspect of the invention relates to the manufacture of a medicament for the treatment of inflammation comprising administering an effective amount of a compound according to any one of the above embodiments.

Another aspect of the invention relates to the manufacture of a medicament for the treatment of rheumatoid arthritis, Pagets disease, osteoporosis, multiple myeloma, uveititis, acute or chronic myelogenous leukemia, pancreatic β cell destruction, osteoarthritis, rheumatoid spondylitis, gouty arthritis, inflammatory bowel disease, adult respiratory distress syndrome (ARDS), psoriasis, Crohn's disease, allergic rhinitis, ulcerative colitis, anaphylaxis, contact dermatitis, asthma, muscle degeneration, cachexia, Reiter's syndrome, type I diabetes, type II diabetes, bone resorption diseases, graft vs.

host reaction, Alzheimer's disease, stroke, myocardial infarction, ischemia reperfusion injury, atherosclerosis, brain trauma, multiple sclerosis, cerebral malaria, sepsis, septic shock, toxic shock syndrome, fever, myalgias due to HIV-1, HIV-2, HIV-3, cytomegalovirus (CMV), influenza, adenovirus, the herpes viruses or herpes zoster infection in a mammal comprising administering an effective amount of a compound according to any one of the above embodiments.

The compounds of this invention may have in general several asymmetric centers and are typically depicted in the form of racemic mixtures. This invention is intended to encompass racemic mixtures, partially racemic mixtures and separate enantiomers and diasteromers.

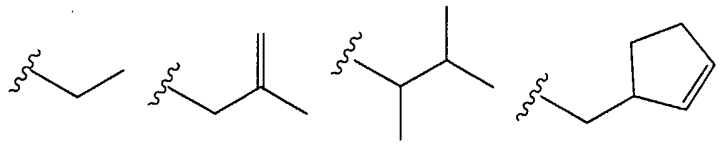
The specification and claims contain listing of species using the language "selected from . . . and . . ." and "is . . . or . . ." (sometimes referred to as Markush groups). When this language is used in this application, unless otherwise stated it is meant to include the group as a whole, or any single members thereof, or any subgroups thereof. The use of this language is merely for shorthand purposes and is not meant in any way to limit the removal of individual elements or subgroups as needed.

Unless otherwise specified, the following definitions apply to terms found in the specification and claims:

"Aryl" means a phenyl or naphthyl radical, wherein the phenyl may be fused with a C_{3-4}cycloalkyl bridge.

"Benzo group", alone or in combination, means the divalent radical C_4H_4=, one representation of which is -CH=CH-CH=CH-, that when vicinally attached to another ring forms a benzene-like ring--for example tetrahydronaphthylene, indole and the like.

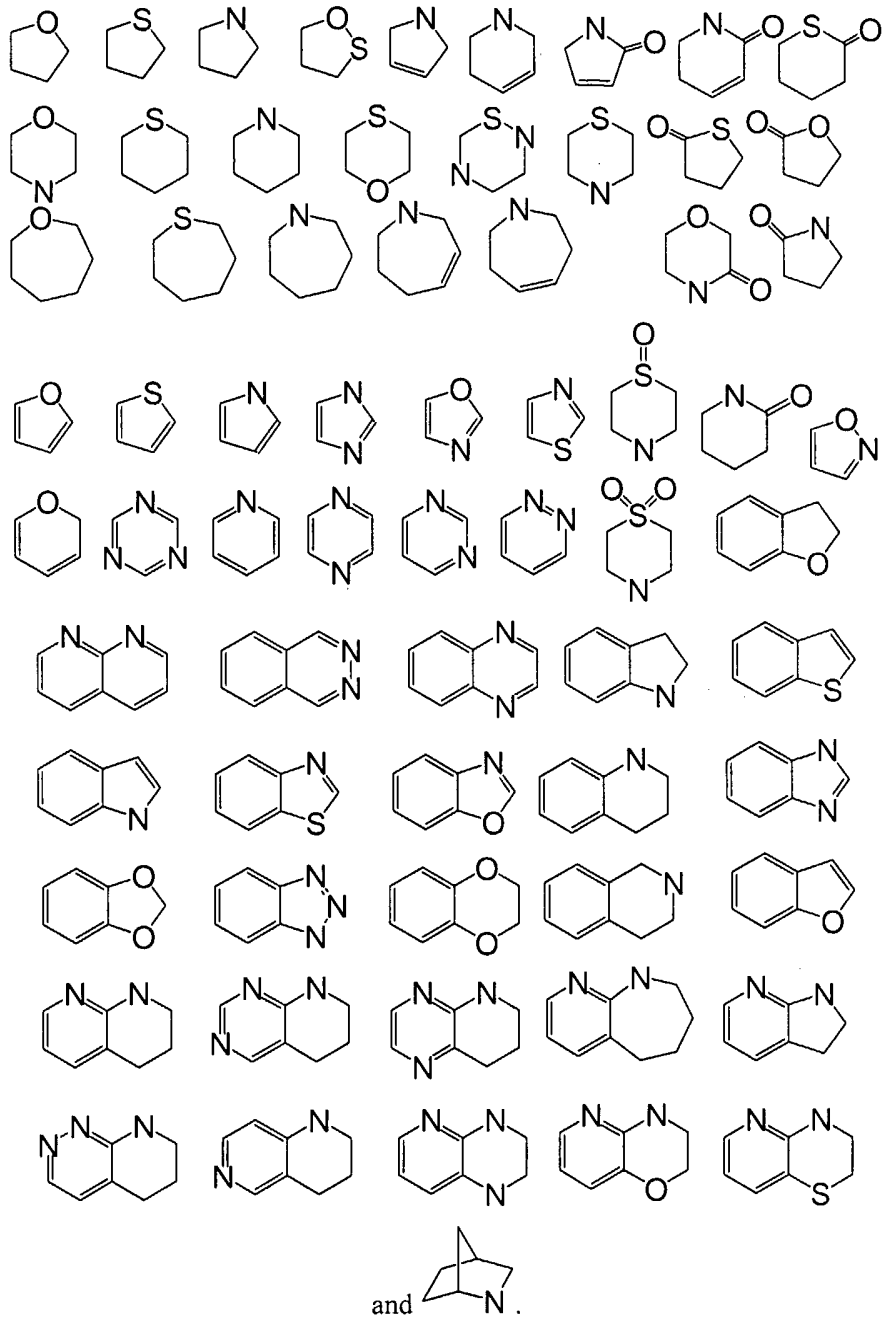
"$C_{\alpha-\beta}$alkyl" means an alkyl group comprising from α to β carbon atoms in a branched, cyclical or linear relationship or any combination of the three. The alkyl groups described in this section may also contain double or triple bonds. Examples of C_{1-8}alkyl include, but are not limited to the following:



"Halogen" and "halo" mean a halogen atoms selected from F, Cl, Br and I.

"$C_{\alpha-\beta}$haloalkyl" means an alkyl group, as described above, wherein any number--at least one--of the hydrogen atoms attached to the alkyl chain are replaced by F, Cl, Br or I.

"Heterocycle" means a ring comprising at least one carbon atom and at least one other atom selected from N, O and S. Examples of heterocycles that may be found in the claims include, but are not limited to, the following:



and .

"Pharmaceutically-acceptable salt" means a salt prepared by conventional means, and are well known by those skilled in the art. The "pharmacologically acceptable salts" include basic salts of inorganic and organic acids, including but not limited to hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulphonic acid, ethanesulfonic

acid, malic acid, acetic acid, oxalic acid, tartaric acid, citric acid, lactic acid, fumaric acid, succinic acid, maleic acid, salicylic acid, benzoic acid, phenylacetic acid, mandelic acid and the like. When compounds of the invention include an acidic function such as a carboxy group, then suitable pharmaceutically acceptable cation pairs for the carboxy group are well known to those skilled in the art and include alkaline, alkaline earth, ammonium, quaternary ammonium cations and the like. For additional examples of "pharmacologically acceptable salts," *see infra* and Berge et al., J. Pharm. Sci., 66:1 (1977).

"Leaving group" generally refers to groups readily displaceable by a nucleophile, such as an amine, a thiol or an alcohol nucleophile. Such leaving groups are well known in the art. Examples of such leaving groups include, but are not limited to, N-hydroxysuccinimide, N-hydroxybenzotriazole, halides, triflates, tosylates and the like. Preferred leaving groups are indicated herein where appropriate.

"Protecting group" generally refers to groups well known in the art which are used to prevent selected reactive groups, such as carboxy, amino, hydroxy, mercapto and the like, from undergoing undesired reactions, such as nucleophilic, electrophilic, oxidation, reduction and the like. Preferred protecting groups are indicated herein where appropriate. Examples of amino protecting groups include, but are not limited to, aralkyl, substituted aralkyl, cycloalkenylalkyl and substituted cycloalkenyl alkyl, allyl, substituted allyl, acyl, alkoxycarbonyl, aralkoxycarbonyl, silyl and the like. Examples of aralkyl include, but are not limited to, benzyl, ortho-methylbenzyl, trityl and benzhydryl, which can be optionally substituted with halogen, alkyl, alkoxy, hydroxy, nitro, acylamino, acyl and the like, and salts, such as phosphonium and ammonium salts. Examples of aryl groups include phenyl, naphthyl, indanyl, anthracenyl, 9-(9-phenylfluorenyl), phenanthrenyl, durenyl and the like. Examples of cycloalkenylalkyl or substituted cycloalkylenylalkyl radicals, preferably have 6-10 carbon atoms, include, but are not limited to, cyclohexenyl methyl and the like. Suitable acyl, alkoxycarbonyl and aralkoxycarbonyl groups include benzyloxycarbonyl, t-butoxycarbonyl, iso-butoxycarbonyl, benzoyl, substituted benzoyl, butyryl, acetyl, tri-fluoroacetyl, tri-chloro acetyl, phthaloyl and the like. A mixture of protecting groups can be used to protect the same amino group, such as a primary amino group can be protected by both an aralkyl group and an aralkoxycarbonyl group. Amino protecting groups can also form a heterocyclic ring with the nitrogen to which they are attached, for example, 1,2-bis(methylene)benzene, phthalimidyl, succinimidyl, maleimidyl and the like and where

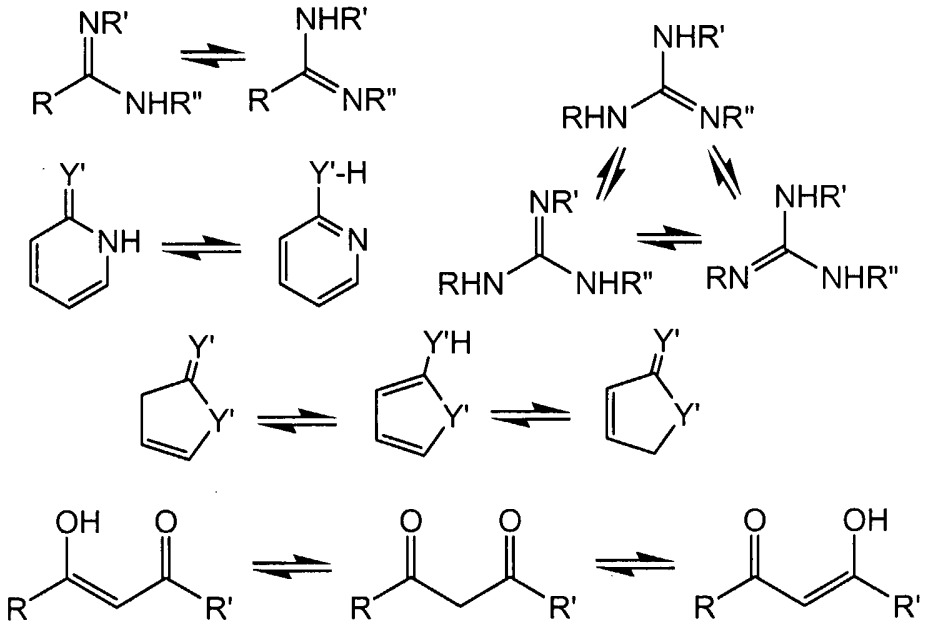
these heterocyclic groups can further include adjoining aryl and cycloalkyl rings. In addition, the heterocyclic groups can be mono-, di- or tri-substituted, such as nitrophthalimidyl. Amino groups may also be protected against undesired reactions, such as oxidation, through the formation of an addition salt, such as hydrochloride, toluenesulfonic acid, trifluoroacetic acid and the like. Many of the amino protecting groups are also suitable for protecting carboxy, hydroxy and mercapto groups. For example, aralkyl groups. Alkyl groups are also suitable groups for protecting hydroxy and mercapto groups, such as tert-butyl.

Silyl protecting groups are silicon atoms optionally substituted by one or more alkyl, aryl and aralkyl groups. Suitable silyl protecting groups include, but are not limited to, trimethylsilyl, triethylsilyl, tri-isopropylsilyl, tert-butyldimethylsilyl, dimethylphenylsilyl, 1,2-bis(dimethylsilyl)benzene, 1,2-bis(dimethylsilyl)ethane and diphenylmethylsilyl. Silylation of an amino groups provide mono- or di-silylamino groups. Silylation of aminoalcohol compounds can lead to a N,N,O-tri-silyl derivative. Removal of the silyl function from a silyl ether function is readily accomplished by treatment with, for example, a metal hydroxide or ammonium fluoride reagent, either as a discrete reaction step or in situ during a reaction with the alcohol group. Suitable silylating agents are, for example, trimethylsilyl chloride, tert-butyl-dimethylsilyl chloride, phenyldimethylsilyl chloride, diphenylmethyl silyl chloride or their combination products with imidazole or DMF. Methods for silylation of amines and removal of silyl protecting groups are well known to those skilled in the art. Methods of preparation of these amine derivatives from corresponding amino acids, amino acid amides or amino acid esters are also well known to those skilled in the art of organic chemistry including amino acid/amino acid ester or aminoalcohol chemistry.

Protecting groups are removed under conditions which will not affect the remaining portion of the molecule. These methods are well known in the art and include acid hydrolysis, hydrogenolysis and the like. A preferred method involves removal of a protecting group, such as removal of a benzyloxycarbonyl group by hydrogenolysis utilizing palladium on carbon in a suitable solvent system such as an alcohol, acetic acid, and the like or mixtures thereof. A t-butoxycarbonyl protecting group can be removed utilizing an inorganic or organic acid, such as HCl or trifluoroacetic acid, in a suitable solvent system, such as dioxane or methylene chloride. The resulting amino salt can readily be neutralized to yield the free amine. Carboxy protecting group, such as methyl,

ethyl, benzyl, tert-butyl, 4-methoxyphenylmethyl and the like, can be removed under hydroylsis and hydrogenolysis conditions well known to those skilled in the art.

It should be noted that compounds of the invention may contain groups that may exist in tautomeric forms, such as cyclic and acyclic amidine and guanidine groups, heteroatom substituted heteroaryl groups (Y' = O, S, NR), and the like, which are illustrated in the following examples:



and though one form is named, described, displayed and/or claimed herein, all the tautomeric forms are intended to be inherently included in such name, description, display and/or claim.

Prodrugs of the compounds of this invention are also contemplated by this invention. A prodrug is an active or inactive compound that is modified chemically through in vivo physiological action, such as hydrolysis, metabolism and the like, into a compound of this invention following administration of the prodrug to a patient. The suitability and techniques involved in making and using prodrugs are well known by those skilled in the art. For a general discussion of prodrugs involving esters see Svensson and Tunek Drug Metabolism Reviews 165 (1988) and Bundgaard Design of Prodrugs, Elsevier (1985). Examples of a masked carboxylate anion include a variety of esters, such as alkyl (for example, methyl, ethyl), cycloalkyl (for example, cyclohexyl), aralkyl (for example, benzyl, p-methoxybenzyl), and alkylcarbonyloxyalkyl (for example, pivaloyloxymethyl). Amines have been masked as arylcarbonyloxymethyl substituted

derivatives which are cleaved by esterases in vivo releasing the free drug and formaldehyde (Bundgaard J. Med. Chem., 2503 (1989)). Also, drugs containing an acidic NH group, such as imidazole, imide, indole and the like, have been masked with N-acyloxymethyl groups (Bundgaard Design of Prodrugs, Elsevier (1985)). Hydroxy groups have been masked as esters and ethers. EP 039,051 (Sloan and Little, 4/11/81) discloses Mannich-base hydroxamic acid prodrugs, their preparation and use.

"Cytokine" means a secreted protein that affects the functions of other cells, particularly as it relates to the modulation of interactions between cells of the immune system or cells involved in the inflammatory response. Examples of cytokines include but are not limited to interleukin 1 (IL-1), preferably IL-1ß, interleukin 6 (IL-6), interleukin 8 (IL-8) and TNF, preferably TNF-α (tumor necrosis factor-α).

"TNF, IL-1, IL-6, and/or IL-8 mediated disease or disease state" means all disease states wherein TNF, IL-1, IL-6, and/or IL-8 plays a role, either directly as TNF, IL-1, IL-6, and/or IL-8 itself, or by TNF, IL-1, IL-6, and/or IL-8 inducing another cytokine to be released. For example, a disease state in which IL-1 plays a major role, but in which the production of or action of IL-1 is a result of TNF, would be considered mediated by TNF.

Compounds according to the invention can be synthesized according to one or more of the following methods. It should be noted that the general procedures are shown as it relates to preparation of compounds having unspecified stereochemistry. However, such procedures are generally applicable to those compounds of a specific stereochemistry, e.g., where the stereochemistry about a group is (S) or (R). In addition, the compounds having one stereochemistry (e.g., (R)) can often be utilized to produce those having opposite stereochemistry (i.e., (S)) using well-known methods, for example, by inversion.

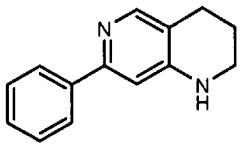
Synthetic Methods

Abbreviations

Ac_2O	acetic anhydride
CH_2Cl_2	dichloromethane, methylene chloride
DCM	dichloromethane
DCE	1,2-dichloroethane
DME	dimethoxyethane, ethylene glycol dimethyl ether
DMF	dimethyl formamide

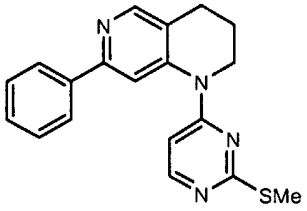
EDC	1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride
Et_2O	diethyl ether
EtOH	ethanol
EtOAc	ethyl acetate
Fmoc	9-fluorenylmethoxycarbonyl
h	hour(s)
MeOH	methanol
NMP	1-methyl-2-pyrrolidinone
i-PrOH	isopropanol
PS-carbodiimide	polymer supported carbodiimide resin from Argonaut
RT	RT
SiO_2	silica
TFA	trifluoroacetic acid
THF	tetrahydrofuran

Example 1



7-Phenyl-1,2,3,4-tetrahydro-1,6-naphthyridine. 7-Phenyl-1,6-naphthyridine (Larcok, R. C. et. al. J. Org. Chem., 67:86-94 (2002), 1.148 g, 5.58 mmol) in MeOH (10 mL) was added Pd (5 % wet w/w on carbon, ~1 g) and the resulting suspension was stirred under 1 atm H_2 overnight. The catalyst was removed with a short pad of Celite and washed with MeOH. Removal of solvent gave the title compound as a pale brown foam. MS m/z 211.1 $(MH)^+$.

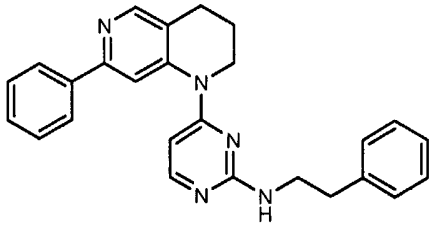
Example 2



1-(2-(Methylthio)pyrimidin-4-yl)-7-phenyl-1,2,3,4-tetrahydro-1,6-naphthyridine

7-Phenyl-1,2,3,4-tetrahydro-1,6-naphthyridine (0.81 g, 3.86 mol) was mixed with *rac*-BINAP (0.12 g, 0.93 mmol), $Pd(OAc)_2$ (43 mg, 0.93 mmol) and sodium *tert*-butoxide (1.85 g, 19.3 mol) in a reaction vial. After purged with N_2 for 10 min, toluene (2 mL) and *tert*-butanol (0.2 mL) were added followed by 4-chloro-2-thiomethylpyrimidine (0.9 mL, 7.7 mmol). The mixture was sealed and heated at 120 °C for 24 h. After cooled, the reaction was quenched with ammonium chloride (sat'd aq) and diluted with water and DCM. After filtrated, the separated aqueous layer was exacted with DCM. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. Removal of volatile material provided the crude product which was purified with flash column chromatography (pure DCM → 1% MeOH in DCM) to provide the title compound as a light yellow solid. MS m/z 335.1 $(M+H)^+$.

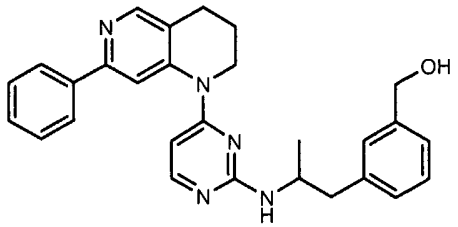
Example 3



***N*-Phenethyl-4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(*2H*)-yl)pyrimidin-2-amine**

m-CPBA (44 mg, ~70%, 0.18 mmol) was added to a cold (0 °C) solution of 1-(2-(methylthio)pyrimidin-4-yl)-7-phenyl-1,2,3,4-tetrahydro-1,6-naphthyridine (60 mg, 1.27 mmol) in DCM (4 mL) and the overall mixture was stirred at the same temperature for 30 min prior to being quenched with saturated aqueous sodium bicarbonate . The aqueous layer was extracted with DCM and the combined organic phases were washed 1 N NaOH(aq) and then dried over Na_2SO_4. Filtration followed by evaporation provided the crude sulfoxide , which was mixed with phenethylamine (0.5 mL) in NMP (1.5 mL). The entire mixture was heated at 100 °C overnight and the volatile material was removed by vacuum distillation. The residue was purified with a flashed column chromatography (pure DCM → 1% MeOH in DCM) to yield the title compound as a pale yellow solid. MS m/z 408.2 $(M+H)^+$.

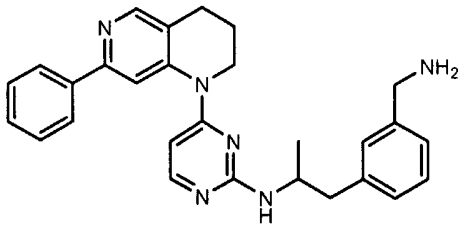
Example 4



(3-(2-(4-(7-Phenyl-3,4-dihydro-1,6-naphthyridin-1(*2H*)-yl)pyrimidin-2-ylamino)-propyl)phenyl)methanol

The title compound was obtained in a similar manner as previously described in Example 3 with (3-(2-aminopropyl)phenyl)methanol (0.42 g, 2.5 mmol) and 1-(2-(methylthio) pyrimidin-4-yl)-7-phenyl-1,2,3,4-tetrahydro-1,6-naphthyridine (0.7 g, 2.01 mmol) to give an off-white solid. MS m/z 452.2 $(M+H)^+$.

Example 5

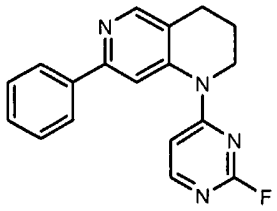


***N*-(1-(3-(Aminomethyl)phenyl)propan-2-yl)-4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(*2H*)-yl)pyrimidin-2-amine**

A THF (10 mL) solution of benzylic alcohol (0.5 g, 1.1 mmol) obtained from Example 4 was treated with DBU (0.33 mL, 2.22 mmoL) and diphenylphosphoryl azide (0.36 mL, 1.67 mmol) at 0 °C and the overall mixture was stirred at RT overnight. After dilution with saturated ammonium chloride aqueous solution, the separated aqueous layer was extracted with ethyl acetate (x2) and the combined organic phases were dried (Na_2SO_4), filtrated, and concentrated to give a crude azide which was immediately treated with 10% Pd/C (0.5 g) in EtOAc (15 mL) under H_2 (1 atm) at RT overnight. Filtration followed by evaporation provided the crude product, which was subjected to a flash column

purification (pure DCM → 3% MeOH in DCM) to yield the title compound. MS m/z 451.3 $(M+H)^+$.

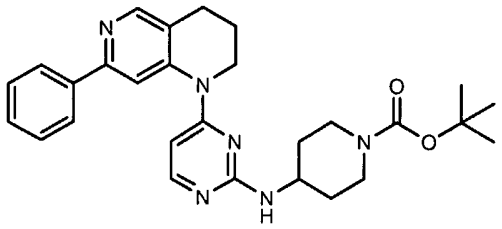
Example 6



1-(2-Fluoropyrimidin-4-yl)-7-phenyl-1,2,3,4-tetrahydro-1,6-naphthyridine

7-Phenyl-1,2,3,4-tetrahydro-1,6-naphthyridine (3.5 g, 16.7 mol) in THF (100 mL) was cooled down to –78 °C and lithium bis(trimethylsilyl) amide (1.5 eq. 25 mmol) added slowly and stirred for 15 min at –78 °C. 2,4-Difluoropyrimidine (33.3 mmol) was added and the resulting mixture was stirred at –78 °C for 1 h. The reaction was quenched with ammonium chloride (sat'd aq) at –78 °C, warmed up to RT and extracted with ethyl acetate and DCM. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. Removal of volatile material provided the crude product, which was purified by flash column chromatography (pure DCM → 1% MeOH in DCM) to provide the title compound as a light yellow solid. MS m/z 307.1 $(M+H)^+$.

Example 7

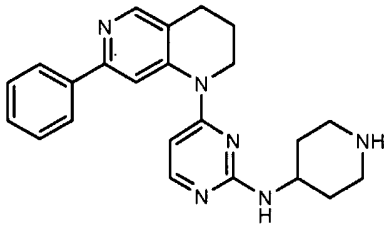


***tert*-Butyl 4-(4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(*2H*)-yl)pyrimidin-2-ylamino)piperidine-1-carboxylate**

m-CPBA (4.4 g, ~70%, 17.14 mmol) was added to a cold (0 °C) solution of 1-(2-(methylthio)pyrimidin-4-yl)-7-phenyl-1,2,3,4-tetrahydro-1,6-naphthyridine (5.0 g, 14.27 mmol) in DCM (250 mL) and the overall mixture was stirred at the same temperature for

30 min prior to being quenched with saturated aqueous sodium bicarbonate. The aqueous layer was extracted with DCM and the combined organic phases were washed 1 N NaOH(aq) and then dried over Na_2SO_4. Filtration followed by evaporation provided the crude sulfoxide (4.85 g, 13.25 mmol). The crude sulfoxide (336 mg, 1.63mmol) was mixed with *tert*-butyl 4-aminopiperdine-1-carboxylate (300 mg, 0.82 mmol) in NMP (25 mL). The entire mixture was heated at 100 °C overnight and the volatile material was removed by vacuum distillation. The residue was purified with a flashed column chromatography (pure DCM → 1% MeOH in DCM) to yield the title compound as a white solid. MS m/z 504.6 $(M+H)^+$.

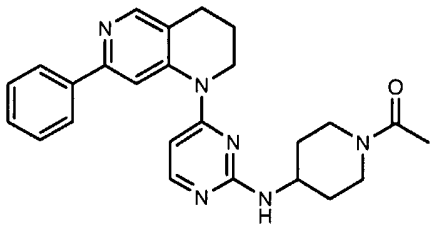
Example 8



4-(7-Phenyl-3,4-dihydro-1,6-naphthyridin-1(*2H*)-yl)-*N*-(piperidin-4-yl)pyrimidin-2-amine

The Boc-amine from Example 7 (0.350 g), was deprotected with 4 N HCl in dioxane (5 mL) at RT for 30 min. Concentration followed by purification (column chromatography, 5% → 10% MeOH in DCM afforded the title compound as an off-white solid. MS m/z 404.6 $(M+H)^+$.

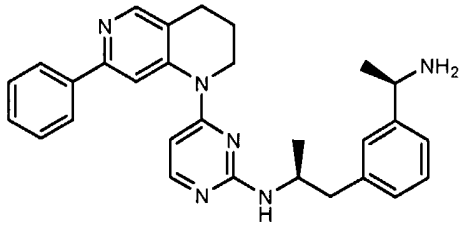
Example 9



1-(4-(4-(7-Phenyl-3,4-dihydro-1,6-naphthyridin-1(*2H*)-yl)pyrimidin-2-ylamino)-piperidin-1-yl)ethanone

To a suspension of PS-Carboiimide (1 g, 1 mmol, 1.31 mmol/g loading) in DCM was added acetic acid (45 mg, 0.74 mmol) and stirred at RT for 10 min. To the resulting suspension 4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(*2H*)-yl)-*N*-(piperidin-4-yl)pyrimidin-2-amine (200 mg, 0.49 mmol) was added and stirred overnight. Filtration followed by concentration and purification (column chromatography, 5% → 10% MeOH in DCM) afforded the title compound as an off-white solid. MS m/z 446.6 $(M+H)^+$.

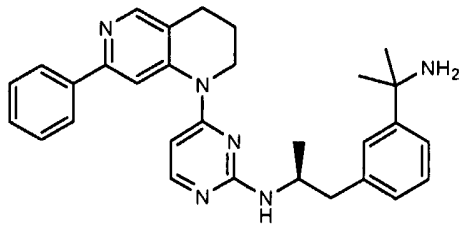
Example 10



***N*-((*S*)-1-(3-((*R*)-1-Aminoethyl)phenyl)propan-2-yl)-4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(*2H*)-yl)pyrimidin-2-amine**

1-(2-Fluoropyrimidin-4-yl)-7-phenyl-1,2,3,4-tetrahydro-1,6-naphthyridine (0.374 g, 1.22 mmol) and tert-butyl (*R*)-1-(3-((*S*)-2-aminopropyl)phenyl)ethylcarbamate (0.408 g, 1.47 mmol) in dioxane (50 mL) were heated at 100 °C overnight. After cooling down to RT the volatile material was removed under reduced pressure. The residue was purified with a flashed column chromatography (1% → 5% MeOH in DCM) to yield the Boc-amine (0.39 g), which was deprotected with 4N HCl in dioxane (5 mL) at RT for 30 min. Concentration followed by purification (column chromatography, 5% → 10% MeOH in DCM) afforded the title compound as an off-white solid. MS m/z 465.3 $(M+H)^+$.

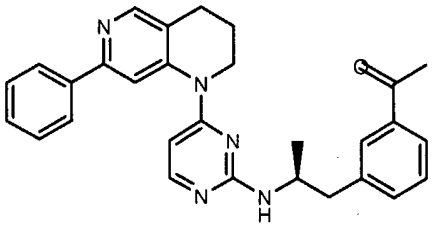
Example 11



***(S)*-*N*-(1-(3-(2-Aminopropan-2-yl)phenyl)propan-2-yl)-4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(*2H*)-yl)pyrimidin-2-amine**

The title compound was obtained with the similar manner as described previously in example 10 with (*S*)-1-(3-(2-aminopropan-2-yl)phenyl)propan-2-amine (0.087 g, 0.453 mmol) and 1-(2-fluoropyrimidin-4-yl)-7-phenyl-1,2,3,4-tetrahydro-1,6-naphthyridine (0.138 g, 0.453 mmol) to give an off-white solid. MS m/z 479.6 $(M+H)^+$.

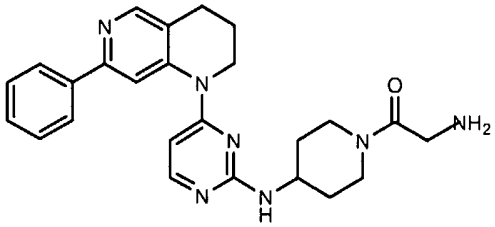
Example 12



(S)-1-(3-(2-(4-(7-Phenyl-3,4-dihydro-1,6-naphthyridin-1(2H)-yl)pyrimidin-2-yl-amino)propyl)phenyl)ethanone

The title compound was obtained with the similar manner as described previously in example 10 with (*S*)-1-(3-(2-aminopropyl)phenyl)ethanone (0.230 g, 0.1.31 mmol) and 1-(2-fluoropyrimidin-4-yl)-7-phenyl-1,2,3,4-tetrahydro-1,6-naphthyridine (0.200 g, 0.65 mmol) to give an off-white solid. MS m/z 464.6 $(M+H)^+$.

Example 13

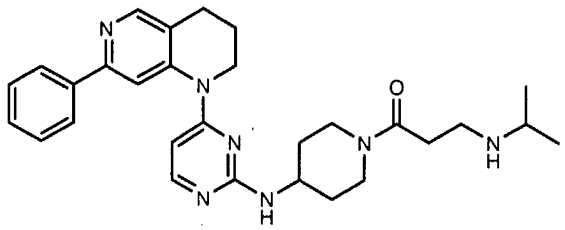


2-Amino-1-(4(4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(*2H*)-yl)pyrimidin-2-yl-amino)piperdin-1- yl)ethanone

To a suspension of PS-carboiimide (2 g, 1 mmol, 1.31 mmol/g loading) in DCM was added 2-(tert-butoxycarbonyl)acetic acid (186 mg, 1.16 mmol) and strrided at RT for 10 min. To the resulting suspension 4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(*2H*)-yl)-*N*-(piperidin-4-yl)pyrimidin-2-amine (300 mg 0.78 mmol) was added and stirred overnight. Filtration followed by concentration and purification (column chromatography, 5% →

10% MeOH in DCM) afforded the Boc-amine (480 mg) as an off-white solid. MS m/z 544.7 $(M+H)^+$, which was deprotected with 4N HCl in dioxane (3 mL) at RT for 30 min. Concentration followed by purification (column chromatography, 5% → 10% MeOH in DCM) afforded the title compound as an off-white solid. MS m/z 445.6 (M+H).

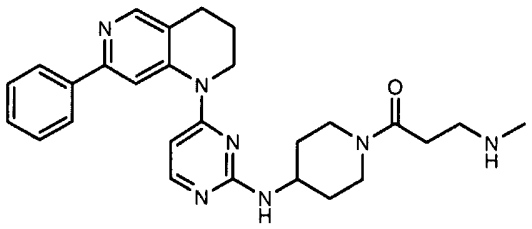
Example 14



3-(Isopropylamino)-1-(4(4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(*2H*)-yl)pyrimidin-2-ylamino)piperdin-1- yl)propan-1-one

To a suspension of PS-carboiimide (6.2 g, 1 mmol, 1.31 mmol/g loading) in DCM was added 3-bromopropanoic acid (714 mg, 4.66 mmol) and stirred at RT for 10 min. To the resulting suspension 4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(*2H*)-yl)-*N*-(piperidin-4-yl)pyrimidin-2-amine (1.2 g 3.11 mmol) was added and stirred overnight. Filtration followed by concentration and purification (column chromatography, 5% → 10% MeOH in DCM) afforded 3-bromo-1-(4(4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(*2H*)-yl)pyrimidin-2-ylamino)piperdin-1-yl)propan-1-one (900 mg) as an off-white solid. MS m/z 521.2 $(M+H)^+$. The bromo compound (250 mg, 0.48 mmol), acetonitrile (10 mL) and isopropyl amine (24 mg, 0.77 mmol) in THF were heated at 50 °C for 4 h. Concentration followed by purification (column chromatography, 5% → 10% MeOH in DCM) afforded the title compound as an off-white solid. MS m/z 500.6 (M+H).

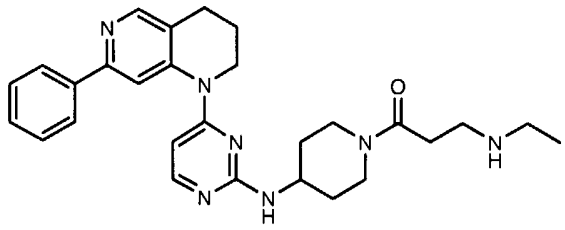
Example 15



3-(Methylamino)-1-(4(4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(*2H*)-yl)-pyrimidin-2-ylamino)piperdin-1- yl)propan-1-one

The title compound was obtained with the similar manner as described previously in example 14 with methyl amine (23 mg, 0.77 mmol) and 3-bromo-1-(4(4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(*2H*)-yl)pyrimidin-2-ylamino)piperdin-1- yl)propan-1-one (0.200 g, 0.38 mmol) to give an off-white solid. MS m/z 472.6 $(M+H)^+$.

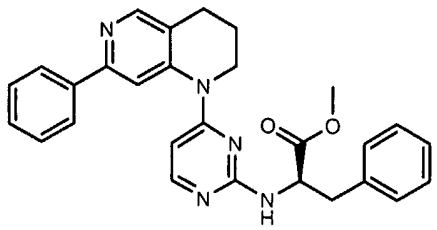
Example 16



3-(Ethylamino)-1-(4(4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(*2H*)-yl)pyrimidin-2-ylamino)piperdin-1- yl)propan-1-one

The title compound was obtained with the similar manner as described previously in example 14 with ethyl amine (35 mg, 0.77 mmol) and 3-bromo-1-(4(4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(2H)-yl)pyrimidin-2-ylamino)piperdin-1- yl)propan-1-one (0.200 g, 0.38 mmol) to give an off-white solid. MS m/z 485.5 $(M+H)^+$.

Example 17

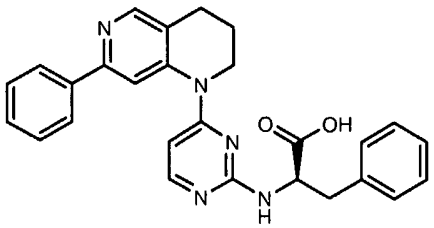


(*R*)-Methyl-3-phenyl-2-(4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(*2H*)-yl)-pyrimidin-2-ylamino)propanoate

1-(2-Fluoropyrimidin-4-yl)-7-phenyl-1,2,3,4-tetrahydro-1,6-naphthyridine (1.2 g, 3.9 mmol) and (*R*)-methyl 2-amino-3-phenylpropanote hydrochloride (1.7 g, 3.9 mmol) in

dioxane (50 mL) was heated at 100 °C overnight and the volatile material was removed under reduced pressure. The residue was purified with a flashed column chromatography (1% → 5% MeOH in DCM) to yield the title compound as an off-white solid. MS m/z 466.6 $(M+H)^+$.

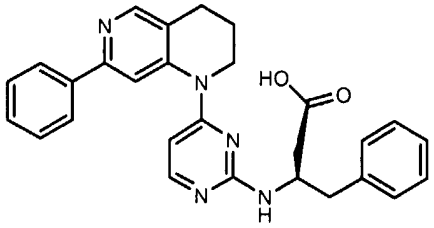
Example 18



(*R*)-3-Phenyl-2-(4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(*2H*)-yl)pyrimidin-2-ylamino)propanoic acid

(*R*)-Methyl-3-phenyl-2-(4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(*2H*)-yl)pyrimidin-2-ylamino)propanoate (1.2 g, 2.72 mmol), thiophenol (0.300 g, 2.72 mmol), potassium carbonate (5% mol) in NMP (20 mL) were heated at 190 °C for 1 h. After cooling down to RT the mixture was diluted with $NaHCO_3$ and extracted with ether. Then the aqueous layer was acidified with HCl (6M), extracted with DCM and concentrated to yield the title compound as an off-white solid. MS m/z 427.5 $(M+H)^+$.

Example 19

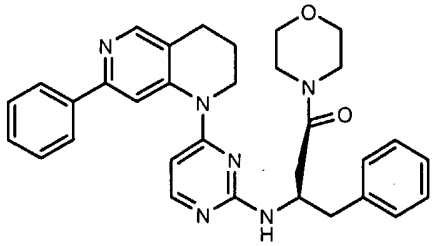


(*R*)-4-Phenyl-3-(4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(*2H*)-yl)pyrimidin-2-ylamino)butanoic acid

1-(2-Fluoropyrimidin-4-yl)-7-phenyl-1,2,3,4-tetrahydro-1,6-naphthyridine (1.1 g, 3.6 mmol) and (*R*)-3-amino-4-phenylbutanoic acid (0.965 g, 5.39 mmol) in dioxane (70 mL) were heated at 100 °C overnight and the volatile material was removed under reduced

pressure. The residue was purified with a flashed column chromatography (1% → 5% MeOH in DCM) to yield the title compound as an off-white solid. MS m/z 466.6 $(M+H)^+$.

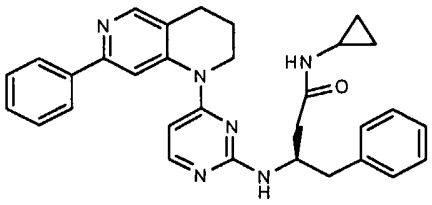
Example 20



(*R*)-1-Morpholino-4-phenyl-3-(4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(*2H*)-yl)pyrimidin-2-ylamino)butan-1-one

The title compound was obtained in a similar manner as described previously in example 9 with morpholine (105 mg, 1.29 mmol) and (*R*)-4-phenyl-3-(4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(*2H*)-yl)pyrimidin-2-ylamino)butanoic acid (0.300 g, 0.65 mmol) to give an off-white solid. MS m/z 535.8 $(M+H)^+$.

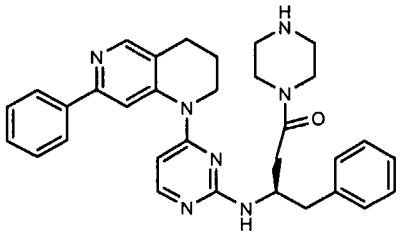
Example 21



(*R*)-*N*-Cyclopropyl-4-phenyl-3-(4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(*2H*)-yl)pyrimidin-2-ylamino)butanamide

The title compound was obtained in a similar manner as described previously in Example 9 with cyclopropylamine (73 mg, 1.29 mmol) and (*R*)-4-phenyl-3-(4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(*2H*)-yl)pyrimidin-2-ylamino)butanoic acid (0.300 g, 0.65 mmol) to give an off-white solid. MS m/z 504.8 $(M+H)^+$.

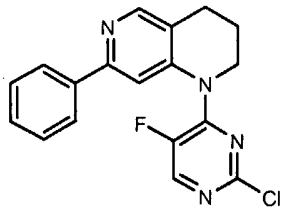
Example 22



(*R*)-4-Phenyl-3-(4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(*2H*)-yl)pyrimidin-2-ylamino)-1-(piperazin-1yl)butan-1-one

The title compound was obtained in a similar manner as described previously in example 9 with piperazine (148 mg, 1.72 mmol) and (*R*)-4-phenyl-3-(4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(*2H*)-yl)pyrimidin-2-ylamino)butanoic acid (0.400 g, 0.86 mmol) to give an off-white solid (170 mg). MS m/z 534.8 $(M+H)^+$.

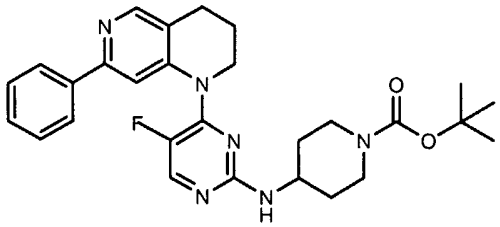
Example 23



1-(2-Chloro-5-fluoropyrimidin-4-yl)-7-phenyl-1,2,3,4-tetrahydro-1,6-naphthyridine

7-Phenyl-1,2,3,4-tetrahydro-1,6-naphthyridine (1.5 g, 7.1 mol) in THF (100 mL) was cooled down to –78 °C and lithium bis(trimethylsilyl) amide (1.5 eq. 10.7 mmol) added slowly and stirred for 15 min at –78 °C. Then 2-chloro-4,5-difuoropyrimidine (14.28 mmol) was added and the resulting mixture was stirred at –78 °C for 1 h. The reaction was quenched with ammonium chloride (sat'd aq) at –78 °C and warmed up to RT. After extracted with ethyl acetate and DCM, the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. Removal of volatile material provided the crude product, which was purified by flash column chromatography (pure DCM → 1% MeOH in DCM) to provide the title compound as a light yellow solid. MS m/z 341.1 $(M+H)^+$.

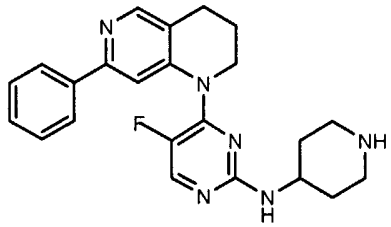
Example 24



***tert*-Butyl-4-(5-fluoro-4(7-phenyl-3,4-dihydro-1,6-naphthylridin-1(*2H*)-pyrimidin-2-ylamino)piperidine-1-carboxylate**

1-(2-Chloro-5-fluoropyrimidin-4-yl)-7-phenyl-1,2,3,4-tetrahydro-1,6-naphthyridine (250 mg, 0.735 mmol) in isopropyl alcohol (1 mL), catalytic amount of PTSA and tert-butyl 4-aminopiperdine-1- carboxylate (294 mg, 1.47 mmol) were heated in a microwave synthesizer at 140 °C for 1 h. Concentration followed by purification (column chromatography, 5% → 10% MeOH in DCM) afforded the title compound as an off-white solid. MS m/z 505.6 (M+H).

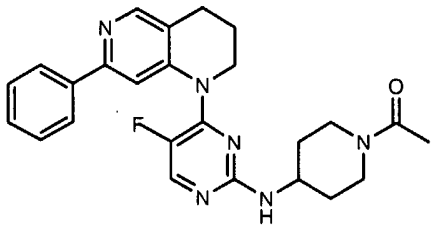
Example 25



5-Fluoro-4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(2H)-yl)-N-(piperidin-4-yl)pyrimidin-2-amine

The Boc-amine from Example 24 (0.090 g), was deprotected with 4 N HCl in dioxane (5 mL) at RT for 30 min. Concentration followed by purification (column chromatography, 5% → 10% MeOH in DCM) afforded the title compound as an off-white solid. MS m/z 405.6 $(M+H)^+$.

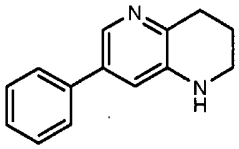
Example 26



1-(4-(5-Fluoro-4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(*2H*)-yl)pyrimidin-2-yl-amino)piperidin-1-yl)ethanone

To a suspension of PS-Carboiimide (1 g, 1 mmol, 1.31 mmol/g loading) in DCM was added acetic acid (45 mg, 0.74 mmol) and stirred at RT for 10 min. To the resulting suspension 4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(*2H*)-yl)-*N*-(piperidin-4-yl)pyrimidin-2-amine (175 mg 0.433 mmol) was added and stirred overnight. Filtration followed by concentration and purification (column chromatography, 5% → 10% MeOH in DCM) afforded the title compound as an off-white solid. MS m/z 447.5 $(M+H)^+$.

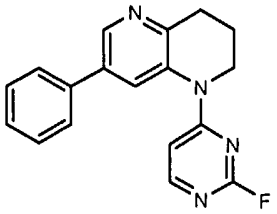
Example 27



7-Phenyl-1,2,3,4-tetrahydro-1,5-naphthyridine

To a solution of 7-phenyl-1,5-naphthyridine (3.8 g, 18 mmol) in dioxane (100 mL) was added Pd (5 % wet w/w on carbon, ~4 g) and the resulting suspension was stirred under 1 atm H_2 overnight. The catalyst was removed with a short pad of Celite and washed with MeOH. Removal of solvent gave the title compound as a pale brown foam. MS m/z 211.1 $(M+H)^+$.

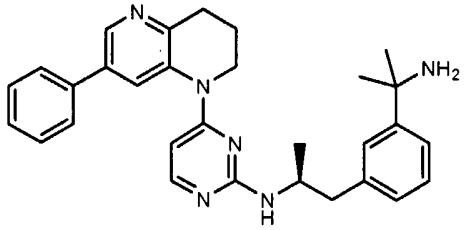
Example 28



1-(2-Fluoropyrimidin-4-yl)-7-phenyl-1,2,3,4-tetrahydro-1,5-naphthyridine

7-Phenyl-1,2,3,4-tetrahydro-1,5-naphthyridine (3.2 g, 15 mol) in THF (100 mL) was cooled down to –78 °C and lithium bis(trimethylsilyl) amide (1.5 eq. 23 mmol) added slowly and stirred for 15 min at –78 °C. Then 2,4-difuoropyrimidine (32.33 mmol) was added and the resulting mixture was stirred at –78 °C for 1 h. The reaction was quenched with ammonium chloride (sat'd aq) at –78 °C, warmed up to RT and extracted with ethyl acetate and DCM. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. Removal of volatile material provided the crude product, which was purified by flash column chromatography (pure DCM → 1% MeOH in DCM) to provide the title compound as a light yellow solid. MS m/z 307.1 $(M+H)^+$.

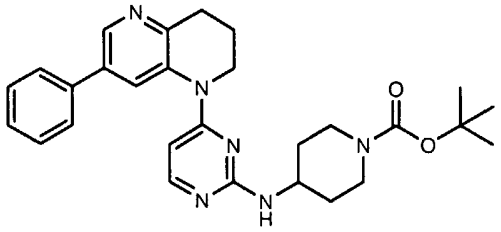
Example 29



(*S*)-*N*-(1-(3-(2-Aminopropan-2-yl)phenyl)propan-2-yl)-4-(7-phenyl-3,4-dihydro-1,5-naphthyridin-1(*2H*)-yl)pyrimidin-2-amine

The title compound was obtained with a similar manner as described previously in example 10 with *(S)*-1-(3-(2-aminopropan-2-yl)phenyl)propan-2-amine (0.087 g, 0.453 mmol) and 1-(2-fluoropyrimidin-4-yl)-7-phenyl-1,2,3,4-tetrahydro-1,5-naphthyridine (0.138 g, 0.453 mmol) to give an off-white solid. MS m/z 479.6 $(M+H)^+$.

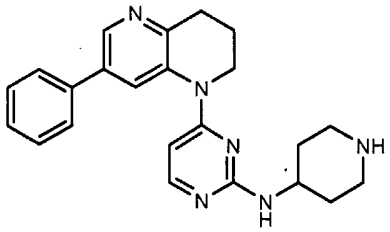
Example 30



***tert*-Butyl-4(7-phenyl-3,4-dihydro-1,5-naphthylridin-1(*2H*)-pyrimidin-2-ylamino)-piperidine-1-carboxylate**

1-(2-Fluoropyrimidin-4-yl)-7-phenyl-1,2,3,4-tetrahydro-1,5-naphthyridine (0.700 g, 2.28 mmol) and *tert*-butyl 4-aminopiperidine-1- carboxylate (915 mg, 4.58 mmol) in dioxane (150 mL) were heated at 100 °C overnight and the volatile material was removed under reduced pressure. The residue was purified by flash column chromatography (1% → 5% MeOH in DCM) to yield the title compound as an off-white solid. MS m/z 487.7 $(M+H)^+$.

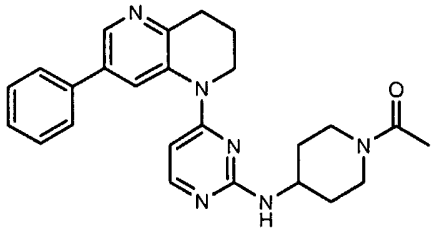
Example 31



4-(7-Phenyl-3,4-dihydro-1,5-naphthyridin-1(*2H*)-yl)-*N*-(piperidin-4-yl)pyrimidin-2-amine

The Boc-amine from example 30 (0.500 g), was deprotected with 4 N HCl in dioxane (5 mL) at RT for 30 min. Concentration followed by purification (column chromatography, 5% → 10% MeOH in DCM) afforded the title compound as an off-white solid. MS m/z 404.6 $(M+H)^+$.

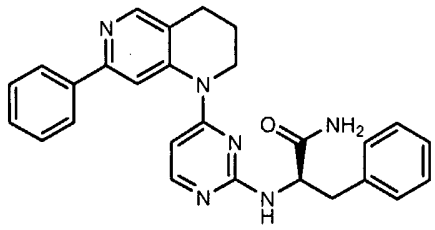
Example 32



1-(4-(4-(7-Phenyl-3,4-dihydro-1,5-naphthyridin-1(*2H*)-yl)pyrimidin-2-ylamino)-piperidin-1-yl)ethanone

To a suspension of PS-Carboiimide (2 g, 1 mmol, 1.31 mmol/g loading) in DCM was added acetic acid (93 mg, 1.55 mmol) and stirred at RT for 10 min. To the resulting suspension 4-(7-phenyl-3,4-dihydro-1,5-naphthyridin-1(*2H*)-yl)-*N*-(piperidin-4-yl)pyrimidin-2-amine (300 mg, 0.776 mmol) was added and stirred overnight. Filtration followed by concentration and purification (column chromatography, 5% → 10% MeOH in DCM) afforded the title compound as an off-white solid. MS m/z 429.6 $(M+H)^+$.

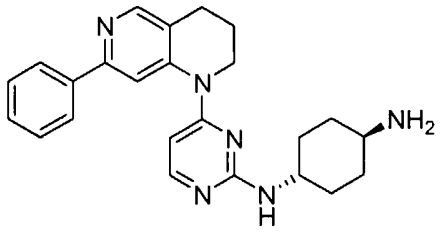
Example 33



(*R*)-3-Phenyl-2-(4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(*2H*)-yl)pyrimidin-2-ylamino)propanamide

(*R*)-Methyl 3-phenyl-2-(4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(*2H*)-yl)pyrimidin-2-ylamino)propanoate (0.150 g, 0.322 mmol), ammonium hydroxide (10 mL) and a 2 M solution of ammonia in methanol (10 mL) were heated at 80 °C overnight in a sealable tube. Concentrate purification (column chromatography, 5% → 10% MeOH in DCM) afforded the title compound as an off-white solid. MS m/z 451.6 $(M+H)^+$.

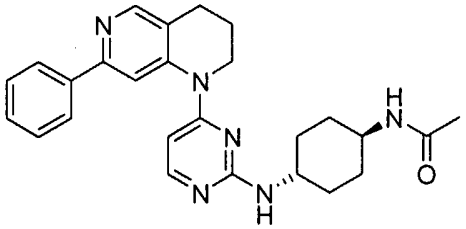
Example 34



(*1R,4R*)-*N*^{1}-(4-(7-Phenyl-3,4-dihydro-1,6-naphthyridin-1(2*H*)-yl)pyrimidin-2-yl)cyclohexane-1, 4-diamine

1-(2-Fluoropyrimidin-4-yl)-7-phenyl-1,2,3,4-tetrahydro-1,6-naththyridine (200 mg, 0.65 mmol) was mixed with trans-1,4-diaminocyclohexane (200 mg, 1.75 mmol) in dioxane (5 mL). The entire mixture was sealed and heated at 100 °C overnight and the volatile material was removed by vacuum distillation. The residue was purified by flash column chromatography (5%-10% MeOH in DCM) to yield the title compound as an off-white solid. MS m/z 401 $(M+H)^+$.

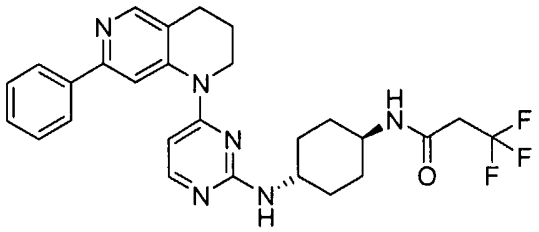
Example 35



***N*-((*1R,4R*)-4-(4-(7-Phenyl-3,4-dihydro-1,6-naphthyridin-1(2*H*)-yl)pyrimidin-2-ylamino)cyclohexyl) acetamide**

To the stirring suspension of acetic acid (100 mg, 2 mmol) and PS-carbodiimide (0.2 g, 0.26 mmol, loading 1.3 mmol/g) in DCM (5 mL), (*1R,4R*)-*N*^{1}- (4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1 (2*H*)-yl) pyrimidin-2-yl) cyclohexane-1, 4-diamine (100 mg, 0.25 mmol) was added. The suspension was stirred at RT overnight and filtered off. The filtrate was concentrated under vacuum and the crude product was precipitated in ether to provide the title compound as an off-white solid. MS m/z 443 $(M+H)^+$.

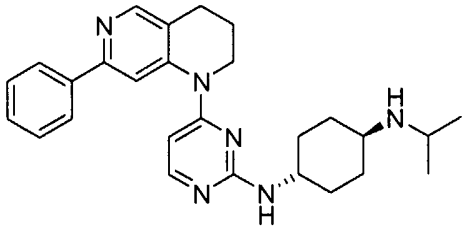
Example 36



3,3,3-Trifluoro-*N*-((*1R,4R*)-4-(4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(2*H*)-yl)-pyrimidin-2-ylamino)cyclohexyl)propanamide

To a stirring suspension of 3,3,3-trifluoropropionic acid (100 mg, 0.8 mmol) and PS-carbodiimide (0.3 g, 0.36 mmol, loading 1.3 mmol/g), in DCM (5 mL), (*1R,4R*)-*N*^{1}-(4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(2*H*)-yl) pyrimidin-2-yl) cyclohexane-1,4-diamine (100 mg, 0.25 mmol) was added. The suspension was stirred at RT overnight and then filtered out. The filtrate was concentrated under vacuum and the crude product purified by flash column chromatography (2% MeOH in DCM) to yield the title compound as an off-white solid. MS m/z 511 $(M+H)^+$.

Example 37

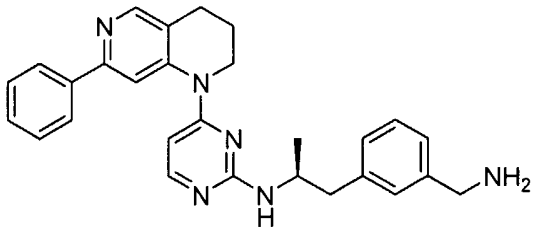


(*1R,4R*)-*N*^{1}-Isopropyl-*N*^{4}-(4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(2*H*)-yl)-pyrimidin-2-yl) cyclohexane-1,4-diamine

To a stirring solution of (*1R,4R*)-*N*^{1}-(4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(2*H*)-yl)pyrimidin-2-yl) cyclohexane-1,4-diamine (100 mg, 0.25 mmol) and acetone (5 mL), sodium triacetoxyborohydride (100 mg, 0.5 mmol) with catalytic amount of acetic acid was added. The suspension was stirred at RT overnight, and then the mixture was quenched with ammonium chloride (sat'd aq) and diluted with water and DCM. The separated aqueous layer was exacted several times with DCM. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. Removal of

volatile material provided the crude product, which was purified by flash column chromatography (pure DCM → 2% MeOH in DCM) to provide the title compound as an off-white solid. MS m/z 443 $(M+H)^+$.

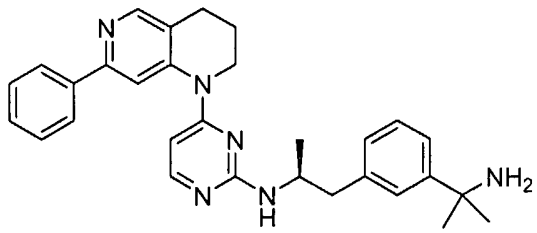
Example 38



(*S*)-*N*-(1-(3-(Aminoethyl)phenyl)propan-2-yl)-4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(2*H*)-yl) pyrimidin-2-amine

1-(2-Fluoropyrimidin-4-yl)-7-phenyl-1,2,3,4-tetrahydro-1,6-naphthyridine (300. mg, 0.98 mmol) was mixed with (*S*)-*tert*-butyl(3-(2-aminopropyl)benzyl)carbamate (310 mg, 1.17 mmol) in dioxane (5 mL) then sealed and heated at 100 °C overnight. After removal of the volatile material by reduced pressure, the residue was purified by flash column chromatography (2%-5% MeOH in DCM) to yield (*S*)-*tert*-butyl(3-(2-(4-(7-phenyl-3,4-dihydro-1,6-naththyridin-1(2*H*)-yl)pyrimidin-2-ylamino)propyl)phenyl)methyl carbamate as an off-white solid. MS m/z 551 $(M+H)^+$. The Boc-amine (0.15 g) was deprotected with TFA (2mL) in DCM (2 mL) at RT for 30 min. Concentration followed by purification (column chromatography, 5%MeOH in DCM) afforded the title compound as an off-white solid. MS m/z 451 $(M+H)^+$.

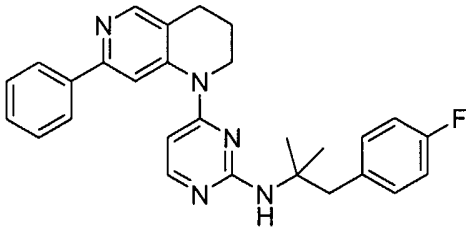
Example 39



(*S*)-*N*-(1-(3-(2-Aminopropan-2-yl)phenyl)propan-2-yl)-4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(2*H*)-yl) pyrimidin-2-amine

1-(2-Fluoropyrimidin-4-yl)-7-phenyl-1,2,3,4-tetrahydro-1,6-naththyridine (100 mg, 0.32 mmol) was mixed with (*S*)-1-(3-(2-aminopropan-2-yl)phenyl)propan-2-amine (70. mg, 0.36 mmol) in dioxane (5 mL), then sealed and heated at 90 °C overnight. The volatile material was removed by reduced pressure and the residue purified by flash column chromatography (5%-10% MeOH in DCM) to yield the title compound as a yellow solid. MS m/z 479(M+H)$^+$.

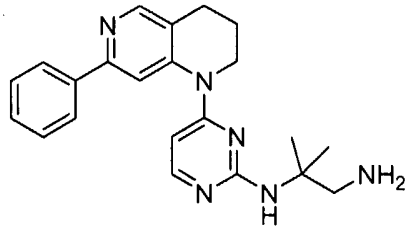
Example 40



***N*-(1-(4-Fluorophenyl)-2-methylpropan-2-yl)-4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(2*H*)-yl) pyrimidin-2-amine**

1-(2-Fluoropyrimidin-4-yl)-7-phenyl-1,2,3,4-tetrahydro-1,6-naththyridine (100 mg, 0.32 mmol) was mixed with 1-(4-fluorophenyl)-2-methylpropan-2-amine (100 mg, 0.6 mmol) in dioxane (5 mL) then sealed and heated at 100 °C overnight. The volatile material was removed by reduced pressure and the residue purified by flash column chromatography (5% MeOH in DCM) to yield the title compound as a yellow solid. MS m/z 454(M+H)$^+$.

Example 41

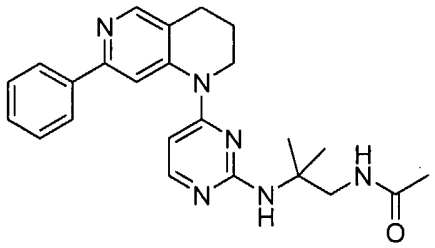


***N*-(1-Amino-2-methylpropan-2-yl)-4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(2*H*)-yl)pyrimidin-2-amine**

1-(2-Fluoropyrimidin-4-yl)-7-phenyl-1,2,3,4-tetrahydro-1,6-naththyridine (300 mg, 0.98 mmol) was mixed with 2-amino-2-methyl-propyl-carbamic acid *tert*-butyl ester (250. mg,

1.33 mmol) in dioxane (5 mL), then sealed and heated at 100 °C overnight. The volatile material was removed by reduced pressure and the residue purified by flash column chromatograpy (2% MeOH in DCM) to yield *tert*-butyl 2-methyl-2-(4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(2*H*)-yl)pyrimidin-2-ylamino) propyl carbamate as a white solid. MS m/z 475 $(M+H)^+$. The resulted Boc-amine (0.1 g) was deprotected with TFA (2 mL) in DCM (2 mL) at RT for 30 min. Concentration followed by purification (column chromatography, 5%MeOH in DCM) afforded the title compound as an off-white solid. MS m/z 375 $(M+H)^+$.

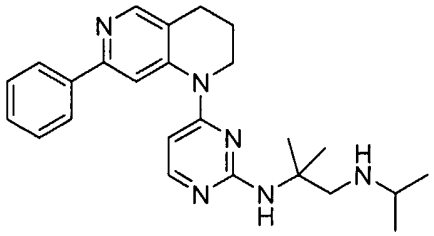
Example 42



***N*-(2-Methyl-2-(4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(2*H*)-yl)pyrimidin-2-ylamino)propyl) acetamide**

To the stirring suspension of acetic acid (100 mg, 1.6 mmol) and PS-carbodiimide (0.2 g, 0.26 mmol, loading 1.3 mmol/g) in DCM (5 mL) was added *N*-(1-amino-2-methylpropan-2-yl)-4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(2*H*)-yl) pyrimidin-2-amine (80 mg, 0.2 mmol). The suspension was stirred at RT overnight and filtered out. The filtrate was concentrated under vacuum and the crude product was purified by flash column chromatography (pure DCM → 2% MeOH in DCM) to provide the title compound (40 mg) as an off-white solid. MS m/z 443 $(M+H)^+$.

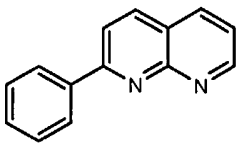
Example 43



***N*-(1-(Isopropylamino)-2-methylpropan-2-yl)-4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(2*H*)-yl) pyrimidin-2-amine**

To the stirring solution of (*1R,4R*)-*N'*-(4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(2*H*)-yl) pyrimidin-2-yl)cyclohexane-1,4-diamine (50 mg, 0.13 mmol) in acetone (5 mL) was added sodium triacetoxyborohydride (50 mg, 0.24 mmol) with catalytic amount of acetic acid. Then the suspension was stirred at RT overnight. The mixture was quenched with ammonium chloride (sat'd aq) and diluted with water and DCM. The separated aqueous layer was extracted with DCM and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. Removal of volatile material provided the crude product, which was purified by flash column chromatography (pure DCM → 2% MeOH in DCM) to provide the title compound as an off-white solid. MS m/z 417 $(M+H)^+$.

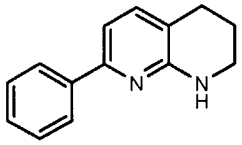
Example 44



2-Phenyl-1,8-naphthyridine

To a solution of 2-aminonicotinaldehyde (1.3 g, 10.6 mmol) in EtOH (10 mL) was added acetophenone (2.5 g, 21.2 mmol) and several drops of 10% NaOH. Them the mixture was heated under reflux for 24 h. After that the solvent was removed and the residue triturated with hexanes and filtered off to give the title compound as a yellow solid. MS m/z 207 $(MH)^+$.

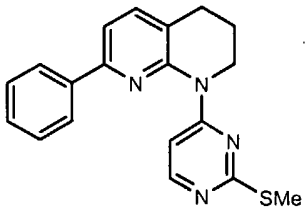
Example 45



7-Phenyl-1,2,3,4-tetrahydro-1,8-naphthyridine

To a solution of 2-phenyl-1,8-naphthyridine (596 mg, 2.9 mmol) in EtOH (5 mL) was added Pd (5 % wet w/w on carbon, ~0.5 g) and the resulting suspension was stirred under 1 atm H_2 overnight. The catalyst was removed with a short pad of Celite and washed with EtOH. The residue was purified by flash chromatography (hex: EtOAc, 2:1) to give the title compound as a light yellow solid (290 mg). MS m/z 211 $(MH)^+$.

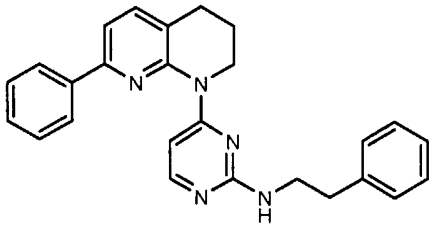
Example 46



1-(2-(Methylthio)pyrimidin-4-yl)-7-phenyl-1,2,3,4-tetrahydro-1,8-naphthyridine

7-Phenyl-1,2,3,4-tetrahydro-1,8-naphthyridine (280 mg, 1.3 mmol) was mixed with *rac*-BINAP (25 mg, 0.04 mmol), $Pd(OAc)_2$ (9 mg, 0.04 mmol) and sodium *tert*-butoxide (250 mg, 2.6 mmol) in a reaction vial. After purged with N_2 for 10 min, toluene (2 mL) was added followed by 4-chloro-2-thiomethylpyrimidine (0.23 mL, 1.9 mmol). The mixture was sealed and heated at 100 °C for 7 h. After cooling down to RT the reaction mixture was quenched with ammonium chloride (sat'd aq) and diluted with water and DCM. The separated aqueous layer was extracted several times with DCM. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. Removal of volatile material provided the crude product, which was purified by flash column chromatography (5 % EtOAc in hex → 20 % EtOAc in hex) to provide the title compound as a white solid. MS m/z 335 $(M+H)^+$.

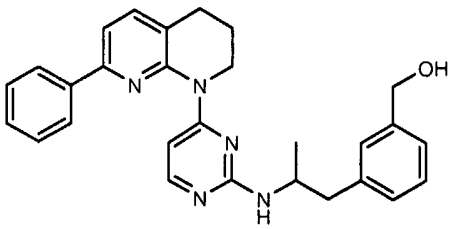
Example 47



***N*-Phenethyl-4-(7-phenyl-3,4-dihydro-1,8-naphthyridin-1(*2H*)-yl)pyrimidin-2-amine**

m-CPBA (468 mg, ~70%, 1.9 mmol) was added to a cold (0 °C) solution of 1-(2-(methylthio)pyrimidin-4-yl)-7-phenyl-1,2,3,4-tetrahydro-1,8-naphthyridine (423 mg, 1.27 mmol) in DCM (10 mL) and the overall mixture was stirred at the same temperature for 30 min prior to being quenched with saturated aqueous sodium bicarbonate. The aqueous layer was extracted several times with DCM and the combined organic phases were washed 1 N NaOH(aq) and then dried over Na_2SO_4. Filtration followed by evaporation provided the crude sulfoxide, which was mixed with phenethylamine (1 mL) in NMP (1.5 mL). The entire mixture was heated at 100 °C overnight and the volatile material was removed by vacuum distillation. The residue was purified with a flashed column chromatography (pure DCM → 2% 2M NH_3 /MeOH in DCM) to yield the title compound as a pale yellow solid. MS m/z 408 $(M+H)^+$.

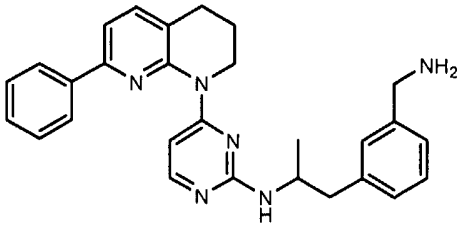
Example 48



(3-(2-(4-(7-Phenyl-3,4-dihydro-1,8-naphthyridin-1(*2H*)-yl)pyrimidin-2-yl-amino)propyl)phenyl)methanol

The title compound was obtained in a similar manner as described in Example 47 with (3-(2-aminopropyl)phenyl)methanol (0.17 g, 1 mmol) and 1-(2-(methylthio)pyrimidin-4-yl)-7-phenyl-1,2,3,4-tetrahydro-1,6-naphthyridine (0.21 g, 0.67 mmol) to give an off-white solid. MS m/z 452.2 $(M+H)^+$.

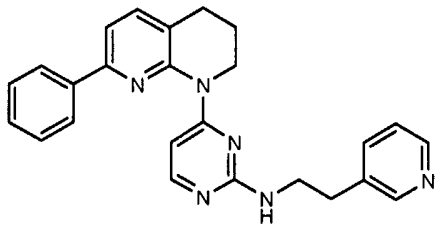
Example 49



***N*-(1-(3-(Aminomethyl)phenyl)propan-2-yl)-4-(7-phenyl-3,4-dihydro-1,8-naphthyridin-1(*2H*)-yl)pyrimidin-2-amine**

A THF (10 mL) solution of the benzylic alcohol (0.3 g, 0.66 mmol) obtained from example 48 was treated with DBU (0.2 mL, 1.32 mmol), diphenylphosphoryl azide (0.29 mL, 1.32 mmol) at 0 °C and the overall mixture was stirred at RT overnight. After dilution with saturated ammonium chloride aqueous solution, the separated aqueous layer was extracted with ethyl acetate (x2) and the combined organic phases were dried (Na_2SO_4), filtrated, and concentrated to give a crude azide. This was immediately treated with Zn (216 mg, 3.3 mmol) in EtOH (5 mL) and 1 mL of NH_4Cl sat solution and heated under reflux for 2 h. After cooling down to RT the mixture was diluted with EtOAc and washed with sat $NaHCO_3$ and brine. The residue was purified by flash column chromatography (2% 2M NH_3 /MeOH in DCM → 4% 2M NH_3 /MeOH in DCM) to yield the title compound as a white solid. MS m/z 451 $(M+H)^+$.

Example 50

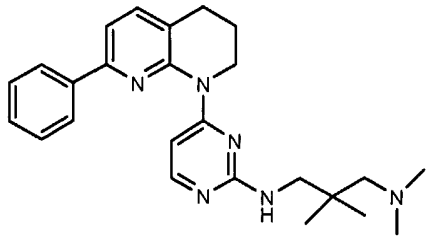


4-(7-Phenyl-3,4-dihydro-1,8-naphthyridin-1(*2H*)-yl)-*N*-(2-(pyridin-3-yl)ethyl)-pyrimidin-2-amine

1-(2-Fluoropyrimidin-4-yl)-7-phenyl-1,2,3,4-tetrahydro-1,8-naphthyridine (0.26 g, 0.78 mmol) and 2-(pyridin-3-yl)ethanamine (0.285 g, 2.34 mmol) in NMP (2 mL) were heated

at 100 °C overnight. After cooling down to RT the volatile material was removed under reduced pressure. The residue was purified by flash column chromatography (5% NH_3 /MeOH in DCM) to yield the title compound as an off-white solid. MS m/z 409 $(M+H)^+$.

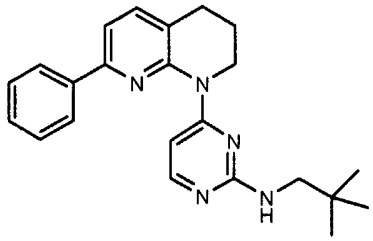
Example 51



***N*-(3-(Dimethylamino)-2,2-dimethylpropyl)-4-(7-phenyl-3,4-dihydro-1,8-naphthyridin-1(*2H*)-yl)pyrimidin-2-amine**

1-(2-Fluoropyrimidin-4-yl)-7-phenyl-1,2,3,4-tetrahydro-1,8-naphthyridine (0.19 g, 0.55 mmol) and N^1,N^1,2,2-tetramethylpropane-1,3-diamine (0.215 g, 1.65 mmol) in dioxane (2 mL) were heated at 100 °C overnight. After cooling down to RT the volatile material was removed under reduced pressure. The residue was purified by flash column chromatography (2% 2M NH_3 /MeOH in DCM → 4% 2M NH_3 /MeOH in DCM) to yield the title compound as an off-white solid. MS m/z 417 $(M+H)^+$.

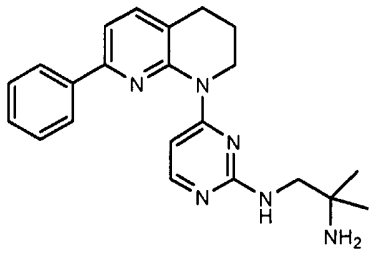
Example 52



***N*-Neopentyl-4-(7-phenyl-3,4-dihydro-1,8-naphthyridin-1(*2H*)-yl)pyrimidin-2-amine**

The title compound was obtained in a similar manner as described previously on Example 51 to give an off-white solid. MS m/z 374 $(M+H)^+$.

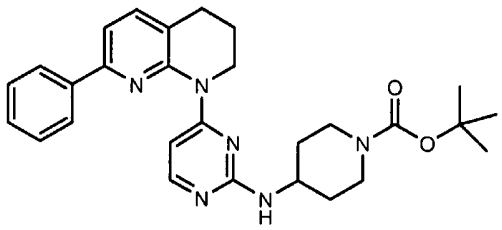
Example 53



***N*-(2-Amino-2-methylpropyl)-4-(7-phenyl-3,4-dihydro-1,8-naphthyridin-1(*2H*)-yl)-pyrimidin-2-amine**

The title compound was obtained in a similar manner as described previously on Example 51 to give an off-white solid. MS m/z 375 $(M+H)^+$.

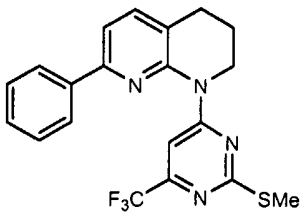
Example 54



***tert*-Butyl 4-(4-(7-phenyl-3,4-dihydro-1,8-naphthyridin-1(*2H*)-yl)pyrimidin-2-yl-amino)piperidine-1-carboxylate**

The title compound was obtained in a similar manner as described previously on Example 51 to give an off-white solid. MS m/z 487 $(M+H)^+$.

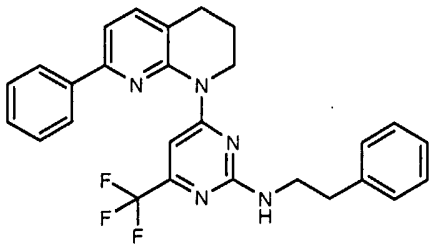
Example 55



1-(2-(Methylthio)-6-(trifluoromethyl)pyrimidin-4-yl)-7-phenyl-1,2,3,4-tetrahydro-1,8-naphthyridine

7-Phenyl-1,2,3,4-tetrahydro-1,8-naphthyridine (1.2 g, 5.7 mmol) was mixed with 2-dicyclohexylphosphino-2'-(*N,N*-dimethylamino)biphenyl (224 mg, 0.57 mmol) and $Pd_2(dba)_3$ (260 mg, 0.28 mmol) in a reaction vial. After purged with N_2 for 10 min, dioxane (3 mL) was added followed by LHMDS (1M in THF, 8.6 mmol, 8.6 mL) and 4-chloro-2-(methylthio)-6-(trifluoromethyl)pyrimidine (1.96 g, 8.6 mmol). The mixture was sealed and heated at 150 °C for 30 min in a microwave synthesizer. After cooled to RT, the reaction was diluted with EtOAc and washed with sat $NaHCO_3$ and water. Removal of volatile material provided the crude product, which was purified by flash column chromatography (5 % EtOAc in hex → 20 % EtOAc in hex) to provide the title compound as a white solid. MS m/z 403 $(M+H)^+$.

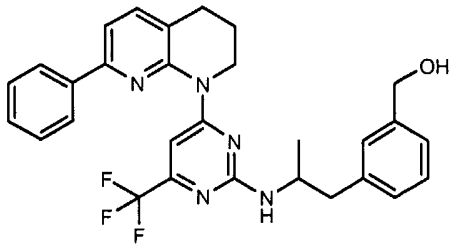
Example 56



***N*-Phenethyl-4-(7-phenyl-3,4-dihydro-1,8-naphthyridin-1(*2H*)-yl)-6-(trifluoromethyl)pyrimidin-2-amine**

m-CPBA (430 mg, ~70%, 2.6 mmol) was added to a cold (0 °C) solution of 1-(2-(methylthio)-6-(trifluoromethyl)pyrimidin-4-yl)-7-phenyl-1,2,3,4-tetrahydro-1,8-naphthyridine (690 mg, 1.7 mmol) in DCM (10 mL) and the overall mixture was stirred at the same temperature for 30 min prior to being quenched with saturated aqueous sodium bicarbonate. The aqueous layer was extracted with DCM and the combined organic phases were washed 1 N NaOH(aq) and then dried over Na_2SO_4. Filtration followed by evaporation provided the crude sulfoxide, which was mixed with phenethylamine (1 mL) in dioxane (1.5 mL). The entire mixture was heated at 100 °C overnight and the volatile material was removed by vacuum distillation. The residue was purified by flash column chromatography (2% 2M NH_3 /MeOH in DCM) to yield the title compound as a white solid. MS m/z 476 $(M+H)^+$.

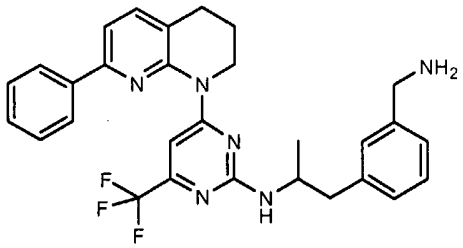
Example 57



(3-(2-(4-(7-Phenyl-3,4-dihydro-1,8-naphthyridin-1(*2H*)-yl)-6-(trifluoromethyl)-pyrimidin-2-ylamino)propyl)phenyl)methanol

The title compound was obtained with the similar manner as described previously on Example 56 with (3-(2-aminopropyl)phenyl)methanol (0.74 g, 4.48 mmol) and 1-(2-(methylthio)-6-(trifluoromethyl)pyrimidin-4-yl)-7-phenyl-1,2,3,4-tetrahydro-1,8-naphthyridine (0.9 g, 2.24 mmol) to give an off-white solid. MS m/z 520 $(M+H)^+$.

Example 58

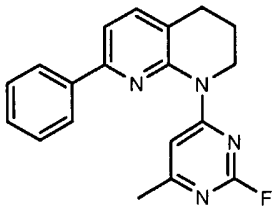


***N*-(1-(3-(Aminomethyl)phenyl)propan-2-yl)-4-(7-phenyl-3,4-dihydro-1,8-naphthyridin-1(*2H*)-yl)-6-(trifluoromethyl)pyrimidin-2-amine**

A THF (5 mL) solution of benzylic alcohol (0.6 g, 1.1 mmol) obtained on example 57 was treated with DBU (0.32 mL, 2.2 mmol) and diphenylphosphoryl azide (0.48 mL, 2.2 mmol) at 0 °C and the overall mixture was stirred at RT overnight. After dilution with saturated ammonium chloride aqueous solution, the separated aqueous layer was extracted with ethyl acetate (2x) and the combined organic phases were dried (Na_2SO_4), filtrated, and concentrated to give a crude azide. and concentrated to give a crude azide which was immediately treated with 10% Pd/C (0.5 g) in EtOH (15 mL) under H_2 (1 atm) at RT overnight. Filtration followed by evaporation provided the crude product, which

was subjected to flash column purification (2% 2M NH_3 /MeOH in DCM → 4% 2M NH_3 /MeOH in DCM) to yield the title compound as a white solid. MS m/z 519 $(M+H)^+$.

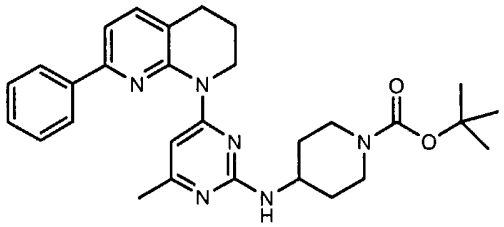
Example 59



1-(2-Fluoro-6-methylpyrimidin-4-yl)-7-phenyl-1,2,3,4-tetrahydro-1,8-naphthyridine

To a solution of 7-phenyl-1,2,3,4-tetrahydro-1,8-naphthyridine (1.76 g, 8.5 mmol) in THF (10 mL) under N_2 at –78 °C was added LHMDS (1M in THF, 10.2 mL, 10.2 mmol) and then 2,4-difluoro-6-methylpyrimidine (1.2 g, 9.3 mmol). The mixture was stirred at –78 °C for 2 h and then quenched with saturated aqueous sodium bicarbonate. Then the reaction was diluted with EtOAc and washed with sat $NaHCO_3$ and water. Removal of volatile material provided the crude product, which was purified by flash column chromatography (25 % EtOAc in hex) to provide the title compound as a white solid. MS m/z 321 $(M+H)^+$.

Example 60

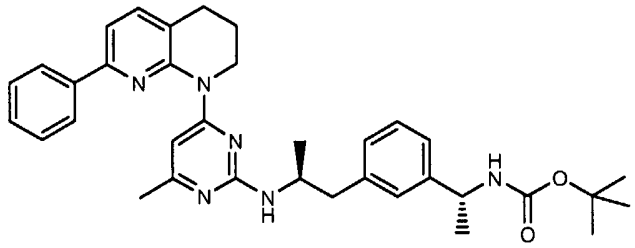


***tert*-Butyl 4-(4-methyl-6-(7-phenyl-3,4-dihydro-1,8-naphthyridin-1(*2H*)-yl)-pyrimidin-2-ylamino)piperidine-1-carboxylate**

1-(2-Fluoro-6-methylpyrimidin-4-yl)-7-phenyl-1,2,3,4-tetrahydro-1,8-naphthyridine (0.16 g, 0.5 mmol) and *tert*-butyl 4-aminopiperidine-1-carboxylate (0.200 g, 1.00 mmol) in dioxane (2 mL) were heated at 90 °C for 24 h. Then, the volatile material was removed under reduced pressure. The residue was purified by flash column chromatography (2%

2M NH_3 /MeOH in DCM) to yield the title compound as a white solid. MS m/z 501 $(M+H)^+$.

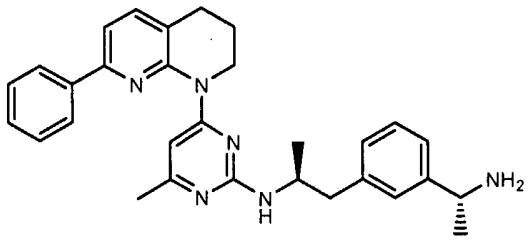
Example 61



***tert*-Butyl (*R*)-1-(3-((*S*)-2-(4-methyl-6-(7-phenyl-3,4-dihydro-1,8-naphthyridin-1(*2H*)-yl)pyrimidin-2-ylamino)propyl)phenyl)ethylcarbamate**

The title compound was obtained with the similar manner as described previously on Example 60 with *tert*-butyl (*R*)-1-(3-((*S*)-2-aminopropyl)phenyl)ethylcarbamate (0.28 g, 1.00 mmol) and 1-(2-fluoro-6-methylpyrimidin-4-yl)-7-phenyl-1,2,3,4-tetrahydro-1,8-naphthyridine (215 mg, 0.67 mmol) to give an off-white solid. MS m/z 579 $(M+H)^+$.

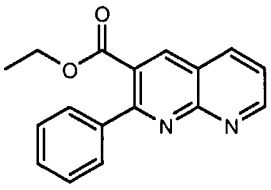
Example 62



***N*-((*S*)-1-(3-((*R*)-1-Aminoethyl)phenyl)propan-2-yl)-4-methyl-6-(7-phenyl-3,4-dihydro-1,8-naphthyridin-1(*2H*)-yl)pyrimidin-2-amine**

A solution of *tert*-butyl (*R*)-1-(3-((*S*)-2-(4-methyl-6-(7-phenyl-3,4-dihydro-1,8-naphthyridin-1(*2H*)-yl)pyrimidin-2-ylamino)propyl)phenyl)ethylcarbamate (165 mg, 0.28 mmol) in (1:1, DCM:TFA) (5 mL) was stirred at RT for 30 min, and then the volatile material was removed under reduced pressure. The residue dissolved in EtOAc and washed with sat $NaHCO_3$, water and brine, then dried over Na_2SO_4 and concentrated to give the title compound as an off-white solid. MS m/z 479 $(M+H)^+$.

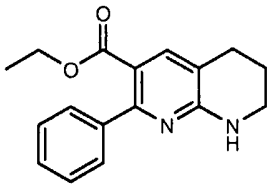
Example 63



Ethyl 2-phenyl-1,8-naphthyridine-3-carboxylate

A mixture of 2-aminonicotinaldehyde (0.58 g, 4.72 mmol), ethyl 3-oxo-3-phenylpropanoate (906 mg, 4.72 mmol) and piperidine (401 mg, 4.72 mmol) was heated in the microwave at 120 °C for 5 min. Them the mixture was diluted with EtOAc, washed with water and brine to give the title compound that was used without further purification. MS m/z 279 $(MH)^+$.

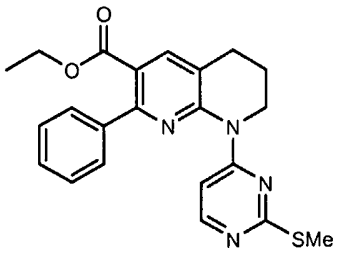
Example 64



Ethyl 2-phenyl-5,6,7,8-tetrahydro-1,8-naphthyridine-3-carboxylate

To a solution of ethyl 2-phenyl-1,8-naphthyridine-3-carboxylate 2-phenyl-1,8-naphthyridine (4.72 mmol crude from Example 63) in EtOH (30 mL) was added Pd (5 % wet w/w on carbon, ~1 g) and the resulting suspension was stirred under 1 atm H_2 overnight. The catalyst was removed with a short pad of Celite® and washed with EtOH. The residue was purified by trituration with a 1:1 mixture of EtOAc and hexanes to give the title compound as a light yellow solid. MS m/z 283 $(MH)^+$.

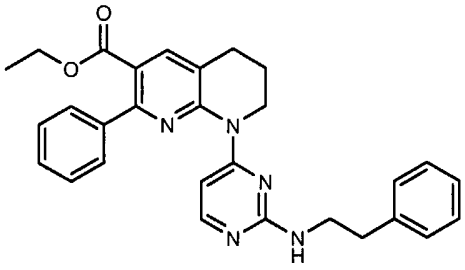
Example 65



Ethyl 8-(2-(methylthio)pyrimidin-4-yl)-2-phenyl-5,6,7,8-tetrahydro-1,8-naphthyridine-3-carboxylate

The title compound was obtained with the similar manner as described previously on Example 55 with ethyl 2-phenyl-5,6,7,8-tetrahydro-1,8-naphthyridine-3-carboxylate (0.48 g, 1.7 mmol) and 4-chloro-2-thiomethylpyrimidine (409 mg, 2.6 mmol) to give a white solid. MS m/z 407 $(M+H)^+$.

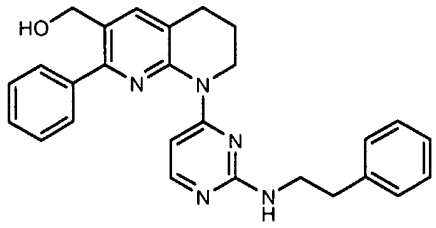
Example 66



Ethyl 8-(2-(Phenethylamino)pyrimidin-4-yl)-2-phenyl-5,6,7,8-tetrahydro-1,8-naphthyridine-3-carboxylate

The title compound was obtained with the similar manner as described previously on Example 47 with ethyl 8-(2-(methylthio)pyrimidin-4-yl)-2-phenyl-5,6,7,8-tetrahydro-1,8-naphthyridine-3-carboxylate (690 mg, 1.7 mmol) to give a white solid (455 mg). MS m/z 480 $(M+H)^+$.

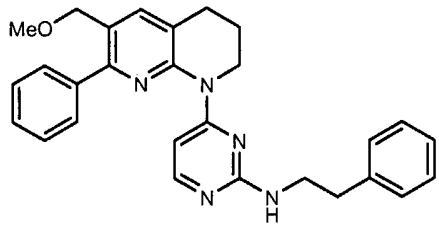
Example 67



(8-(2-(Phenethylamino)pyrimidin-4-yl)-2-phenyl-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)methanol

To a solution of ethyl 8-(2-(phenethylamino)pyrimidin-4-yl)-2-phenyl-5,6,7,8-tetrahydro-1,8-naphthyridine-3-carboxylate (188 mg, 0.39 mmol) in THF (3 mL) at 0 °C was added $LiAlH_4$ (1M in THF, 1.2 mL, 1.2 mmol) and then the mixture was stirred at 0 °C for 1.5 h and at RT for 1 h. After cooling down to 0 °C Na_2SO_4. 6 H_2O (390 mg, 1.6 mmol) was added and the mixture stirred at RT for 15 min and at 50 °C for 15 min. Then the solids were filtered off and the filtrate was concentrated to provide the crude product, which was purified by flash column chromatography (3% 2M NH_3 /MeOH in DCM → 4% 2M NH_3 /MeOH in DCM) to yield the title compound as a white solid. MS m/z 438 $(M+H)^+$.

Example 68

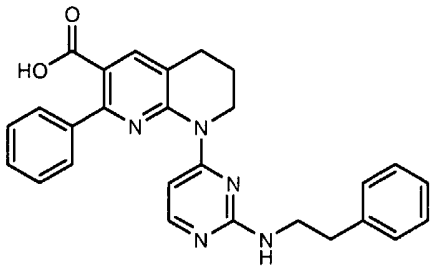


4-(6-(Methoxymethyl)-7-phenyl-3,4-dihydro-1,8-naphthyridin-1(*2H*)-yl)-*N*-phenethylpyrimidin-2-amine

To a solution of (8-(2-(phenethylamino)pyrimidin-4-yl)-2-phenyl-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)methanol (72 mg, 0.16 mmol) in THF (4 mL) at 0 °C was added NaH (8 mg, 60% oil, 0.19 mmol) and stirred for 15 min. Then methyl iodide (10 μL, 0.16 mmol) was added and the mixture was stirred at 0 °C for 10 min and 12 h at RT. Removal of volatile material provided the crude product which was purified by flash

column chromatography (2% 2M NH_3 /MeOH in DCM → 3% 2M NH_3 /MeOH in DCM) to yield the title compound (47 mg) as a white solid. MS m/z 452 $(M+H)^+$.

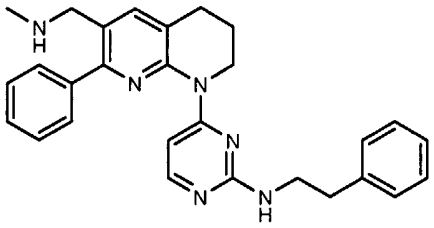
Example 69



8-(2-(Phenethylamino)pyrimidin-4-yl)-2-phenyl-5,6,7,8-tetrahydro-1,8-naphthyridine-3-carboxylic acid

A mixture of ethyl 8-(2-(phenethylamino)pyrimidin-4-yl)-2-phenyl-5,6,7,8-tetrahydro-1,8-naphthyridine-3-carboxylate (460 mg, 0.96 mmol) and 10 % HCl (1 mL) in dioxane (3 mL) was heated under reflux for 50 h. After cooling down to RT NaOH (5 N, 1 mL) and water (5 mL) were added and the solids were filtered off and washed several times with water. The title compound was obtained as a tan solid (sodium salt). MS m/z 474 $(M+H)^+$.

Example 70



4-(6-((Methylamino)methyl)-7-phenyl-3,4-dihydro-1,8-naphthyridin-1(*2H*)-yl)-*N*-phenethylpyrimidin-2-amine

Step A: 8-(2-(Phenethylamino)pyrimidin-4-yl)-2-phenyl-5,6,7,8-tetrahydro-1,8-naphthyridine-3-carbaldehyde.

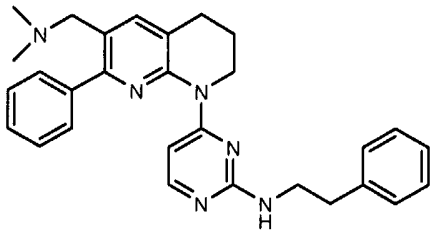
To a solution of (8-(2-(phenethylamino)pyrimidin-4-yl)-2-phenyl-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)methanol (843 mg, 1.9 mmol) in DCM (15 mL) at RT was added Dess-

Martin periodinane (982 mg, 2.28 mmol) and stirred at RT for 1 h. Then an additional amount of Dess-Martin periodinane (1.6 g, 3.8 mmol) was added and the mixture was stirred for 1 h more at RT. After that it was diluted with DCM and washed with $NaHCO_3$ and water. Removal of volatile material provided the crude product, which was purified by chromatography (2% 2M NH_3 /MeOH in DCM) to yield the title compound as a white solid. MS m/z 436 $(M+H)^+$.

Step B: 4-(6-((Methylamino)methyl)-7-phenyl-3,4-dihydro-1,8-naphthyridin-1(*2H*)-yl)-*N*-phenethylpyrimidin-2-amine.

To a solution of 8-(2-(phenethylamino)pyrimidin-4-yl)-2-phenyl-5,6,7,8-tetrahydro-1,8-naphthyridine-3-carbaldehyde (96 mg, 0.22 mmol) in $CHCl_3$ (2 mL) was added methyl amine (2 M in THF, 0.88 mL, 0.88 mmol) and $Na(OAc)_3BH$ (93 mg, 0.44 mmol), then it was stirred 0.5 h at RT and 2 h at 50 °C. After cooling down to RT, the mixture was diluted with DCM and washed with $NaHCO_3$ and water. Removal of volatile material provided the crude product, which was purified by flash chromatography (3% 2M NH_3 /MeOH in DCM → 4% 2M NH_3 /MeOH in DCM) to yield the title compound as a white solid. MS m/z 488 $(M+H)^+$.

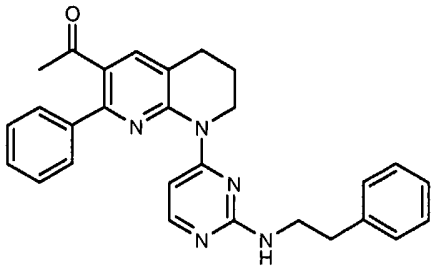
Example 71



4-(6-((Dimethylamino)methyl)-7-phenyl-3,4-dihydro-1,8-naphthyridin-1(*2H*)-yl)-N-phenethylpyrimidin-2-amine

The title compound was obtained with the similar manner as described previously on Example 70 with 8-(2-(phenethylamino)pyrimidin-4-yl)-2-phenyl-5,6,7,8-tetrahydro-1,8-naphthyridine-3-carbaldehyde (101 mg, 0.23 mmol) and dimethylamine (2M in THF, 0.4 mL, 0.8 mmol) to give the title compound as a white solid. MS m/z 502 $(M+H)^+$.

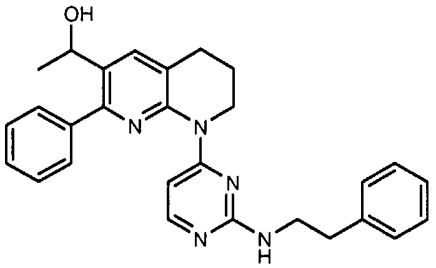
Example 72



1-(8-(2-(Phenethylamino)pyrimidin-4-yl)-2-phenyl-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)ethanone

To a solution of ethyl 8-(2-(phenethylamino)pyrimidin-4-yl)-2-phenyl-5,6,7,8-tetrahydro-1,8-naphthyridine-3-carboxylate (420 mg, 0.87 mmol) in THF (6 mL) under N_2 at –78 °C was added dropwise methyl magnesium bromide (3 M in ether, 1.5 mL, 4.5 mmol) and then stirred for 1 h at RT and 2 h at 50 °C. The reaction was quenched with MeOH (1 mL) and the volatiles were removed. After that it was diluted with DCM and washed with $NaHCO_3$ and water. Removal of volatile material provided the crude product, which was purified by flash chromatography (DCM → 4% 2M NH_3 /MeOH in DCM) to yield the title compound as a yellow solid. MS m/z 450 $(M+H)^+$.

Example 73

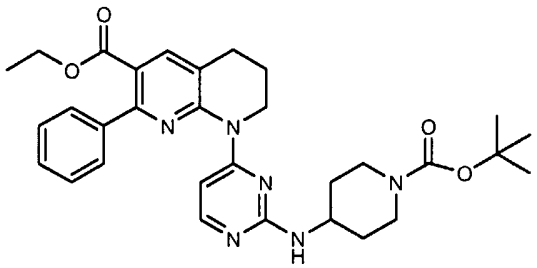


1-(8-(2-(Phenethylamino)pyrimidin-4-yl)-2-phenyl-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)ethanol

To a suspension of 1-(8-(2-(phenethylamino)pyrimidin-4-yl)-2-phenyl-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)ethanone (120 mg, 0.27 mmol) in MeOH:THF (3:1) (4 mL) at 0 °C was added $NaBH_4$ (20 mg, 0.54 mmol) and then stirred for 1 h at RT. The reaction was quenched with $NaHCO_3$ (1 mL) and MeOH (1 mL) and the volatiles were removed. After

that, it was diluted with EtOAc and washed with $NaHCO_3$ and water. Removal of volatile material provided the crude product, which was purified by trituration with ether:EtOAc (4:1) to yield the title compound as a white solid. MS m/z 452 $(M+H)^+$.

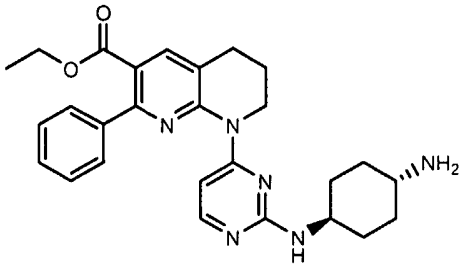
Example 74



Ethyl 8-(2-(1-(tert-butoxycarbonyl)piperidin-4-ylamino)pyrimidin-4-yl)-2-phenyl-5,6,7,8-tetrahydro-1,8-naphthyridine-3-carboxylate

The title compound was obtained with the similar manner as described previously on Example 47 with ethyl 8-(2-(methylthio) pyrimidin-4-yl)-2-phenyl-5,6,7,8-tetrahydro-1,8-naphthyridine-3-carboxylate (520 mg, 1.3 mmol). Off-white solid. MS m/z 559 $(M+H)^+$.

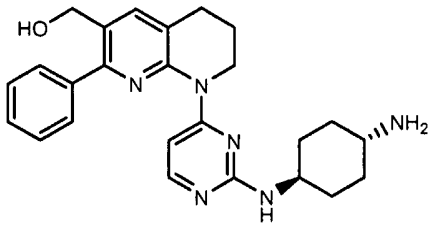
Example 75



Ethyl 8-(2-((*1R,4R*)-4-aminocyclohexylamino)pyrimidin-4-yl)-2-phenyl-5,6,7,8-tetrahydro-1,8-naphthyridine-3-carboxylate

The title compound was obtained with the similar manner as described previously on Example 47 with ethyl 8-(2-(methylthio)pyrimidin-4-yl)-2-phenyl-5,6,7,8-tetrahydro-1,8-naphthyridine-3-carboxylate (350 mg, 0.83 mmol). White solid. MS m/z 473 $(M+H)^+$.

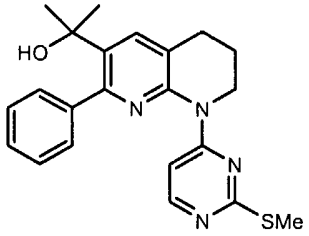
Example 76



(8-(2-((*1R,4R*)-4-Aminocyclohexylamino)pyrimidin-4-yl)-2-phenyl-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)methanol

The title compound was obtained in a similar manner as described previously on Example 67 with ethyl 8-(2-((*1R,4R*)-4-aminocyclohexylamino)pyrimidin-4-yl)-2-phenyl-5,6,7,8-tetrahydro-1,8-naphthyridine-3-carboxylate (126 mg, 0.27 mmol). White solid. MS m/z 431 $(M+H)^+$.

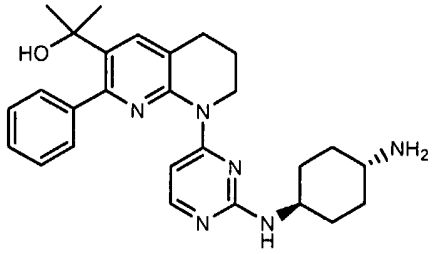
Example 77



2-(8-(2-(Methylthio)pyrimidin-4-yl)-2-phenyl-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)propan-2-ol

To a solution of ethyl 8-(2-(methylthio)pyrimidin-4-yl)-2-phenyl-5,6,7,8-tetrahydro-1,8-naphthyridine-3-carboxylate (298 mg, 0.7 mmol) in dry THF (3 mL) under N_2 at –78 °C was added dropwise methyl magnesium bromide (1.4 M in THF/toluene, 2.5 mL, 3.5 mmol) and then stirred at RT overnight. The reaction was quenched with MeOH (1 mL) and the volatiles were removed. After that it was diluted with EtOAc and washed with $NaHCO_3$ and water. Removal of volatile material provided the crude product which was purified by flash chromatography (40% EtOAc in hexane → 80% EtOAc in hexane) to yield the title compound as a yellow solid. MS m/z 393 $(M+H)^+$.

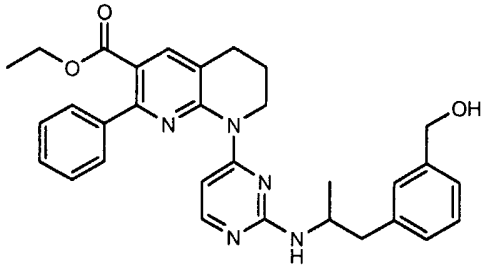
Example 78



2-(8-(2-((*1R,4R*)-4-Aminocyclohexylamino)pyrimidin-4-yl)-2-phenyl-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)propan-2-ol

The title compound was obtained with the similar manner as described previously on Example 47 with 2-(8-(2-(methylthio)pyrimidin-4-yl)-2-phenyl-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)propan-2-ol (130 mg, 0.33 mmol). Off-white solid. MS m/z 459 $(M+H)^+$.

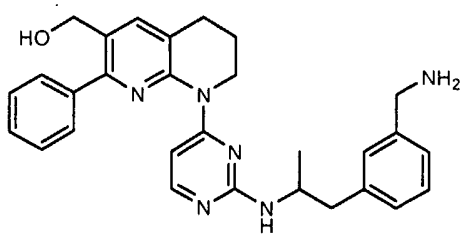
Example 79



Ethyl 8-(2-(1-(3-(hydroxymethyl)phenyl)propan-2-ylamino)pyrimidin-4-yl)-2-phenyl-5,6,7,8-tetrahydro-1,8-naphthyridine-3-carboxylate

The title compound was obtained with the similar manner as described previously on Example 47 with ethyl 8-(2-(methylthio)pyrimidin-4-yl)-2-phenyl-5,6,7,8-tetrahydro-1,8-naphthyridine-3-carboxylate (1.5 g, 3.7 mmol). Off-white solid. MS m/z 524 $(M+H)^+$.

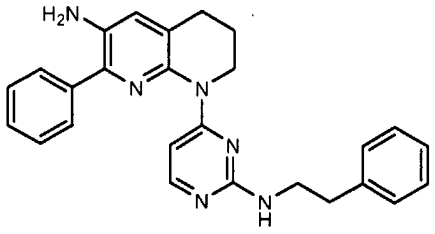
Example 80



(8-(2-(1-(3-(Aminomethyl)phenyl)propan-2-ylamino)pyrimidin-4-yl)-2-phenyl-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)methanol

A THF (5 mL) solution of ethyl 8-(2-(1-(3-(hydroxymethyl)phenyl)propan-2-ylamino)pyrimidin-4-yl)-2-phenyl-5,6,7,8-tetrahydro-1,8-naphthyridine-3-carboxylate (0.71 g, 1.36 mmol) was treated with DBU (0.41 mL, 2.72 mmol) and diphenylphosphoryl azide (0.59 mL, 2.72 mmol) at 0 °C and the overall mixture was stirred at RT overnight. After dilution with saturated ammonium chloride aqueous solution, the separated aqueous layer was extracted with ethyl acetate(x2) and the combined organic phases were dried (Na_2SO_4), filtrated, and concentrated to give the crude azide. This was immediately treated with $LiAlH_4$ (1M in THF, 6.8 mL, 6.8 mmol) in THF (3 mL) at 0 °C for 0.5 h and at RT for 45 min. under H_2 (1 atm) at RT overnight. After cooling down to 0 °C, Na_2SO_4. 6 H_2O (3 g) was added and the mixture stirred at RT for 15 min and at 50 °C for 15 min. Then the solids were filtered off and the filtrate was concentrated to provide the crude product, which was purified by flash column chromatography (5% 2M NH_3 /MeOH). The title compound was obtained as a white solid. MS m/z 481 $(M+H)^+$.

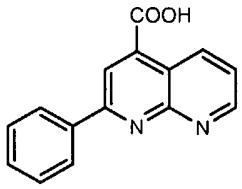
Example 81



8-(2-(Phenethylamino)pyrimidin-4-yl)-2-phenyl-5,6,7,8-tetrahydro-1,8-naphthyridin-3-amine

A solution of 8-(2-(phenethylamino)pyrimidin-4-yl)-2-phenyl-5,6,7,8-tetrahydro-1,8-naphthyridine-3-carboxylic acid (142 mg, 0.31 mmol) in *t*-BuOH (2 mL) was treated with Et_3N (0.18 mL, 1.24 mmol) and diphenylphosphoryl azide (0.21 mL, 0.68 mmol) at RT and the overall mixture was stirred at 100 °C for 3 h. After cooling down to RT it was diluted with EtOAc and washed with $NaHCO_3$ and water. Removal of volatile materials provided the crude product, which was purified by chromatography (2% 2M NH_3 /MeOH). This was treated with HCl (4M in dioxane) at RT for 1 h. After removal of the solvent the residue was dissolved in EtOAc and washed with $NaHCO_3$ and water. Removal of volatile materials provided the crude product, which was purified by flash column chromatography (4% 2M NH_3 /MeOH in DCM → 7% 2M NH_3 /MeOH in DCM) to yield the title compound as an off-white solid. MS m/z 459 $(M+H)^+$.

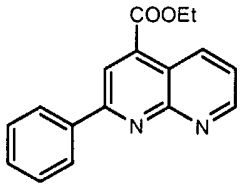
Example 82



2-Phenyl-1,8-naphthyridine-4-carboxylic acid

The title compound was obtained with the similar manner as described previously on Example 44 to give a white solid. MS m/z 251 $(M+H)^+$.

Example 83

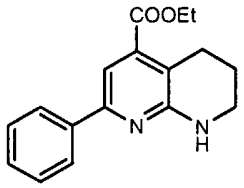


Ethyl 2-phenyl-1,8-naphthyridine-4-carboxylate

To a solution of 2-phenyl-1,8-naphthyridine-4-carboxylic acid (3.15 g, 12.5 mmol) in dry DCM (70 mL) at 0 °C under N_2 was added oxalyl chloride (2 M in DCM, 7 mL, 14 mmol) and several drops of DMF. Then the reaction mixture was stirred at RT for 1 h. Removal of the volatile materials provides crude acid chloride. This was dissolved in dry

THF (60 mL) and EtOH (2 mL) was added. The mixture was then stirred at RT for 1 h. Removal of the solvent provided the title compound. MS m/z 279 $(M+H)^+$.

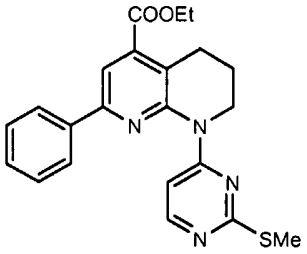
Example 84



Ethyl 2-phenyl-5,6,7,8-tetrahydro-1,8-naphthyridine-4-carboxylate

The title compound was obtained with the similar manner as described previously on Example 64 with ethyl 2-phenyl-1,8-naphthyridine-4-carboxylate. MS m/z 283 $(M+H)^+$.

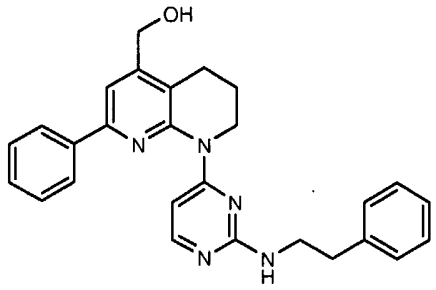
Example 85



Ethyl 8-(2-(methylthio)pyrimidin-4-yl)-2-phenyl-5,6,7,8-tetrahydro-1,8-naphthyridine-4-carboxylate

The title compound was obtained with the similar manner as described previously on Example 55 with ethyl 2-phenyl-5,6,7,8-tetrahydro-1,8-naphthyridine-4-carboxylate (1.67 g, 5.9 mmol) and 4-chloro-2-thiomethylpyrimidine (1.42 g, 8.85 mmol). White solid. MS m/z 407 $(M+H)^+$.

Example 86



(8-(2-(Phenethylamino)pyrimidin-4-yl)-2-phenyl-5,6,7,8-tetrahydro-1,8-naphthyridin-4-yl)methanol

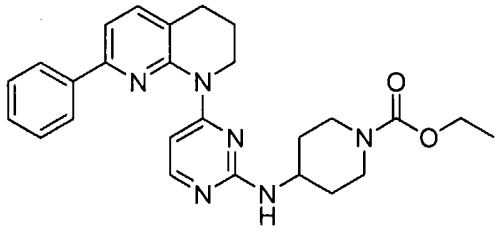
Step A: Ethyl 8-(2-(phenethylamino)pyrimidin-4-yl)-2-phenyl-5,6,7,8-tetrahydro-1,8-naphthyridine-4-carboxylate.

The title compound was obtained with the similar manner as described previously on Example 47 with ethyl 8-(2-(methylthio)pyrimidin-4-yl)-2-phenyl-5,6,7,8-tetrahydro-1,8-naphthyridine-4-carboxylate (240 mg, 0.59 mmol). MS m/z 480 $(M+H)^+$.

Step B: (8-(2-(Phenethylamino)pyrimidin-4-yl)-2-phenyl-5,6,7,8-tetrahydro-1,8-naphthyridin-4-yl)methanol.

The title compound was obtained with the similar manner as described previously on Example 67. White solid. MS m/z 438 $(M+H)^+$.

Example 87

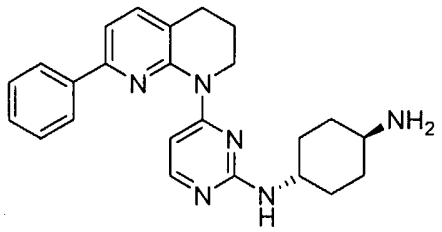


Ethyl-4-(4-(7-phenyl-3,4-dihydro-1,8-naphthyridin-1(2*H*)-yl)pyrimidin-2-ylamino)-piperidine-1-carboxylate

1-(2-Fluoropyrimidin-4-yl)-7-phenyl-1, 2,3,4-tetrahydro-1, 8-naththyridine (200. mg, 0.65 mmol) was mixed with ethyl 4-amino-1-piperidine carboxylate (0.3 mL, 1.73 mmol) in dioxane (5 mL). The entire mixture was heated at 100 °C overnight and the volatile

material was removed by vacuum distillation. The residue was purified by flash column chromatography (pure DCM → 2% MeOH in DCM) to yield the title compound as a white solid. MS m/z 459 $(M+H)^+$.

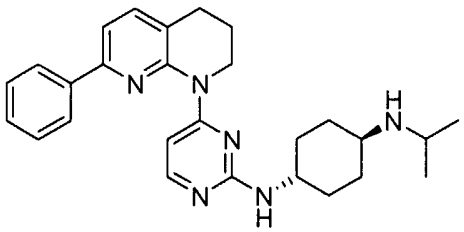
Example 88



(*1R,4R*)-N^1-(4-(7-Phenyl-3,4-dihydro-1,8-naphthyridin-1(2*H*)-ylpyrimidin-2-yl)-cyclohexane-1,4-diamine

1-(2-Fluoropyrimidin-4-yl)-7-phenyl-1,2,3,4-tetrahydro-1,8-naththyridine (500. mg, 1.6 mmol) was mixed with *trans*-1,4-diaminocyclohexane (376 mg, 3.3 mmol) in dioxane (5 mL). The entire mixture was sealed and heated at 100 °C overnight; the volatile material was removed by vacuum distillation. The residue was purified by flash column chromatography (5%-10% MeOH in DCM) to yield the title compound as a white solid. MS m/z 401 $(M+H)^+$.

Example 89

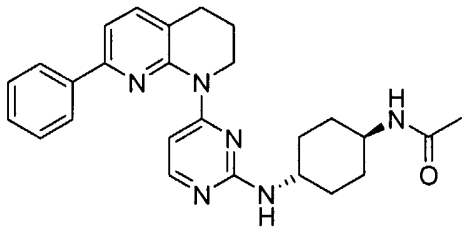


(*1R,4R*)-N^1-Isopropyl-N^4-(4-(7-phenyl-3,4-dihydro-1,8-naphthyridin-1(2*H*)-yl)pyrimidin-2-yl) cyclohexane-1,4-diamine

To the stirring solution of (*1R,4R*)-N^1-(4-(7-phenyl-3,4-dihydro-1,8-naphthyridin-1(*2H*)-yl)pyrimidin-2-yl) cyclohexane-1,4-diamine (80 mg, 0.2 mmol) in acetone (5 mL) was added sodium triacetoxyborohydride (100 mg, 0.5 mmol) with a catalytic amount of acetic acid. The suspension was stirred at RT overnight. The mixture was quenched with

ammonium chloride (sat'd aq) and diluted with water and DCM, the separated aqueous layer was extracted with DCM. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. Removal of volatile material provided the crude product, which was purified by flash column chromatography (pure DCM → 2% MeOH in DCM) to provide the title compound as a white solid. MS m/z 443 $(M+H)^+$.

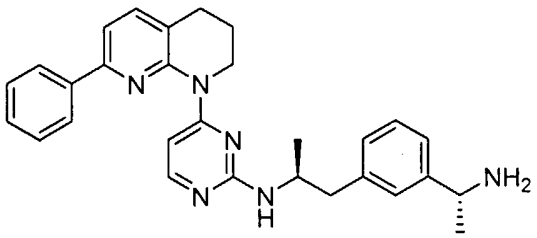
Example 90



***N*-((*1R*,,*4*R)-4-(4-(7-Phenyl-3,4-dihydro-1,8-naphthyridin-1(2*H*)-yl)pyrimidin-2-ylamino)cyclohexyl) acetamide**

To the stirring suspension of acetic acid (60 mg, 1 mmol) and PS-carbodiimide (0.3 g , 0.4 mmol, loading 1.3 mmol/g) in DCM (5 mL) was added (*1R,4R*)-*N'*-(4-(7-phenyl-3,4-dihydro-1,8-naphthyridin-1 (2*H*)-yl) pyrimidin-2-yl) cyclohexane-1,4-diamine (80 mg, 0.2 mmol). The suspension was stirred at RT overnight and then filtered out. The filtrate was concentrated under vacuum and the product was precipitated with ether to provide the title compound as a white solid. MS m/z 443 $(M+H)^+$.

Example 91

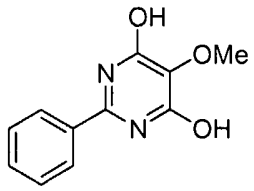


***N*-((*S*)-1-(3-((*R*)-1-Aminoethyl) phenyl) propan-2-yl)-4-(7-phenyl-3, 4-dihydro-1, 8-naphthyridin-1(2*H*)-yl) pyrimidin-2-amine**

To a stirred solution of 1-(2-fluoropyrimidin-4-yl)-7-phenyl-1,2,3,4-tetrahydro-1,8-naphthyridine (120 mg, 0.4 mmol) in dioxane (5 mL) was added *N,N*-

diisopropylethylamine and *tert*-butyl (*S*)-1-(3-((*S*)-2-aminopropyl) phenyl) ethyl carbamate (110 mg, 0.4 mmol). The mixture was sealed and heated at 100 °C overnight. After cooling down to RT the volatile material was removed by vacuum distillation. The residue was purified by flash column chromatography (2%-5% MeOH in DCM) to yield *tert*-butyl(*R*) –1-(3-((*S*)-2-(4-(7-phenyl-3, 4-dihydro-1,8-naphthyridin-1(2*H*)-yl) pyrimidin-2-ylamino) propyl) phenyl) ethyl carbamate as a white solid. MS m/z 565 $(M+H)^+$. The Boc-amine (0.09 g) was deprotected with TFA (2 mL) in DCM (2 mL) at RT for 30 min. Concentration followed by purification (column chromatography, 5%MeOH in DCM) afforded the title compound as an off-white solid. MS m/z 465 $(M+H)^+$.

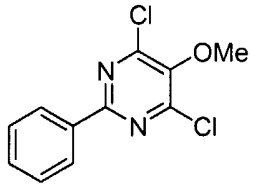
Example 92



5-Methoxy-2-phenylpyrimidine-4,6-diol

To a suspension of sodium methoxide (11 g, 205 mmol) in anhydrous methanol (MeOH) (100 mL) at 0 °C were added dimethyl methoxymalonate (8.8 mL, 64 mmol) and benzamidine (10. g, 64 mmol). The resulting suspension was stirred at 0 °C for 30 min then heated to reflux for 1 h. The mixture was cooled to RT, put in an ice-bath followed by the addition of concentrated hydrochloric acid (34 mL). A green yellow precipitate was formed which was filtered off and dried under high vacuum. MS m/z 219 $(M+H)^+$.

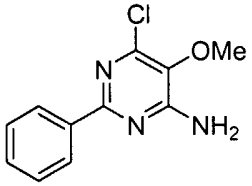
Example 93



4,6-Dichloro-5-methoxy-2-phenylpyrimidine

A mixture of 5-methoxy-2-phenylpyrimidine-4,6-diol (11.96 g, 55 mmol) and phosphoryl trichloride (35 mL) was heated to reflux for 20 h. The mixture was brought to RT and concentrated. To the residue obtained was added ice (500 mL) and stirred for 2 h. A pale yellow precipitate was formed which was filtered off, washed with water, dried with toluene and high vacuum. MS m/z 255 $(M+H)^+$.

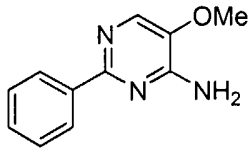
Example 94



6-Chloro-5-methoxy-2-phenylpyrimidin-4-amine

A mixture of 4,6-dichloro-5-methoxy-2-phenylpyrimidine (5.14 g, 20.2 mmol) and concentrated ammonium hydroxide (50 mL) in a sealed tube was heated to 100 °C for 17 h. The mixture was brought to RT and extracted with dichloromethane (CH_2Cl_2). The organic extracts were combined, dried over magnesium sulfate, concentrated and chromatographed on silica gel using 3:1 hexanes/ ethyl acetate to afford a white solid. MS m/z 236 $(M+H)^+$.

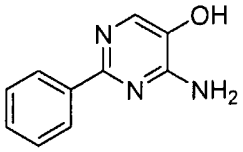
Example 95



5-Methoxy-2-phenylpyrimidin-4-amine

Through a mixture of 6-chloro-5-methoxy-2-phenylpyrimidin-4-amine (2 g, 8.5 mmol) and Pd/C (1.7 g) in methanol (30 mL) was bubbled hydrogen through a balloon for 15 h. The mixture was filtered through celite and concentrated to provide the title compound. MS m/z 202 $(M+H)^+$.

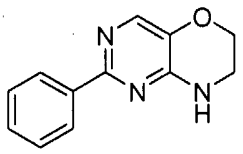
Example 96



4-Amino-2-phenylpyrimidin-5-ol

A mixture of 5-methoxy-2-phenylpyrimidin-4-amine (0.32 g, 1.6 mmol), benzenethiol (0.16 mL, 1.6 mmol), K_2CO_3 (catalytic) in 1-methyl-2-pyrrolidinone (2 mL) was heated to 190 °C for 1 h. The mixture was brought to RT and made alkaline with 5% aqueous NaOH (sodium hydroxide) and extracted with ether. The aqueous layer was acidified with diluted hydrochloric acid and extracted with 3:1 chloroform/isopropanol. The organic extracts were combined, dried over magnesium sulfate, concentrated and chromatographed on silica gel using 8% $2MNH_3MeOH/CH_2Cl_2$ to afford the title compound as a brown oil. MS m/z 188 $(M+H)^+$.

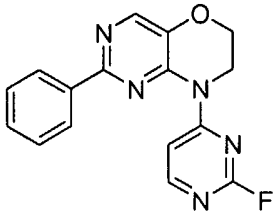
Example 97



2-Phenyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazine

To a solution of 4-amino-2-phenylpyrimidin-5-ol (0.55 g, 2.9 mmol) in dimethylformamide (25 mL) was added potassium carbonate (1.62 g, 11.8 mmol) and stirred at RT for 5 min followed by the addition of 1,2-dibromoethane (0.25 mL, 2.9 mmol). The resulting suspension was heated to 100 °C for 15 h. The mixture was brought to RT, poured into water and extracted with ethyl acetate. The organic extracts were combined, dried over magnesium sulfate, concentrated and chromatographed on silica gel using 0-4% $MeOH/CH_2Cl_2$ to give the title compound. MS m/z 214 $(M+H)^+$.

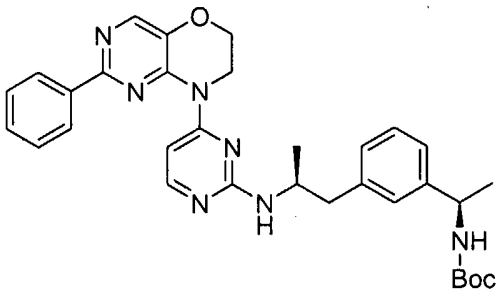
Example 98



8-(2-Fluoropyrimidin-4-yl)-2-phenyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazine

A solution of 2-phenyl-7,8-dihydro-*6H*-pyrimido[5,4-b][1,4]oxazine (70 mg, 0.33 mmol) in THF (2 mL) was brought to 0 °C followed by the addition of lithium bis(trimethylsilyl)amide (1.0 M in THF). After 15 min 2,4-difluoropyrimidine was added and the resulting orange solution was stirred at 0 °C for 2 h. The mixture was quenched with saturated NH_4Cl. The organic phase was separated, washed with saturated NH_4Cl, brine, dried over magnesium sulfate, concentrated and chromatographed on silica gel using 2:1 hexanes/ethyl acetate to give the title compound. MS m/z 310 $(M+H)^+$.

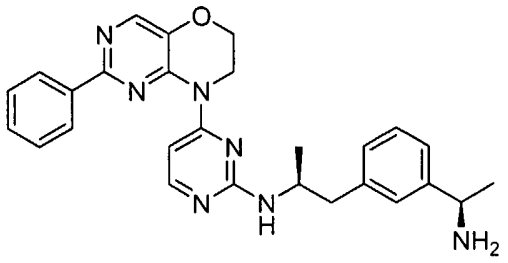
Example 99



***tert*-Butyl (*R*)-1-(3-((*S*)-2-(4-(2-phenyl-6,7-dihydropyrimido[5,4-b][1,4]oxazin-8-yl)pyrimidin-2-ylamino)propyl)phenyl)ethylcarbamate**

A mixture of 8-(2-fluoropyrimidin-4-yl)-2-phenyl-7,8-dihydro-*6H*-pyrimido[5,4-b][1,4]oxazine (30 mg, 0.10 mmol), *tert*-butyl (*R*)-1-(3-((*S*)-2-aminopropyl)phenyl) ethylcarbamate (31 mg, 0.11 mmol), *N,N*-diisopropylethylamine (17 μL, 0.10 mmol) in dioxane (2 mL) was heated to 100 °C for 15 h. The mixture was brought to RT, diluted in ethyl acetate, washed with saturated NH_4Cl, brine, dried over magnesium sulfate, concentrated and chromatographed on silica gel using 0-4% $MeOH/CH_2Cl_2$. MS m/z 568 $(M+H)^+$.

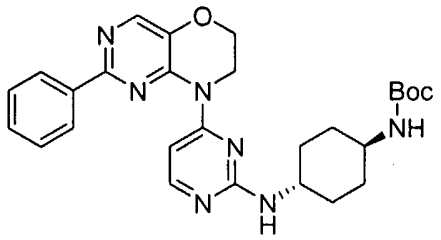
Example 100



***N*-((*S*)-1-(3-((*R*)-1-Aminoethyl)phenyl)propan-2-yl)-4-(2-phenyl-6,7-dihydro-pyrimido[5,4-b][1,4]oxazin-8-yl)pyrimidin-2-amine**

A mixture of *tert*-butyl (*R*)-1-(3-((*S*)-2-(4-(2-phenyl-6,7-dihydropyrimido[5,4-b][1,4]oxazin-8-yl)pyrimidin-2-ylamino)propyl)phenyl)ethylcarbamate (50 mg, 0.09 mmol) and trifluoroacetic acid (3 mL) in dichloromethane (3 mL) was stirred at RT for 30 min and quenched with saturated $NaHCO_3$. The organic phase was separated, washed again with saturated $NaHCO_3$ (3x), brine, dried over magnesium sulfate and concentrated. MS m/z 468 $(M+H)^+$.

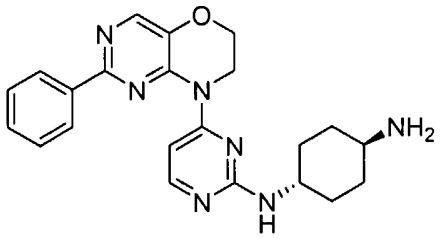
Example 101



***tert*-Butyl (*1R,4R*)-4-(4-(2-phenyl-6,7-dihydropyrimido[5,4-b][1,4]oxazin-8-yl)-pyrimidin-2-ylamino)cyclohexylcarbamate**

The title compound was obtained using the same procedure as on example 99 with 8-(2-fluoropyrimidin-4-yl)-2-phenyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazine (0.10 g, 0.28 mmol) and tert-butyl (1r,4r)-4-aminocyclohexylcarbamate (78 mg, 0.36 mmol) to afford a yellow oil. MS m/z 504 $(M+H)^+$.

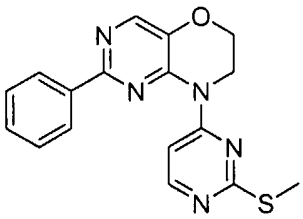
Example 102



(*1R,4R*)-*N*^{1}-(4-(2-Phenyl-6,7-dihydropyrimido[5,4-b][1,4]oxazin-8-yl)pyrimidin-2-yl)cyclohexane-1,4-diamine

The title compound was obtained as an off-white solid using the same procedure as in example 100 with *tert*-butyl (*1R,4R*)-4-(4-(2-phenyl-6,7-dihydropyrimido[5,4-b][1,4]oxazin-8-yl)pyrimidin-2-ylamino)cyclohexylcarbamate (0.18 g, 0.36 mmol) and TFA (5 mL) in CH_2Cl_2. MS m/z 404 $(M+H)^+$.

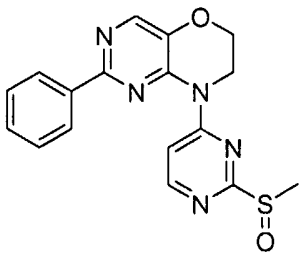
Example 103



8-(2-(Methylthio)pyrimidin-4-yl)-2-phenyl-7,8-dihydro-*6H*-pyrimido[5,4-b][1,4]-oxazine

A mixture of 2-phenyl-7,8-dihydro-*6H*-pyrimido[5,4-b][1,4]oxazine (0.69 g, 3.2 mmol), 4-chloro-2-(methylthio)pyrimidine (0.48 mL, 4.16 mmol), tris(dibenzylideneacetone) dipalladium(0) (9.5 mg, 0.16 mmol), rac-2-2'-bis(diphenylphosphino)-1,1'-bynaphthyl (0.20 g, 0.32 mmol), sodium *tert*-butoxide (0.40 g, 4.16 mmol) in toluene was heated to 90 °C for 3 h. The mixture was brought to RT, diluted in EtOAc, washed with saturated NH_4Cl, brine, dried over magnesium sulfate, concentrated and chromatographed on silica gel using 3:1 hexanes/EtOAc. MS m/z 338 $(M+H)^+$.

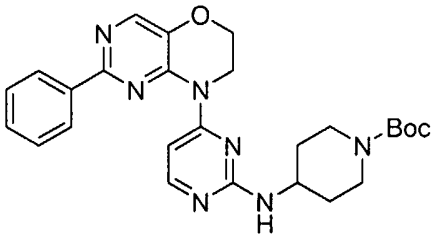
Example 104



8-(2-(Methylsulfinyl)pyrimidin-4-yl)-2-phenyl-7,8-dihydro-*6H*-pyrimido[5,4-b]-[1,4]oxazine

A mixture of 8-(2-(methylthio)pyrimidin-4-yl)-2-phenyl-7,8-dihydro-*6H*-pyrimido[5,4-b][1,4]oxazine (0.73 g, 2.2 mmol) and *m*-chloroperoxybenzoic acid (0.65 g, 2.2 mmol) in CH_2Cl_2 (5 mL) was stirred at RT for 3 h. The mixture was washed with saturated $NaHCO_3$, brine, dried over magnesium sulfate, and concentrated to be used as is to afford a light yellow solid. MS m/z 354 $(M+H)^+$.

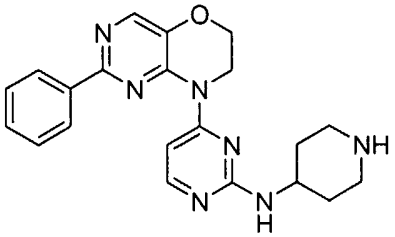
Example 105



***tert*-Butyl-4-(4-(2-phenyl-6,7-dihydropyrimido[5,4-b][1,4]oxazin-8-yl)pyrimidin-2-ylamino)piperidine-1-carboxylate**

A mixture of 8-(2-(methylsulfinyl)pyrimidin-4-yl)-2-phenyl-7,8-dihydro-6H-pyrimido [5,4-b][1,4]oxazine (0.22 g, 0.60 mmol) and *tert*-butyl 4-aminopiperidine-1-carboxylate (0.16 g, 0.78 mmol) in N-methylpyrrolidone (3 mL) was heated to 100 °C for 48 h.. The mixture was brought to RT, poured into water, and extracted with EtOAc. The organic extracts were combined, washed with saturated $NaHCO_3$, brine, dried over magnesium sulfate, concentrated and chromatographed on silica gel using 0-4-8% MeOH/ CH_2Cl_2. MS m/z 490 $(M+H)^+$.

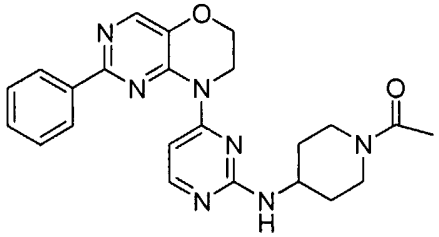
Example 106



4-(2-Phenyl-6,7-dihydropyrimido[5,4-b][1,4]oxazin-8-yl)-*N*-(piperidin-4-yl)-pyrimidin-2-amine

The title compound was obtained using the same procedure as on example 100 using *tert*-butyl-4-(4-(2-phenyl-6,7-dihydropyrimido[5,4-b][1,4]oxazin-8-yl)pyrimidin-2-ylamino)piperidine-1-carboxylate (0.13 g, 0.27 mmol). MS m/z 390 $(M+H)^+$.

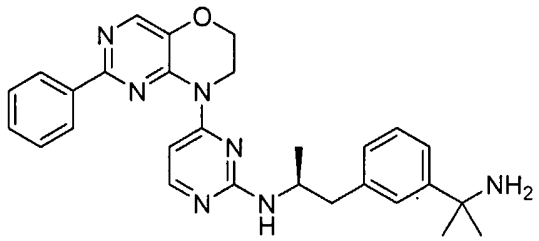
Example 107



1-(4-(4-(2-Phenyl-6,7-dihydropyrimido[5,4-b][1,4]oxazin-8-yl)pyrimidin-2-yl-amino)piperidin-1-yl)ethanone

A mixture of acetic acid (11 μL, 0.20 mmol) and PS-carbodiimide (0.20 g, 0.26 mmol) was stirred at RT for 15 min followed by the addition of 4-(2-phenyl-6,7-dihydropyrimido[5,4-b][1,4]oxazin-8-yl)-*N*-(piperidin-4-yl)pyrimidin-2-amine (50 mg, 0.13 mmol). The resulting mixture was stirred at RT for 2 h, filtered and the filtrate was washed with saturated $NaHCO_3$, brine, dried over magnesium sulfate, concentrated and chromatographed on silica gel using 0-8% 2M NH_3 in $MeOH/CH_2Cl_2$ to afford the title compound as a white solid. MS m/z 432 $(M+H)^+$.

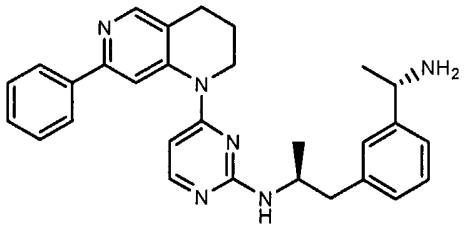
Example 108



(*S*)-*N*-(1-(3-(2-Aminopropan-2-yl)phenyl)propan-2-yl)-4-(2-phenyl-6,7-dihydro-pyrimido[5,4-b][1,4]oxazin-8-yl)pyrimidin-2-amine

The title compound was obtained the same was as example 105 using 8-(2-(methylsulfinyl)pyrimidin-4-yl)-2-phenyl-7,8-dihydro-6H-pyrimido[5,4-b][1,4]oxazine (90 mg, 0.25 mmol) and (*S*)-1-(3-(2-aminopropan-2-yl)phenyl)propan-2-amine (90 mg, 0.48 mmol). MS m/z 482 $(M+H)^+$.

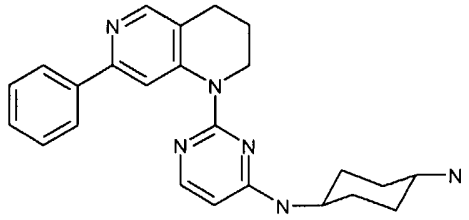
Example 109



***N*-((*S*)-1-(3-((*S*)-1-Aminoethyl)phenyl)propan-2-yl)-4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(*2H*)-yl)pyrimidin-2-amine**

1-(2-Fluoropyrimidin-4-yl)-7-phenyl-1,2,3,4-tetrahydro-1,6-naphthyridine (0.374 g, 1.22 mmol) and *tert*-butyl (*S*)-1-(3-((*S*)-2-aminopropyl)phenyl)ethylcarbamate (0.408 g, 1.47 mmol) in dioxane (3 mL) was heated at 100 °C overnight and the volatile material was removed under reduced pressure. The residue was purified by flash column chromatography (1% → 5% MeOH in DCM) to yield the Boc-amine (0.39 g), which was deprotected with 4N HCl in dioxane (3 mL) at RT for 30 min. Concentration followed by purification (column chromatography, 5% → 10% MeOH in DCM) afforded the title compound as an off-white solid. MS m/z 465.3 $(M+H)^+$.

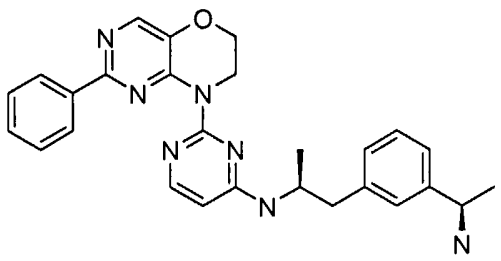
Example 110



'N-(4-aminocyclohexyl)-N-(2-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(2H)-yl)-4-pyrimidinyl)amine

$C_{24}H_{28}N_6$; 401 (M+H+).

Example 111



$C_{27}H_{29}N_7O$; 468 (M+H+).

Biological Assays

The following assays were used to characterize the ability of compounds of the invention to inhibit the production of TNF-α and IL-1-β. The second assay can be used to measure the inhibition of TNF-α and/or IL-1-β in mice after oral administration of the test compounds. The third assay, a glucagon binding inhibition *in vitro* assay, can be used to characterize the ability of compounds of the invention to inhibit glucagon binding. The fourth assay, a cyclooxygenase enzyme (COX-1 and COX-2) inhibition activity in vitro assay, can be used to characterize the ability of compounds of the invention to inhibit COX-1 and/or COX-2. The fifth assay, a Raf-kinase inhibition assay, can be used to characterize the compounds of the invention to inhibit phosphorylation of MEK by activated Raf-kinase.

Lipopolysaccharide-activated monocyte TNF production assay

Isolation of monocytes

Test compounds were evaluated *in vitro* for the ability to inhibit the production of TNF by monocytes activated with bacterial lipopolysaccharide (LPS). Fresh residual source leukocytes (a byproduct of plateletpheresis) were obtained from a local blood bank, and peripheral blood mononuclear cells (PBMCs) were isolated by density gradient centrifugation on Ficol-Paque Plus (Pharmacia). PBMCs were suspended at 2 x 10^6/mL in DMEM supplemented to contain 2% FCS, 10 mM, 0.3 mg/mL glutamate, 100 U/mL penicillin G and 100 mg/mL streptomycin sulfate (complete media). Cells were plated into Falcon flat bottom, 96 well culture plates (200 µL/well) and cultured overnight at 37 °C and 6% CO_2. Non-adherent cells were removed by washing with 200 µl/well of fresh medium. Wells containing adherent cells (~70% monocytes) were replenished with 100 µL of fresh medium.

Preparation of test compound stock solutions

Test compounds were dissolved in DMZ. Compound stock solutions were prepared to an initial concentration of 10 - 50µM. Stocks were diluted initially to 20 – 200 µM in complete media. Nine two-fold serial dilutions of each compound were then prepared in complete medium.

Treatment of cells with test compounds and activation of TNF production with lipopolysaccharide

One hundred microliters of each test compound dilution were added to microtiter wells containing adherent monocytes and 100 µL complete medium. Monocytes were cultured with test compounds for 60 min at which time 25 µL of complete medium containing 30 ng/mL lipopolysaccharide from *E. coli* K532 were added to each well. Cells were cultured an additional 4 h. Culture supernatants were then removed and TNF presence in the supernatants was quantified using an ELISA.

TNF ELISA

Flat bottom, 96 well Corning High Binding ELISA plates were coated overnight (4 °C) with 150 µL/well of 3 µg/mL murine anti-human TNF-α MAb (R&D Systems #MAB210). Wells were then blocked for 1 h at RT with 200 µL/well of $CaCl_2$-free

ELISA buffer supplemented to contain 20 mg/mL BSA (standard ELISA buffer: 20 mM, 150 mM NaCl, 2 mM $CaCl_2$, 0.15mM thimerosal, pH 7.4). Plates were washed and replenished with 100 μL of test supernatants (diluted 1:3) or standards. Standards consisted of eleven 1.5-fold serial dilutions from a stock of 1 ng/mL recombinant human TNF (R&D Systems). Plates were incubated at RT for 1 h on orbital shaker (300 rpm), washed and replenished with 100 μL/well of 0.5 μg/mL goat anti-human TNF-α (R&D systems #AB-210-NA) biotinylated at a 4:1 ratio. Plates were incubated for 40 min, washed and replenished with 100 μL/well of alkaline phosphatase-conjugated streptavidin (Jackson ImmunoResearch #016-050-084) at 0.02 μg/mL. Plates were incubated 30 min, washed and replenished with 200 μL/well of 1 mg/mL of p-nitrophenyl phosphate. After 30 min, plates were read at 405 nm on a V_{max} plate reader.

Data analysis

Standard curve data were fit to a second order polynomial and unknown TNF-α concentrations determined from their OD by solving this equation for concentration. TNF concentrations were then plotted vs. test compound concentration using a second order polynomial. This equation was then used to calculate the concentration of test compounds causing a 50% reduction in TNF production.

Compounds of the invention can also be shown to inhibit LPS-induced release of IL-1β, IL-6 and/or IL-8 from monocytes by measuring concentrations of IL-1β, IL-6 and/or IL-8 by methods well known to those skilled in the art. In a similar manner to the above described assay involving the LPS induced release of TNF–α from monocytes, compounds of this invention can also be shown to inhibit LPS induced release of IL-1β, IL-6 and/or IL-8 from monocytes by measuring concentrations of IL-1β, IL-6 and/or IL-8 by methods well known to those skilled in the art. Thus, the compounds of the invention may lower elevated levels of TNF-α, IL-1, IL-6, and IL-8 levels. Reducing elevated levels of these inflammatory cytokines to basal levels or below is favorable in controlling, slowing progression, and alleviating many disease states. All of the compounds are useful in the methods of treating disease states in which TNF-α, IL-1β, IL-6, and IL-8 play a role to the full extent of the definition of TNF-α-mediated diseases described herein.

Lipopolysaccharide-activated THP1 Cell TNF production assay

THP1 cells are resuspended in fresh THP1 media (RPMI 1640, 10% heat-inactivated FBS, 1XPGS, 1XNEAA, plus 30μM βME) at a concentration of 1E6/mL. One hundred microliters of cells per well are plated in a polystyrene 96-well tissue culture. One microgram per mL of bacterial LPS is prepared in THP1 media and is transferred to the wells. Test compounds are dissolved in 100% DMSO and are serially diluted 3-fold in a polypropylene 96-well microtiter plate (drug plate). HI control and LO control wells contain only DMSO. One microliter of test compound from the drug plate followed by 10 μL of LPS are transferred to the cell plate. The treated cells are induced to synthesize and secrete TNF-α at 37 °C for 3 h. Forty microliters of conditioned media are transferred to a 96-well polypropylene plate containing 110 μL of ECL buffer (50mM Tris-HCl pH 8.0, 100 mM NaCl, 0.05% Tween 20, 0.05% NaN_3 and 1%FBS) supplemented with 0.44 nM MAB610 monoclonal Ab (R&D Systems), 0.34 nM ruthenylated AF210NA polyclonal Ab (R&D Systems) and 44 μg/mL sheep anti-mouse M280 Dynabeads (Dynal). After a 2 h incubation at RT with shaking, the reaction is read on the ECL M8 Instrument (IGEN Inc.). A low voltage is applied to the ruthenylated TNF-α immune complexes, which in the presence of TPA (the active component in Origlo), results in a cyclical redox reaction generating light at 620 nM. The amount of secreted TNF-α in the presence of compound compared with that in the presence of DMSO vehicle alone (HI control) is calculated using the formula:% control (POC) = (cpd – average LO)/(average HI - average LO)*100. Data (consisting of POC and inhibitor concentration in μM) is fitted to a 4-parameter equation (y = A + ((B-A)/(1 + ((x/C)^D))), where A is the minimum y (POC) value, B is the maximum y (POC), C is the x (cpd concentration) at the point of inflection and D is the slope factor) using a Levenburg-Marquardt non-linear regression algorithm.

The following compounds exhibit activities in the THP1 cell assay (LPS induced TNF release) with IC_{50} values of 20 μM or less:

N-Phenethyl-4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(*2H*)-yl)pyrimidin-2-amine;

(3-(2-(4-(7-Phenyl-3,4-dihydro-1,6-naphthyridin-1(*2H*)-yl)pyrimidin-2-ylamino)-propyl)phenyl)methanol;

N-(1-(3-(Aminomethyl)phenyl)propan-2-yl)-4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(*2H*)-yl)pyrimidin-2-amine;

N-((*S*)-1-(3-((*S*)-1-Aminoethyl)phenyl)propan-2-yl)-4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(*2H*)-yl)pyrimidin-2-amine;

tert-Butyl-4-4(7-phenyl-3,4-dihydro-1,6-naphthylridin-1(*2H*)-pyrimidin-2-ylamino)-piperidine-1-carboxylate;

4-(7-Phenyl-3,4-dihydro-1,6-naphthyridin-1(*2H*)-yl)-*N*-(piperidin-4-yl)pyrimidin-2-amine;

1-(4-(4-(7-Phenyl-3,4-dihydro-1,6-naphthyridin-1(*2H*)-yl)pyrimidin-2-ylamino)piperidin-1-yl)ethanone;

N-((*S*)-1-(3-((*R*)-1-Aminoethyl)phenyl)propan-2-yl)-4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(*2H*)-yl)pyrimidin-2-amine;

(S)-N-(1-(3-(2-Aminopropan-2-yl)phenyl)propan-2-yl)-4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(*2H*)-yl)pyrimidin-2-amine;

(S)-1-(3-(2-(4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(*2H*)-yl)pyrimidin-2-ylamino)-propyl)phenyl)ethanone;

2-Amino-1-(4(4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(*2H*)-yl)pyrimidin-2-yl-amino)piperdin-1- yl)ethanone;

3-(Isopropylamino)-1-(4(4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(*2H*)-yl)pyrimidin-2-ylamino)piperdin-1- yl)propan-1-one;

3-(Methylamino)-1-(4(4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(*2H*)-yl)pyrimidin-2-ylamino)piperdin-1- yl)propan-1-one;

3-(Ethylamino)-1-(4(4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(*2H*)-yl)pyrimidin-2-ylamino)piperdin-1- yl)propan-1-one;

(*R*)-Methyl-3-phenyl-2-(4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(*2H*)-yl)pyrimidin-2-ylamino)propanoate;

(R)-3-Phenyl-2-(4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(*2H*)-yl)pyrimidin-2-ylamino)propanoic acid;

(*R*)-4-Phenyl-3-(4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(*2H*)-yl)pyrimidin-2-ylamino)butanoic acid;

(*R*)-1-Morpholino-4-phenyl-3-(4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(*2H*)-yl)pyrimidin-2-ylamino)butan-1-one;

(*R*)-*N*-Cyclopropyl-4-phenyl-3-(4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(*2H*)-yl)pyrimidin-2-ylamino)butanamide;

(*R*)-4-Phenyl-3-(4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(*2H*)-yl)pyrimidin-2-ylamino)-1-(piperazin-1yl)butan-1-one;

tert-Butyl-4-(5-fluoro-4(7-phenyl-3,4-dihydro-1,6-naphthylridin-1(*2H*)-pyrimidin-2-ylamino)piperidine-1-carboxylate;

5-Fluoro-4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(2H)-yl)-N-(piperidin-4-yl) pyrimidin-2-amine;

1-(4-(5-Fluoro-4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(*2H*)-yl)pyrimidin-2-yl-amino)piperidin-1-yl)ethanone;

(*S*)-*N*-(1-(3-(2-Aminopropan-2-yl)phenyl)propan-2-yl)-4-(7-phenyl-3,4-dihydro-1,5-naphthyridin-1(*2H*)-yl)pyrimidin-2-amine;

tert-Butyl-4(7-phenyl-3,4-dihydro-1,5-naphthylridin-1(*2H*)-pyrimidin-2-ylamino)-piperidine-1-carboxylate;

4-(7-Phenyl-3,4-dihydro-1,5-naphthyridin-1(*2H*)-yl)-*N*-(piperidin-4-yl)pyrimidin-2-amine;

1-(4-(4-(7-Phenyl-3,4-dihydro-1,5-naphthyridin-1(*2H*)-yl)pyrimidin-2-ylamino)piperidin-1-yl)ethanone;

(*R*)-3-Phenyl-2-(4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(*2H*)-yl)pyrimidin-2-ylamino)propanamide;

(*1R,4R*)-N^1-(4-(7-Phenyl-3,4-dihydro-1,6-naphthyridin-1(2*H*)-yl)pyrimidin-2-yl) cyclohexane-1, 4-diamine;

N-((*1R,4R*)-4-(4-(7-Phenyl-3,4-dihydro-1,6-naphthyridin-1(2*H*)-yl)pyrimidin-2-ylamino) cyclohexyl) acetamide;

3,3,3-Trifluoro-*N*-((*1R,4R*)-4-(4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(2*H*)-yl)-pyrimidin-2-ylamino)cyclohexyl)propanamide;

(*1R,4R*)-N^1-Isopropyl-N^4-(4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(2*H*)-yl)pyrimidin-2-yl) cyclohexane-1,4-diamine;

(*S*)-*N*-(1-(3-(Aminoethyl)phenyl)propan-2-yl)-4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(2*H*)-yl) pyrimidin-2-amine;

(*S*)-*N*-(1-(3-(2-Aminopropan-2-yl)phenyl)propan-2-yl)-4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(2*H*)-yl) pyrimidin-2-amine;

N-(1-(4-Fluorophenyl)-2-methylpropan-2-yl)-4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(2*H*)-yl) pyrimidin-2-amine;

N-(1-Amino-2-methylpropan-2-yl)-4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(2*H*)-yl)pyrimidin-2-amine;

N-(2-Methyl-2-(4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(2*H*)-yl)pyrimidin-2-ylamino)propyl) acetamide;

N-(1-(Isopropylamino)-2-methylpropan-2-yl)-4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(2*H*)-yl) pyrimidin-2-amine;

N-Phenethyl-4-(7-phenyl-3,4-dihydro-1,8-naphthyridin-1(*2H*)-yl)pyrimidin-2-amine;

(3-(2-(4-(7-Phenyl-3,4-dihydro-1,8-naphthyridin-1(*2H*)-yl)pyrimidin-2-ylamino)propyl) phenyl)methanol;

N-(1-(3-(Aminomethyl)phenyl)propan-2-yl)-4-(7-phenyl-3,4-dihydro-1,8-naphthyridin-1(*2H*)-yl)pyrimidin-2-amine;

4-(7-Phenyl-3,4-dihydro-1,8-naphthyridin-1(*2H*)-yl)-*N*-(2-(pyridin-3-yl)ethyl)pyrimidin-2-amine;

N-(3-(Dimethylamino)-2,2-dimethylpropyl)-4-(7-phenyl-3,4-dihydro-1,8-naphthyridin-1(*2H*)-yl)pyrimidin-2-amine;

N-Neopentyl-4-(7-phenyl-3,4-dihydro-1,8-naphthyridin-1(*2H*)-yl)pyrimidin-2-amine;

N-(2-Amino-2-methylpropyl)-4-(7-phenyl-3,4-dihydro-1,8-naphthyridin-1(*2H*)-yl)-pyrimidin-2-amine;

*t*ert-Butyl 4-(4-(7-phenyl-3,4-dihydro-1,8-naphthyridin-1(*2H*)-yl)pyrimidin-2-yl-amino)piperidine-1-carboxylate;

N-Phenethyl-4-(7-phenyl-3,4-dihydro-1,8-naphthyridin-1(*2H*)-yl)-6-(trifluoromethyl) pyrimidin-2-amine;

(3-(2-(4-(7-Phenyl-3,4-dihydro-1,8-naphthyridin-1(*2H*)-yl)-6-(trifluoromethyl)pyrimidin-2-ylamino)propyl)phenyl)methanol;

N-(1-(3-(Aminomethyl)phenyl)propan-2-yl)-4-(7-phenyl-3,4-dihydro-1,8-naphthyridin-1(*2H*)-yl)-6-(trifluoromethyl)pyrimidin-2-amine;

1-(2-Fluoro-6-methylpyrimidin-4-yl)-7-phenyl-1,2,3,4-tetrahydro-1,8-naphthyridine;

tert-Butyl 4-(4-methyl-6-(7-phenyl-3,4-dihydro-1,8-naphthyridin-1(*2H*)-yl)pyrimidin-2-ylamino)piperidine-1-carboxylate;

tert-Butyl (*R*)-1-(3-((*S*)-2-(4-methyl-6-(7-phenyl-3,4-dihydro-1,8-naphthyridin-1(*2H*)-yl)pyrimidin-2-ylamino)propyl)phenyl)ethylcarbamate;

N-((*S*)-1-(3-((*R*)-1-Aminoethyl)phenyl)propan-2-yl)-4-methyl-6-(7-phenyl-3,4-dihydro-1,8-naphthyridin-1(*2H*)-yl)pyrimidin-2-amine;

Ethyl 8-(2-(Phenethylamino)pyrimidin-4-yl)-2-phenyl-5,6,7,8-tetrahydro-1,8-naphthyridine-3-carboxylate;

(8-(2-(Phenethylamino)pyrimidin-4-yl)-2-phenyl-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)methanol;

4-(6-(Methoxymethyl)-7-phenyl-3,4-dihydro-1,8-naphthyridin-1(*2H*)-yl)-N-phenethylpyrimidin-2-amine;

8-(2-(Phenethylamino)pyrimidin-4-yl)-2-phenyl-5,6,7,8-tetrahydro-1,8-naphthyridine-3-carboxylic acid;

4-(6-((Methylamino)methyl)-7-phenyl-3,4-dihydro-1,8-naphthyridin-1(*2H*)-yl)-*N*-phenethylpyrimidin-2-amine;

4-(6-((Dimethylamino)methyl)-7-phenyl-3,4-dihydro-1,8-naphthyridin-1(*2H*)-yl)-N-phenethylpyrimidin-2-amine;

1-(8-(2-(Phenethylamino)pyrimidin-4-yl)-2-phenyl-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)ethanone;

1-(8-(2-(Phenethylamino)pyrimidin-4-yl)-2-phenyl-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)ethanol;

Ethyl 8-(2-(1-(tert-butoxycarbonyl)piperidin-4-ylamino)pyrimidin-4-yl)-2-phenyl-5,6,7,8-tetrahydro-1,8-naphthyridine-3-carboxylate;

Ethyl 8-(2-((*1R,4R*)-4-aminocyclohexylamino)pyrimidin-4-yl)-2-phenyl-5,6,7,8-tetrahydro-1,8-naphthyridine-3-carboxylate;

(8-(2-((*1R,4R*)-4-Aminocyclohexylamino)pyrimidin-4-yl)-2-phenyl-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)methanol;

2-(8-(2-((*1R,4R*)-4-Aminocyclohexylamino)pyrimidin-4-yl)-2-phenyl-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)propan-2-ol;

Ethyl 8-(2-(1-(3-(hydroxymethyl)phenyl)propan-2-ylamino)pyrimidin-4-yl)-2-phenyl-5,6,7,8-tetrahydro-1,8-naphthyridine-3-carboxylate;

(8-(2-(1-(3-(Aminomethyl)phenyl)propan-2-ylamino)pyrimidin-4-yl)-2-phenyl-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)methanol;

8-(2-(Phenethylamino)pyrimidin-4-yl)-2-phenyl-5,6,7,8-tetrahydro-1,8-naphthyridin-3-amine;

(8-(2-(Phenethylamino)pyrimidin-4-yl)-2-phenyl-5,6,7,8-tetrahydro-1,8-naphthyridin-4-yl)methanol;

Ethyl-4-(4-(7-phenyl-3,4-dihydro-1,8-naphthyridin-1(2*H*)-yl)pyrimidin-2-ylamino)-piperidine-1-carboxylate;

(*1R,4R*)-N^1-(4-(7-Phenyl-3,4-dihydro-1,8-naphthyridin-1(2*H*)-ylpyrimidin-2-yl)-cyclohexane-1,4-diamine;

(*1R,4R*)-N^1-Isopropyl-N^4-(4-(7-phenyl-3,4-dihydro-1,8-naphthyridin-1(2*H*)-yl)pyrimidin-2-yl) cyclohexane-1,4-diamine;

N-((*1R*,,*4*R)-4-(4-(7-Phenyl-3,4-dihydro-1,8-naphthyridin-1(2*H*)-yl)pyrimidin-2-ylamino) cyclohexyl) acetamide;

N-((*S*)-1-(3-((*R*)–1-Aminoethyl) phenyl) propan-2-yl)-4-(7-phenyl-3, 4-dihydro-1, 8-naphthyridin-1(2*H*)-yl) pyrimidin-2-amine;

tert-Butyl (*R*)-1-(3-((*S*)-2-(4-(2-phenyl-6,7-dihydropyrimido[5,4-b][1,4]oxazin-8-yl)pyrimidin-2-ylamino)propyl)phenyl)ethylcarbamate;

N-((*S*)-1-(3-((*R*)-1-Aminoethyl)phenyl)propan-2-yl)-4-(2-phenyl-6,7-dihydropyrimido-[5,4-b][1,4]oxazin-8-yl)pyrimidin-2-amine;

(*1R,4R*)-N^1-(4-(2-Phenyl-6,7-dihydropyrimido[5,4-b][1,4]oxazin-8-yl)pyrimidin-2-yl) cyclohexane-1,4-diamine;

4-(2-Phenyl-6,7-dihydropyrimido[5,4-b][1,4]oxazin-8-yl)-*N*-(piperidin-4-yl)pyrimidin-2-amine;

1-(4-(4-(2-Phenyl-6,7-dihydropyrimido[5,4-b][1,4]oxazin-8-yl)pyrimidin-2-ylamino) piperidin-1-yl)ethanone; and

(*S*)-*N*-(1-(3-(2-Aminopropan-2-yl)phenyl)propan-2-yl)-4-(2-phenyl-6,7-dihydropyrimido [5,4-b][1,4]oxazin-8-yl)pyrimidin-2-amine.

Inhibition of LPS-Induced TNF-α production in mice

Male DBA/1LACJ mice are dosed with vehicle or test compounds in a vehicle (the vehicle consisting of 0.5% tragacanth in 0.03 N HCl) 30 minutes prior to lipopolysaccharide (2 mg/Kg, I.V.) injection. Ninety minutes after LPS injection, blood is collected and the serum is analyzed by ELISA for TNF-α levels.

Compounds of the invention may be shown to have anti-inflammatory properties in animal models of inflammation, including carageenan paw edema, collagen induced arthritis and adjuvant arthritis, such as the carageenan paw edema model (C. A. Winter et al Proc. Soc. Exp. Biol. Med., 111:544 (1962); K. F. Swingle, in R. A. Scherrer and M.

W. Whitehouse, Eds., Anti-inflammatory Agents, Chemistry and Pharmacology, 13-II:33, Academic, New York (1974) and collagen induced arthritis (D. E. Trentham et al., J. Exp. Med., 146:857 (1977); J. S. Courtenay, Nature (New Biol.), 283:666 (1980).

^{125}I-Glucagon Binding Screen with CHO/hGLUR Cells

The assay is described in WO 97/16442, which is incorporated herein by reference in its entirety.

Reagents

The reagents can be prepared as follows: (a) prepare fresh 1 M o-Phenanthroline (Aldrich) (198.2 mg/mL ethanol); (b) prepare fresh 0.5 M DTT (Sigma); (c) Protease Inhibitor Mix (1000 X): 5 mg leupeptin, 10 mg benzamidine, 40 mg bacitracin and 5 mg soybean trypsin inhibitor per mL DMSO and store aliquots at -20 °C; (d) 250 μM human glucagon (Peninsula): solubilize 0.5 mg vial in 575 μl 0.1N acetic acid (1 μL yields 1 μM final concentration in assay for non-specific binding) and store in aliquots at -20 °C; (e) Assay Buffer: 20 mM Tris (pH 7.8), 1mM DTT and 3mM o-phenanthroline; (f) Assay Buffer with 0.1% BSA (for dilution of label only; 0.01% final in assay): 10 μL 10% BSA (heat-inactivated) and 990 μL Assay Buffer; (g) ^{125}I-Glucagon (NEN, receptor-grade, 2200 Ci/mmol): dilute to 50,000 cpm/25 μL in assay buffer with BSA (about 50pM final concentration in assay).

Harvesting of CHO/hGLUR Cells for Assay

1. Remove media from confluent flask then rinse once each with PBS (Ca, Mg-free) and Enzyme-free Dissociation Fluid (Specialty Media, Inc.).

2. Add 10 mL Enzyme-free Dissoc. Fluid and hold for about 4 min at 37 °C.

3. Gently tap cells free, triturate, take aliquot for counting and centrifuge remainder for 5 min at 1000 rpm.

4. Resuspend pellet in Assay Buffer at 75000 cells per 100 μL.

Membrane preparations of CHO/hGLUR cells can be used in place of whole cells at the same assay volume. Final protein concentration of a membrane preparation is determined on a per batch basis.

Assay

The determination of inhibition of glucagon binding can be carried out by measuring the reduction of I^{125}-glucagon binding in the presence of compounds of Formula I. The reagents are combined as follows:

	Compound/ Vehicle	250 μM Glucagon	^{125}I-Glucagon	CHO/hGLUR Cells
Total Binding	--/5 μl	--	25 μL	100 μL
+ Compound	5 μl/--	--	25 μL	100 μL
Nonspecific Binding	--/5 μl	1 μl	25 μL	100 μL

The mixture is incubated for 60 min at 22 °C on a shaker at 275 rpm. The mixture is filtered over pre-soaked (0.5% polyethylimine (PEI)) GF/C filtermat using an Innotech Harvester or Tomtec Harvester with four washes of ice-cold 20 mM Tris buffer (pH 7.8). The radioactivity in the filters is determined by a gamma-scintillation counter.

Thus, compounds of the invention may also be shown to inhibit the binding of glucagon to glucagon receptors.

Cyclooxygenase Enzyme Activity Assay

The human monocytic leukemia cell line, THP-1, differentiated by exposure to phorbol esters expresses only COX-1; the human osteosarcoma cell line 143B expresses predominantly COX-2. THP-1 cells are routinely cultured in RPMI complete media supplemented with 10% FBS and human osteosarcoma cells (HOSC) are cultured in minimal essential media supplemented with 10% fetal bovine serum (MEM-10%FBS); all cell incubations are at 37 °C in a humidified environment containing 5% CO_2.

COX-1 Assay

In preparation for the COX-1 assay, THP-1 cells are grown to confluency, split 1:3 into RPMI containing 2% FBS and 10mM phorbol 12-myristate 13-acetate (TPA), and incubated for 48 h on a shaker to prevent attachment. Cells are pelleted and resuspended in Hank's Buffered Saline (HBS) at a concentration of 2.5×10^6 cells/mL and plated in 96-well culture plates at a density of 5×10^5 cells/mL. Test compounds are diluted in HBS and added to the desired final concentration and the cells are incubated

for an additional 4 hours. Arachidonic acid is added to a final concentration of 30 mM, the cells incubated for 20 min. at 37 °C, and enzyme activity determined as described below.

COX-2 Assay

For the COX-2 assay, subconfluent HOSC are trypsinized and resuspended at 3×10^6 cells/mL in MEM-FBS containing 1 ng human IL-1b/mL, plated in 96-well tissue culture plates at a density of 3×10^4 cells per well, incubated on a shaker for 1 hour to evenly distribute cells, followed by an additional 2 h static incubation to allow attachment. The media is then replaced with MEM containing 2% FBS (MEM-2%FBS) and 1 ng human IL-1b/mL, and the cells incubated for 18-22 h. Following replacement of media with 190 mL MEM, 10 mL of test compound diluted in HBS is added to achieve the desired concentration and the cells incubated for 4 h. The supernatants are removed and replaced with MEM containing 30 mM arachidonic acid, the cells incubated for 20 min at 37 °C, and enzyme activity determined as described below.

COX Activity Determined

After incubation with arachidonic acid, the reactions are stopped by the addition of 1 N HCl, followed by neutralization with 1 N NaOH and centrifugation to pellet cell debris. Cyclooxygenase enzyme activity in both HOSC and THP-1 cell supernatants is determined by measuring the concentration of PGE_2 using a commercially available ELISA (Neogen #404110). A standard curve of PGE_2 is used for calibration, and commercially available COX-1 and COX-2 inhibitors are included as standard controls.

Raf Kinase assay

In vitro Raf kinase activity is measured by the extent of phosphorylation of the substrate MEK (Map kinase/ERK kinase) by activated Raf kinase, as described in GB 1,238,959 (incorporated herein by reference in its entirety). Phosphorylated MEK is trapped on a filter and incorporation of radiolabeled phosphate is quantified by scintillation counting.

MATERIALS:

Activated Raf is produced by triple transfection of Sf9 cells with baculoviruses expressing "Glu-Glu"-epitope tagged Raf,val^{12}-H-Ras, and Lck. The "Glu-Glu"-epitope, Glu-Try-Met-Pro-Met-Glu, was fused to the carboxy-terminus of full-length c-Raf.

Catalytically inactive MEK (K97A mutation) is produced in Sf9 cells transfected with a baculovirus expressing c-terminus "Glu-Glu" epitope-tagged K97A MEK1.

Anti "Glu-Glu" antibody was purified from cells grown as described in: Grussenmeyer, et al., Proceedings of the National Academy of Science, U.S.A., 7952-7954 (1985).

Column buffer: 20 mM Tris pH 8, 100 mM NaCl, 1 mM EDTA, 2.5 mM EGTA, 10 mM $MgCl_2$, 2mM DTT, 0.4 mM AEBSF, 0.1% n-octylglucopyranoside, 1nM okadeic acid, and 10 μg/mL each of benzamidine, leupeptin, pepstatin, and aprotinin.

5x Reaction buffer: 125 mM HEPES pH=8, 25 mM $MgCl_2$, 5 mM EDTA, 5 mM Na_3VO_4, 100 μg/mL BSA.

Enzyme dilution buffer: 25 mM HEPES pH 8, 1 mM EDTA, 1 mM Na_3VO_4, 400 μg/mL BSA.

Stop solution: 100 mM EDTA, 80mM sodium pyrophosphate.

Filter plates: Milipore multiscreen # SE3MO78E3, Immobilon-P (PVDF).

METHODS:

Protein purification: Sf9 cells were infected with baculovirus and grown as described in Williams, et al., Proceedings of the National Academy of Science, U.S.A., 2922-2926 (1992). All subsequent steps were preformed on ice or at 4 °C. Cells were pelleted and lysed by sonication in column buffer. Lysates were spun at 17,000 xg for 20 min, followed by 0.22 μm filtration. Epitope tagged proteins were purified by chromatography over GammaBind Plus affinity column to which the "Glu-Glu" antibody was coupled. Proteins were loaded on the column followed by sequential washes with two column volumes of column buffer, and eluted with 50 μg/mL Glu-Tyr-Met-Pro-Met-Glu in column buffer.

Raf kinase assay: Test compounds were evaluated using ten 3-fold serial dilutions starting at 10 – 100 μM. 10 μL of the test inhibitor or control, dissolved in 10% DMSO, was added to the assay plate followed by the addition of 30 μL of the a mixture containing 10 μL 5x reaction buffer, 1 mM ^{33}P-γ-ATP (20 μCi/mL), 0.5 μL MEK (2.5 mg/mL), 1 μL 50 mM β-mercaptoethanol. The reaction was started by the addition of 10

μL of enzyme dilution buffer containing 1 mM DTT and an amount of activated Raf that produces linear kinetics over the reaction time course. The reaction was mixed and incubated at RT for 90 min and stopped by the addition of 50 μL stop solution. 90 μL aliquots of this stopped solution were transferred onto GFP-30 cellulose microtiter filter plates (Polyfiltronics), the filter plates washed in four well volumes of 5% phosphoric acid, allowed to dry, and then replenished with 25 μL scintillation cocktail. The plates were counted for ^{33}P gamma emission using a TopCount Scintillation Reader.

While the compounds of the invention can be administered as the sole active pharmaceutical agent, they can also be used in combination with one or more compounds of the invention or other agents. When administered as a combination, the therapeutic agents can be formulated as separate compositions or medicaments (used herein synonymously with composition) that are given at the same time or different times, or the therapeutic agents can be given as a single composition or medicament.

The foregoing is merely illustrative of the invention and is not intended to limit the invention to the disclosed compounds. Variations and changes, which are obvious to one skilled in the art, are intended to be within the scope and nature of the invention, which are defined, in the appended claims.

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

For the treatment of TNF-α, IL-1β, IL-6, and IL-8 mediated diseases, cancer, and/or hyperglycemia, the compounds of the present invention may be administered orally, parentally, by inhalation spray, rectally, or topically in dosage unit formulations containing conventional pharmaceutically acceptable carriers, adjuvants, and vehicles. The term parenteral as used herein includes, subcutaneous, intravenous, intramuscular, intrasternal, infusion techniques or intraperitoneally.

Treatment of diseases and disorders herein is intended to also include the prophylactic administration of a compound of the invention, a pharmaceutical salt thereof, or a pharmaceutical composition of either to a subject (*i.e.*, an animal, preferably a mammal, most preferably a human) believed to be in need of preventative treatment, such as, for example, pain, inflammation and the like.

The dosage regimen for treating a TNF-α, IL-1, IL-6, and IL-8 mediated diseases, cancer, and/or hyperglycemia with the compounds of this invention and/or compositions of this invention is based on a variety of factors, including the type of disease, the age, weight, sex, medical condition of the patient, the severity of the condition, the route of administration, and the particular compound employed. Thus, the dosage regimen may vary widely, but can be determined routinely using standard methods. Dosage levels of the order from about 0.01 mg to 30 mg per kilogram of body weight per day, preferably from about 0.1 mg to 10 mg/kg, more preferably from about 0.25 mg to 1 mg/kg are useful for all methods of use disclosed herein.

The pharmaceutically active compounds of this invention can be processed in accordance with conventional methods of pharmacy to produce medicinal agents for administration to patients, including humans and other mammals.

For oral administration, the pharmaceutical composition may be in the form of, for example, a capsule, a tablet, a suspension, or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a given amount of the active ingredient. For example, these may contain an amount of active ingredient from about 1 to 2000 mg, preferably from about 1 to 500 mg, more preferably from about 5 to 150 mg. A suitable daily dose for a human or other mammal may vary widely depending on the condition of the patient and other factors, but, once again, can be determined using routine methods.

The active ingredient may also be administered by injection as a composition with suitable carriers including saline, dextrose, or water. The daily parenteral dosage regimen will be from about 0.1 to about 30 mg/kg of total body weight, preferably from about 0.1 to about 10 mg/kg, and more preferably from about 0.25 mg to 1 mg/kg.

Injectable preparations, such as sterile injectable aqueous or oleaginous suspensions, may be formulated according to the known are using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed, including

synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Suppositories for rectal administration of the drug can be prepared by mixing the drug with a suitable non-irritating excipient such as cocoa butter and polyethylene glycols that are solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum and release the drug.

A suitable topical dose of active ingredient of a compound of the invention is 0.1 mg to 150 mg administered one to four, preferably one or two times daily. For topical administration, the active ingredient may comprise from 0.001% to 10% w/w, *e.g.*, from 1% to 2% by weight of the formulation, although it may comprise as much as 10% w/w, but preferably not more than 5% w/w, and more preferably from 0.1% to 1% of the formulation.

Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin (*e.g.*, liniments, lotions, ointments, creams, or pastes) and drops suitable for administration to the eye, ear, or nose.

For administration, the compounds of this invention are ordinarily combined with one or more adjuvants appropriate for the indicated route of administration. The compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanoic acids, stearic acid, talc, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulphuric acids, acacia, gelatin, sodium alginate, polyvinyl-pyrrolidine, and/or polyvinyl alcohol, and tableted or encapsulated for conventional administration. Alternatively, the compounds of this invention may be dissolved in saline, water, polyethylene glycol, propylene glycol, ethanol, corn oil, peanut oil, cottonseed oil, sesame oil, tragacanth gum, and/or various buffers. Other adjuvants and modes of administration are well known in the pharmaceutical art. The carrier or diluent may include time delay material, such as glyceryl monostearate or glyceryl distearate alone or with a wax, or other materials well known in the art.

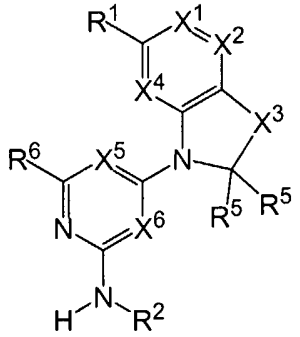
The pharmaceutical compositions may be made up in a solid form (including granules, powders or suppositories) or in a liquid form (*e.g.*, solutions, suspensions, or emulsions). The pharmaceutical compositions may be subjected to conventional pharmaceutical operations such as sterilization and/or may contain conventional adjuvants, such as preservatives, stabilizers, wetting agents, emulsifiers, buffers etc.

Solid dosage forms for oral administration may include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound may be admixed with at least one inert diluent such as sucrose, lactose, or starch. Such dosage forms may also comprise, as in normal practice, additional substances other than inert diluents, *e.g.*, lubricating agents such as magnesium stearate. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

Liquid dosage forms for oral administration may include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting, sweetening, flavoring, and perfuming agents.

WHAT IS CLAIMED IS:

1. A compound of the Formula I



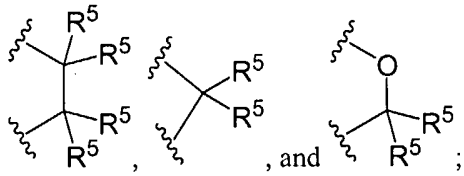
I

or a pharmaceutically acceptable salt or hydrate thereof, wherein

X^1 is N or CR^3;

X^2 is N or CR^4;

X^3 is selected from



, and ;

X^4 is N or CR^4;

X^5 is N or CR^6;

X^6 is N or CR^6;

R^1 is a saturated, partially saturated or unsaturated 5-, 6- or 7-membered, ring containing 0, 1, 2 or 3 atoms selected from N, O and S, wherein the ring is substituted by 0, 1, 2 or 3 substituents selected from C_{1-8}alkyl, C_{1-4}haloalkyl, halo, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^b$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}$alkylNR^aR^a, $-OC_{2-6}$alkylOR^a, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}$alkylNR^aR^a and $-NR^aC_{2-6}$alkylOR^a;

R^2 is C_{1-8}alkyl substituted by 0, 1, 2 or 3 substituents selected from C_{1-2}haloalkyl, halo, oxo, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}$alkylNR^aR^a,

$-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$, $-NR^aC_{2-6}alkylOR^a$, $-C(=O)R^g$, $-C(=O)OR^g$, $-C(=O)NR^aR^g$, $-C(=NR^a)NR^aR^g$, $-OR^g$, $-OC(=O)R^g$, $-OC(=O)NR^aR^g$, $-OC(=O)N(R^a)S(=O)_2R^g$, $-OC_{2-6}alkylNR^aR^g$, $-OC_{2-6}alkylOR^g$, $-SR^g$, $-S(=O)R^g$, $-S(=O)_2R^g$, $-S(=O)_2NR^aR^g$, $-NR^aR^g$, $-N(R^a)C(=O)R^g$, $-N(R^a)C(=O)OR^g$, $-N(R^a)C(=O)NR^aR^g$, $-C(=O)R^e$, $-C(=O)OR^e$, $-C(=O)NR^aR^e$, $-C(=NR^a)NR^aR^e$, $-OR^e$, $-OC(=O)R^e$, $-OC(=O)NR^aR^e$, $-OC(=O)N(R^a)S(=O)_2R^e$, $-OC_{2-6}alkylNR^aR^e$, $-OC_{2-6}alkylOR^e$, $-SR^e$, $-S(=O)R^e$, $-S(=O)_2R^e$, $-S(=O)_2NR^aR^e$, $-NR^aR^e$, $-N(R^a)C(=O)R^e$, $-N(R^a)C(=O)OR^e$ and $-N(R^a)C(=O)NR^aR^e$, and additionally substituted by 0, 1 or 2 saturated, partially saturated or unsaturated 5-, 6- or 7-membered monocyclic or 6-, 7-, 8-, 9-, 10- or 11-membered bicyclic rings containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, wherein the carbon atoms of the rings are substituted by 0, 1 or 2 oxo groups and the rings is substituted by 0, 1, 2 or 3 substituents selected from R^e, R^g, $C_{1-8}alkyl$, $C_{1-4}haloalkyl$, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ and $-NR^aC_{2-6}alkylOR^a$; or

R^2 is a saturated, partially saturated or unsaturated 5-, 6- or 7-membered monocyclic or 6-, 7-, 8-, 9-, 10- or 11-membered bicyclic rings containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, wherein the carbon atoms of the rings are substituted by 0, 1 or 2 oxo groups and the rings is substituted by 0, 1, 2 or 3 substituents selected from R^e, R^g, $C_{1-8}alkyl$, $C_{1-4}haloalkyl$, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ and $-NR^aC_{2-6}alkylOR^a$, and additionally substituted by 0, 1 or 2 $C_{1-8}alkyl$ groups, each being substituted by 0, 1, 2 or 3 substituents selected from $C_{1-2}haloalkyl$, halo, oxo, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$,

-C(=O)NR^aR^a, -C(=NR^a)NR^aR^a, -OR^a, -OC(=O)R^b, -OC(=O)NR^aR^a, -OC(=O)$N(R^a)S(=O)_2R^b$, -OC_{2-6}alkylNR^aR^a, -OC_{2-6}alkylOR^a, -SR^a, -S(=O)R^b, -$S(=O)_2R^b$, -$S(=O)_2NR^aR^a$, -$S(=O)_2N(R^a)C(=O)R^b$, -$S(=O)_2N(R^a)C(=O)OR^b$, -$S(=O)_2N(R^a)C(=O)NR^aR^a$, -$NR^aR^a$, -$N(R^a)C(=O)R^b$, -$N(R^a)C(=O)OR^b$, -$N(R^a)C(=O)NR^aR^a$, -$N(R^a)C(=NR^a)NR^aR^a$, -$N(R^a)S(=O)_2R^b$, -$N(R^a)S(=O)_2NR^aR^a$, -$NR^aC_{2-6}$alkyl$NR^aR^a$, -$NR^aC_{2-6}$alkyl$OR^a$, -C(=O)$R^g$, -C(=O)$OR^g$, -C(=O)$NR^aR^g$, -C(=$NR^a$)$NR^aR^g$, -$OR^g$, -OC(=O)$R^g$, -OC(=O)$NR^aR^g$, -OC(=O)$N(R^a)S(=O)_2R^g$, -$OC_{2-6}$alkyl$NR^aR^g$, -$OC_{2-6}$alkyl$OR^g$, -$SR^g$, -S(=O)$R^g$, -$S(=O)_2R^g$, -$S(=O)_2NR^aR^g$, -$NR^aR^g$, -$N(R^a)C(=O)R^g$, -$N(R^a)C(=O)OR^g$, -$N(R^a)C(=O)NR^aR^g$, -C(=O)$R^e$, -C(=O)$OR^e$, -C(=O)$NR^aR^e$, -C(=$NR^a$)$NR^aR^e$, -$OR^e$, -OC(=O)$R^e$, -OC(=O)$NR^aR^e$, -OC(=O)$N(R^a)S(=O)_2R^e$, -$OC_{2-6}$alkyl$NR^aR^e$, -$OC_{2-6}$alkyl$OR^e$, -$SR^e$, -S(=O)$R^e$, -$S(=O)_2R^e$, -$S(=O)_2NR^aR^e$, -$NR^aR^e$, -$N(R^a)C(=O)R^e$, -$N(R^a)C(=O)OR^e$ and -$N(R^a)C(=O)NR^aR^e$, and additionally substituted by 0, 1 or 2 saturated, partially saturated or unsaturated 5-, 6- or 7-membered monocyclic or 6-, 7-, 8-, 9-, 10- or 11-membered bicyclic rings containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, wherein the carbon atoms of the rings are substituted by 0, 1 or 2 oxo groups and the rings is substituted by 0, 1, 2 or 3 substituents selected from R^e, R^g, C_{1-8}alkyl, C_{1-4}haloalkyl, cyano, nitro, -C(=O)R^b, -C(=O)OR^b, -C(=O)NR^aR^a, -C(=NR^a)NR^aR^a, -OR^a, -OC(=O)R^b, -OC(=O)NR^aR^a, -OC(=O)$N(R^a)S(=O)_2R^b$, -OC_{2-6}alkylNR^aR^a, -OC_{2-6}alkylOR^a, -SR^a, -S(=O)R^b, -$S(=O)_2R^b$, -$S(=O)_2NR^aR^a$, -$S(=O)_2N(R^a)C(=O)R^b$, -$S(=O)_2N(R^a)C(=O)OR^b$, -$S(=O)_2N(R^a)C(=O)NR^aR^a$, -$NR^aR^a$, -$N(R^a)C(=O)R^b$, -$N(R^a)C(=O)OR^b$, -$N(R^a)C(=O)NR^aR^a$, -$N(R^a)C(=NR^a)NR^aR^a$, -$N(R^a)S(=O)_2R^b$, -$N(R^a)S(=O)_2NR^aR^a$, -$NR^aC_{2-6}$alkyl$NR^aR^a$ and -NR^aC_{2-6}alkylOR^a; wherein any part of R^2 is additionally substituted by 0, 1, 2, 3, 4, 5 or 6 atoms selected from Br, Cl, F and I;

R^3 is independently, in each instance, selected from H, R^e, C_{1-4}haloalkyl, halo, cyano, nitro, -C(=O)R^b, -C(=O)OR^b, -C(=O)NR^aR^a, -C(=NR^a)NR^aR^a, -OR^b, -OR^e, -OC(=O)R^b, -OC(=O)NR^aR^a, -OC(=O)$N(R^a)S(=O)_2R^b$, -OC_{2-6}alkylNR^aR^a, -OC_{2-6}alkylOR^a, -SR^a, -S(=O)R^b, -$S(=O)_2R^b$, -$S(=O)_2NR^aR^a$, -$S(=O)_2N(R^a)C(=O)R^b$, -$S(=O)_2N(R^a)C(=O)OR^b$, -$S(=O)_2N(R^a)C(=O)NR^aR^a$, -$NR^aR^a$, -$NR^aR^e$, -$N(R^a)C(=O)R^b$, -$N(R^a)C(=O)OR^b$, -$N(R^a)C(=O)NR^aR^a$, -$N(R^a)C(=NR^a)NR^aR^a$, -$N(R^a)S(=O)_2R^b$, -$N(R^a)S(=O)_2NR^aR^a$, -$NR^aC_{2-6}$alkyl$NR^aR^a$ and -NR^aC_{2-6}alkylOR^a;

R^4 is independently in each instance H, R^e, C_{1-4}haloalkyl, halo, cyano, nitro, -C(=O)R^b, -C(=O)OR^b, -C(=O)NR^aR^a, -C(=NR^a)NR^aR^a, -OR^b, -OR^e, -OC(=O)R^b,

$-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-NR^aR^e$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ or $-NR^aC_{2-6}alkylOR^a$;

R^5 is independently in each instance H, R^e, C_{1-4}haloalkyl, halo, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^b$, $-OR^e$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-NR^aR^e$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ or $-NR^aC_{2-6}alkylOR^a$;

R^6 is independently in each instance H, C_{1-8}alkyl, C_{1-4}haloalkyl, $-NR^aR^a$, $-OR^a$, or halo;

R^a is independently, at each instance, H or R^b;

R^b is independently, at each instance, phenyl, benzyl or C_{1-6}alkyl, the phenyl, benzyl and C_{1-6}alkyl being substituted by 0, 1, 2 or 3 substituents selected from halo, C_{1-4}alkyl, C_{1-3}haloalkyl, $-OC_{1-4}$alkyl, $-NH_2$, $-NHC_{1-4}$alkyl, $-N(C_{1-4}alkyl)C_{1-4}$alkyl;

R^d is independently at each instance C_{1-8}alkyl, C_{1-4}haloalkyl, halo, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ or $-NR^aC_{2-6}alkylOR^a$;

R^e is independently at each instance C_{1-6}alkyl substituted by 0, 1, 2 or 3 substituents independently selected from R^d and additionally substituted by 0 or 1 substituents selected from R^g; and

R^g is independently at each instance a saturated, partially saturated or unsaturated 5-, 6- or 7-membered monocyclic or 6-, 7-, 8-, 9-, 10- or 11-membered bicyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, wherein the carbon atoms of the ring are substituted by 0, 1 or 2 oxo groups and the ring is substituted by 0, 1, 2 or 3 substituents selected from R^b, C_{1-4}haloalkyl, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$,

$-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ and $-NR^aC_{2-6}alkylOR^a$, and additionally substituted by 0, 1, 2, 3, 4, 5 or 6 atoms selected from Br, Cl, F and I.

2. The compound according to Claim 1, wherein

R^1 is a ring selected from phenyl, pyridyl, pyrimidinyl, pyridazine, pyrazine, pyrazole, imidazole, triazole, thiophene, furan, thiazole and oxazole, wherein the ring is substituted by 0, 1, 2 or 3 substituents selected from $C_{1-4}alkyl$, $C_{1-4}haloalkyl$, halo, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ and $-NR^aC_{2-6}alkylOR^a$;

R^2 is $C_{2-8}alkyl$ substituted by 1 or 2 substituents selected from $C_{1-2}haloalkyl$, halo, oxo, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$, $-NR^aC_{2-6}alkylOR^a$, $-C(=O)R^g$, $-C(=O)OR^g$, $-C(=O)NR^aR^g$, $-C(=NR^a)NR^aR^g$, $-OR^g$, $-OC(=O)R^g$, $-OC(=O)NR^aR^g$, $-OC(=O)N(R^a)S(=O)_2R^g$, $-OC_{2-6}alkylNR^aR^g$, $-OC_{2-6}alkylOR^g$, $-SR^g$, $-S(=O)R^g$, $-S(=O)_2R^g$, $-S(=O)_2NR^aR^g$, $-NR^aR^g$, $-N(R^a)C(=O)R^g$, $-N(R^a)C(=O)OR^g$, $-N(R^a)C(=O)NR^aR^g$, $-C(=O)R^e$, $-C(=O)OR^e$, $-C(=O)NR^aR^e$, $-C(=NR^a)NR^aR^e$, $-OR^e$, $-OC(=O)R^e$, $-OC(=O)NR^aR^e$, $-OC(=O)N(R^a)S(=O)_2R^e$, $-OC_{2-6}alkylNR^aR^e$, $-OC_{2-6}alkylOR^e$, $-SR^e$, $-S(=O)R^e$, $-S(=O)_2R^e$, $-S(=O)_2NR^aR^e$, $-NR^aR^e$, $-N(R^a)C(=O)R^e$, $-N(R^a)C(=O)OR^e$, $-N(R^a)C(=O)NR^aR^e$ and a ring selected from phenyl, pyridyl, pyrimidinyl, pyridazine, pyrazine, pyrazole, imidazole, triazole, thiophene, furan, thiazole and oxazole, wherein

the ring is substituted by 0, 1 or 2 substituents selected from R^e, R^g, C_{1-8}alkyl, C_{1-4}haloalkyl, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}$alkylNR$^aR^a$, $-OC_{2-6}$alkylOR^a, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}$alkylNR$^aR^a$ and $-NR^aC_{2-6}$alkylOR^a; wherein any part of R^2 is additionally substituted by 0, 1, 2, 3, 4, 5 or 6 atoms selected from Br, Cl, F and I;

R^3 is H;

R^4 is H;

R^5 is H; and

R^6 is H.

3. The compound according to Claim 1 that is selected from:

N-Phenethyl-4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(*2H*)-yl)pyrimidin-2-amine;

(3-(2-(4-(7-Phenyl-3,4-dihydro-1,6-naphthyridin-1(*2H*)-yl)pyrimidin-2-ylamino)-propyl)phenyl)methanol;

N-(1-(3-(Aminomethyl)phenyl)propan-2-yl)-4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(*2H*)-yl)pyrimidin-2-amine;

N-((*S*)-1-(3-((*S*)-1-Aminoethyl)phenyl)propan-2-yl)-4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(*2H*)-yl)pyrimidin-2-amine;

tert-Butyl-4-4(7-phenyl-3,4-dihydro-1,6-naphthylridin-1(*2H*)-pyrimidin-2-ylamino)-piperidine-1-carboxylate;

4-(7-Phenyl-3,4-dihydro-1,6-naphthyridin-1(*2H*)-yl)-*N*-(piperidin-4-yl)pyrimidin-2-amine;

1-(4-(4-(7-Phenyl-3,4-dihydro-1,6-naphthyridin-1(*2H*)-yl)pyrimidin-2-ylamino)piperidin-1-yl)ethanone;

N-((*S*)-1-(3-((*R*)-1-Aminoethyl)phenyl)propan-2-yl)-4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(*2H*)-yl)pyrimidin-2-amine;

(S)-N-(1-(3-(2-Aminopropan-2-yl)phenyl)propan-2-yl)-4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(*2H*)-yl)pyrimidin-2-amine;

(S)-1-(3-(2-(4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(*2H*)-yl)pyrimidin-2-ylamino)-propyl)phenyl)ethanone;

2-Amino-1-(4(4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(*2H*)-yl)pyrimidin-2-ylamino) piperdin-1- yl)ethanone;

3-(Isopropylamino)-1-(4(4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(*2H*)-yl)pyrimidin-2-ylamino)piperdin-1- yl)propan-1-one;

3-(Methylamino)-1-(4(4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(*2H*)-yl)pyrimidin-2-ylamino)piperdin-1- yl)propan-1-one;

3-(Ethylamino)-1-(4(4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(*2H*)-yl)pyrimidin-2-ylamino)piperdin-1- yl)propan-1-one;

(*R*)-Methyl-3-phenyl-2-(4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(*2H*)-yl)pyrimidin-2-ylamino)propanoate;

(R)-3-Phenyl-2-(4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(*2H*)-yl)pyrimidin-2-ylamino)propanoic acid;

(*R*)-4-Phenyl-3-(4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(*2H*)-yl)pyrimidin-2-ylamino)butanoic acid;

(*R*)-1-Morpholino-4-phenyl-3-(4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(*2H*)-yl) pyrimidin-2-ylamino)butan-1-one;

(*R*)-*N*-Cyclopropyl-4-phenyl-3-(4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(*2H*)-yl) pyrimidin-2-ylamino)butanamide;

(*R*)-4-Phenyl-3-(4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(*2H*)-yl)pyrimidin-2-ylamino)-1-(piperazin-1yl)butan-1-one;

tert-Butyl-4-(5-fluoro-4(7-phenyl-3,4-dihydro-1,6-naphthylridin-1(*2H*)-pyrimidin-2-ylamino)piperidine-1-carboxylate;

5-Fluoro-4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(2H)-yl)-N-(piperidin-4-yl) pyrimidin-2-amine;

1-(4-(5-Fluoro-4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(*2H*)-yl)pyrimidin-2-yl-amino)piperidin-1-yl)ethanone;

(*S*)-*N*-(1-(3-(2-Aminopropan-2-yl)phenyl)propan-2-yl)-4-(7-phenyl-3,4-dihydro-1,5-naphthyridin-1(*2H*)-yl)pyrimidin-2-amine;

tert-Butyl-4(7-phenyl-3,4-dihydro-1,5-naphthylridin-1(*2H*)-pyrimidin-2-ylamino)-piperidine-1-carboxylate;

4-(7-Phenyl-3,4-dihydro-1,5-naphthyridin-1(*2H*)-yl)-*N*-(piperidin-4-yl)pyrimidin-2-amine;

1-(4-(4-(7-Phenyl-3,4-dihydro-1,5-naphthyridin-1(*2H*)-yl)pyrimidin-2-ylamino)piperidin-1-yl)ethanone;

(*R*)-3-Phenyl-2-(4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(*2H*)-yl)pyrimidin-2-ylamino)propanamide;

(*1R,4R*)-N^1-(4-(7-Phenyl-3,4-dihydro-1,6-naphthyridin-1(2*H*)-yl)pyrimidin-2-yl) cyclohexane-1, 4-diamine;

N-((*1R,4R*)-4-(4-(7-Phenyl-3,4-dihydro-1,6-naphthyridin-1(2*H*)-yl)pyrimidin-2-ylamino) cyclohexyl) acetamide;

3,3,3-Trifluoro-*N*-((*1R,4R*)-4-(4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(2*H*)-yl)-pyrimidin-2-ylamino)cyclohexyl)propanamide;

(*1R,4R*)-N^1-Isopropyl-N^4-(4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(2*H*)-yl)pyrimidin-2-yl) cyclohexane-1,4-diamine;

(*S*)-*N*-(1-(3-(Aminoethyl)phenyl)propan-2-yl)-4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(2*H*)-yl) pyrimidin-2-amine;

(*S*)-*N*-(1-(3-(2-Aminopropan-2-yl)phenyl)propan-2-yl)-4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(2*H*)-yl) pyrimidin-2-amine;

N-(1-(4-Fluorophenyl)-2-methylpropan-2-yl)-4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(2*H*)-yl) pyrimidin-2-amine;

N-(1-Amino-2-methylpropan-2-yl)-4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(2*H*)-yl)pyrimidin-2-amine;

N-(2-Methyl-2-(4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(2*H*)-yl)pyrimidin-2-ylamino) propyl) acetamide;

N-(1-(Isopropylamino)-2-methylpropan-2-yl)-4-(7-phenyl-3,4-dihydro-1,6-naphthyridin-1(2*H*)-yl) pyrimidin-2-amine;

N-Phenethyl-4-(7-phenyl-3,4-dihydro-1,8-naphthyridin-1(*2H*)-yl)pyrimidin-2-amine;

(3-(2-(4-(7-Phenyl-3,4-dihydro-1,8-naphthyridin-1(*2H*)-yl)pyrimidin-2-ylamino)propyl) phenyl)methanol;

N-(1-(3-(Aminomethyl)phenyl)propan-2-yl)-4-(7-phenyl-3,4-dihydro-1,8-naphthyridin-1(*2H*)-yl)pyrimidin-2-amine;

4-(7-Phenyl-3,4-dihydro-1,8-naphthyridin-1(*2H*)-yl)-*N*-(2-(pyridin-3-yl)ethyl)pyrimidin-2-amine;

N-(3-(Dimethylamino)-2,2-dimethylpropyl)-4-(7-phenyl-3,4-dihydro-1,8-naphthyridin-1(*2H*)-yl)pyrimidin-2-amine;

N-Neopentyl-4-(7-phenyl-3,4-dihydro-1,8-naphthyridin-1(*2H*)-yl)pyrimidin-2-amine;

N-(2-Amino-2-methylpropyl)-4-(7-phenyl-3,4-dihydro-1,8-naphthyridin-1(*2H*)-yl)-pyrimidin-2-amine;

*t*ert-Butyl 4-(4-(7-phenyl-3,4-dihydro-1,8-naphthyridin-1(*2H*)-yl)pyrimidin-2-ylamino) piperidine-1-carboxylate;

N-Phenethyl-4-(7-phenyl-3,4-dihydro-1,8-naphthyridin-1(*2H*)-yl)-6-(trifluoromethyl) pyrimidin-2-amine;

(3-(2-(4-(7-Phenyl-3,4-dihydro-1,8-naphthyridin-1(*2H*)-yl)-6-(trifluoromethyl)pyrimidin-2-ylamino)propyl)phenyl)methanol;

N-(1-(3-(Aminomethyl)phenyl)propan-2-yl)-4-(7-phenyl-3,4-dihydro-1,8-naphthyridin-1(*2H*)-yl)-6-(trifluoromethyl)pyrimidin-2-amine;

1-(2-Fluoro-6-methylpyrimidin-4-yl)-7-phenyl-1,2,3,4-tetrahydro-1,8-naphthyridine;

tert-Butyl 4-(4-methyl-6-(7-phenyl-3,4-dihydro-1,8-naphthyridin-1(*2H*)-yl)pyrimidin-2-ylamino)piperidine-1-carboxylate;

tert-Butyl (*R*)-1-(3-((*S*)-2-(4-methyl-6-(7-phenyl-3,4-dihydro-1,8-naphthyridin-1(*2H*)-yl) pyrimidin-2-ylamino)propyl)phenyl)ethylcarbamate;

N-((*S*)-1-(3-((*R*)-1-Aminoethyl)phenyl)propan-2-yl)-4-methyl-6-(7-phenyl-3,4-dihydro-1,8-naphthyridin-1(*2H*)-yl)pyrimidin-2-amine;

Ethyl 8-(2-(Phenethylamino)pyrimidin-4-yl)-2-phenyl-5,6,7,8-tetrahydro-1,8-naphthyridine-3-carboxylate;

(8-(2-(Phenethylamino)pyrimidin-4-yl)-2-phenyl-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)methanol;

4-(6-(Methoxymethyl)-7-phenyl-3,4-dihydro-1,8-naphthyridin-1(*2H*)-yl)-N-phenethylpyrimidin-2-amine;

8-(2-(Phenethylamino)pyrimidin-4-yl)-2-phenyl-5,6,7,8-tetrahydro-1,8-naphthyridine-3-carboxylic acid;

4-(6-((Methylamino)methyl)-7-phenyl-3,4-dihydro-1,8-naphthyridin-1(*2H*)-yl)-*N*-phenethylpyrimidin-2-amine;

4-(6-((Dimethylamino)methyl)-7-phenyl-3,4-dihydro-1,8-naphthyridin-1(*2H*)-yl)-N-phenethylpyrimidin-2-amine;

1-(8-(2-(Phenethylamino)pyrimidin-4-yl)-2-phenyl-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)ethanone;

1-(8-(2-(Phenethylamino)pyrimidin-4-yl)-2-phenyl-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)ethanol;

Ethyl 8-(2-(1-(tert-butoxycarbonyl)piperidin-4-ylamino)pyrimidin-4-yl)-2-phenyl-5,6,7,8-tetrahydro-1,8-naphthyridine-3-carboxylate;

Ethyl 8-(2-((*1R,4R*)-4-aminocyclohexylamino)pyrimidin-4-yl)-2-phenyl-5,6,7,8-tetrahydro-1,8-naphthyridine-3-carboxylate;

(8-(2-((*1R,4R*)-4-Aminocyclohexylamino)pyrimidin-4-yl)-2-phenyl-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)methanol;

2-(8-(2-((*1R,4R*)-4-Aminocyclohexylamino)pyrimidin-4-yl)-2-phenyl-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)propan-2-ol;

Ethyl 8-(2-(1-(3-(hydroxymethyl)phenyl)propan-2-ylamino)pyrimidin-4-yl)-2-phenyl-5,6,7,8-tetrahydro-1,8-naphthyridine-3-carboxylate;

(8-(2-(1-(3-(Aminomethyl)phenyl)propan-2-ylamino)pyrimidin-4-yl)-2-phenyl-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)methanol;

8-(2-(Phenethylamino)pyrimidin-4-yl)-2-phenyl-5,6,7,8-tetrahydro-1,8-naphthyridin-3-amine;

(8-(2-(Phenethylamino)pyrimidin-4-yl)-2-phenyl-5,6,7,8-tetrahydro-1,8-naphthyridin-4-yl)methanol;

Ethyl-4-(4-(7-phenyl-3,4-dihydro-1,8-naphthyridin-1(2*H*)-yl)pyrimidin-2-ylamino)-piperidine-1-carboxylate;

(*1R,4R*)-N^1-(4-(7-Phenyl-3,4-dihydro-1,8-naphthyridin-1(2*H*)-ylpyrimidin-2-yl)-cyclohexane-1,4-diamine;

(*1R,4R*)-N^1-Isopropyl-N^4-(4-(7-phenyl-3,4-dihydro-1,8-naphthyridin-1(2*H*)-yl)pyrimidin-2-yl) cyclohexane-1,4-diamine;

N-((*1R*,,*4*R)-4-(4-(7-Phenyl-3,4-dihydro-1,8-naphthyridin-1(2*H*)-yl)pyrimidin-2-ylamino)cyclohexyl) acetamide;

N-((*S*)-1-(3-((*R*)–1-Aminoethyl) phenyl) propan-2-yl)-4-(7-phenyl-3, 4-dihydro-1, 8-naphthyridin-1(2*H*)-yl) pyrimidin-2-amine;

tert-Butyl (*R*)-1-(3-((*S*)-2-(4-(2-phenyl-6,7-dihydropyrimido[5,4-b][1,4]oxazin-8-yl) pyrimidin-2-ylamino)propyl)phenyl)ethylcarbamate;

N-((*S*)-1-(3-((*R*)-1-Aminoethyl)phenyl)propan-2-yl)-4-(2-phenyl-6,7-dihydropyrimido-[5,4-b][1,4]oxazin-8-yl)pyrimidin-2-amine;

(*1R,4R*)-*N*^{1}-(4-(2-Phenyl-6,7-dihydropyrimido[5,4-b][1,4]oxazin-8-yl)pyrimidin-2-yl) cyclohexane-1,4-diamine;

4-(2-Phenyl-6,7-dihydropyrimido[5,4-b][1,4]oxazin-8-yl)-*N*-(piperidin-4-yl)pyrimidin-2-amine;

1-(4-(4-(2-Phenyl-6,7-dihydropyrimido[5,4-b][1,4]oxazin-8-yl)pyrimidin-2-ylamino) piperidin-1-yl)ethanone; and

(*S*)-*N*-(1-(3-(2-Aminopropan-2-yl)phenyl)propan-2-yl)-4-(2-phenyl-6,7-dihydropyrimido [5,4-b][1,4]oxazin-8-yl)pyrimidin-2-amine; or

a pharmaceutically-acceptable salt or hydrate thereof.

4. A pharmaceutical composition comprising a compound according to any of Claims 1-3 and a pharmaceutically acceptable carrier.

5. A method of treatment of inflammation comprising administering an effective amount of a compound according to any of Claims 1-3.

6. A method of treatment of rheumatoid arthritis, Pagets disease, osteoporosis, multiple myeloma, uveititis, acute or chronic myelogenous leukemia, pancreatic β cell destruction, osteoarthritis, rheumatoid spondylitis, gouty arthritis, inflammatory bowel disease, adult respiratory distress syndrome (ARDS), psoriasis, Crohn's disease, allergic rhinitis, ulcerative colitis, anaphylaxis, contact dermatitis, asthma, muscle degeneration, cachexia, Reiter's syndrome, type I diabetes, type II diabetes, bone resorption diseases, graft vs. host reaction, Alzheimer's disease, stroke, myocardial infarction, ischemia reperfusion injury, atherosclerosis, brain trauma, multiple sclerosis, cerebral malaria, sepsis, septic shock, toxic shock syndrome, fever, myalgias due to HIV-1, HIV-2, HIV-3, cytomegalovirus (CMV), influenza, adenovirus, the herpes viruses or herpes zoster infection in a mammal comprising administering an effective amount of a compound according to any of Claims 1-3.

7. A method of lowering plasma concentrations of either or both TNF-α and IL-1 comprising administering an effective amount of a compound according to any of Claims 1-3.

8. A method of lowering plasma concentrations of either or both IL-6 and IL-8 comprising administering an effective amount of a compound according to any of Claims 1-3.

9. A method of treatment of diabetes disease in a mammal comprising administering an effective amount of a compound according to any of Claims 1-3 to produce a glucagon antagonist effect.

10. A method of treatment of a pain disorder in a mammal comprising administering an effective amount of a compound according to any of Claims 1-3.

11. A method of decreasing prostaglandins production in a mammal comprising administering an effective amount of a compound according to any of Claims 1-3.

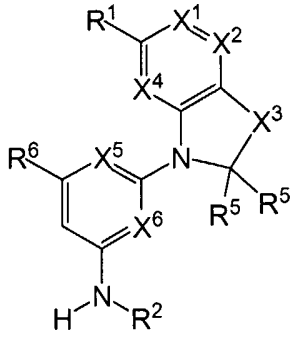
12. A method of decreasing cyclooxygenase enzyme activity in a mammal comprising administering an effective amount of a compound according to any of Claims 1-3.

13. A medicament comprising a compound according to any of Claims 1-3 and a pharmaceutically acceptable carrier.

14. The medicament of claim 13 useful for treatment of rheumatoid arthritis, Pagets disease, osteoporosis, multiple myeloma, uveititis, acute or chronic myelogenous leukemia, pancreatic β cell destruction, osteoarthritis, rheumatoid spondylitis, gouty arthritis, inflammatory bowel disease, adult respiratory distress syndrome (ARDS), psoriasis, Crohn's disease, allergic rhinitis, ulcerative colitis, anaphylaxis, contact dermatitis, asthma, muscle degeneration, cachexia, Reiter's syndrome, type I diabetes, type II diabetes, bone resorption diseases, graft vs. host reaction, Alzheimer's disease, stroke, myocardial infarction, ischemia reperfusion injury, atherosclerosis, brain trauma, multiple sclerosis, cerebral malaria, sepsis, septic shock, toxic shock syndrome, fever, myalgias due to HIV-1, HIV-2, HIV-3, cytomegalovirus (CMV), influenza, adenovirus, the herpes viruses or herpes zoster infection in a mammal.

15. The medicament of claim 13 useful for at least one of lowering plasma concentrations of either or both IL-6 and IL-8, treatment of diabetes disease, treatment of a pain disorder, decreasing prostaglandins production and decreasing cyclooxygenase enzyme activity in a mammal.

16. A compound of the Formula II



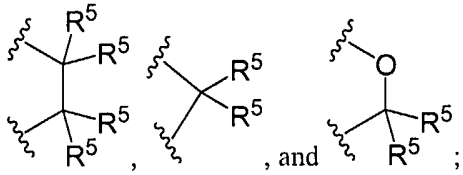
II

or a pharmaceutically acceptable salt or hydrate thereof, wherein

X^1 is N or CR^3;

X^2 is N or CR^4;

X^3 is selected from



;

X^4 is N or CR^4;

X^5 is N or CR^6;

X^6 is N or CR^6, provided that at least one of X^5 and X^6 is N;

R^1 is a saturated, partially saturated or unsaturated 5-, 6- or 7-membered, ring containing 0, 1, 2 or 3 atoms selected from N, O and S, wherein the ring is substituted by 0, 1, 2 or 3 substituents selected from C_{1-8}alkyl, C_{1-4}haloalkyl, halo, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^b$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}$alkylNR^aR^a, $-OC_{2-6}$alkylOR^a, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$,

$-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ and $-NR^aC_{2-6}alkylOR^a$;

R^2 is C_{1-8}alkyl substituted by 0, 1, 2 or 3 substituents selected from C_{1-2}haloalkyl, halo, oxo, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$, $-NR^aC_{2-6}alkylOR^a$, $-C(=O)R^g$, $-C(=O)OR^g$, $-C(=O)NR^aR^g$, $-C(=NR^a)NR^aR^g$, $-OR^g$, $-OC(=O)R^g$, $-OC(=O)NR^aR^g$, $-OC(=O)N(R^a)S(=O)_2R^g$, $-OC_{2-6}alkylNR^aR^g$, $-OC_{2-6}alkylOR^g$, $-SR^g$, $-S(=O)R^g$, $-S(=O)_2R^g$, $-S(=O)_2NR^aR^g$, $-NR^aR^g$, $-N(R^a)C(=O)R^g$, $-N(R^a)C(=O)OR^g$, $-N(R^a)C(=O)NR^aR^g$, $-C(=O)R^e$, $-C(=O)OR^e$, $-C(=O)NR^aR^e$, $-C(=NR^a)NR^aR^e$, $-OR^e$, $-OC(=O)R^e$, $-OC(=O)NR^aR^e$, $-OC(=O)N(R^a)S(=O)_2R^e$, $-OC_{2-6}alkylNR^aR^e$, $-OC_{2-6}alkylOR^e$, $-SR^e$, $-S(=O)R^e$, $-S(=O)_2R^e$, $-S(=O)_2NR^aR^e$, $-NR^aR^e$, $-N(R^a)C(=O)R^e$, $-N(R^a)C(=O)OR^e$ and $-N(R^a)C(=O)NR^aR^e$, and additionally substituted by 0, 1 or 2 saturated, partially saturated or unsaturated 5-, 6- or 7-membered monocyclic or 6-, 7-, 8-, 9-, 10- or 11-membered bicyclic rings containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, wherein the carbon atoms of the rings are substituted by 0, 1 or 2 oxo groups and the rings is substituted by 0, 1, 2 or 3 substituents selected from R^e, R^g, C_{1-8}alkyl, C_{1-4}haloalkyl, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ and $-NR^aC_{2-6}alkylOR^a$; or

R^2 is a saturated, partially saturated or unsaturated 5-, 6- or 7-membered monocyclic or 6-, 7-, 8-, 9-, 10- or 11-membered bicyclic rings containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, wherein the carbon atoms of the rings are substituted by 0, 1 or 2 oxo groups and the rings is substituted by 0, 1, 2 or 3 substituents selected from R^e, R^g, C_{1-8}alkyl, C_{1-4}haloalkyl, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$,

$-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ and $-NR^aC_{2-6}alkylOR^a$, and additionally substituted by 0, 1 or 2 C_{1-8}alkyl groups, each being substituted by 0, 1, 2 or 3 substituents selected from C_{1-2}haloalkyl, halo, oxo, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$, $-NR^aC_{2-6}alkylOR^a$, $-C(=O)R^g$, $-C(=O)OR^g$, $-C(=O)NR^aR^g$, $-C(=NR^a)NR^aR^g$, $-OR^g$, $-OC(=O)R^g$, $-OC(=O)NR^aR^g$, $-OC(=O)N(R^a)S(=O)_2R^g$, $-OC_{2-6}alkylNR^aR^g$, $-OC_{2-6}alkylOR^g$, $-SR^g$, $-S(=O)R^g$, $-S(=O)_2R^g$, $-S(=O)_2NR^aR^g$, $-NR^aR^g$, $-N(R^a)C(=O)R^g$, $-N(R^a)C(=O)OR^g$, $-N(R^a)C(=O)NR^aR^g$, $-C(=O)R^e$, $-C(=O)OR^e$, $-C(=O)NR^aR^e$, $-C(=NR^a)NR^aR^e$, $-OR^e$, $-OC(=O)R^e$, $-OC(=O)NR^aR^e$, $-OC(=O)N(R^a)S(=O)_2R^e$, $-OC_{2-6}alkylNR^aR^e$, $-OC_{2-6}alkylOR^e$, $-SR^e$, $-S(=O)R^e$, $-S(=O)_2R^e$, $-S(=O)_2NR^aR^e$, $-NR^aR^e$, $-N(R^a)C(=O)R^e$, $-N(R^a)C(=O)OR^e$ and $-N(R^a)C(=O)NR^aR^e$, and additionally substituted by 0, 1 or 2 saturated, partially saturated or unsaturated 5-, 6- or 7-membered monocyclic or 6-, 7-, 8-, 9-, 10- or 11-membered bicyclic rings containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, wherein the carbon atoms of the rings are substituted by 0, 1 or 2 oxo groups and the rings is substituted by 0, 1, 2 or 3 substituents selected from R^e, R^g, C_{1-8}alkyl, C_{1-4}haloalkyl, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ and $-NR^aC_{2-6}alkylOR^a$; wherein any part of R^2 is additionally substituted by 0, 1, 2, 3, 4, 5 or 6 atoms selected from Br, Cl, F and I;

R^3 is independently, in each instance, selected from H, R^e, C_{1-4}haloalkyl, halo, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^b$, $-OR^c$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$,

$-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-NR^aR^e$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ and $-NR^aC_{2-6}alkylOR^a$;

R^4 is independently in each instance H, R^e, C_{1-4}haloalkyl, halo, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^b$, $-OR^e$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-NR^aR^e$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ or $-NR^aC_{2-6}alkylOR^a$;

R^5 is independently in each instance H, R^e, C_{1-4}haloalkyl, halo, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^b$, $-OR^e$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-NR^aR^e$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ or $-NR^aC_{2-6}alkylOR^a$;

R^6 is independently in each instance H, C_{1-8}alkyl, C_{1-4}haloalkyl, $-NR^aR^a$, $-OR^a$, or halo;

R^a is independently, at each instance, H or R^b;

R^b is independently, at each instance, phenyl, benzyl or C_{1-6}alkyl, the phenyl, benzyl and C_{1-6}alkyl being substituted by 0, 1, 2 or 3 substituents selected from halo, C_{1-4}alkyl, C_{1-3}haloalkyl, $-OC_{1-4}$alkyl, $-NH_2$, $-NHC_{1-4}$alkyl, $-N(C_{1-4}alkyl)C_{1-4}alkyl$;

R^d is independently at each instance C_{1-8}alkyl, C_{1-4}haloalkyl, halo, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ or $-NR^aC_{2-6}alkylOR^a$;

R^e is independently at each instance C_{1-6}alkyl substituted by 0, 1, 2 or 3 substituents independently selected from R^d and additionally substituted by 0 or 1 substituents selected from R^g; and

R^g is independently at each instance a saturated, partially saturated or unsaturated 5-, 6- or 7-membered monocyclic or 6-, 7-, 8-, 9-, 10- or 11-membered bicyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, wherein the carbon atoms of the ring are substituted by 0, 1 or 2 oxo groups and the ring is substituted by 0, 1, 2 or 3 substituents selected from R^b, C_{1-4}haloalkyl, cyano, nitro, $-C(=O)R^b$, $-C(=O)OR^b$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^b$, $-OC_{2-6}$alkylNR^aR^a, $-OC_{2-6}$alkylOR^a, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^b$, $-S(=O)_2N(R^a)C(=O)OR^b$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}$alkylNR^aR^a and $-NR^aC_{2-6}$alkylOR^a, and additionally substituted by 0, 1, 2, 3, 4, 5 or 6 atoms selected from Br, Cl, F and I.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2005/046652

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/04 C07D498/04 A61K31/4375 A61K31/5383 A61P29/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 01/40215 A (PFIZER PRODUCTS INC; BLUMENKOPF, TODD, ANDREW; MUELLER, EILEEN, ELLIOT) 7 June 2001 (2001-06-07) Examples 1-18, pages 37-39. Claims 1, 19, 23, 24, 28, 29, 32.	1,4-13, 16
A	WO 02/092090 A (BRISTOL-MYERS SQUIBB PHARMA COMPANY) 21 November 2002 (2002-11-21) Table 1, pages 79-90. Claim 23	1,4-13, 16

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 April 2006	04/05/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Menchaca, R

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2005/046652

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 5-12 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2005/046652

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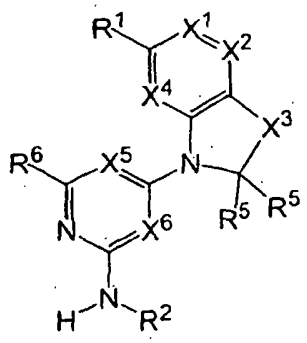
		PL 366577 A1	07-02-2005
		SK 13752003 A3	03-11-2004
		ZA 200308729 A	10-02-2005

Box No. IV Text of the abstract (Continuation of item 5 of the first sheet)

The present invention relates to nitrogen-containing compounds according to formula (I) and pharmaceutically acceptable salts thereof. Also included is a method of treatment of inflammation, rheumatoid arthritis, Pagets disease, osteoporosis, multiple myeloma, uveititis, acute or chronic myelogenous leukemia, pancreatic ß cell destruction, osteoarthritis, rheumatoid spondylitis, gouty arthritis, inflammatory bowel disease, adult respiratory distress syndrome (ARDS), psoriasis, Crohn's disease, allergic rhinitis, ulcerative colitis, anaphylaxis, contact dermatitis, asthma, muscle degeneration, cachexia, Reiter's syndrome, type I diabetes, type II diabetes, bone resorption diseases, graft vs. host reaction, Alzheimer's disease, stroke, myocardial infarction, ischemia reperfusion injury, atherosclerosis, brain trauma, multiple sclerosis, cerebral malaria, sepsis, septic shock, toxic shock syndrome, fever, myalgias due to HIV-1, HIV-2, HIV-3, cytomegalovirus (CMV), influenza, adenovirus, the herpes viruses or herpes zoster infection in a mammal comprising administering an effective amount a compound as described above.



(I)