CERTAIN 1,4,5-TRI-SUBSTITUTED IMIDAZOLE COMPOUNDS USEFUL AS CYTOKINE

This invention relates to a novel group of imidazole compounds, processes for the preparation thereof, the use thereof in treating cytokine mediated diseases and pharmaceutical compositions for use in such therapy.

BACKGROUND OF THE INVENTION

Interleukin-1 (IL-1) and Tumor Necrosis Factor (TNF) are biological substances produced by a variety of cells, such as monocytes or macrophages. IL-1 has been demonstrated to mediate a variety of biological activities thought to be important in immunoregulation and other physiological conditions such as inflammation [See, e.g., Dinarello et al., Rev. Infect. Disease, 6, 51 (1984)]. The myriad of known biological activities of IL-1 include the activation of T helper cells, induction of fever, stimulation of prostaglandin or collagenase production, neutrophil chemotaxis, induction of acute phase proteins and the suppression of plasma iron levels.

There are many disease states in which excessive or unregulated IL-1 production is implicated in exacerbating and/or causing the disease. These include rheumatoid arthritis, osteoarthritis, endotoxemia and/or toxic shock syndrome, other acute or chronic inflammatory disease states such as the inflammatory reaction induced by endotoxin or inflammatory bowel disease; tuberculosis, atherosclerosis, muscle degeneration, cachexia, psoriatic arthritis, Reiter's syndrome, rheumatoid arthritis, gout, traumatic arthritis, rubella arthritis, and acute synovitis. Recent evidence also links IL-1 activity to diabetes and pancreatic ß cells.

Dinarello, J. Clinical Immunology, 5 (5), 287-297 (1985), reviews the biological activities which have been attributed to IL-1. It should be noted that some of these effects have been described by others as indirect effects of IL-1.

Excessive or unregulated TNF production has been implicated in mediating or exacerbating a number of diseases including rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions; sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoisosis, bone resorption diseases, reperfusion injury, graft vs. host reaction, allograft rejections, fever and myalgias due to infection, such as influenza, cachexia secondary to infection or malignancy, cachexia, secondary to acquired immune deficiency syndrome (AIDS), AIDS, ARC (AIDS related complex), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis, or pyresis.

AIDS results from the infection of T lymphocytes with Human Immunodeficiency Virus (HIV). At least three types or strains of HIV have been identified, i.e., HIV-1, HIV-2 and HIV-3. As a consequence of HIV infection, T-cell mediated immunity is impaired and infected individuals manifest severe opportunistic infections and/or unusual neoplasms. HIV entry into the T lymphocyte requires T lymphocyte activation. Other viruses, such as HIV-1, HIV-2 infect T lymphocytes after T Cell activation and such virus protein expression and/or replication is mediated or maintained by such T cell activation. Once an activated T lymphocyte is infected with HIV, the T lymphocyte must continue to be maintained in an activated state to permit HIV gene expression and/or HIV replication. Monokines, specifically TNF, are implicated in activated T-cell mediated HIV protein expression and/or virus replication by playing a role in maintaining T lymphocyte activation. Therefore, interference with monokine activity such as by inhibition of monokine production, notably TNF, in an HIV-infected individual aids in limiting the maintenance of T cell activation, thereby reducing the progression of HIV infectivity to previously uninfected cells which results in a slowing or elimination of the progression of immune dysfunction caused by HIV infection. Monocytes, macrophages, and related cells, such as kupffer and glial cells, have also been implicated in maintenance of the HIV infection. These cells, like T-cells, are targets for viral replication and the level of viral replication is dependent upon the activation state of the cells. [See Rosenberg et al., The Immunopathogenesis of HIV Infection, Advances in Immunology, Vol. 57, (1989)]. Monokines, such as TNF, have been shown to activate HIV replication in monocytes and/or macrophages [See Poli, et al., Proc. Natl. Acad. Sci., 87:782-784 (1990)], therefore, inhibition of monokine production or activity aids in limiting HIV progression as stated above for T-cells.

TNF has also been implicated in various roles with other viral infections, such as the cytomegalia virus (CMV), influenza virus, and the herpes virus for similar reasons as those noted.

Interleukin-8 (IL-8) is a chemotactic factor first identified and characterized in 1987. IL-8 is produced by several cell types including mononuclear cells, fibroblasts, endothelial cells, and keratinocytes. Its production from endothelial cells is induced by IL-1, TNF, or lipopolysachharide (LPS). Human IL-8 has been shown to act on Mouse, Guinea Pig, Rat, and Rabbit Neutrophils. Many different names have been applied to IL-8, such as neutrophil attractant/activation protein-1 (NAP-1), monocyte derived neutrophil chemotactic factor (MDNCF), neutrophil activating factor (NAF), and T-cell lymphocyte chemotactic factor.

IL-8 stimulates a number of functions in vitro. It has been shown to have chemoattractant properties for neutrophils, T-lymphocytes, and basophils. In addition it induces histamine release from basophils from both normal and atopic individuals as

well as lysozomal enzyme release and respiratory burst from neutrophils. IL-8 has also been shown to increase the surface expression of Mac-1 (CD11b/CD18) on neutrophils without de novo protein synthesis, this may contribute to increased adhesion of the neutrophils to vascular endothelial cells. Many diseases are characterized by massive neutrophil infiltration. Conditions associated with an increased in IL-8 production (which is responsible for chemotaxis of neutrophil into the inflammatory site) would benefit by compounds which are suppressive of IL-8 production.

IL-1 and TNF affect a wide variety of cells and tissues and these cytokines as well as other leukocyte derived cytokines are important and critical inflammatory mediators of a wide variety of disease states and conditions. The inhibition of these cytokines is of benefit in controlling, reducing and alleviating many of these disease states.

There remains a need for treatment, in this field, for compounds which are cytokine suppressive anti-inflammatory drugs, i.e. compounds which are capable of inhibiting cytokines, such as IL-1, IL-6, IL-8 and TNF.

SUMMARY OF THE INVENTION

This invention relates to the novel compounds of Formula (I), and (II) and pharmaceutical compositions comprising a compound of Formula (I) or (II) and a pharmaceutically acceptable diluent or carrier.

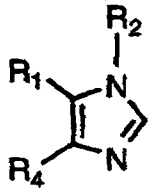
This invention also relates to a method of inhibiting cytokines and the treatment of a cytokine mediated disease, in a mammal in need thereof, which comprises administering to said mammal an effective amount of a compound of Formula (I) or (II).

This invention more specifically relates to a method of inhibiting the production of IL-1 in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of Formula (I) or (II).

This invention more specifically relates to a method of inhibiting the production of IL-8 in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of Formula (I) or (II).

This invention more specifically relates to a method of inhibiting the production of TNF in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of Formula (I) or (II).

Accordingly, the present invention provides a compound of Formula (I):



(I)

R_1 is 4-pyridyl, pyrimidinyl, quinolyl, isoquinolinyl, quinazolin-4-yl, 1-imidazolyl or 1-benzimidazolyl, which heteroaryl ring is substituted with $N(R_{10})C(O)R_a$ or a halo substituted mono or di- C_{1-6} alkyl substituted amino and which ring is further optionally substituted with C_{1-4} alkyl, halogen, hydroxyl, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} alkylsulfinyl, CH_2OR_{12}, amino, mono and di- C_{1-6} alkyl substituted amino, or an N-heterocyclyl ring which ring has from 5 to 7 members NR_{15};

R_4 is phenyl, naphth-1-yl or naphth-2-yl, or a heteroaryl, which is optionally substituted by one or two substituents, each of which is independently selected, and which, for a 4-phenyl, 4-naphth-1-yl, 5-naphth-2-yl or 6-naphth-2-yl substituent, is halogen, cyano, nitro, $-C(Z)NR_7R_{17}$, $-C(Z)OR_{16}$, $-(CR_{10}R_{20})_vCOR_{12}$, $-SR_5$, $-SOR_5$, $-OR_{12}$, halo-substituted-C_{1-4} alkyl, C_{1-4} alkyl, $-ZC(Z)R_{12}$, $-NR_{10}C(Z)R_{16}$, or $-(CR_{10}R_{20})_vNR_{10}R_{20}$ and which, for other positions of substitution, is halogen, cyano, $-C(Z)NR_{13}R_{14}$, $-C(Z)OR_3$, $-(CR_{10}R_{20})_{m''}COR_3$, $-S(O)_mR_3$, $-OR_3$, $-OR_{12}$, halo substituted C_{1-4} alkyl, C_{1-4} alkyl, $-(CR_{10}R_{20})_{m''}NR_{10}C(Z)R_3$, $-NR_{10}S(O)_{m'}R_8$, $-NR_{10}S(O)_{m'}NR_7R_{17}$, $-ZC(Z)R_3$, $-ZC(Z)R_{12}$, or $-(CR_{10}R_{20})_{m''}NR_{13}R_{14}$;

v is 0, or an integer having a value of 1 or 2;

m is 0, or the integer 1 or 2;

m' is an integer having a value of 1 or 2,

m" is 0, or an integer having a value of 1 to 5;

R_2 is C_{1-10} alkyl N_3, $-(CR_{10}R_{20})_{n'}OR_9$, heterocyclyl, heterocyclylC_{1-10} alkyl, C_{1-10}alkyl, halo-substituted C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{3-7}cycloalkylC_{1-10} alkyl, C_{5-7} cycloalkenyl, C_{5-7}cycloalkenylC_{1-10}alkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10}alkyl, $(CR_{10}R_{20})_nOR_{11}$, $(CR_{10}R_{20})_nS(O)_mR_{18}$, $(CR_{10}R_{20})_nNHS(O)_2R_{18}$, $(CR_{10}R_{20})_nNR_{13}R_{14}$, $(CR_{10}R_{20})_nNO_2$, $(CR_{10}R_{20})_nCN$, $(CR_{10}R_{20})_{n'}SO_2R_{18}$, $(CR_{10}R_{20})_nS(O)_{m'}NR_{13}R_{14}$, $(CR_{10}R_{20})_nC(Z)R_{11}$, $(CR_{10}R_{20})_nOC(Z)R_{11}$, $(CR_{10}R_{20})_nC(Z)OR_{11}$, $(CR_{10}R_{20})_nC(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nC(Z)NR_{11}OR_9$, $(CR_{10}R_{20})_nNR_{10}C(Z)R_{11}$, $(CR_{10}R_{20})_nNR_{10}C(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nN(OR_6)C(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nN(OR_6)C(Z)R_{11}$, $(CR_{10}R_{20})_nC(=NOR_6)R_{11}$, $(CR_{10}R_{20})_nNR_{10}C(=NR_{19})NR_{13}R_{14}$, $(CR_{10}R_{20})_nOC(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nNR_{10}C(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nNR_{10}C(Z)OR_{10}$, 5-$(R_{18})$-1,2,4-oxadizaol-3-yl or 4-(R_{12})-5-$(R_{18}R_{19})$-4,5-dihydro-1,2,4-oxadiazol-3-yl; wherein the aryl, arylalkyl, heteroaryl, heteroaryl alkyl, cyclcoalkyl, cycloalkyl alkyl, heterocyclic and heterocyclic alkyl groups may be optionally substituted;

n is an integer having a value of 1 to 10;

n' is 0, or an integer having a value of 1 to 10;

Z is oxygen or sulfur;

Ra is hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, aryl, arylC_{1-4} alkyl, heteroaryl, heteroarylC_{1-4}alkyl, heterocyclyl, or heterocyclylC_{1-4} alkyl;

R_3 is heterocyclyl, heterocyclylC_{1-10} alkyl or R_8;

R_5 is hydrogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl or NR_7R_{17}, excluding the moieties $-SR_5$ being $-SNR_7R_{17}$ and $-S(O)R_5$ being -SOH;

R_6 is hydrogen, a pharmaceutically acceptable cation, C_{1-10} alkyl, C_{3-7} cycloalkyl, aryl, arylC_{1-4} alkyl, heteroaryl, heteroaryl$_{1-10}$alkyl, heterocyclyl, aroyl, or C_{1-10} alkanoyl ;

R_7 and R_{17} is each independently selected from hydrogen or C_{1-4} alkyl or R_7 and R_{17} together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR_{15};

R_8 is C_{1-10} alkyl, halo-substituted C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{5-7} cycloalkenyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, $(CR_{10}R_{20})_nOR_{11}$, $(CR_{10}R_{20})_nS(O)_mR_{18}$, $(CR_{10}R_{20})_nNHS(O)_2R_{18}$, $(CR_{10}R_{20})_nNR_{13}R_{14}$; wherein the aryl, arylalkyl, heteroaryl, heteroaryl alkyl may be optionally substituted;

R_9 is hydrogen, $-C(Z)R_{11}$, optionally substituted C_{1-10} alkyl, $S(O)_2R_{18}$, optionally substituted aryl or optionally substituted aryl-C_{1-4} alkyl;

R_{10} and R_{20} is each independently selected from hydrogen or C_{1-4} alkyl;

R_{11} is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, heterocyclyl, heterocyclyl C_{1-10}alkyl, aryl, arylC_{1-10} alkyl, heteroaryl or heteroarylC_{1-10} alkyl;

R_{12} is hydrogen or R_{16};

R_{13} and R_{14} is each independently selected from hydrogen or optionally substituted C_{1-4} alkyl, optionally substituted aryl or optionally substituted aryl-C_{1-4} alkyl, or together with the nitrogen which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR_9;

R_{15} is R_{10} or $C(Z)$-C_{1-4} alkyl;

R_{16} is C_{1-4} alkyl, halo-substituted-C_{1-4} alkyl, or C_{3-7} cycloalkyl;

R_{18} is C_{1-10} alkyl, C_{3-7} cycloalkyl, heterocyclyl, aryl, aryl$_{1-10}$alkyl, heterocyclyl, heterocyclyl-C_{1-10}alkyl, heteroaryl or heteroaryl$_{1-10}$alkyl;

R_{19} is hydrogen, cyano, C_{1-4} alkyl, C_{3-7} cycloalkyl or aryl;

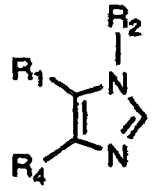
or a pharmaceutically acceptable salt thereof.

DETAILED DESCRIPTION OF THE INVENTION

The novel compounds of Formula (I) may also be used in association with the veterinary treatment of mammals, other than humans, in need of inhibition of cytokine

inhibition or production. In particular, cytokine mediated diseases for treatment, therapeutically or prophylactically, in animals include disease states such as those noted herein in the Methods of Treatment section, but in particular viral infections. Examples of such viruses include, but are not limited to, lentivirus infections such as, equine infectious anaemia virus, caprine arthritis virus, visna virus, or maedi virus or retrovirus infections, such as but not limited to feline immunodeficiency virus (FIV), bovine immunodeficiency virus, or canine immunodeficiency virus or other retroviral infections.

Another aspect of the present invention is the preferred selection of a compound of the formula:



(II)

R_1 is 4-pyridyl, or pyrimidinyl ring substituted with a C_{1-4}alkyl amino group which ring may be further optionally substituted with C_{1-4} alkyl, halogen, hydroxyl, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} alkylsulfinyl, CH_2OR_{12}, amino, mono and di- C_{1-6} alkyl substituted amino, or an N-heterocyclyl ring which ring has from 5 to 7 members and optionally contains an additional heteroatom selected from oxygen, sulfur or NR_{15};

R_4 is phenyl, naphth-1-yl or naphth-2-yl, or a heteroaryl, which is optionally substituted by one or two substituents, each of which is independently selected, and which, for a 4-phenyl, 4-naphth-1-yl, 5-naphth-2-yl or 6-naphth-2-yl substituent, is halogen, cyano, nitro, $-C(Z)NR_7R_{17}$, $-C(Z)OR_{16}$, $-(CR_{10}R_{20})_vCOR_{12}$, $-SR_5$, $-SOR_5$, $-OR_{12}$, halo-substituted-C_{1-4} alkyl, C_{1-4} alkyl, $-ZC(Z)R_{12}$, $-NR_{10}C(Z)R_{16}$, or $-(CR_{10}R_{20})_vNR_{10}R_{20}$ and which, for other positions of substitution, is halogen, cyano, $-C(Z)NR_{13}R_{14}$, $-C(Z)OR_3$, $-(CR_{10}R_{20})_{m"}COR_3$, $-S(O)_mR_3$, $-OR_3$, $-OR_{12}$, halo substituted C_{1-4} alkyl, C_{1-4} alkyl, $-(CR_{10}R_{20})_{m"}NR_{10}C(Z)R_3$, $-NR_{10}S(O)_{m'}R_8$, $-NR_{10}S(O)_{m'}NR_7R_{17}$, $-ZC(Z)R_3$, $-ZC(Z)R_{12}$, or $-(CR_{10}R_{20})_{m"}NR_{13}R_{14}$;

v is 0, or an integer having a value of 1 or 2;

m is 0, or the integer 1 or 2;

m' is an integer having a value of 1 or 2,

m" is 0, or an integer having a value of 1 to 5;

R_2 is C_{1-10} alkyl N_3, $-(CR_{10}R_{20})_{n'}OR_9$, heterocyclyl, heterocyclylC_{1-10} alkyl, C_{1-10}alkyl, halo-substituted C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{3-7}cycloalkylC_{1-10} alkyl, C_{5-7} cycloalkenyl, C_{5-7}cycloalkenylC_{1-10}alkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10}alkyl,

$(CR_{10}R_{20})_nOR_{11}$, $(CR_{10}R_{20})_nS(O)_mR_{18}$, $(CR_{10}R_{20})_nNHS(O)_2R_{18}$, $(CR_{10}R_{20})_nNR_{13}R_{14}$, $(CR_{10}R_{20})_nNO_2$, $(CR_{10}R_{20})_nCN$, $(CR_{10}R_{20})_{n'}SO_2R_{18}$, $(CR_{10}R_{20})_nS(O)_{m'}NR_{13}R_{14}$, $(CR_{10}R_{20})_nC(Z)R_{11}$, $(CR_{10}R_{20})_nOC(Z)R_{11}$, $(CR_{10}R_{20})_nC(Z)OR_{11}$, $(CR_{10}R_{20})_nC(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nC(Z)NR_{11}OR_9$, $(CR_{10}R_{20})_nNR_{10}C(Z)R_{11}$, $(CR_{10}R_{20})_nNR_{10}C(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nN(OR_6)C(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nN(OR_6)C(Z)R_{11}$, $(CR_{10}R_{20})_nC(=NOR_6)R_{11}$, $(CR_{10}R_{20})_nNR_{10}C(=NR_{19})NR_{13}R_{14}$, $(CR_{10}R_{20})_nOC(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nNR_{10}C(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nNR_{10}C(Z)OR_{10}$, 5-$(R_{18})$-1,2,4-oxadizaol-3-yl or 4-(R_{12})-5-$(R_{18}R_{19})$-4,5-dihydro-1,2,4-oxadiazol-3-yl; wherein the aryl, arylalkyl, heteroaryl, heteroaryl alkyl, cyclcoalkyl, cycloalkyl alkyl, heterocyclic and heterocyclic alkyl groups may be optionally substituted;

n is an integer having a value of 1 to 10;

n' is 0, or an integer having a value of 1 to 10;

Z is oxygen or sulfur;

Ra is hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, aryl, arylC_{1-4} alkyl, heteroaryl, heteroarylC_{1-4}alkyl, heterocyclyl, or heterocyclylC_{1-4} alkyl;

R_3 is heterocyclyl, heterocyclylC_{1-10} alkyl or R_8;

R_5 is hydrogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl or NR_7R_{17}, excluding the moieties -SR_5 being -SNR_7R_{17} and -$S(O)R_5$ being -SOH;

R_6 is hydrogen, a pharmaceutically acceptable cation, C_{1-10} alkyl, C_{3-7} cycloalkyl, aryl, arylC_{1-4} alkyl, heteroaryl, heteroaryl$_{1-10}$alkyl, heterocyclyl, aroyl, or C_{1-10} alkanoyl;

R_7 and R_{17} is each independently selected from hydrogen or C_{1-4} alkyl or R_7 and R_{17} together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR_{15};

R_8 is C_{1-10} alkyl, halo-substituted C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{5-7} cycloalkenyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, $(CR_{10}R_{20})_nOR_{11}$, $(CR_{10}R_{20})_nS(O)_mR_{18}$, $(CR_{10}R_{20})_nNHS(O)_2R_{18}$, $(CR_{10}R_{20})_nNR_{13}R_{14}$; wherein the aryl, arylalkyl, heteroaryl, heteroaryl alkyl may be optionally substituted;

R_9 is hydrogen, -$C(Z)R_{11}$, optionally substituted C_{1-10} alkyl, $S(O)_2R_{18}$, optionally substituted aryl or optionally substituted aryl-C_{1-4} alkyl;

R_{10} and R_{20} is each independently selected from hydrogen or C_{1-4} alkyl;

R_{11} is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, heterocyclyl, heterocyclyl C_{1-10}alkyl, aryl, arylC_{1-10} alkyl, heteroaryl or heteroarylC_{1-10} alkyl;

R_{12} is hydrogen or R_{16};

R_{13} and R_{14} is each independently selected from hydrogen or optionally substituted C_{1-4} alkyl, optionally substituted aryl or optionally substituted aryl-C_{1-4} alkyl, or together with the nitrogen which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR_9 ;

R_{15} is R_{10} or C(Z)-C_{1-4} alkyl;

R_{16} is C_{1-4} alkyl, halo-substituted-C_{1-4} alkyl, or C_{3-7} cycloalkyl;

R_{18} is C_{1-10} alkyl, C_{3-7} cycloalkyl, heterocyclyl, aryl, aryl$_{1-10}$alkyl, heterocyclyl, heterocyclyl-C_{1-10}alkyl, heteroaryl or heteroaryl$_{1-10}$alkyl;

R_{19} is hydrogen, cyano, C_{1-4} alkyl, C_{3-7} cycloalkyl or aryl;

or a pharmaceutically acceptable salt thereof.

In Formula (I), suitable R_1 moieties includes 4-pyridyl, 4-pyrimidinyl, 4-quinolyl, 6-isoquinolinyl, 4-quinazolinyl, 1-imidazolyl and 1-benzimidazolyl, of which the 4-pyridyl, 4-pyrimidinyl and 4-quinolyl are preferred. More preferred is the 4-pyrimidinyl or 4-pyridyl moiety, and most preferred is the 4-pyrimidinyl.

The R_1 heteroaryl ring is substituted by $N(R_{10})C(O)R_a$ or a halo substituted mono or di- C_{1-6} alkyl substituted amino. When the R_1 substituent is $N(R_{10})C(O)$ R_a, R_a is hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, aryl, arylC_{1-4} alkyl, heteroaryl, heteroarylC_{1-4}alkyl, heterocyclyl, or heterocyclylC_{1-4}alkyl C_{1-4} alkyl, R_a is preferably C1-6 alkyl; preferably R_{10} is hydrogen. It is also recognized that the R_a moieties, in particular the C_{1-6} alkyl group may be optionally substituted, preferably from one to three times, preferably with halogen, such as fluorine, as in trifluoromethyl or trifluroethyl.

When the R_1 substituent is a halo substituted mono- and di-C_{1-6} alkylsubstituted amino, preferably where the amino group is mono-substituted, more preferably with methyl. The alkyl group in the mono- and di-C_{1-6} alkylsubstituted amino moiety is halo substituted, such as in trifluoro- i.e., trifluoromethyl or trifluroethyl.

The R_1 heteroaryl ring may contain an additional substituent group such as C_{1-4} alkyl, halo, OH, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} alkylsulfinyl, CH_2OR_{12}, amino, mono- and di-C_{1-6} alkylsubstituted amino, or an N-heterocyclyl ring which ring has from 5 to 7 members and optionally contains an additional heteroatom selected from oxygen, sulfur or NR_{15}.

A preferred ring placement of the R_1 substituent on the 4-pyridyl derivative is the 2-position, such as 2-methyl-4-pyridyl. A preferred ring placement on the 4-pyrimidinyl ring is also at the 2-position, such as in 2-methyl-pyrimidinyl, 2-amino pyrimidinyl or 2-methylaminopyrimidinyl .

Suitably, for compounds of Formula (II), R_1 is a 4-pyridyl, or pyrimidinyl ring substituted with a C_{1-4} alkyl amino group. The C_{1-4} alkyl amino group is suitably

methylamino, ethylamino, isopropyl amino, n-butylamino, or t-butylamino. Preferably, the ring is a 4-pyrimidinyl ring. A preferred ring placement on the 4-pyrimidinyl ring is at the 2-position, such as in 2-methylamino-pyrimidinyl. A preferred ring placement of the R_1 substituent on the 4-pyridyl derivative is the 2-position, such as 2-methylamino-4-pyridyl. The pyridyl or pyriminidyl ring may contain an additional substituent group such as a C_{1-4} alkyl, halogen, hydroxyl, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} alkylsulfinyl, CH_2OR_{12}, amino, mono and di- C_{1-6} alkyl substituted amino, or an N-heterocyclyl ring which ring has from 5 to 7 members and optionally contains an additional heteroatom selected from oxygen, sulfur or NR_{15}.

Suitably, for compounds of Formula (I) and (II), R_4 is phenyl, naphth-1-yl or naphth-2-yl, or a heteroaryl, which is optionally substituted by one or two substituents. More preferably R_4 is a phenyl or naphthyl ring. Suitable substitutions for R_4 when this is a 4-phenyl, 4-naphth-1-yl, 5-naphth-2-yl or 6-naphth-2-yl moiety are one or two substituents each of which are independently selected from halogen, $-SR_5$, $-SOR_5$, $-OR_{12}$, CF_3, or $-(CR_{10}R_{20})_vNR_{10}R_{20}$, and for other positions of substitution on these rings preferred substitution is halogen, $-S(O)_mR_3$, $-OR_3$, CF_3, $-(CR_{10}R_{20})_{m''}NR_{13}R_{14}$, $-NR_{10}C(Z)R_3$ and $-NR_{10}S(O)_{m'}R_8$. Preferred substituents for the 4-position in phenyl and naphth-1-yl and on the 5-position in naphth-2-yl include halogen, especially fluoro and chloro and $-SR_5$ and $-SOR_5$ wherein R_5 is preferably a C_{1-2} alkyl, more preferably methyl; of which the fluoro and chloro is more preferred, and most especially preferred is fluoro. Preferred substituents for the 3-position in phenyl and naphth-1-yl rings include: halogen, especially fluoro and chloro; $-OR_3$, especially C_{1-4} alkoxy; CF_3, $NR_{10}R_{20}$, such as amino; $-NR_{10}C(Z)R_3$, especially $-NHCO(C_{1-10}$ alkyl); $-NR_{10}S(O)_{m'}R_8$, especially $-NHSO_2(C_{1-10}$ alkyl), and $-SR_3$ and $-SOR_3$ wherein R_3 is preferably a C_{1-2} alkyl, more preferably methyl. When the phenyl ring is disubstituted preferably it is two independent halogen moieties, such as fluoro and chloro, preferably di-chloro and more preferably in the 3,4-position. It is also preferred that for the 3-position of both the $-OR_3$ and $-ZC(Z)R_3$ moieties, R_3 may also include hydrogen.

Preferably, the R_4 moiety is an unsubstituted or substituted phenyl moiety. More preferably, R_4 is phenyl or phenyl substituted at the 4-position with fluoro and/or substituted at the 3-position with fluoro, chloro, C_{1-4} alkoxy, methane-sulfonamido or acetamido, or R_4 is a phenyl di-substituted at the 3,4-position independently with chloro or fluoro, more preferably chloro. Most preferably, R_4 is a 4-fluorophenyl.

Suitably, for compounds of Formula (I) and (II), Z is oxygen or sulfur, preferably oxygen.

Suitably, for compounds of Formula (I) and (II), R_2 is C_{1-10} alkyl N_3, $-(CR_{10}R_{20})_{n'}OR_9$, heterocyclyl, heterocyclylC_{1-10} alkyl, C_{1-10}alkyl, halo-substituted C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{3-7}cycloalkylC_{1-10} alkyl, C_{5-7} cycloalkenyl, C_{5-7} cycloalkenyl C_{1-10} alkyl, aryl, arylC_{1-10} alkyl, heteroaryl,

heteroarylC1-10 alkyl, $(CR_{10}R_{20})_nOR_{11}$, $(CR_{10}R_{20})_nS(O)_mR_{18}$, $(CR_{10}R_{20})_nNHS(O)_2R_{18}$, $(CR_{10}R_{20})_nNR_{13}R_{14}$, $(CR_{10}R_{20})_nNO_2$, $(CR_{10}R_{20})_nCN$, $(CR_{10}R_{20})_{n'}SO_2R_{18}$, $(CR_{10}R_{20})_nS(O)_{m'}NR_{13}R_{14}$, $(CR_{10}R_{20})_nC(Z)R_{11}$, $(CR_{10}R_{20})_nOC(Z)R_{11}$, $(CR_{10}R_{20})_nC(Z)OR_{11}$, $(CR_{10}R_{20})_nC(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nC(Z)NR_{11}OR_9$, $(CR_{10}R_{20})_nNR_{10}C(Z)R_{11}$, $(CR_{10}R_{20})_nNR_{10}C(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nN(OR_6)C(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nN(OR_6)C(Z)R_{11}$, $(CR_{10}R_{20})_nC(=NOR_6)R_{11}$, $(CR_{10}R_{20})_nNR_{10}C(=NR_{19})NR_{13}R_{14}$, $(CR_{10}R_{20})_nOC(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nNR_{10}C(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nNR_{10}C(Z)OR_{10}$, 5-($R_{18}$)-1,2,4-oxadizaol-3-yl or 4-(R_{12})-5-($R_{18}R_{19}$)-4,5-dihydro-1,2,4-oxadiazol-3-yl;wherein the cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclic, and heterocyclic alkyl moieties may be optionally substituted; wherein n is an integer having a value of 1 to 10, m is 0, or the integer 1 or 2: n' is 0, or an integer having a value of 1 to 10; and m' is 1 or 2. Preferably n is 1 to 4.

Preferably R_2 is an optionally substituted heterocyclyl ring, and optionally substituted heterocyclylC1-10 alkyl, an optionally substituted C1-10 alkyl, an optionally substituted C3-7cycloalkyl, an optionally substituted C3-7cycloalkyl C1-10 alkyl, $(CR_{10}R_{20})_nC(Z)OR_{11}$ group, $(CR_{10}R_{20})_nNR_{13}R_{14}$, $(CR_{10}R_{20})_nNHS(O)_2R_{18}$, $(CR_{10}R_{20})_nS(O)_mR_{18}$, an optionally substituted aryl; an optionally substituted arylC1-10 alkyl, $(CR_{10}R_{20})_nOR_{11}$, $(CR_{10}R_{20})_nC(Z)R_{11}$, or $(CR_{10}R_{20})_nC(=NOR_6)R_{11}$ group.

More preferably R_2 is an optionally substituted heterocyclyl ring, and optionally substituted heterocyclylC1-10 alkyl, optionally substituted C3-7cycloalkyl, an optionally substituted C3-7cycloalkyl C1-10 alkyl, an optionally substituted aryl, $(CR_{10}R_{20})_nNR_{13}R_{14}$, or $(CR_{10}R_{20})_nC(Z)OR_{11}$ group.

When R_2 is an optionally substituted heterocyclyl the ring is preferably a morpholino, pyrrolidinyl, or a piperidinyl group. When the ring is optionally substituted the substituents may be directly attached to the free nitrogen, such as in the piperidinyl group or pyrrole ring, or on the ring itself. Preferably the ring is a piperidine or pyrrole, more preferably piperidine. The heterocyclyl ring may be optionally substituted one to four times independently by halogen; C1-4 alkyl; halosubstituted C1-4 alkyl, such as trifluoromethyl or trifluoroethyl: aryl, such as phenyl; aryl alkyl, such as benzyl, wherein the aryl or aryl alkyl moieties themselves may be optionally substituted (as in the definition section below); $C(O)OR_{11}$, such as the C(O)C1-4 alkyl or C(O)OH moieties; C(O)H; C(O)C1-4 alkyl, hydroxy substituted C1-4 alkyl, C1-4 alkoxy, $S(O)_mC_{1-4}$ alkyl (wherein m is 0, 1, or 2), $NR_{10}R_{20}$ (wherein R_{10} and R_{20} are independently hydrogen or C1-4alkyl).

Preferably if the ring is a piperidine, the ring is attached to the imidazole at the 4-position, and the substituents are directly on the available nitrogen, i.e. a 1-formyl-4-piperidine, 1-benzyl-4-piperidine, 1-methyl-4-piperidine, 1-ethoxy-carbonyl-4-piperidine, 2,2,2-trifluoroethyl-4-piperidine, or 1-trifluoroacetyl-4-piperidine. If the ring is substituted by an alkyl group and the ring is attached in the 4-position, it is preferably substituted in the 2 or 6 position or both, such as 2,2,6,6-tetramethyl-4-piperidine. Similarly, if the ring is a pyrrole, the ring is attached to the imidazole at the 3-position, and the substituents are all directly on the available nitrogen.

When R_2 is an optionally substituted heterocyclyl C_{1-10} alkyl group, the ring is preferably a morpholino, pyrrolidinyl, or a piperidinyl group. Preferably this alkyl moiety is from 1 to 4, more preferably 3 or 4, and most preferably 3, such as in a propyl group. Preferred heterocyclic alkyl groups include but are not limited to, morpholino ethyl, morpholino propyl, pyrrolidinyl propyl, and piperidinyl propyl moieties. The heterocyclic ring herein is also optionally substituted in a similar manner to that indicated above for the direct attachment of the heterocyclyl.

When R_2 is an optionally substituted C_{3-7}cycloalkyl, or an optionally substituted C_{3-7}cycloalkyl C_{1-10} alkyl, the cycloalkyl group is preferably a C_5 to C6 ring which ring may be optionally substituted 1 or more times independently by halogen, such as fluorine, chlorine, bromine or iodine; hydroxy; C_{1-10} alkoxy, such as methoxy or ethoxy; $S(O)_m$ alkyl, wherein m is 0, 1, or 2, such as methyl thio, methylsulfinyl or methyl sulfonyl; amino, mono & di-substituted amino, such as in the NR_7R_{17} group; or where the R_7R_{17} may cyclize together with the nitrogen to which they are attached to form a 5 to 7 membered ring which optionally includes an additional heteroatom selected from O/N/S; C_{1-10} alkyl, such as methyl, ethyl, propyl, isopropyl, or t-butyl; halosubstituted alkyl, such as CF_3 or trifluroethyl; hydroxy substituted C_{1-10}alkyl; $C(O)OR_{11}$, such as the free acid or methyl ester derivative; an optionally substituted aryl, such as phenyl; an optionally substituted arylalkyl, such as benzyl of phenethyl; and further where these aryl moieties may also be substituted one to two times by halogen; hydroxy; C_{1-10} alkoxy; $S(O)_m$ alkyl; amino, mono & di-substituted amino, such as in the NR_7R_{17} group; alkyl or halosubstituted alkyl.

When R_2 is $(CR_{10}R_{20})_nNR_{13}R_{14}$, R_{13} and R_{14} are as defined in Formula (I), that is R_{13} and R_{14} are each independently selected from hydrogen, optionally substituted C_{1-4} alkyl, optionally substituted aryl or an optionally substituted aryl-C_{1-4} alkyl, or together with the nitrogen which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR_9. It is recognized that in some instances this can yield the same moiety as a heterocyclic C_{1-10} alkyl moiety noted above which is also a suitable R_2 variable. If the $NR_{13}R_{14}$ ring is cyclized it may be optionally substituted as defined

herein. Preferably R_{13} and R_{14} are independently hydrogen, C_{1-4} alkyl, preferably methyl, or benzyl. The n term is preferably 1 to 4, more preferably 3 or 4, and most preferably 3, such as in a propyl group. Preferred groups include, but are not limited to, aminopropyl, (N-methyl-N-benzyl)aminopropyl, (N-Phenylmethyl)amino-1-propyl, or diethylamino propyl.

When R_2 is a $(CR_{10}R_{20})_nC(Z)OR_{11}$ group, R_{11} is suitably hydrogen, C_{1-4} alkyl, especially methyl. The n term is preferably 1 to 4, more preferably 2 or 3, such as in an ethyl or propyl group. Preferred groups include, but are not limited to, carboxymethyl-1-butyl, carboxy-1-propyl, or 2-acetoxyethyl.

When R_2 is a $(CR_{10}R_{20})_nS(O)_mR_{18}$ group m is 0, 1, or 2, and R_{18} is preferably aryl, especially phenyl, or C_{1-10} alkyl, especially methyl. The n term is preferably 1 to 4, more preferably 2 or 3, such as in an ethyl or propyl group.

When R_2 is a $(CR_{10}R_{20})_nOR_{11}$ group, R_{11} is suitably hydrogen, aryl, especially phenyl, or C_{1-10} alkyl, especially methyl or ethyl. The n term is preferably 1 to 4, more preferably 2 or 3, such as in an ethyl or propyl group.

When R_2 is a $(CR_{10}R_{20})_nNHS(O)_2R_{18}$ group, R_{18} is suitably alkyl, especially methyl. The n term is preferably 1 to 4, more preferably 2 or 3, such as in an ethyl or propyl group.

When R_2 is a optionally substituted aryl, the aryl is preferably phenyl. The aryl ring may be optionally substituted one or more times, preferably by one or two substituents, independently selected from C_{1-4} alkyl, halosubstituted C_{1-4} alkyl such as trifluromethyl or trifluoroethyl, halogen, especially fluoro or chloro, $(CR_{10}R_{20})_tOR_{11}$, $-(CR_{10}R_{20})_tNR_{10}R_{20}$, especially amino or mono- or di-alkylamino $-(CR_{10}R_{20})_tS(O)_mR_{18}$, wherein m is 0, 1 or 2 ; - SH-, $-(CR_{10}R_{20})_nNR_{13}R_{14}$, $-NR_{10}C(Z)R_3$ (such -NHCO(C_{1-10} alkyl)); $-NR_{10}S(O)_mR_8$ (such as $-NHSO_2$(C_{1-10} alkyl)); and t is 0, or an integer of 1 to 4. Preferably the phenyl is substituted in the 3 or 4- position by $-(CR_{10}R_{20})_tS(O)_mR_{18}$, and R_{18} is preferably C_{1-10}alkyl, especially methyl.

When R_2 is an optionally substituted heteroaryl or heteroarylalkyl group the ring may be optionally substituted one or more times, preferably by one or two substituents, independently selected from one or more times, by C_{1-4} alkyl, halosubstituted C_{1-4} alkyl such as trifluromethyl or trifluoroethyl, halogen, especially fluoro or chloro, $(CR_{10}R_{20})_tOR_{11}$, $-(CR_{10}R_{20})_tNR_{10}R_{20}$, especially amino or mono- or di-alkylamino $-(CR_{10}R_{20})_tS(O)_mR_{18}$, wherein m is 0, 1 or 2 ; -SH-, $-(CR_{10}R_{20})_n$-$NR_{13}R_{14}$, $-NR_{10}C(Z)R_3$ (such -NHCO(C_{1-10} alkyl)); $-NR_{10}S(O)_mR_8$ (such as $-NHSO_2$(C_{1-10} alkyl)); t is 0, or an integer of 1 to 4.

One skilled in the art would readily recognize that when R_2 is a $(CR_{10}R_{20})_nOC(Z)R_{11}$, or $(CR_{10}R_{20})_nOC(Z)NR_{13}R_{14}$ moiety, or any similarly

substituted group that n is preferably at least 2 which will allow for the synthesis of stable compounds.

Preferably R_2 is a C_{1-4} alkyl (branched and unbranched), especially methyl, methylthio propyl, a methylsulfinyl propyl, an amino propyl, N-methyl-N-benzylamino propyl group, diethylamino propyl, cyclopropyl methyl, morpholinyl butyl, morpholinyl propyl, a morpholinyl ethyl, a piperidine or a substituted piperidine. More preferably R_2 is a methyl, isopropyl, butyl, t-butyl, n-propyl, methylthiopropyl, or methylsulfinyl propyl, morpholino propyl, morpholinyl butyl, phenyl substituted by halogen, thioalkyl or sulfinyl alkyl such as a methylthio, methylsulfinyl or methylsulfonyl moiety; piperidinyl, 1-formyl-4-piperidine, 1-benzyl-4-piperidine, 1-methyl-4-piperidine, 1-ethoxycarbonyl-4-piperidine, 2,2,2-trifluoroethyl-4-piperidine, or 1-trifluoroacetyl-4-piperidine.

In all instances herein where there is an alkenyl or alkynyl moiety as a substituent group, the unsaturated linkage, i.e., the vinylene or acetylene linkage is preferably not directly attached to the nitrogen, oxygen or sulfur moieties, for instance in OR_3, or for certain R_2 moieties.

As used herein, "optionally substituted" unless specifically defined shall mean such groups as halogen, such as fluorine, chlorine, bromine or iodine; hydroxy; hydroxy substituted C_{1-10}alkyl; C_{1-10} alkoxy, such as methoxy or ethoxy; S(O)m alkyl, wherein m is 0, 1 or 2, such as methyl thio, methylsulfinyl or methyl sulfonyl; amino, mono & di-substituted amino, such as in the NR_7R_{17} group; or where the R_7R_{17} may together with the nitrogen to which they are attached cyclize to form a 5 to 7 membered ring which optionally includes an additional heteroatom selected from O/N/S; C_{1-10} alkyl, cycloalkyl, or cycloalkyl alkyl group, such as methyl, ethyl, propyl, isopropyl, t-butyl, etc. or cyclopropyl methyl; halosubstituted C_{1-10} alkyl, such CF_3; or trifluroethyl, an optionally substituted aryl, such as phenyl, or an optionally substituted arylalkyl, such as benzyl or phenethyl, wherein these aryl moieties may also be substituted one to two times by halogen; hydroxy; hydroxy substituted alkyl; C_{1-10} alkoxy; $S(O)_m$ alkyl; amino, mono & di-substituted amino, such as in the NR_7R_{17} group; alkyl, or CF_3.

In a preferred subgenus of compounds of Formula (I), R_2 is morpholinyl propyl, aminopropyl, piperidinyl, N-benzyl-4-piperidinyl, N-methyl-4-piperidinyl, or 2,2,6,6-tetramethylpiperidin-4-yl, 2,2,2-trifluoroethyl-4-piperidine, or 1-trifluoroacetyl-4-piperidine; and R_4 is phenyl or phenyl substituted one or two times by fluoro, chloro, C_{1-4} alkoxy, $-S(O)_m$ alkyl, methanesulfonamido or acetamido.

In a preferred subgenus of compounds of Formula (II), R_1 is 2-methylamino-4-pyrimidinyl or 2-methylamino-4-pyridyl; R_2 is morpholinyl propyl, aminopropyl, piperidinyl, N-benzyl-4-piperidinyl, N-methyl-4-piperidinyl, or 2,2,6,6-

tetramethylpiperidin-4-yl; and R_4 is phenyl or phenyl substituted one or two times by fluoro, chloro, C_{1-4} alkoxy, $-S(O)_m$ alkyl, methanesulfonamido or acetamido.

Suitable pharmaceutically acceptable salts are well known to those skilled in the art and include basic salts of inorganic and organic acids, such as hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methane sulphonic acid, ethane sulphonic acid, acetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid and mandelic acid. In addition, pharmaceutically acceptable salts of compounds of Formula (I) may also be formed with a pharmaceutically acceptable cation, for instance, if a substituent group comprises a carboxy moiety. Suitable pharmaceutically acceptable cations are well known to those skilled in the art and include alkaline, alkaline earth, ammonium and quaternary ammonium cations.

The following terms, as used herein, refer to:

- "halo" or "halogens", include the halogens: chloro, fluoro, bromo and iodo.
- "C_{1-10}alkyl" or "alkyl" - both straight and branched chain radicals of 1 to 10 carbon atoms, unless the chain length is otherwise limited, including, but not limited to, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *tert*-butyl, *n*-pentyl and the like.
- The term "cycloalkyl" is used herein to mean cyclic radicals, preferably of 3 to 8 carbons, including but not limited to cyclopropyl, cyclopentyl, cyclohexyl, and the like.
- The term "cycloalkenyl" is used herein to mean cyclic radicals, preferably of 5 to 8 carbons, which have at least one bond including but not limited to cyclopentenyl, cyclohexenyl, and the like.
- The term "alkenyl" is used herein at all occurrences to mean straight or branched chain radical of 2-10 carbon atoms, unless the chain length is limited thereto, including, but not limited to ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl and the like.
- "aryl" - phenyl and naphthyl;
- "heteroaryl" (on its own or in any combination, such as "heteroaryloxy", or "heteroaryl alkyl") - a 5-10 membered aromatic ring system in which one or more rings contain one or more heteroatoms selected from the group consisting of N, O or S, such as, but not limited, to pyrrole, pyrazole, furan, thiophene, quinoline, isoquinoline, quinazolinyl, pyridine, pyrimidine, oxazole, thiazole, thiadiazole, triazole, imidazole, or benzimidazole.
- "heterocyclic" (on its own or in any combination, such as "heterocyclylalkyl") - a saturated or partially unsaturated 4-10 membered ring system in which one or more

rings contain one or more heteroatoms selected from the group consisting of N, O, or S: such as, but not limited to, pyrrolidine, piperidine, piperazine, morpholine, tetrahydro pyran, or imidazolidine.

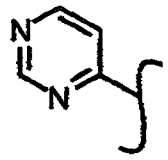
• The term "aralkyl" or "heteroarylalkyl" or "heterocyclicalkyl" is used herein to mean C_{1-4} alkyl as defined above attached to an aryl, heteroaryl or heterocyclic moiety as also defined herein unless otherwise indicate.

• "sulfinyl" - the oxide S (O) of the corresponding sulfide, the term "thio" refers to the sulfide, and the term "sulfonyl" refers to the fully oxidized S $(O)_2$ moiety.

• "aroyl" - a C(O)Ar, wherein Ar is as phenyl, naphthyl, or aryl alkyl derivative such as defined above, such group include but are not limited to benzyl and phenethyl.

• "alkanoyl" - a $C(O)C_{1-10}$ alkyl wherein the alkyl is as defined above.

For the purposes herein the "core" 4-pyrimidinyl moiety for R_1 or R_2 is



referred to as the formula:

The compounds of the present invention may contain one or more asymmetric carbon atoms and may exist in racemic and optically active forms. All of these compounds are included within the scope of the present invention.

Exemplified compounds of Formula (I) include:

5-(2-Acetamido-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(4-morpholino-3-propyl)-imidazole;

5-(2-Acetamido-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(1-methyl-4-piperidinyl)-imidazole.

Exemplified compounds of Formula (II) include:

5-[4-(2-Methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(1-methylpiperidin-4-yl)-imidazole;

5-[4-(2-Methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-morpholino-3-propyl)imidazole;

5-[4-(2-Methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(piperidin-4-yl)imidazole;

5-[(2-Ethylamino)pyrimidin-4-yl]-4-(4-fluorophenyl)-1-(1-methylpiperdin-4-yl)-imidazole:

4-(4-Fluorophenyl)-5-[2-(isopropyl)aminopyrimidiny-4-yl]-1-(1-methylpiperdin-4-yl)imidazole;

5-[4-(2-Methylamino-4-pyrimidinyl)]-4-(4-fluorophenyl)-1-(2,2,6,6-tetra-methyl-piperidin-4-yl)imidazole;

5-(2-Methylamino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(2-cyanoethyl)imidazole;

5-(2-Methylamino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-[1-(2,2,2-trifluoroethyl)-4-piperidinyl] imidazole;

5-(2-amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-[1-(2,2,2-trifluoroethyl)-4-piperidinyl] imidazole;

5-(2-Amino-4-pyrimidinyl]-4-(4-fluorophenyl)-1-[(1-trifluoroacetyl)-4-piperidinyl]imidazole.

Preferred compounds of Formula (II) include:

5-[4-(2-Methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-morpholino-3-propyl)imidazole;

5-[4-(2-Methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(1-methylpiperidin-4-yl)-imidazole;

5-[4-(2-Methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-piperidine)imidazole.

The present invention additionally includes novel species as exemplified below:

5-[4-(2-Methylthio)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-piperidine)imidazole;

4-(Fluorophenyl)-1-(1-methylpiperidin-4-yl)-5-(2-methylthio-4-pyrimidinyl)imidazole;

4-(Fluorophenyl)-1-(1-methylpiperidin-4-yl)-5-(2-methysulfinyl-4-pyrimidinyl)imidazole;

1-tert-Butyl-4-(4-fluorophenyl)-5-(2-methysulfinyl-4-pyrimidinyl)imidazole;

5-(2-Amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(tetrahydro-4-thiopyranyl)-imidazole;

5-(2-Amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(tetrahydro-4-pyranyl)imidazole;

5-(2-Amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(tetrahydro-4-sulfinylpyranyl)-imidazole;

5-(2-Amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(tetrahydro-4-sulfonylpyranyl)-imidazole;

5-(2-Amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(1-trifluoroacetylpiperidin-4-yl)-imidazole;

5-(4-Pyridyl)-4-(4-fluorophenyl)-1-(4-piperidinyl) imidazole;

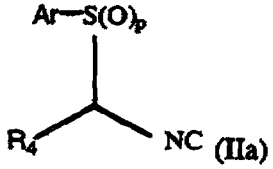
5-(4-Pyridyl)-4-(4-fluorophenyl)-1-(1-t-butoxy carbonyl-4-piperidinyl) imidazole.

For purposes herein the dosage ranges, formulation details, and methods of making for compounds of Formula (II) are analogous to the compounds of Formula (I). Further, the dosage ranges, and formulation details for use of the compounds of Formula

(A) as COX-2 and PGHS inhibitors are analogous to the compounds of Formula (I) as described herein.

In a further aspect the present invention provides for the synthesis of compounds of Formula (I) and (II) as illustrated above and further, for compounds of Formula (A) wherein R_1 is 4-pyridyl, pyrimidinyl, quinolyl, isoquinolinyl, quinazolin-4-yl, 1-imidazolyl or 1-benzimidazolyl, which heteroaryl ring is optionally substituted with one or two substituents each of which is independently selected from C_{1-4} alkyl, halogen, hydroxyl, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} alkylsulfinyl, CH_2OR_{12}, amino, mono or di-C_{1-6} alkyl substituted amino, $N(R_{10})C(O)R_a$ or an N-heterocyclyl ring which ring has from 5 to 7 members and optionally contains an additional heteroatom selected from oxygen, sulfur or NR_{15}; and wherein all the substituent groups in R_1, R_2 and R_4 are the same as in Formulas (I) and (II). For use in the synthetic section herein, synthesis of "compounds of Formula (I)" will also refer to this broader description of R_1.

In a further aspect the present invention provides for compounds of the Formula (IIa) having the structure:



(IIa)

wherein p is 0, or 2; R_4 is as defined for Formula (I) and Ar is an optionally substituted aryl as defined herein. Suitably, Ar is phenyl optionally substituted by C_{1-4}alkyl, C_{1-4} alkoxy or halo. Preferably Ar is phenyl or 4-methylphenyl, i.e. a tosyl derivative.

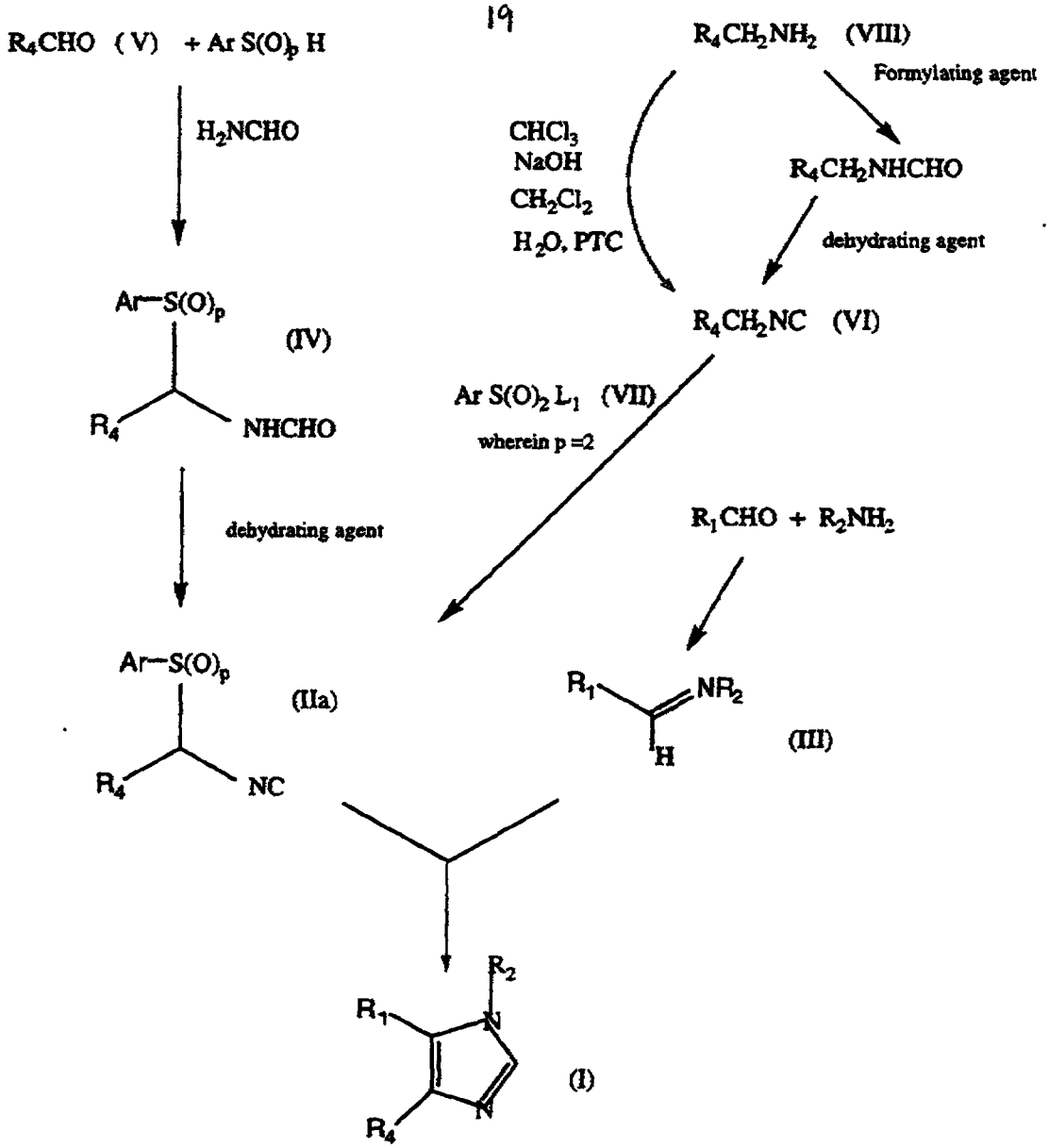
The compounds of Formula (I) and (II) may be obtained by applying synthetic procedures, some of which are illustrated in Schemes I to XI herein. The synthesis provided for in these Schemes is applicable for the producing compounds of Formula (I) having a variety of different R_1, R_2, and R_4 groups which are reacted, employing optional substituents which are suitably protected, to achieve compatibility with the reactions outlined herein. Subsequent deprotection, in those cases, then affords compounds of the nature generally disclosed. Once the imidazole nucleus has been established, further compounds of Formula (I) and (II) may be prepared by applying standard techniques for functional group interconversion, well known in the art.

For instance: $-C(O)NR_{13}R_{14}$ from $-CO_2CH_3$ by heating with or without catalytic metal cyanide, e.g. NaCN, and $HNR_{13}R_{14}$ in CH_3OH; $-OC(O)R_3$ from -OH with e.g., $ClC(O)R_3$ in pyridine; $-NR_{10}-C(S)NR_{13}R_{14}$ from $-NHR_{10}$ with an alkylisothiocyante or thiocyanic acid; $NR_6C(O)OR_6$ from $-NHR_6$ with the alkyl chloroformate; $-NR_{10}C(O)NR_{13}R_{14}$ from $-NHR_{10}$ by treatment with an isocyanate.

e.g. HN=C=O or $R_{10}N$=C=O; -NR_{10}-C(O)R_8 from -NHR_{10} by treatment with Cl-C(O)R_3 in pyridine: -C(=NR_{10})$NR_{13}R_{14}$ from -C($NR_{13}R_{14}$)SR_3 with $H_3NR_3^+OAc^-$ by heating in alcohol; -C($NR_{13}R_{14}$)SR_3 from -C(S)$NR_{13}R_{14}$ with R_6-I in an inert solvent, e.g. acetone; -C(S)$NR_{13}R_{14}$ (where R_{13} or R_{14} is not hydrogen) from -C(S)NH_2 with $HNR_{13}R_{14}$-C(=NCN)-$NR_{13}R_{14}$ from -C(=$NR_{13}R_{14}$)-SR_3 with NH_2CN by heating in anhydrous alcohol, alternatively from -C(=NH)-$NR_{13}R_{14}$ by treatment with BrCN and NaOEt in EtOH; -NR_{10}-C(=NCN)SR_8 from -NHR_{10} by treatment with $(R_8S)_2$C=NCN; -$NR_{10}SO_2R_3$ from -NHR_{10} by treatment with $ClSO_2R_3$ by heating in pyridine; -NR_{10}C(S)R_3 from -NR_{10}C(O)R_8 by treatment with Lawesson's reagent [2,4-*bis*(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide]; -$NR_{10}SO_2CF_3$ from -NHR_6 with triflic anhydride and base wherein R_3, R_6, R_{10}, R_{13} and R_{14} are as defined in Formula (I) herein.

Precursors of the groups R_1, R_2 and R_4 can be other R_1, R_2 and R_4 groups which can be interconverted by applying standard techniques for functional group inter-conversion. For example a compound of the formula (I) wherein R_2 is halo -substituted C_{1-10} alkyl can be converted to the corresponding C_{1-10} alkylN_3 derivative by reacting with a suitable azide salt, and thereafter if desired can be reduced to the corresponding C_{1-10}alkylNH_2 compound, which in turn can be reacted with $R_{18}S(0)_2X$ wherein X is halo (e.g., chloro) to yield the corresponding C_{1-10}alkylNHS$(0)_2R_{18}$ compound.

Alternatively a compound of the formula (I) where R_2 is halo-substituted C_{1-10}-alkyl can be reacted with an amine $R_{13}R_{14}NH$ to yield the corresponding C_{1-10}-alkyl$NR_{13}R_{14}$ compound, or can be reacted with an alkali metal salt of $R_{18}SH$ to yield the corresponding C_{1-10}alkylSR_{18} compound.



SCHEME I

Referring to Scheme I the compounds of Formula (I) are suitably prepared by reacting a compound of the Formula (IIa) with a compound of the Formula (III) wherein p is 0 or 2, R_1, R_2 and R_4 are as defined herein, for Formula (I), or are precursors of the groups R_1, R_2 and R_4, and Ar is an optionally substituted phenyl group, and thereafter if necessary converting a precursor of R_1, R_2 and R_4 to a group R_1, R_2 and R_4. It is recognized that R2NH2 which is reacted with R1CHO to form the imine, Formula (III) the R_2 moiety when it contains a reactive functional group, such as a primary or secondary amine, an alcohol, or thiol compound the group must be suitably protected. Suitable protecting groups may be found in, Protecting Groups in Organic Synthesis, Greene T W, Wiley-Interscience, New York, 1981. whose disclosure is incorporated

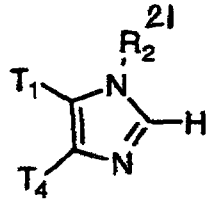
herein by reference. For instance, when R_2 is a heterocyclic ring, such as a piperidine ring, the nitrogen is protected with groups such as t-Boc, CO_2R_{18}, or a substitued arylalkyl moiety.

Suitably, the reaction is performed at ambient temperature or with cooling (e.g. -50° to 10°) or heating in an inert solvent such as methylene chloride, DMF, tetrahydrofuran, toluene, acetonitrile, or dimethoxyethane in the presence of an appropriate base such as K_2CO_3, t-buNH$_2$, 1,8-diazabicyclo [5.4.0.] undec-7-ene (DBU), or a guanidine base such as 1,5,7-triaza-bicyclo [4.4.0] dec-5-ene (TBD). The intermediates of formula (II) have been found to be very stable and capable of storage for a long time. Preferably, p is 2.

Reaction a compound of the Formula (IIa) wherein p = 2, with a compound of the Formula (III)-Scheme I gives consistently higher yields of compounds of Formula (I) than when p=0. In addition, the reaction of Formula (IIa) compounds wherein p = 2 is more environmentally and economically attractive. When p=0, the preferred solvent used is methylene chloride, which is environmentally unattractive for large scale processing, and the preferred base, TBD, is also expensive, and produces some byproducts and impurities, than when using the commercially attractive synthesis (p=2) as further described herein.

As noted, Scheme I utilizes the 1,3-dipolar cycloadditions of an anion of a substituted aryl thiomethylisocyanide (when p=0) to an imine. More specifically, this reaction requires a strong base, such as an amine base, to be used for the deprotonation step. The commercially available TBD is preferred although t-butoxide, Li+ or Na+, or K+ hexamethyldisilazide may also be used. While methylene chloride is the prefered solvent, other halogenated solvents, such as chloroform or carbon tetrachloride; ethers, such as THF, DME, DMF, diethylether, t-butyl methyl ether; as well as acetonitrile, toluene or mixtures thereof can be utiltized. The reaction may take place from about -20°C to about 40°C, preferably from about 0°C to about 23°C, more preferably from about 0°C to about 10°C, and most preferably about 4°C for reactions involving an R_1 group of pyrimidine. For compounds wherein R_1 is pyridine, it is recognized that varying the reations conditions of both temperature and solvent may be necessary, such as decreasing temperatures to about -50°C or changing the solvent to THF.

In a further process, compounds of Formula (I) may be prepared by coupling a suitable derivative of a compound of Formula (IX):



(IX)

wherein T_1 is hydrogen and T_4 is R_4, or alternatively T_1 is R_1 and T_4 is H in which R_1, R_2 and R_4 are as hereinbefore defined; with: (i) when T_1 is hydrogen, a suitable derivative of the heteroaryl ring R_1H, under ring coupling conditions, to effect coupling of the heteroaryl ring R_1 to the imidazole nucleus at position 5; (ii) when T_4 is hydrogen, a suitable derivative of the aryl ring R_4H, under ring coupling conditions, to effect coupling of the aryl ring R_4 to the imidazole nucleus at position 4.

Such aryl/heteroaryl coupling reactions are well known to those skilled in the art. In general, an organometallic synthetic equivalent of an anion of one component is coupled with a reactive derivative of the second component, in the presence of a suitable catalyst. The anion equivalent may be formed from either the imidazole of Formula (IX), in which case the aryl/heteroaryl compound provides the reactive derivative, or the aryl/heteroaryl compound in which case the imidazole provides the reactive derivative. Accordingly, suitable derivatives of the compound of Formula (IX) or the aryl/heteroaryl rings include organometallic derivatives such as organomagnesium, organozinc, organostannane and boronic acid derivatives and suitable reactive derivatives include the bromo, iodo, fluorosulfonate and trifluoromethanesulphonate derivatives. Suitable procedures are described in WO 91/19497, the disclosure of which is incorporated by reference herein.

Suitable organomagnesium and organozinc derivatives of a compound of Formula (IX) may be reacted with a halogen, fluorosulfonate or triflate derivative of the heteroaryl or aryl ring, in the presence of a ring coupling catalyst, such as a palladium (O) or palladium (II) catalyst, following the procedure of Kumada *et al.*, Tetrahedron Letters, **22**, 5319 (1981). Suitable such catalysts include *tetrakis*-(triphenylphosphine)palladium and $PdCl_2$[1,4-*bis*-(diphenylphosphino)-butane], optionally in the presence of lithium chloride and a base, such as triethylamine. In addition, a nickel (II) catalyst, such as Ni(II)Cl_2(1,2-biphenylphosphino)ethane, may also be used for coupling an aryl ring, following the procedure of Pridgen et al., J. Org. Chem, 1982, **47**, 4319. Suitable reaction solvents include hexamethylphosphor-amide. When the heteroaryl ring is 4-pyridyl, suitable derivatives include 4-bromo- and 4-iodo-pyridine and the fluorosulfonate and triflate esters of 4-hydroxy pyridine. Similarly, suitable derivatives for when the aryl ring is phenyl include the bromo, fluorosulfonate, triflate and, preferably, the iodo-derivatives. Suitable organomagnesium and organozinc derivatives may be obtained by treating a compound

of Formula (IX) or the bromo derivative thereof with an alkyllithium compound to yield the corresponding lithium reagent by deprotonation or transmetallation, respectively. This lithium intermediate may then be treated with an excess of a magnesium halide or zinc halide to yield the corresponding organometallic reagent.

A trialkyltin derivative of the compound of Formula (IX) may be treated with a bromide, fluorosulfonate, triflate, or, preferably, iodide derivative of an aryl or heteroaryl ring compound, in an inert solvent such as tetrahydrofuran, preferably containing 10% hexamethylphosphoramide, in the presence of a suitable coupling catalyst, such as a palladium (0) catalyst, for instance *tetrakis*-(triphenylphosphine)-palladium, by the method described in by Stille, J. Amer. Chem. Soc, 1987, **109**, 5478, US Patents 4,719,218 and 5,002,942, or by using a palladium (II) catalyst in the presence of lithium chloride optionally with an added base such as triethylamine, in an inert solvent such as dimethyl formamide. Trialkyltin derivatives may be conveniently obtained by metallation of the corresponding compound of Formula (IX) with a lithiating agent, such as *s*-butyl-lithium or *n*-butyllithium, in an ethereal solvent, such as tetrahydrofuran, or treatment of the bromo derivative of the corresponding compound of Formula (IX) with an alkyl lithium, followed, in each case, by treatment with a trialkyltin halide. Alternatively, the bromo- derivative of a compound of Formula (IX) may be treated with a suitable heteroaryl or aryl trialkyl tin compound in the presence of a catalyst such as *tetrakis*-(triphenyl-phosphine)-palladium, under conditions similar to those described above.

Boronic acid derivatives are also useful. Hence, a suitable derivative of a compound of Formula (IX), such as the bromo, iodo, triflate or fluorosulphonate derivative, may be reacted with a heteroaryl- or aryl-boronic acid, in the presence of a palladium catalyst such as *tetrakis*-(triphenylphosphine)-palladium or $PdCl_2$[1,4-*bis*-(diphenyl-phosphino)-butane] in the presence of a base such as sodium bicarbonate, under reflux conditions, in a solvent such as dimethoxyethane (see Fischer and Haviniga, Rec. Trav. Chim. Pays Bas, **84**, 439, 1965, Snieckus, V., Tetrahedron Lett., **29**, 2135, 1988 and Terashimia, M., Chem. Pharm. Bull., **11**, 4755, 1985). Non-aqueous conditions, for instance, a solvent such as DMF, at a temperature of about 100°C, in the presence of a Pd(II) catalyst may also be employed (see Thompson W J *et al*, J Org Chem, **49**, 5237, 1984). Suitable boronic acid derivatives may be prepared by treating the magnesium or lithium derivative with a trialkylborate ester, such as triethyl, tri-*iso*-propyl or tributylborate, according to standard procedures.

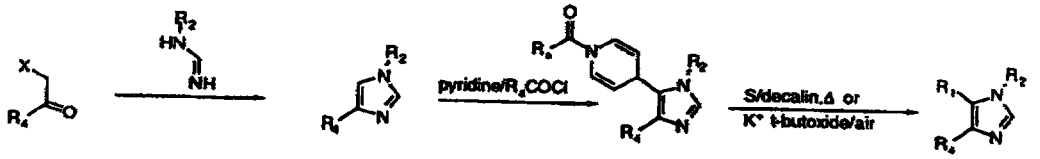
In such coupling reactions, it will be readily appreciated that due regard must be exercised with respect to functional groups present in the compounds of Formula (IX). Thus, in general, amino and sulfur substituents should be non-oxidised or protected.

Compounds of Formula (IX) are imidazoles and may be obtained by any of the procedures herein before described for preparing compounds of Formula (I). In

particular, an α-halo-ketone or other suitably activated ketones R_4COCH_2Hal (for compounds of Formula (IX) in which T_1 is hydrogen) or R_1COCH_2Hal (for compounds of Formula (IX) in which T_4 is hydrogen) may be reacted with an amidine of the formula R_2NH-C=NH, wherein R_2 is as defined in Formula (I), or a salt thereof, in an inert solvent such as a halogenated hydrocarbon solvent, for instance chloroform, at a moderately elevated temperature, and, if necessary, in the presence of a suitable condensation agent such as a base. The preparation of suitable a-halo-ketones is described in WO 91/19497. Suitable reactive esters include esters of strong organic acids such as a lower alkane sulphonic or aryl sulphonic acid, for instance, methane or *p*-toluene sulphonic acid. The amidine is preferably used as the salt, suitably the hydrochloride salt, which may then be converted into the free amidine *in situ* , by employing a two phase system in which the reactive ester is in an inert organic solvent such as chloroform, and the salt is in an aqueous phase to which a solution of an aqueous base is slowly added, in dimolar amount, with vigorous stirring. Suitable amidines may be obtained by standard methods, see for instance, Garigipati R, Tetrahedron Letters, 190, 31, 1989.

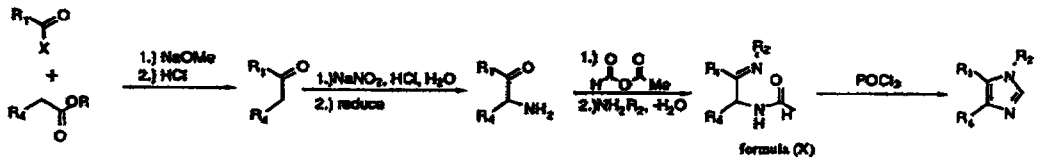
Compounds of Formula (I) may also be prepared by a process which comprises reacting a compound of Formula (IX), wherein T_1 is hydrogen, with an N-acyl heteroaryl salt, according to the method disclosed in US patent 4,803,279, US patent 4,719,218 and US patent 5,002.942, to give an intermediate in which the heteroaryl ring is attached to the imidazole nucleus and is present as a 1,4-dihydro derivative thereof, which intermediate may then be subjected to oxidative-deacylation conditions (Scheme II). The heteroaryl salt, for instance a pyridinium salt, may be either preformed or, more preferably, prepared *in situ* by adding a substituted carbonyl halide (such as an acyl halide, an aroyl halide, an arylalkyl haloformate ester, or, preferably, an alkyl haloformate ester, such as acetyl bromide, benzoylchloride, benzyl chloroformate, or, preferably, ethyl chloroformate) to a solution of the compound of Formula (IX) in the heteroaryl compound R_1H or in an inert solvent such as methylene chloride to which the heteroaryl compound has been added. Suitable deacylating and oxidising conditions are described in U.S. Patent Nos. 4,803,279, 4,719,218 and 5,002,942, which references are hereby incorporated by reference in their entirety. Suitable oxidizing systems include sulfur in an inert solvent or solvent mixture, such as decalin, decalin and diglyme, *p*-cymene, xylene or mesitylene, under reflux conditions, or, preferably, potassium *t*-butoxide in *t*-butanol with dry air or oxygen.

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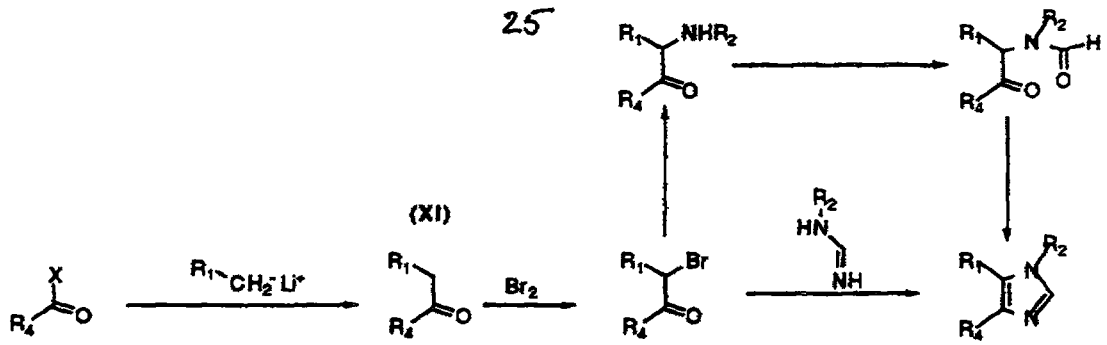
SCHEME II

In a further process, illustrated in Scheme III below, compounds of Formula (I) may be prepared by treating a compound of Formula (X) thermally or with the aid of a cyclising agent such as phosphorus oxychloride or phosphorus pentachloride (see Engel and Steglich, Liebigs Ann Chem, 1978, 1916 and Strzybny *et al.*, J Org Chem, 1963, 28, 3381). Compounds of Formula (X) may be obtained, for instance, by acylating the corresponding a-keto-amine with an activated formate derivative such as the corresponding anhydride, under standard acylating conditions followed by formation of the imine with R_2NH_2. The aminoketone may be derived from the parent ketone by oxamination and reduction and the requisite ketone may in turn be prepared by decarboxylation of the beta-ketoester obtained from the condensation of an aryl (heteroaryl) acetic ester with the R_1COX component.



SCHEME III

In Scheme IV illustrated below, two (2) different routes which use ketone (formula XI) for preparing a compound of Formula (I). A heterocyclic ketone (XI) is prepared by adding the anion of the alkyl heterocycle such as 4-methyl-quinoline (prepared by treatment thereof with an alkyl lithium, such as *n*-butyl lithium) to an N-alkyl-O-alkoxybenzamide, ester, or any other suitably activated derivative of the same oxidation state. Alternatively, the anion may be condensed with a benzaldehyde, to give an alcohol which is then oxidised to the ketone (XI).



SCHEME IV

In a further process, N-substituted compounds of Formula (I) may be prepared by treating the anion of an amide of Formula (XII):

$$R_1CH_2NR_2COH \qquad (XII)$$

wherein R_1 and R_2 with:

(a) a nitrile of the Formula (XIII):

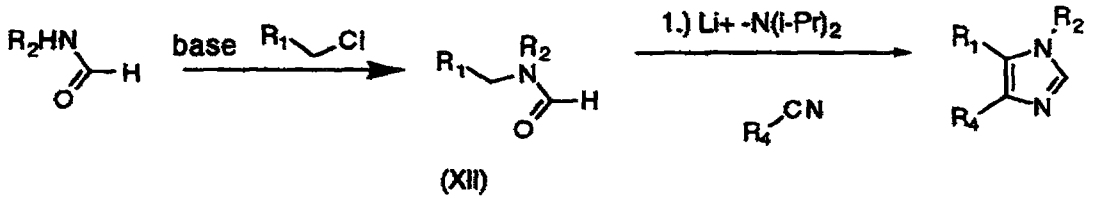
$$R_4CN \qquad (XIII)$$

wherein R_4 is as hereinbefore defined, or

(b) an excess of an acyl halide, for instance an acyl chloride, of the Formula (XIV):

$$R_4COHal \qquad (XIV)$$

wherein R_4 is as hereinbefore defined and Hal is halogen, or a corresponding anhydride, to give a *bis*-acylated intermediate which is then treated with a source of ammonia, such as ammonium acetate.



SCHEME V

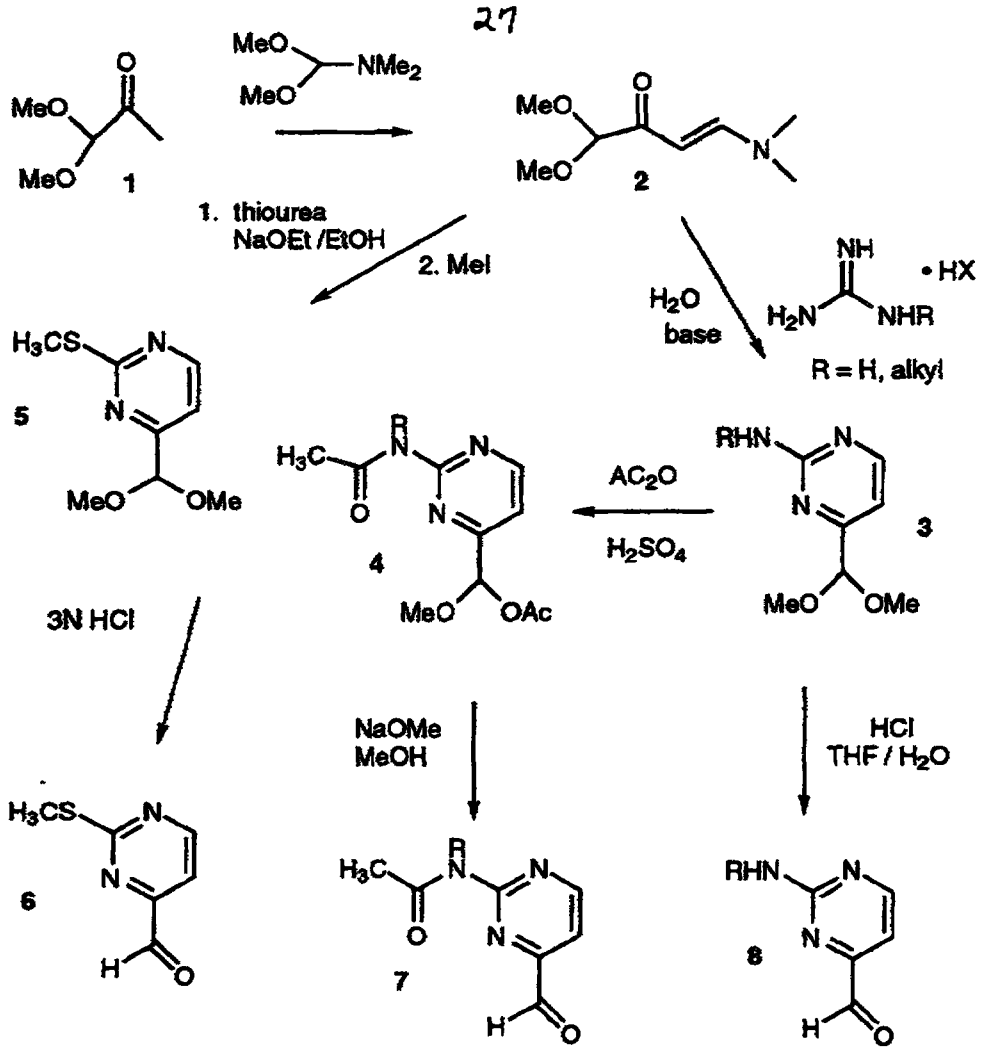
One variation of this approach is illustrated in Scheme V above. A primary amine (R_2NH_2) is treated with a halomethyl heterocycle of Formula R_1CH_2X to give the secondary amine which is then converted to the amide by standard techniques. Alternatively the amide may be prepared as illustrated in scheme V by alkylation of the formamide with R_1CH_2X. Deprotonation of this amide with a strong amide base, such as lithium di-*iso*-propyl amide or sodium *bis*-(trimethylsilyl)amide, followed by addition of an excess of an aroyl chloride yields the *bis*-acylated compound which is then closed to an imidazole compound of Formula (I), by heating in acetic acid

containing ammonium acetate. Alternatively, the anion of the amide may be reacted with a substituted aryl nitrile to produce the imidazole of Formula (I) directly.

The following description and schemes are further exemplification of the process as previously described above in Scheme I. Various pyrimidine aldehyde derivatives 6, 7 and 8 as depicted in scheme VI below, can be prepared by modification of the procedures of Bredereck et al. (*Chem. Ber.* **1964**, *97*, 3407) whose disclosure is incorporated by reference herein. These pyrimidine aldehydes are then utilized as intermediates in the synthesis as further described herein. The unprotected amino aldehyde derivative, e.g. 8, can be somewhat unstable. Use of an acetolysis procedure, as described in Scheme VI, wherein the aldehyde 7 is isolated as the acetamide derivative, (compound 3 is converted to 7, via the intermediate 4) and leads to a more stable compound for use in the cycloaddition reaction to make compounds of Formula (I).

General acetolysis conditions, for such a reaction are employed and are well known to those of skill in the art. Suitable conditions are exemplified, for instance in Example 83. In greater detail, the reaction employs heating the 2-amino pyrimidine dialkoxy acetal with acetic anhydride in the presence of a catalytic amount of concentrated sulfuric acid, which simultaneously acetylates the amine and leads to the exchange of one of the alkoxy groups for an acetoxy group. The resultant compound is converted to the aldehyde by deacetylation with a catalytic amount of an alkoxide salt and the corresponding alcohol solvent, e.g. Na+ methoxide and methanol. Alternatively, higher yields can be obtained by first acetylating the amine with acetic anhydride and then affecting exchange by subsequent addition of concentrated sulfuric acid.

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Scheme VI

The reaction of imines with tosylmethyl isonitriles was first reported by van Leusen (van Leusen, et al., *J. Org. Chem.* **1977**, *42*, 1153.) Reported were the following conditions: tert butyl amine(*t*BuNH$_2$) in dimethoxyethane (DME), K_2CO_3 in MeOH, and NaH in DME. Upon re-examination of these conditions each was found to produce low yields. The desired product for instance, 5-[(2-(1-methylamino)-pyrimidin-4-yl]-4-(4-fluorophenyl)-1-(1-methylpiperdin-4-yl)imidazole was isolated at yields less than 50%, using t-BuNH$_2$ in DME at room temperature, but a second pathway involving amine exchange to produce the t-butyl imine followed by reaction with the isocyanide 1 to produce the *t*Bu imidazole was also operating. This will likely occur using any primary amine as a base. The secondary amines, while not preferred may be used, but may also decompose the isonitrile slowly. Reactions will likely require about 3 equivalents of amine to go to completion, resulting in approximately 50% isolated yields. Hindered secondary amines (diisopropylamine) while usable are very slow and generally not too effective. Use of tertiary and aromatic amines, such as pyridine, and triethyl-

amine gave no reaction under certain test conditions, but more basic types such as DBU, and 4-dimethylamino pyridine (DMAP) while slow, did produce some yields and hence may be suitable for use herein.

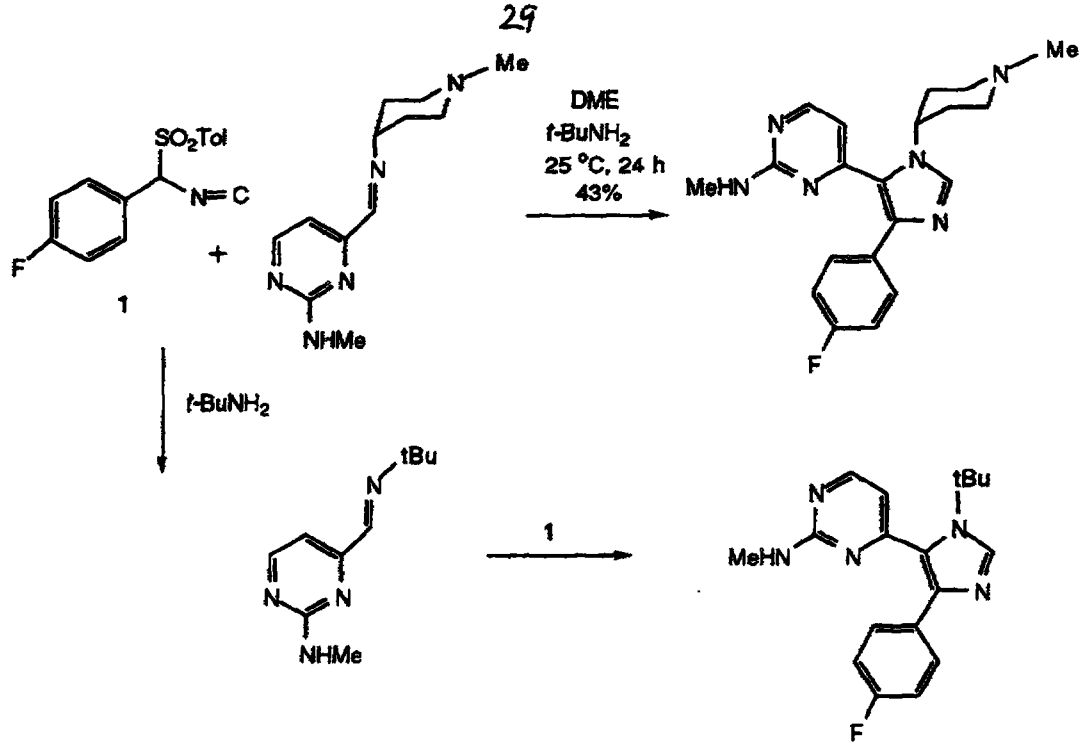
As depicted in Schemes VII and VIII below, the pyrimidine aldehydes of Scheme VI, can be condensed with a primary amine, to generate an imine, which may suitably be isolated or reacted in situ, with the desired isonitrile in the presence of a variety of suitable bases, and solvents as described herein to afford the 5-(4-pyrimidinyl)-imidazoles, wherein R_2 and R_4 are as defined herein for Formula (I) compounds.

One preferred method for preparing compounds of Formula (I) is shown below in Scheme VII. The imines, prepared and isolated in a separate step were often tars, which are hard to handle. The black color is also often carried over into the final product. The yield for making the imines varied, and environmentally less-acceptable solvents, such as CH_2Cl_2 were often used in their preparation.

This reaction, wherein p=2, requires a suitable base for the reaction to proceed. The reaction requires a base strong enough to deprotonate the isonitrile. Suitable bases include an amine, a carbonate, a hydride, or an alkyl or aryl lithium reagent; or mixtures thereof. Bases include, but are not limited to, potassium carbonate, sodium carbonate, primary and secondary amines, such as t-butylamine, diisopropyl amine, morpholine, piperidine, pyrrolidine, and other non-nucleophilic bases, such as DBU, DMAP and 1,4-diazabicyclo[2.2.2]octane (DABCO).

Suitable solvents for use herein, include but are not limited to N,N-dimethyl-formamide (DMF). MeCN, halogenated solvents, such as methylene chloride or chloroform, tetrahydrofuran (THF), dimethylsulfoxide (DMSO), alcohols, such as methanol or ethanol, benzene, toluene, DME, or EtOAc. Preferably the solvent is DMF, DME, THF, or MeCN, more preferably DMF. Product isolation may generally be accomplished by adding water and filtering the product as a clean compound.

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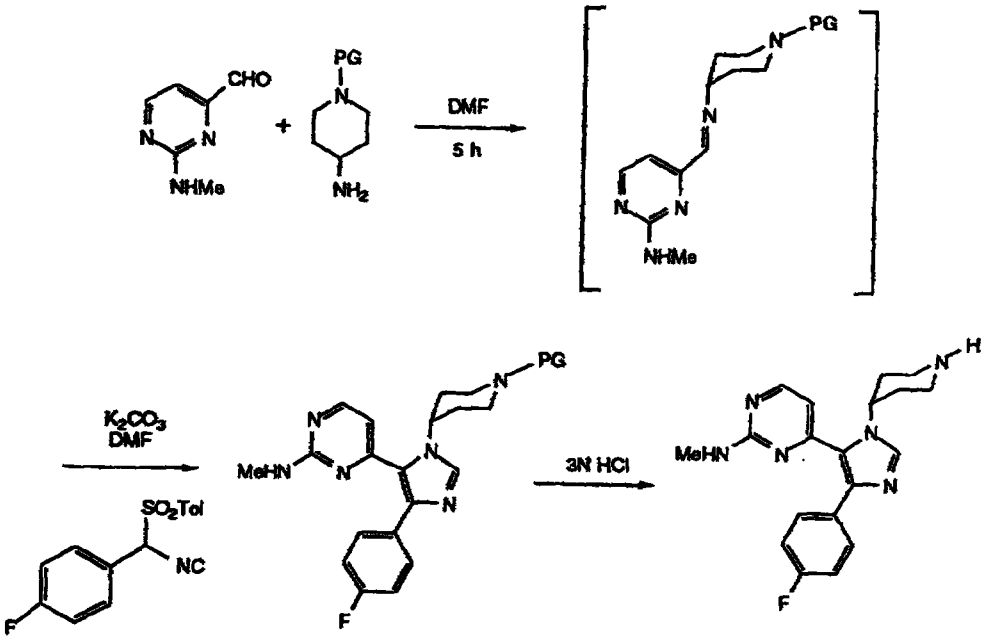
SCHEME VII

While not convenient for large scale work, addition of NaH, instead of t-bu lamine, to the isonitrile, perhaps with temperatures lower than 25°C (in THF) are needed. Additionally, BuLi has also been reported to be an effective base for tonating tosyl benzylisonitriles at -50°C. (DiSanto, R.; Costi, R.; Massa, S.; Artico, *th. Commun.* **1995**, *25*, 795).

Various temperature conditions may be utilized depending upon the preferred b. r instance, using $tBuNH_2$/DME and K_2CO_3/MeOH, reactions were tried at 0, ro perature, 40, about 64, and 80°C. At temperatures above 40°C, the yields may dro ut 20%, although not much difference has been seen between 0°C and room tem . Using K_2CO_3 in DMF, reactions were tried at 0°C and 25°C, with virtually no di e in product, quality or yield. Consequently, temperature ranges below 0°C , and at °C are contemplated as also being within the scope of this invention. Prefera temperature ranges are from about 0°C to about 25°C. For purposes herein, m mpature, which is depicted as 25°C, but it is recognized that this may vary from 20° °C.

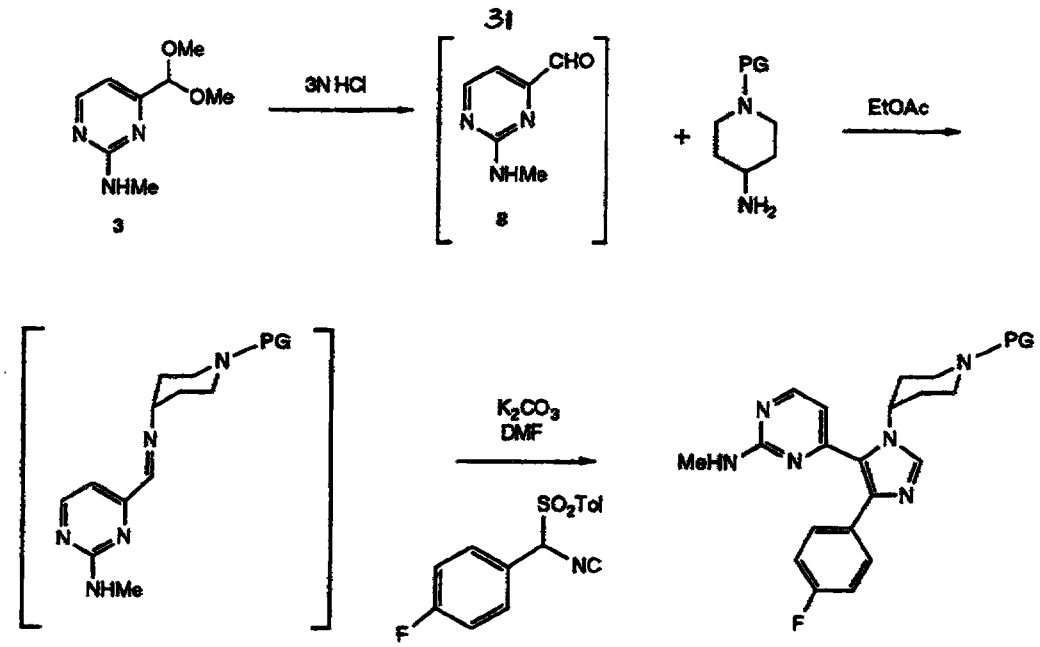
As shown in Scheme VIII below, the imine is preferably formed in situ in a solvent. This preferred synthesis, is a process which occurs as a one-pot synthesis. Suitably, when the primary amine is utilized as a salt, such as in the dihydrochloride salt in the Examples, the reaction may further include a base, such as potassium carbonate prior to the addition of the isonitrile. Alternatively, the piperidine nitrogen may be required to be protected (PG) as shown below, suitably the PG is BOC or C(O)2R,

wherein R is preferably alkyl, aryl, arylalkyl moieties well known to those skilled in the art. Reaction conditions, such as solvents, bases, temperatures, etc. are similar to those illustrated and discussed above for the isolated imine as shown in Scheme VII. One skilled in the art would readily recognize that under some circumstances, the in situ formation of the imine may require dehydrating conditions, or may require acid catalysis.



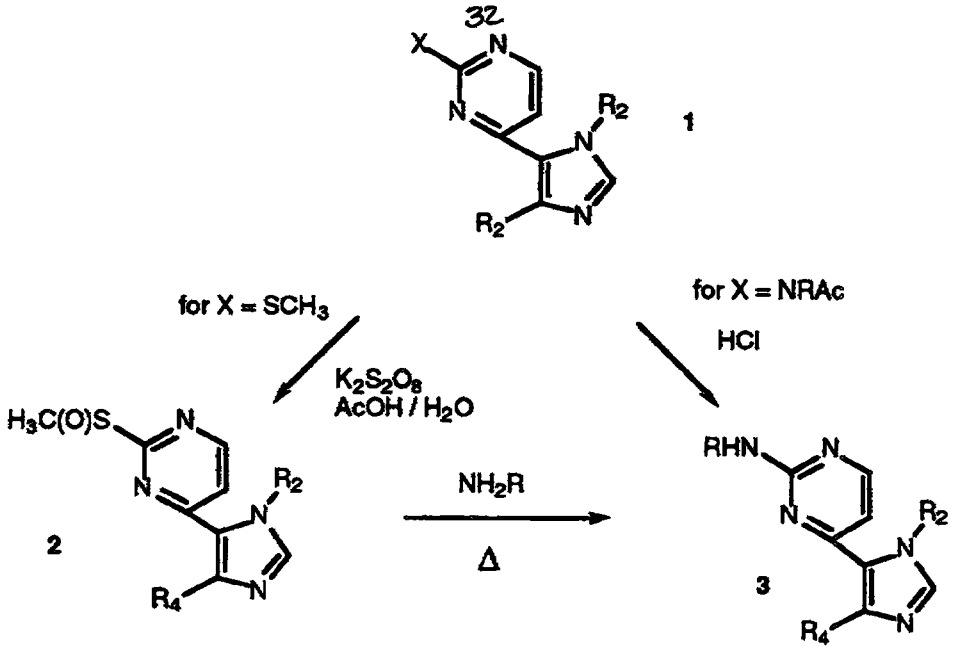
SCHEME VIII

Another method for preparing compounds of Formula (I) is shown below in Scheme VIIIa. To avoid the difficulty associated with isolating the pyrimidine aldehyde 8, it is possible to hydrolyze the acetal 3 to aldehyde 8 as described in Example 3, part b. The aldehyde 8, formed in situ, can be treated sequentially with a primary amine, ethyl acetate, and $NaHCO_3$ to form the corresponding imine in situ, which is extracted into the ethyl acetate. Addition of the isonitrile, a carbonate base and DMF allows for the formation of the 5-(4-pyrimidinyl)-imidazoles, wherein R_2 and R_4 are as defined herein for Formula (A) compounds.



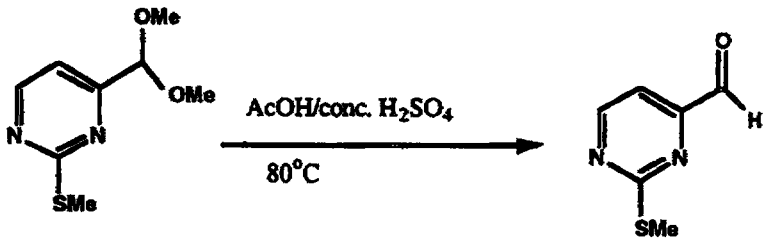
SCHEME VIIIa

The preferred method of synthesis for compounds of Formula (I) also provides for a suitable and reliable method for introduction of an $S(O)_m$alkyl moiety on the pyrimidine (R_1 group) by using, for instance, the 2-methylthio pyrimidine aldehyde derivative, as is described in the Examples section. In scheme IX below, compound 1 (X = S methyl), while a final product may also be used as a precursor, as previously noted to make further compounds of formula (I). In this particular instance the methylthio moiety is oxidized to the methyl sulfinyl moiety which may additionally be further modified to a substituted amino group.



Scheme IX

Another embodiment of the present invention is the novel hydrolysis of 2-thiomethyl-pyrimidine acetal to 2-thiomethylpyrimidine aldehyde, as shown in Scheme X below. Hydrolysis of the acetal to aldehyde using various known reaction conditions, such as formic acid, did not produce a satisfactory yield of the aldehyde, <13% was obtained. One method of synthesis involves the use of AcOH (fresh) as solvent and concentrated H_2SO_4 under heating conditions, preferably a catalytic amount of sulfuric acid. Heating conditions include temperatures from about 60° to 85°C, preferably from about 70° to about 80°C as higher temperatures show a darkening of the reaction mixture. After the reaction is completeed the mixture is cooled to about room temperature and the acetic acid is removed. A more preferred procedure involves heating the acetal in 3N HCL at 40°C for 18 hours, cooling and extracting the bicarbonate neutralized solution into EtOAc. Examples of these two procedures are described herein as Examples 6b and 25.



Scheme X

The final 2-aminopyrimidin-4-yl imidazole compounds of Formula (I), as well as similar pyridine containing compounds can be prepared by one of three methods: 1) direct reaction of the 2-aminopyrimidine imine with the isonitrile; 2) condensation of the 2-acetamidopyrimidine imine with the isonitrile followed by removal of the acetamido group; and 3) oxidation of the 2-methylthiopyrimidine derivative to the corresponding sulfoxide followed by displacement with the desired amine.

While these schemes herein are presented, for instance, with an optionally substituted piperidine moiety for the resultant R_2 position, or a 4-fluoro phenyl for R_4, any suitable R_2 moiety or R_4 moiety may be added in this manner if it can be prepared on the primary amine. Similarly, any suitable R_4 can be added via the isonitrile route.

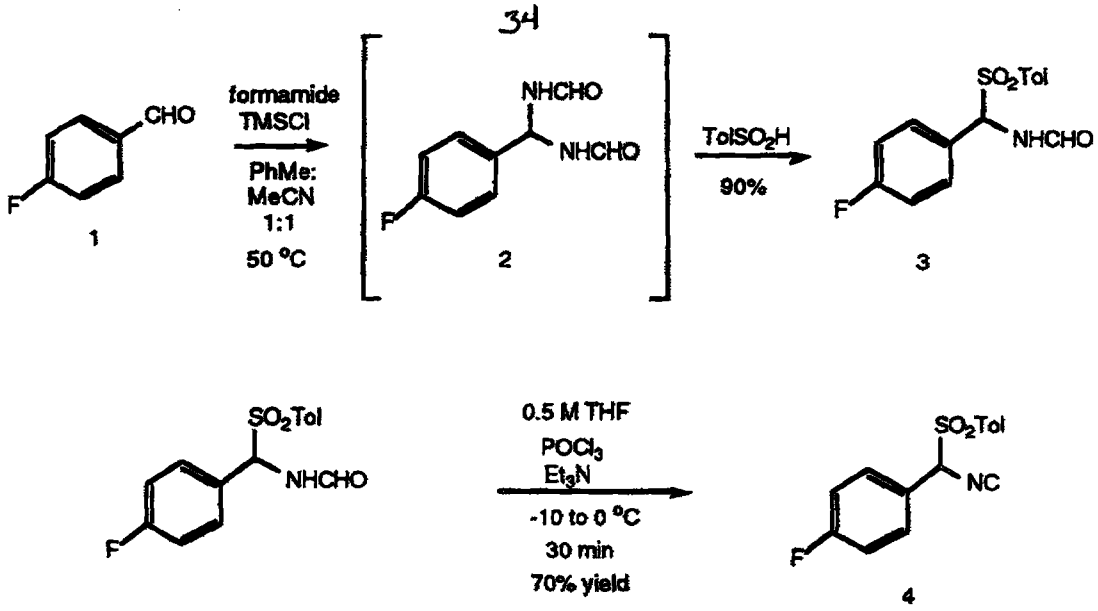
The compounds of Formula (IIa), in Scheme I, may be prepared by the methods of van Leusen et al., supra. For example a compound of the Formula (IIa) may be prepared by dehydrating a compound of the Formula (IV)-Scheme I, wherein Ar, R_4 and p are as defined herein.

Suitable dehydrating agents include phosphorus oxychloride, oxalyl chloride, thionyl chloride, phosgene, or tosyl chloride in the presence of a suitable base such as triethylamine or diisopropylethylamine, or similar bases, etc. such as pyridine. Suitable solvents are dimethoxy ether, tetrahydrofuran, or halogenated solvents, preferably THF. The reaction is most efficent when the reaction temperatures are kept between -10°C and 0°C. At lower temperatures incomplete reaction occurs and at higher temperatures, the solution turns dark and the product yield drops.

The compounds of formula (IV)-Scheme I may be prepared by reacting a compound of the formula (V)-Scheme I, R_4CHO where R_4 is as defined herein, with $ArS(0)_pH$ and formamide with or without water removal, preferably under dehydrating conditions, at ambient or elevated temperature e.g. 30° to 150°, conveniently at reflux, optionally in the presence of an acid catalyst. Alternatively trimethysilylchloride can be used in place of the acid catalyst. Examples of acid catalysts include camphor-10-sulphonic acid, formic acid, p-toluenesulphonic acid, hydrogen chloride or sulphuric acid.

An optimal method of making an isonitrile of Formula (IIa) is illustrated below, in Scheme XI, and in the Examples section, Example 10 herein.

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SCHEME XI

The conversion of the substituted aldehyde to the tosylbenzyl formamide may be accomplished by heating the aldehyde, 1-Scheme XI, with an acid, such as p-toluene-sulfonic acid, formic acid or camphorsulfonic acid; with formamide and p-toluene-sulfinic acid [under reaction conditions of about 60°C for about 24 hours]. Preferably, no solvent is used. The reaction, may give poor yields (< 30%) when solvents, such as DMF, DMSO, toluene, acetonitrile, or excess formamide are used. Temperatures less than 60°C are generally poor at producing the desired product, and temperatures in excess of 60°C may produce a product which decomposes, or obtain a benzylic bis-formamide 2- Scheme XI. In Example 23 (a), described in WO 95/02591, Adams et al., synthesizes 4-Fluorophenyl-tosylmethylformamide, a compound of Formula (IV) -Scheme I, wherein p = 2. This procedure differs from that presently described herein in Example 10 by the following conditions, using the sodium salt of toluene sulfinic acid, neat which process results in uneven heating, lower yields and lower reproduceability then the present invention, as described herein which uses sulfinic acid and allows for use of non-aqueous conditions.

Conditions for making α-(p-Toluenesulfonyl)-4-fluorobenzylisonitrileas described in Example 23 (b), of WO 95/02591, Adams et al., used as a solvent MeCl to extract the product and DME as solvent. The present invention improves upon this process by utiizing less expensive solvents, such as THF and EtOAc to extract. Further higher yields are obtained by recrystalizing with an alcohol, such as 1-propanol, although other alcohols, such as methanol, ethanol and butanols are acceptable. Previously, the compound was partially purifed using chromatography techniques, and hazardous solvents for additional purifications.

Another embodiment of the present invention is the synthesis of the tosyl benzyl formamide compound, achieved by reacting the bisformamide intermediate 2- Scheme XI with p-toluenesulfinic acid. In this preferred route, preparation of the bis-formamide from the aldehyde is accomplished by heating the aldehyde with formamide, in a suitable solvent with acid catalysis. Suitable solvents are toluene, acetonitrile, DMF, and DMSO or mixtures thereof. Acid catalysts, are those well known in the art, and include but are not limited to hydrogen chloride, p-toluenesulfonic acid, camphorsulfonic acid, and other anhydrous acids. The reaction can be conducted at temperatures ranging from about 25°C to 110°C, preferably about 50°C, suitably for about 4 to about 5 hours, longer reaction times are also acceptable. Product decomposition and lower yields may be observed at higher temperatures (>70°C) at prolonged reactions times. Complete conversion of the product generally requires water removal from the reaction mixture.

Preferred conditions for converting a bis-formamide derivative to the tosyl benzyl formamide are accomplished by heating the bisformamide in a suitable solvent with an acid catalyst and p-toluenesulfinic acid. Solvents for use in this reaction include but are not limited to toluene, and acetonitrile or mixtures thereof. Additional mixtures of these solvents with DMF, or DMSO may also be used but may result in lower yields. Temperatures may range from about 30°C to about 100°C. Temperatures lower than 40°C and higher than 60°C are not preferred as the yield and rate decreases. Preferably the range is from about 40° to 60°C, most preferably about 50°C. The optimal time is about 4 to 5 hours, although it may be longer. Preferably, acids used include but are not limited to, toluenesulfonic acid, camphorsulfonic acid, and hydrogen chloride and other anhydrous acids. Most preferably the bisformamide is heated in toluene:acetonitrile in a 1:1 ratio, with p-toluenesulfinic acid and hydrogen chloride.

Another embodiment of the present invention is the preferred synthetic route for synthesis of the tosylbenzyl formamide compound which is accomplished using a one-pot procedure. This process first converts the aldehyde to the bis-formamide derivative and subsequently reacts the bis-formamide derivative with toluenesulfinic acid. This procedure combines the optimized conditions into a single, efficient process. High yields, >90% of the aryl (tosyl) benzylformamide may be obtained in such a manner.

Preferred reaction conditions employ a catalyst, such as trimethylsilyl chloride (TMSCl), in a preferred solvent, toluene:acetonitrile, preferably in a 1:1 ratio. A reagent, such as TMSCl , is preferred which reacts with water produced therein and at the same time produces hydrogen chloride to catalyze the reaction. Also preferred is use of hydrogen chloride and p-toluenesulfonic acid. Therefore, three suitable reaction conditions for use herein include 1) use of a dehydrating agent which also provides hydrogen chloride, such as TMSCl or p-toluene sulfinic acid: or by 2) use of a suitable dehydrating agent and a suitable source of acid source, such as but not limited to,

camphorsulfonic acid, hydrogen chloride or p-toluenesulfonic acid; and 3) alternative dehydrating conditions, such as the azeotropic removal of water, and using an acid catalyst and p-toluene sulfinic acid.

Compounds of the formula (IIa) where p is 2 may also be prepared by reacting in the presence of a strong base a compound of the formula (VI) -Scheme I, R_4CH_2NC with a compound of the formula (VII)-Scheme I, $ArSO_2L_1$ wherein R_4 and Ar are as defined herein and L_1 is a leaving group such as halo, e.g. fluoro. Suitable strong bases include, but are not limited to, alkyl lithiums such as butyl lithium or lithium diisopropylamide (Van Leusen et al., Tetrahedron Letters, No. 23, 2367-68 (1972)).

The compounds of formula (VI)-Scheme I may be prepared by reacting a compound of the formula (VIII)-Scheme I, $R_4CH_2NH_2$ with an alkyl formate (e.g. ethylformate) to yield an intermediate amide which can be converted to the desired isonitrile by reacting with well known dehydrating agent, such as but not limited to oxalyl chloride, phosphorus oxychloride or tosyl chloride in the presence of a suitable base such as triethylamine.

Alternatively a compound of the formula (VIII) - Scheme I may be converted to a compound of the formula (VI)- Scheme I by reaction with chloroform and sodium hydroxide in aqueous dichloromethane under phase transfer catalysis.

The compounds of the formula (III) - Scheme I may be prepared by reacting a compound of the formula R_1CHO with a primary amine R_2NH_2.

The amino compounds of the formula (VIII) - Scheme I are known or can be prepared from the corresponding alcohols, oximes or amides using standard functional group interconversions.

Suitable protecting groups for use with hydroxyl groups and the imidazole nitrogen are well known in the art and described in many references, for instance, Protecting Groups in Organic Synthesis, Greene T W, Wiley-Interscience, New York, 1981. Suitable examples of hydroxyl protecting groups include silyl ethers, such as t-butyldimethyl or t-butyldiphenyl, and alkyl ethers, such as methyl connected by an alkyl chain of variable link, $(CR_{10}R_{20})_n$. Suitable examples of imidazole nitrogen protecting groups include tetrahydropyranyl.

Pharmaceutically acid addition salts of compounds of Formula (I) may be obtained in known manner, for example, by treatment thereof with an appropriate amount of acid in the presence of a suitable solvent.

METHODS OF TREATMENT

The compounds of Formula (I) or (II) or a pharmaceutically acceptable salt thereof can be used in the manufacture of a medicament for the prophylactic or

therapeutic treatment of any disease state in a human, or other mammal, which is exacerbated or caused by excessive or unregulated cytokine production by such mammal's cell, such as but not limited to monocytes and/or macrophages.

Compounds of Formula (I) or (II) are capable of inhibiting proinflammatory cytokines, such as IL-1, IL-6, IL-8 and TNF and are therefore of use in therapy. IL-1, IL-6, IL-8 and TNF affect a wide variety of cells and tissues and these cytokines, as well as other leukocyte-derived cytokines, are important and critical inflammatory mediators of a wide variety of disease states and conditions. The inhibition of these pro-inflammatory cytokines is of benefit in controlling, reducing and alleviating many of these disease states.

Accordingly, the present invention provides a method of treating a cytokine-mediated disease which comprises administering an effective cytokine-interfering amount of a compound of Formula (I) or (II) or a pharmaceutically acceptable salt thereof.

In particular, compounds of Formula (I) or (II) or a pharmaceutically acceptable salt thereof are of use in the prophylaxis or therapy of any disease state in a human, or other mammal, which is exacerbated by or caused by excessive or unregulated IL-1, IL-8 or TNF production by such mammal's cell, such as, but not limited to, monocytes and/or macrophages.

Another aspect of the present invention are wherein compounds of Formula (A), Formula (I) and Formula (II) are capable of inhibiting inducible proinflammatory proteins, such as COX-2, also referred to by many other names such as prostaglandin endoperoxide synthase-2 (PGHS-2) and are therefore of use in therapy. These proinflammatory lipid mediators of the cyclooxygenase (CO) pathway are produced by the inducible COX-2 enzyme. Regulation, therefore of COX-2 which is responsible for the these products derived from arachidonic acid, such as prostaglandins affect a wide variety of cells and tissues are important and critical inflammatory mediators of a wide variety of disease states and conditions. Expression of COX-1 is not effected by compounds of Formula (I). This selective inhibition of COX-2 may alleviate or spare ulcerogenic liability associated with inhibition of COX-1 thereby inhibiting prostoglandins essential for cytoprotective effects. Thus inhibition of these pro-inflammatory mediators is of benefit in controlling, reducing and alleviating many of these disease states. Most notably these inflammatory mediators, in particular prostaglandins, have been implicated in pain, such as in the sensitization of pain receptors, or edema. This aspect of pain management therefore includes treatment of neuromuscular pain, headache, cancer pain, and arthritis pain. Compounds of Formula (I) or a pharmaceutically acceptable salt thereof, are of use in the prophylaxis or therapy in a human, or other mammal, by inhibition of the synthesis of the COX-2 enzyme.

Accordingly, the present invention provides a method of inhibiting the synthesis of COX-2 which comprises administering an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof. The present invention also provides for a method of prophylaxis treatment in a human, or other mammal, by inhibition of the synthesis of the COX-2 enzyme.

Accordingly, in another aspect, this invention relates to a method of inhibiting the production of IL-1 in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of Formula (I) or (II) or a pharmaceutically acceptable salt thereof.

There are many disease states in which excessive or unregulated IL-1 production is implicated in exacerbating and/or causing the disease. These include rheumatoid arthritis, osteoarthritis, stroke, endotoxemia and/or toxic shock syndrome, other acute or chronic inflammatory disease states such as the inflammatory reaction induced by endotoxin or inflammatory bowel disease, tuberculosis, atherosclerosis, muscle degeneration, multiple sclerosis, cachexia, bone resorption, psoriatic arthritis, Reiter's syndrome, rheumatoid arthritis, gout, traumatic arthritis, rubella arthritis and acute synovitis. Recent evidence also links IL-1 activity to diabetes, pancreatic ß cells and Alzheimer's disease.

In a further aspect, this invention relates to a method of inhibiting the production of TNF in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of Formula (I) or (II) or a pharmaceutically acceptable salt thereof.

Excessive or unregulated TNF production has been implicated in mediating or exacerbating a number of diseases including rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions, sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, stroke, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoisosis, bone resorption diseases, such as osteoporosis, reperfusion injury, graft vs. host reaction, allograft rejections, fever and myalgias due to infection, such as influenza, cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome (AIDS), AIDS, ARC (AIDS related complex), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis and pyresis.

Compounds of Formula (I) are also useful in the treatment of viral infections, where such viruses are sensitive to upregulation by TNF or will elicit TNF production *in vivo*. The viruses contemplated for treatment herein are those that produce TNF as a result of infection, or those which are sensitive to inhibition, such as by decreased replication, directly or indirectly, by the TNF inhibiting-compounds of Formula (I) or (II). Such viruses include, but are not limited to HIV-1, HIV-2 and HIV-3,

Cytomegalovirus (CMV), Influenza, adenovirus and the Herpes group of viruses, such as but not limited to, Herpes Zoster and Herpes Simplex. Accordingly, in a further aspect, this invention relates to a method of treating a mammal afflicted with a human immunodeficiency virus (HIV) which comprises administering to such mammal an effective TNF inhibiting amount of a compound of Formula (I) or (II) or a pharmaceutically acceptable salt thereof.

Compounds of Formula (I) or (II) may also be used in association with the veterinary treatment of mammals, other than in humans, in need of inhibition of TNF production. TNF mediated diseases for treatment, therapeutically or prophylactically, in animals include disease states such as those noted above, but in particular viral infections. Examples of such viruses include, but are not limited to, lentivirus infections such as, equine infectious anaemia virus, caprine arthritis virus, visna virus, or maedi virus or retrovirus infections, such as but not limited to feline immunodeficiency virus (FIV), bovine immunodeficiency virus, or canine immunodeficiency virus or other retroviral infections.

The compounds of Formula (I) or (II) may also be used topically in the treatment or prophylaxis of topical disease states mediated by or exacerbated by excessive cytokine production, such as by IL-1 or TNF respectively, such as inflamed joints, eczema, psoriasis and other inflammatory skin conditions such as sunburn; inflammatory eye conditions including conjunctivitis; pyresis, pain and other conditions associated with inflammation.

Compounds of Formula (I) or (II) have also been shown to inhibit the production of IL-8 (Interleukin-8, NAP). Accordingly, in a further aspect, this invention relates to a method of inhibiting the production of IL-8 in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

There are many disease states in which excessive or unregulated IL-8 production is implicated in exacerbating and/or causing the disease. These diseases are characterized by massive neutrophil infiltration such as, psoriasis, inflammatory bowel disease, asthma, cardiac and renal reperfusion injury, adult respiratory distress syndrome, thrombosis and glomerulonephritis. All of these diseases are associated with increased IL-8 production which is responsible for the chemotaxis of neutrophils into the inflammatory site. In contrast to other inflammatory cytokines (IL-1, TNF, and IL-6), IL-8 has the unique property of promoting neutrophil chemotaxis and activation. Therefore, the inhibition of IL-8 production would lead to a direct reduction in the neutrophil infiltration.

The compounds of Formula (I) or (II) are administered in an amount sufficient to inhibit cytokine, in particular IL-1, IL-6, IL-8 or TNF, production such that it is regulated down to normal levels, or in some case to subnormal levels, so as to

ameliorate or prevent the disease state. Abnormal levels of IL-1, IL-6, IL-8 or TNF, for instance in the context of the present invention, constitute: (i) levels of free (not cell bound) IL-1, IL-6, IL-8 or TNF greater than or equal to 1 picogram per ml; (ii) any cell associated IL-1, IL-6, IL-8 or TNF; or (iii) the presence of IL-1, IL-6, IL-8 or TNF mRNA above basal levels in cells or tissues in which IL-1, IL-6, IL-8 or TNF, respectively, is produced.

The discovery that the compounds of Formula (I) or (II) are inhibitors of cytokines, specifically IL-1, IL-6, IL-8 and TNF is based upon the effects of the compounds of Formulas (I) on the production of the IL-1, IL-8 and TNF in *in vitro* assays which are described herein.

As used herein, the term "inhibiting the production of IL-1 (IL-6, IL-8 or TNF)" refers to:

a) a decrease of excessive *in vivo* levels of the cytokine (IL-1, IL-6, IL-8 or TNF) in a human to normal or sub-normal levels by inhibition of the *in vivo* release of the cytokine by all cells, including but not limited to monocytes or macrophages;

b) a down regulation, at the genomic level, of excessive *in vivo* levels of the cytokine (IL-1, IL-6, IL-8 or TNF) in a human to normal or sub-normal levels;

c) a down regulation, by inhibition of the direct synthesis of the cytokine (IL-1, IL-6, IL-8 or TNF) as a postranslational event; or

d) a down regulation, at the translational level, of excessive *in vivo* levels of the cytokine (IL-1, IL-6, IL-8 or TNF) in a human to normal or sub-normal levels.

As used herein, the term "TNF mediated disease or disease state" refers to any and all disease states in which TNF plays a role, either by production of TNF itself, or by TNF causing another monokine to be released, such as but not limited to IL-1, IL-6 or IL-8. A disease state in which, for instance, IL-1 is a major component, and whose production or action, is exacerbated or secreted in response to TNF, would therefore be considered a disease stated mediated by TNF.

As used herein, the term "cytokine" refers to any secreted polypeptide that affects the functions of cells and is a molecule which modulates interactions between cells in the immune, inflammatory or hematopoietic response. A cytokine includes, but is not limited to, monokines and lymphokines, regardless of which cells produce them. For instance, a monokine is generally referred to as being produced and secreted by a mononuclear cell, such as a macrophage and/or monocyte. Many other cells however also produce monokines, such as natural killer cells, fibroblasts, basophils, neutrophils, endothelial cells, brain astrocytes, bone marrow stromal cells, epideral keratinocytes and B-lymphocytes. Lymphokines are generally referred to as being produced by lymphocyte cells. Examples of cytokines include, but are not limited to, Interleukin-1 (IL-1), Interleukin-6 (IL-6), Interleukin-8 (IL-8), Tumor Necrosis Factor-alpha (TNF-α) and Tumor Necrosis Factor beta (TNF-ß).

As used herein, the term "cytokine interfering" or "cytokine suppressive amount" refers to an effective amount of a compound of Formula (I) or (II) which will cause a decrease in the *in vivo* levels of the cytokine to normal or sub-normal levels, when given to a patient for the prophylaxis or treatment of a disease state which is exacerbated by, or caused by, excessive or unregulated cytokine production.

As used herein, the cytokine referred to in the phrase "inhibition of a cytokine, for use in the treatment of a HIV-infected human" is a cytokine which is implicated in (a) the initiation and/or maintenance of T cell activation and/or activated T cell-mediated HIV gene expression and/or replication and/or (b) any cytokine-mediated disease associated problem such as cachexia or muscle degeneration.

As TNF-ß (also known as lymphotoxin) has close structural homology with TNF-α (also known as cachectin) and since each induces similar biologic responses and binds to the same cellular receptor, both TNF-a and TNF-ß are inhibited by the compounds of the present invention and thus are herein referred to collectively as "TNF" unless specifically delineated otherwise.

A new member of the MAP kinase family, alternatively termed CSBP, p38, or RK, has been identified independently by several laboratories recently. Activation of this novel protein kinase via dual phosphorylation has been observed in different cell systems upon stimulation by a wide spectrum of stimuli, such as physicochemical stress and treatment with lipopolysaccharide or proinflammatory cytokines such as interleukin-1 and tumor necrosis factor. The cytokine biosynthesis inhibitors, of the present invention, compounds of Formula (I), (II) and (A), have been determined to be potent and selective inhibitors of CSBP/p38/RK kinase activity. These inhibitors are of aid in determining the signaling pathways involvement in inflammatory responses. In particular, for the first time a definitive signal transduction pathway can be prescribed to the action of lipopolysaccharide in cytokine production in macrophages.

The cytokine inhibitors were subsequently tested in a number of animal models for anti-inflammatory activity. Model systems were chosen that were relatively insensitive to cyclooxygenase inhibitors in order to reveal the unique activities of cytokine suppressive agents. The inhibitors exhibited significant activity in many such in vivo studies. Most notable are its effectiveness in the collagen-induced arthritis model and inhibition of TNF production in the endotoxic shock model. In the latter study, the reduction in plasma level of TNF correlated with survival and protection from endotoxic shock related mortality. Also of great importance are the compounds effectiveness in inhibiting bone resorption in a rat fetal long bone organ culture system. Griswold et al., (1988) *Arthritis Rheum.* **31**:1406-1412; Badger, et al., (1989) *Circ. Shock* **27**, 51-61; Votta et al., (1994)*in vitro. Bone* **15**, 533-538; Leeet al., (1993). B *Ann. N. Y. Acad. Sci.* **696**, 149-170.

In order to use a compound of Formula (I), (II) or (A) or a pharmaceutically acceptable salt thereof in therapy, it will normally be Formulated into a pharmaceutical composition in accordance with standard pharmaceutical practice. This invention, therefore, also relates to a pharmaceutical composition comprising an effective, non-toxic amount of a compound of Formula (I) or (II) and a pharmaceutically acceptable carrier or diluent. For purposes herein, in the Method of Treatment section, compounds of Formula (II) and (A) are included in and represented by use of the term Formula (I).

Compounds of Formula (I), pharmaceutically acceptable salts thereof and pharmaceutical compositions incorporating such may conveniently be administered by any of the routes conventionally used for drug administration, for instance, orally, topically, parenterally or by inhalation. The compounds of Formula (I) may be administered in conventional dosage forms prepared by combining a compound of Formula (I) with standard pharmaceutical carriers according to conventional procedures. The compounds of Formula (I) may also be administered in conventional dosages in combination with a known, second therapeutically active compound. These procedures may involve mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation. It will be appreciated that the form and character of the pharmaceutically acceptable character or diluent is dictated by the amount of active ingredient with which it is to be combined, the route of administration and other well-known variables. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the Formulation and not deleterious to the recipient thereof.

The pharmaceutical carrier employed may be, for example, either a solid or liquid. Exemplary of solid carriers are lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid and the like. Exemplary of liquid carriers are syrup, peanut oil, olive oil, water and the like. Similarly, the carrier or diluent may include time delay material well known to the art, such as glyceryl mono-stearate or glyceryl distearate alone or with a wax.

A wide variety of pharmaceutical forms can be employed. Thus, if a solid carrier is used, the preparation can be tableted, placed in a hard gelatin capsule in powder or pellet form or in the form of a troche or lozenge. The amount of solid carrier will vary widely but preferably will be from about 25mg. to about 1g. When a liquid carrier is used, the preparation will be in the form of a syrup, emulsion, soft gelatin capsule, sterile injectable liquid such as an ampule or nonaqueous liquid suspension.

Compounds of Formula (I) may be administered topically, that is by non-systemic administration. This includes the application of a compound of Formula (I)

externally to the epidermis or the buccal cavity and the instillation of such a compound into the ear, eye and nose, such that the compound does not significantly enter the blood stream. In contrast, systemic administration refers to oral, intravenous, intraperitoneal and intramuscular administration.

Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin to the site of inflammation such as liniments, lotions, creams, ointments or pastes, and drops suitable for administration to the eye, ear or nose. The active ingredient may comprise, for topical administration, from 0.001% to 10% w/w, for instance from 1% to 2% by weight of the Formulation. It may however comprise as much as 10% w/w but preferably will comprise less than 5% w/w, more preferably from 0.1% to 1% w/w of the Formulation.

Lotions according to the present invention include those suitable for application to the skin or eye. An eye lotion may comprise a sterile aqueous solution optionally containing a bactericide and may be prepared by methods similar to those for the preparation of drops. Lotions or liniments for application to the skin may also include an agent to hasten drying and to cool the skin, such as an alcohol or acetone, and/or a moisturizer such as glycerol or an oil such as castor oil or arachis oil.

Creams, ointments or pastes according to the present invention are semi-solid Formulations of the active ingredient for external application. They may be made by mixing the active ingredient in finely-divided or powdered form, alone or in solution or suspension in an aqueous or non-aqueous fluid, with the aid of suitable machinery, with a greasy or non-greasy base. The base may comprise hydrocarbons such as hard, soft or liquid paraffin, glycerol, beeswax, a metallic soap; a mucilage; an oil of natural origin such as almond, corn, arachis, castor or olive oil; wool fat or its derivatives or a fatty acid such as steric or oleic acid together with an alcohol such as propylene glycol or a macrogel. The Formulation may incorporate any suitable surface active agent such as an anionic, cationic or non-ionic surfactant such as a sorbitan ester or a polyoxyethylene derivative thereof. Suspending agents such as natural gums, cellulose derivatives or inorganic materials such as silicaceous silicas, and other ingredients such as lanolin, may also be included.

Drops according to the present invention may comprise sterile aqueous or oily solutions or suspensions and may be prepared by dissolving the active ingredient in a suitable aqueous solution of a bactericidal and/or fungicidal agent and/or any other suitable preservative, and preferably including a surface active agent. The resulting solution may then be clarified by filtration, transferred to a suitable container which is then sealed and sterilized by autoclaving or maintaining at 98-100°C for half an hour. Alternatively, the solution may be sterilized by filtration and transferred to the container by an aseptic technique. Examples of bactericidal and fungicidal agents suitable for inclusion in the drops are phenylmercuric nitrate or acetate (0.002%), benzalkonium

chloride (0.01%) and chlorhexidine acetate (0.01%). Suitable solvents for the preparation of an oily solution include glycerol, diluted alcohol and propylene glycol.

Compounds of formula (I) may be administered parenterally, that is by intravenous, intramuscular, subcutaneous intranasal, intrarectal, intravaginal or intraperitoneal administration. The subcutaneous and intramuscular forms of parenteral administration are generally preferred. Appropriate dosage forms for such administration may be prepared by conventional techniques. Compounds of Formula (I) may also be administered by inhalation, that is by intranasal and oral inhalation administration. Appropriate dosage forms for such administration, such as an aerosol Formulation or a metered dose inhaler, may be prepared by conventional techniques.

For all methods of use disclosed herein for the compounds of Formula (I), the daily oral dosage regimen will preferably be from about 0.01 to about 30 mg/kg of total body weight, preferably from about 0.01 to 10 mg/kg, more preferably from about 0.01 mg to 5mg. The daily parenteral dosage regimen about 0.001 to about 30 mg/kg of total body weight, preferably from about 0.01 to about 10 mg/kg, and more preferably from about 0.01 mg to 5mg/kg. The daily topical dosage regimen will preferably be from 0.1 mg to 150 mg, administered one to four, preferably two or three times daily. The daily inhalation dosage regimen will preferably be from about 0.01 mg/kg to about 1 mg/kg per day. It will also be recognized by one of skill in the art that the optimal quantity and spacing of individual dosages of a compound of Formula (I) or a pharmaceutically acceptable salt thereof will be determined by the nature and extent of the condition being treated, the form, route and site of administration, and the particular patient being treated, and that such optimums can be determined by conventional techniques. It will also be appreciated by one of skill in the art that the optimal course of treatment, i.e., the number of doses of a compound of Formula (I) or a pharmaceutically acceptable salt thereof given per day for a defined number of days, can be ascertained by those skilled in the art using conventional course of treatment determination tests.

The invention will now be described by reference to the following biological examples which are merely illustrative and are not to be construed as a limitation of the scope of the present invention.

BIOLOGICAL EXAMPLES

The cytokine-inhibiting effects of compounds of the present invention were determined by the following *in vitro* assays:

Interleukin - 1 (IL-1) : Human peripheral blood monocytes were isolated and purified from either fresh blood preparations from volunteer donors, or from blood bank buffy coats, according to the procedure of Colotta *et al*, J Immunol. **132**. 936 (1984). These monocytes ($1x10^6$) were plated in 24-well plates at a concentration of 1-

2 million/ml per well. The cells were allowed to adhere for 2 hours, after which time non-adherent cells were removed by gentle washing. Test compounds were then added to the cells for 1h before the addition of lipopolysaccharide (50 ng/ml), and the cultures were incubated at 37°C for an additional 24h. At the end of this period, culture supernatants were removed and clarified of cells and all debris. Culture supernatants were then immediately assayed for IL-1 biological activity, either by the method of Simon *et al.*, J. Immunol. Methods, **84**, 85, (1985) (based on ability of IL-1 to stimulate a Interleukin 2 producing cell line (EL-4) to secrete IL-2, in concert with A23187 ionophore) or the method of Lee *et al.*, J. ImmunoTherapy, **6** (1), 1-12 (1990) (ELISA assay). The compounds of Formula (I), as evidenced by Examples 1 to 24 were shown to be inhibitors of *in vitro* IL-1 produced by human monocytes.

Tumour Necrosis Factor (TNF): Human peripheral blood monocytes were isolated and purified from either blood bank buffy coats or plateletpheresis residues, according to the procedure of Colotta, R. *et al.*, J Immunol, **132**(2), 936 (1984). The monocytes were plated at a density of $1x10^6$ cells/ml medium/well in 24-well multi-dishes. The cells were allowed to adhere for 1 hour after which time the supernatant was aspirated and fresh medium (1ml, RPMI-1640, Whitaker Biomedical Products, Whitaker, CA) containing 1% fetal calf serum plus penicillin and streptomycin (10 units/ml) added. The cells were incubated for 45 minutes in the presence or absence of a test compound at 1nM-10mM dose ranges (compounds were solubilized in dimethyl sulfoxide/ethanol, such that the final solvent concentration in the culture medium was 0.5% dimethyl sulfoxide/0.5% ethanol). Bacterial lipopoly-saccharide (*E. coli* 055:B5 [LPS] from Sigma Chemicals Co.) was then added (100 ng/ml in 10 ml phosphate buffered saline) and cultures incubated for 16-18 hours at 37°C in a 5% CO_2 incubator. At the end of the incubation period, culture supernatants were removed from the cells, centrifuged at 3000 rpm to remove cell debris. The supernatant was then assayed for TNF activity using either a radio-immuno or an ELISA assay, as described in WO 92/10190 and by Becker *et al.*, J Immunol, 1991, **147**, 4307. The compounds of Formula (I), as evidenced by Examples 1 to 24 were shown to be inhibitors of *in vitro* TNF produced by human monocytes.

IL-1 and TNF inhibitory activity does not seem to correlate with the property of the compounds of Formula (I) in mediating arachidonic acid metabolism inhibition. Further the ability to inhibit production of prostaglandin and/or leukotriene synthesis, by nonsteroidal anti-inflammatory drugs with potent cyclooxygenase and/or lipoxygenase inhibitory activity does not mean that the compound will necessarily also inhibit TNF or IL-1 production, at non-toxic doses.

Interleukin -8 (IL-8): Primary human umbilical cord endothelial cells (HUVEC) (Cell Systems, Kirland, Wa) are maintained in culture medium supplemented with 15% fetal bovine serum and 1% CS-HBGF consisting of aFGF and heparin. The cells are then diluted 20-fold before being plated (250µl) into gelating coated 96-well plates. Prior to use, culture medium are replaced with fresh medium (200µl). Buffer or test compound (25µl, at concentrations between 1 and 10µM) is then added to each well in quadruplicate wells and the plates incubated for 6h in a humidified incubator at 37°C in an atmosphere of 5% CO_2. At the end of the incubation period, supernatant is removed and assayed for IL-8 concentration using an IL-8 ELISA kit obtained from R&D Systems (Minneapolis, MN). All data is presented as mean value (ng/ml) of multiple samples based on the standard curve. IC_{50}'s where appropriate are generated by non-linear regression analysis.

Cytokine Specific Binding Protein Assay

A radiocompetitive binding assay was developed to provide a highly reproducible primary screen for structure-activity studies. This assay provides many advantages over the conventional bioassays which utilize freshly isolated human monocytes as a source of cytokines and ELISA assays to quantify them. Besides being a much more facile assay, the binding assay has been extensively validated to highly correlate with the results of the bioassay. A specific and reproducible cytokine inhibitor binding assay was developed using soluble cystosolic fraction from THP.1 cells and a radiolabeled compound. Patent Application USSN 08/123175 Lee et al., filed September 1993, USSN; Lee et al., PCT 94/10529 filed 16 September 1994 and Lee et al., *Nature* 300, n(72), 739-746 (Dec. 1994) whose disclosures are incorporated by reference herein in its entirety describes the above noted method for screening drugs to identify compounds which interact with and bind to the cytokine specific binding protein (hereinafter CSBP). However, for purposes herein the binding protein may be in isolated form in solution, or in immobilized form, or may be genetically engineered to be expressed on the surface of recombinant host cells such as in phage display system or as fusion proteins. Alternatively, whole cells or cytosolic fractions comprising the CSBP may be employed in the creening protocol. Regardless of the form of the binding protein, a plurality of compounds are contacted with the binding protein under conditions sufficient to form a compound/ binding protein complex and compound capable of forming, enhancing or interfering with said complexes are detected.

Representative final compounds of Formula (I), Examples 3 to 27 all demonstrated positive inhibitory activity, such as from a binding IC50 of about 0.18 to 5 micromolar, in this binding assay, except for Example 12 which compound was not tested.

Prostoglandin endoperoxide synthase-2 (PGHS-2) assay:

The following assay describes a method for determining the inhibitory effects of compounds of Formula (I) on human PGHS-2 protein expression in LPS stimulated human monocytes.

Method: Human peripheal blood monocytes were isolated from buffy coats by centrifugation through Ficoll and Percoll gradients. Cells were seeded at 2 X 10^6/well in 24 well plates and allowed to adhere for 1 hour in RPMI supplemented with 1% human AB serum, 20mM L-glutamine, Penicillin-Streptomycin and 10mM HEPES. Compounds were added at various concentrations and incubated at 37°C for 10 minutes. LPS was added at 50 ng/well (to induce enzyme expression) and incubated overnight at 37°C. The supernatant was removed and cells washed once in cold PBS. The cells were lysed in 100µl of cold lysis buffer(50mM Tris/HCl pH 7.5, 150mM NaCl, 1% NP40, 0.5% sodium deoxycholate, 0.1% SDS, 300ug/ml DNAse, 0.1% TRITON X-100, 1mM PMSF, 1mM leupeptin, 1mM pepstatin). The lysate was centrifuged (10,000 X g for 10 min. at 4°C) to remove debris and the soluble fraction was subjected to SDS PAGE. analysis (12% gel). Protein separated on the gel were transferred onto nitrocellulose membrane by electrophoretic means for 2 hours at 60 volts. The membrane was pretreated for one hour in PBS/0.1% Tween 20 with 5% non-fat dry milk. After washing 3 times in PBS/Tween buffer, the membrane was incubated with a 1:2000 dilution of a monospecific antiserum to PGHS-2 or a 1:1000 dilution of an antiserum to PGHs-1 in PBS/Tween with 1% BSA for one hour with continuous shaking. The membrane was washed 3X in PBS/Tween and then incubated with a 1:3000 dilution of horseradish peroxidase conjugated donkey antiserum to rabbit Ig (Amersham) in PBS/Tween with 1% BSA for one hour with continuous shaking. The membrane was then washed 3X in PBS/Tween and the ECL immunodetection system (Amersham) was used to detect the level of expression of prostaglandin endoperoxide synthases-2.

RESULTS: The following compounds were tested and found to be active (inhibited LPS induced PGHS-2 protein expression in rank order potency similar to that for inhibiting cytokine production as noted in assays indicated):
1-[3-(4-Morpholinyl)propyl]-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole, a representative compound of Formula (I);
6-(4-Fluorophenyl)-2,3-dihydro-5-(4-pyridinyl)imidazo[2,1-b]thiazole;
Dexamethasone

Several compounds were tested and found to be inactive (up to 10uM):
2-(4-Methylsulfinylphenyl)-3-(4-pyridyl)-6,7-dihydro-(5H)-pyrrolo[1,2-a]imidazole rolipram ; phenidone and NDGA. None of the compounds tested was found to inhibit PGHS-1 or cPLA2 protein levels in similar experiments.

SYNTHETIC EXAMPLES

The invention will now be described by reference to the following examples which are merely illustrative and are not to be construed as a limitation of the scope of the present invention. All temperatures are given in degrees centigrade, all solvents are highest available purity and all reactions run under anydrous conditions in an argon atmosphere unless otherwise indicated.

In the Examples, all temperatures are in degrees Centigrade (°C). Mass spectra were performed upon a VG Zab mass spectrometer using fast atom bombardment, unless otherwise indicated. ^{1}H-NMR (hereinafter "NMR") spectra were recorded at 250 MHz using a Bruker AM 250 or Am 400 spectrometer. Multiplicities indicated are: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet and br indicates a broad signal. Sat. indicates a saturated solution, eq indicates the proportion of a molar equivalent of reagent relative to the principal reactant. Flash chromatography is run over Merck Silica gel 60 (230 - 400 mesh).

Example 1

1-[3-(4-Morpholinyl)propyl]-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole

a) 4-fluorophenyl-tolylthiomethylformamide: A solution of p-fluorobenzaldehyde (13.1 milliliters (hereinafter mL), 122 millimoles (hereinafter mmol) thiocresol (16.64 grams (hereinafter g), 122 mmol), formamide (15.0 mL, 445 mmol), and toluene (300 mL) were combined and heated to toluene reflux with azeotropic removal of H_2O for 18 h. The cooled reaction was diluted with EtOAc (500 mL) and washed with satd aq Na_2CO_3(3 x 100 mL), satd aq NaCl (100 mL), dried (Na_2SO_4), and concentrated. The residue was triturated with petroleum ether, filtered and dried in vacuo to afford 28.50 g of the title compound as a white solid (85 %). melting point (hereinafter mp) = 119 - 120°.

b) 4-fluorophenyl-tolylthiomethylisocyanide: The compound of example 1(a) (25 g, 91 mmol) in CH_2Cl_2 (300 mL) was cooled to -30° and with mechanical stirring $POCl_3$ (11 mL, 110 mmol) was added dropwise followed by the dropwise addition of Et_3N (45 mL, 320 mmol) with the temperature maintained below -30°. Stirred at -30° for 30 min and 5° for 2 h, diluted with CH_2Cl_2 (300 mL) and washed with 5% aq Na_2CO_3 (3 x 100 mL), dried (Na_2SO_4) and concentrated to 500 mL. This solution was filtered through a 12 x 16 cm cylinder of silica in a large sintered glass funnel with CH_2Cl_2 to afford 12.5 g (53%) of purified isonitrile as a light brown, waxy solid. IR (CH_2Cl_2) 2130 cm^{-1}.

c) Pyridine-4-carboxaldehyde [4-Morpholinylprop-3-yl]imine: Pyridine-4-carboxaldehyde (2.14 g, 20 mmoL), 4-(3-aminopropyl)morpholine (2.88 g, 20 mmol), toluene (50 mL) and $MgSO_4$ (2 g) were combined and stirred under argon for 18 h. The $MgSO_4$ was filtered off and the filtrate was concentrated and the residue was

reconcentrated from CH_2Cl_2 to afford 4.52 g (97%) of the title compound as a yellow oil containing less than 5% of aldehyde based on ^1H NMR. ^1H NMR (CD_3Cl): d 8.69 (d, J = 4.5 Hz, 2H), 8.28 (s, 1H), 7.58 (d, J = 4.5 Hz, 2H), 3.84 (m, 6H), 2.44 (m, 6H), 1.91 (m, 2H).

d) 1-[3-(4-Morpholinyl)propyl]-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole The compound of example 1(b) (1.41 g, 5.5 mmol), and the compound of example 1(c) (1.17 g, 5.0 mmol) and CH_2Cl_2 (10 mL) were cooled to 5°C. 1.5.7-triazabicyclo-[4.4.0]dec-5-ene, henceforth referred to as TBD, (0.71 g 5.0 mmol) was added and the reaction was kept at 5°C for 16 h, diluted with EtOAc (80 mL) and washed with satd aq Na_2CO_3 (2 x 15 mL). The EtOAc was extracted with 1 N HCl (3 x 15 mL), and the acid phases were washed with EtOAc (2 x 25 mL), layered with EtOAc (25 mL) and made basic by the addition of solid K_2CO_3 til pH 8.0 and then 10% NaOH til pH 10. The phases were separated and the aq was extracted with additional EtOAc (3 x 25 mL). The extracts were dried (K_2CO_3) concentrated and the residue was crystalized from acetone/hexane to afford 0.94 g (51%) of the title compound. mp = 149 - 150°.

Example 2

5-(2-Aminopyrimidin-4-yl)-4-(4-fluorophenyl)-1-[3-(4-Morpholinyl)propyl] imidazole

a) 2-Aminopyrimidine-4-carboxaldehyde dimethyl acetal

Dimethylformamide dimethyl acetal (55 mL, 0.41 mol), and pyruvic aldehyde dimethyl acetal (50 mL, 0.41 mol) were combined and heated to 100° for 18 h. Methanol was removed in vacuo to afford an oil. A solution of NaOH (18 g, 0.45 mol) in H_2O (50 mL) was added to guanidine HCl (43 g, 0.45 mol) in H_2O (100 mL), and the resulting solution was added to the above described oil. The resulting mixture was stirred at 23° for 48 h. Filtration afforded 25g (50%) of the title compound.

b) 2-Aminopyrimidine-4-carboxaldehyde The compund of the previous step (1.69 g, 10 mmol) and 3N HCl (7.3 mL, 22 mmol) were combined and heated to 48° for 14h, cooled, layered with EtOAc (50 mL) and neutralized by the addition of $NaHCO_3$ (2.1g, 25 mmol) in small portions. The aq phase was extracted with EtOAc (5 x 50 mL) and the extracts were dried (Na_2SO_4)and concentrated to afford 0.793 g (64%) of the title compound.

c) 2-Aminopyrimidine-4-carboxaldehyde [3-(4-Morpholinyl)propyl]imine

The compound of the previous step and 4-(3-aminopropyl)morpholine were reacted by the procedure of example 1(c), above, to afford the title compound as a yellow oil.

d) 5-(2-Aminopyrimidin-4-yl)-4-(4-fluorophenyl)-1-[3-(4-Morpholinyl)-propyl] imidazole Following the procedure of example 1(d), above, except using the compound

of the previous step as the imine afforded the title compound as a white solid. ^{1}H NMR (CD_3Cl) δ 8.15(d, J = 5.4 Hz, 1H), 7.62(s,1H), 7.46 (dd, 2H), 7.00(t, J = 8.6Hz, 2H), 6.50(d, J = 5.4 Hz, 1H), 5.09(brd.s, 2H), 4.34(t, J = 7.0 Hz, 2H), 3.69(m, 4H), 2.35(brd.s,4H), 2.24(t, J = 4.6 Hz, 2H), 1.84(m, 2H).

Example 3

5-[4-(2-Methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-morpholino-3-propyl)imidazole

a) 2-Methylaminopyrimidine-4-dimethylacetal Sodium (3.27 g, 142 mmol) was dissolved in absolute ethanol (425 mL). 1-Methylguanidine hydrochloride (15.5 g, 142 mmol) was added and the resulting slurry was stirred for about 10 min. 1,1-Dimethoxy-2-oxo-4-dimethylamino-3-butene (142 mmol) dissolved in ethanol (20 mL) was added and the mixture was stirred at reflux for about 24 hours. The mixture was cooled and filtered. Ethanol was evaporated and the resulting residue was triturated with hot EtOAc. EtOAc washings were combined and solvent was evaporated to afford the title compound (23.5 g, 91% yield) as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 8.35 (d, J = 4.5 Hz, 1H), 6.74 (d, 1H), 5.10 (s, 1H), 3.40 (s, 6H), 3.00 (d, 3H).

b) 2-Methylaminopyrimidine-4-carboxaldehyde Following the procedure of Example 2 (b), above, except using the compound of the previous step (11.75 g, 64.6 mmol) afforded the title compound as a yellow foam (7.3 g, 82.7 % yield). ^{1}H NMR ($CDCl_3$): δ 9.85 (s, J = 4.5 Hz, 1H), 8.52 (s, 1H), 7.03 (d, 1H), 5.52 (s, 1H), 3.10 (d, 3H).

c) 5-[4-(2-Methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-N-morpholino-1-propyl)imidazole The compound of the previous step (5.0g, 36.5 mmol) and 4-(3-aminopropyl) morpholine (5.3 mL, 36.5 mmol) were stirred in CH_2Cl_2 (180 mL). After about 16 h the mixture was cooled to 0°C. Added were the compound of Example 1 (b) (11.3 g, 43.8 mmol) and TBD (8.4 g, 61.32 mmol). The mixture was let stand for about 3 days at about 5°C. The product filtered and triturated with hot EtOH to afford the title compound (6.06 g, 41.9% yield) as a pale yellow solid. mp = 203 - 305°C. ^{1}H NMR ($CDCl_3$/MeOD): δ 8.01 (d, J = 4.5 Hz, 1H), 7.60 (s, 1H), 7.37 (q, 2H), 6.95 (t, 2H), 6.29 (d, 1H), 4.32 (s, 1H), 3.63 (t, 4H), 3.57 (m, 2H), 2.95 (s, 3H). 2.33 (m, 4H), 2.23 (t, 2H), 1.82 (t, 2H).

Example 4

5-[4-(2-Methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(1-methyl-piperidin-4-yl)imidazole

a) The compounds of Example 75 (a), produced as described in WO 95/02591, Adams et al., whose disclosure is incorporated herein by reference in its entirety, (4.25 g,

37.2 mmol) and Example 3(b) as prepared above (5.1 g, 37.2 mmol) were combined in CH_2Cl_2 (150 mL). This mixture was stirred for about 16 hours at room temperature, and cooled to 0°C. The compound of Example 1(b), above and TBD were added and the resulting mixture was stirred at room temperature for about 3 days. The mixture was poured directly on a silica gel column and was purified by flash chromatography eluting with 0% - 5% MeOH/CH_2Cl_2. The resulting oil was washed in acetone/hexane and the precipitate was filtered, washing with acetone to afford the title compound (1.36 g, 10% yield) as a pale yellow solid. mp = 209 - 210°C. ^{1}H NMR ($CDCl_3$): δ 8.16 (d, J = 4.5 Hz, 1H), 7.77 (s, 1H), 7.45 (q, 2H), 6.98 (t, 2H) 6.41 (d, 1H), 5.20 (d, 1H), 4.66 (s,1 H), 3.05, (d, 3H), 2.98 (d, 2H), 2.32 (s, 3H), 2.14 (m, 2H), 2.01 (m, 4H).

The above noted conditions employ a compound of Formula (IIa)-Scheme I wherein p=0. In an analogous procedure to that of part (a), but using a compound of Formula (IIa)-Scheme I wherein p=2, and an isolated imine, were employed.

Base	Solvent	Temp. °C
t-butylamine	DME	25, 50, 85
t-butylamine	THF	25
K_2CO_3	MeOH	25, 65
K_2CO_3	EtOH	25
K_2CO_3	DMF	0
pyrrolidine	THF	25
DBU	THF	0, 25
piperidine	THF	0
morpholine	THF	0
morpholine	acetonitrile	0

In methods analogous to those described above, the following compound may be prepared:

Example 5

5-[4-(2-Methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-piperidine)imidazole

a) 5-[4-(2-Methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-N-Boc-piperidine)-imidazole A solution of 2-methylamino-4-pyrimidine carboxaldehyde (2.47 g, 17.99 mmol) and t-butyl 4-amino-1-piperidine carboxylate (as described in example 46 (a) in WO 95/02591, Adams et al., (3.96 g, 19.79 mmol) in 36 mL of DMF was stirred at about 25°C for about 5 to 6 h. After cooling to about 0°C, the isonitrile of step (b), Example 10(b), below (6.24 g, 21.60 mmol) and powdered K_2CO_3 (2.98 g, 21.60 mmol) were added. The solution was gradually warmed to about 25°C over about 3 h. After about 16 h , 100 mL of H_2O was added and the resulting mixture was filtered, washed with 20 mL of H_2O and 50 mL of t-butyl methyl ether. After drying, 6.85 g (84%) of the title product

was obtained as a white powder. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (1H, d, J = 5.0 Hz), 7.72 (1H, s), 7.45 (2H, m), 6.99 (2H, t, J = 8.7 Hz), 6.40 (1H, d, J = 5.1 Hz), 5.20 (1H, m), 4.80 (1H, m), 4.28 (2H, m), 3.03 (3H, d, J = 5.0 Hz), 2.76 (2H, t, J = 12.2 Hz), 2.17 (2H, d, J = 12.2 Hz), 1.86 (2H, dq, J = 4.3, 12.4 Hz), 1.48 (9H, s).

b) 5-[4-(2-Methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-piperidine)-imidazole To a stirred suspension of the N-BOC derivative of Step (a) above, (31 g, 68 mmoles) in ethyl acetate (310 mL, 10 volumes) was added 3N aqueous HCl (160 mL, 476 mmoles, 7 equiv.) at 25°C. The resulting cloudy yellow solution was stirred at 25°C for 2 hours. The pH of the reaction mixture was adjusted to 12-13 by the slow addition of 50% aqueous NaOH. The phases were separated and the aqueous was extracted twice with methylene chloride (200 mL each). The combined organic extracts were washed with water, dried over $MgSO_4$ and rotary evaporated to dryness. The resulting light-yellow residue was slurried in hot ethyl acetate/methylene chloride (200 mL of a 9:1 mixture) and allowed to cool to 25°C. The product was collected by suction filtration and rinsed with ethyl acetate (25 mL). The white solid was dried to a constant weight at 50°C/<1 mm to give 19 g (54 mmoles) of the desired titled product, affording a 79% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (1H, d, J = 5.0 Hz), 7.77 (1H, s), 7.45 (2H, m), 6.99 (2H, t, J = 8.7 Hz), 6.40 (1H, d, J = 5.1 Hz), 5.23 (1H, m), 4.76 (1H, m), 3.22 (2H, d, J = 12.4 Hz), 3.05 (3H, d, J = 5.1 Hz), 2.67 (2H, dt, J = 2.0, 12.3 Hz), 2.16 (2H, d, J = 11.8 Hz), 1.86 (2H, dq, J = 3.9, 12.2 Hz).

In an alternative synthesis the title compound may be prepared as follows:
5-[4-(2-Methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(piperidin-4-yl)-imidazole
i) 5-[4-(2-Methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-N-carboxyethyl-piperidine)-imidazole A solution of 2-methylaminopyrimidine-4-carboxaldehyde dimethyl acetal (1.88 g, 10.3 mmol) in 10 mL of 3 N HCl was heated at 47°C for 14 h, until no starting material remained by HPLC. The reaction was cooled to 25°C and ethyl 4-amino-1-piperidine carboxylate (1.95 g, 11.3 mmol), ethyl acetate (30 mL) and $NaHCO_3$ (3.45 g, 41.1 mmol) were added sequentially. After 7 h, DMF (5 mL), the isonitrile of step (b), Example 10 (b) (2.97 g, 10.3 mmol) and powdered K_2CO_3 (1.56 g, 11.3 mmol) were added. The reaction was stirred for 14 h, diluted with 50 mL of EtOAc, washed with water (2 X 50 mL), saturated K_2CO_3 solution (50 mL), and brine (30 mL), and the organic phase was concentrated. The product was recrystallized from ethyl acetate to give the title compound (1.96 g, 45%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (1H, d, J = 5.0 Hz), 7.72 (1H, s), 7.45 (2H, m), 7.00 (2H, t, J = 8.7 Hz), 6.41 (1H, d, J = 5.0 Hz), 5.19 (1H, m), 4.84 (1H, m), 4.35 (2H, m),4.16 (2H, q, J = 7.1 Hz), 3.04 (3H, d, J = 5.0 Hz), 2.82 (2H, m), 2.20 (2H, m), 1.88 (2H, dq, J = 4.4, 12.5 Hz), 1.28 (3H, t, J = 7.1 Hz).

ii) 5-[4-(2-Methylamino)pyrimidinyl}-4-(4-fluorophenyl)-1-(piperidin-4-yl)-imidazole

To a stirred solution of the above compound (2.1 g, 4.64 mmol) in EtOH (40 mL) and water (20 mL) was added NaOH (1.48 g, 37.2 mmol) and the solution was heated at reflux for 36 h. The solution was cooled to room temperature and toluene (20 mL) was added. The solution was concentrated in vacuo, toluene was added (20 mL) and reconcentrated in vacuo. Water (30 mL) and toluene (30 mL) were added and the white solid which had formed was filtered and dried to yield the title compound (1.26 g, 77%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (1H, d, J = 5.0 Hz), 7.77 (1H, s), 7.45 (2H, m), 6.99 (2H, t, J = 8.7 Hz), 6.40 (1H, d, J = 5.1 Hz), 5.23 (1H, m), 4.76 (1H, m), 3.22 (2H, d, J = 12.4 Hz), 3.05 (3H, d, J = 5.1 Hz), 2.67 (2H, dt, J = 2.0, 12.3 Hz), 2.16 (2H, d, J = 11.8 Hz), 1.86 (2H, dq, J = 3.9, 12.2 Hz).

In yet another alternative emobidiment of the present invention the protecting group has been changed from t-BOC to carboxyethyl and synthesized using similar conditions to parts (a) and (b) above:

5-[4-(2-N-Methylamino)pyrimidinyl}-4-(4-fluorophenyl)-1- (4-N-carboxyethyl-piperidine)-imidazole A solution of 2-methylamino-4-pyrimidine carboxaldehyde (2.47 g, 17.99 mmol) and ethyl 4-amino-1-piperidine carboxylate (3.25 g, 18.9 mmol) in 36 mL of DMF was stirred at room temperature for about 3.3 h. The isonitrile of step (b), Example 10 (b) (6.0 g, 20.7 mmol) and powdered K_2CO_3 (3.11 g, 22.5 mmol) were added. After about 16 h , 250 mL of H_2O, 30 mL of TBME, and 30 mL of EtOAc were added and the resulting mixture was filtered, washed with 200 mL of H_2O and TBME (2 X 100 mL). The isolated material was recrystallized from EtOAc/Et2O to give 5.3 g (65%) of the title product as a white powder. mp 205-206°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (1H, d, J = 5.0 Hz), 7.72 (1H, s), 7.45 (2H, m), 7.00 (2H, t, J = 8.7 Hz), 6.41 (1H, d, J = 5.0 Hz), 5.19 (1H, m), 4.84 (1H, m), 4.35 (2H, m),4.16 (2H, q, J = 7.1 Hz), 3.04 (3H, d, J = 5.0 Hz), 2.82 (2H, m). 2.20 (2H, m), 1.88 (2H, dq, J = 4.4, 12.5 Hz), 1.28 (3H, t, J = 7.1 Hz).

In yet another alternative emobidiment of the present invention using acid hydrolysis of the ethyl carbamate affords the title compound: 5-[4-(2-Methyl-amino)pyrimidinyl}-4-(4-fluorophenyl)-1-(4-piperidine)imidazole

Concentrated hydrochloric acid (12 mL) was added to 4-[[1-(1-ethoxycarbonyl)-4-piperdinyl)]- 4-(4-fluoropheyl)-1H-imidazol-5-yl]-N-methyl-2-pyrimidinamine (25 g, 0.059 mol) and heated to reflux for 18 h. The reaction mixture was cooled to 0°C and neutralized with 50% aqueous sodium hydroxide. The resulting precipitate was collected by filtration, washed with water, air-dried and dried in vacuo at 40°C to afford the title compound as a white solid in 62% yield.

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Example 6

5-[(2-Ethylamino)pyrimidin-4-yl]-4-(4-fluorophenyl)-1-(1-methylpiperdin-4-yl)imidazole

a) 2-Methylthiopyrimidine-4-carboxaldehyde dimethyl acetal Pyruvaldehyde dimethyl acetal (19.2 mL, 159.1 mmol) and N,N-dimethylformamide dimethyl acetal (21.12 mL, 159.1 mmol) were combined in a 500 mL flask and heated at 100°C. After 4.5 h the flask was removed from the heat, thiourea (11.0 g, 144.5 mmol), NaOMe (25 wt. % solution in MeOH, 39.7 mL, 173 mmol) and 30 mL of MeOH were added and heating was continued at 65°C. After 18 h the solution was cooled to 25°C and MeI (10.8 mL, 173 mmol) was added over 5 min (exothermic). After 3 h, the solution was diluted with 250 mL of H_2O and extracted with EtOAc (3 X 100 mL). The organics were combined, dried over Na_2SO_4 and concentrated to give the title compound (26.8 g, 93%) as a brown oil.

b) 2-Methylthiopyrimidine-4-carboxaldehyde 2-Methylthiopyrimidine-4-carboxaldehyde dimethyl acetal (30.0 g, 150 mmol) was dissolved in 300 mL of glacial AcOH and 3 mL of conc. H_2SO_4 and heated at about 70- 80°C. After 10 h, the solution was cooled to 25°C and the AcOH was removed *in vacuo*, leaving a brown oil residue. This residue was diluted in 200 mL of CH_2Cl_2 and washed with saturated $NaHCO_3$ (3 X 50 mL), H_2O (50 mL) and brine (50 mL). The organics were dried over $MgSO_4$ and concentrated to yield 22.1 g (96%) of the title compound as a brown oil.

c) 2-Methylthiopyrimidine-4-carboxaldehyde (1-methylpiperdin-4-yl)imine 2-Methylthiopyrimidine-4-carboxaldehyde (5.6 g, 36 mmol) and 4- amino-1-methylpiperidine dihydrochloride (6.73 g, 36 mmol) were dissolved in 200 mL of CH_2Cl_2 and $NaHCO_3$ (10.6 g, 126 mmol) was added. After 20 h, the solution was filtered and concentrated to yield 8.9 g (98%) of the title compound as a brown oil.

d) 4-(Fluorophenyl)-1-(1-methylpiperidin-4-yl)-5-(2-methylthio-4-pyrimidinyl)-imidazole *t*-$BuNH_2$ (3.90 mL, 37.08 mmol) was added rapidly to a solution of 2-methylthiopyrimidine-4-carboxaldehyde(1-methylpiperdin-4-yl)imine (3.71 g, 14.83 mmol) and 4-fluorophenyl-tosylmethylisocyanide (5.15 g, 17.8 mmol) dissolved in 50 mL of DME at 25°C. After 14 h, the solution was diluted with 50 mL of EtOAc and washed with 50 mL of sat. $NaHCO_3$ and 25 mL of brine. The organics were dried over Na_2SO_4 and concentrated. Crystallization from the crude residue using EtOAc/hexanes yielded 2.85 g (50%) of the product as a light brown crystal. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.31 (1H, d, J = 5.1 Hz), 7.78 (1H, s), 7.40 (2H, m), 6.99 (2H, t, J = 8.7 Hz), 6.76 (1H, d, J = 5.2 Hz), 4.67 (1H, m), 2.97 (2H, m), 2.58 (3H, s), 2.31 (3H, s), 2.06 (6H, m).

Alternatively for the synthesis in part (d) above additional reaction conditions were employed with other amine bases and solvents:

a) t-butylamine and THF; b) diisopropyl amine and THF; c) pyrrolidine and THF; d) potassium carbonate and ethanol.

e) 4-(Fluorophenyl)-1-(1-methylpiperidin-4-yl)-5-(2-methysulfinyl-4-pyrimidinyl)-imidazole Potassium persulfate (3.2 g, 7.0 mmol) in water (75 mL) was added to a solution of 4-(fluorophenyl)-1-(1-methylpiperidin-4-yl)-5-(2-methylthio-4-pyrimidinyl)-imidazole (2.7 g, 7.0 mmol) in glacial AcOH (150 mL). After stirring at ambient temperature for 72 h, the reaction mixture was neutralized by the portion-wise addition of concentrated aqueous NH_4OH and extracted with CH_2Cl_2. The organic extract was washed with brine, dried (MgSO4) and concentrated. The residue was triturated with ethyl ether to afford the title compound as an off-white solid; yield 2.3 g (83%).

f) 5-[(2-Ethylamino)pyrimidin-4-yl]-4-(4-fluorophenyl)-1-(1-methylpiperdin-4-yl)imidazole 4-(Fluorophenyl)-1-(1-methylpiperidin-4-yl)-5-(2-methysulfinyl-4-pyrimid-inyl)imidazole (0.25 g, 0.65 mmol) and 70% aqueous ethylamine (2.5 mL) were heated to 120°C in a sealed reaction vessel for 18 h. After cooling to ambient temperature, volatiles were evaporated and the residue was triturated with ethyl ether to afford the title compound as a white solid; yield 0.13 g (53%): ES (+) MS m/e = 381 (MH^+).

Example 7

4-(4-Fluorophenyl)-5-[2-(isopropyl)aminopyrimidiny-4-yl]-1-(1-methylpiperdin-4-yl)imidazole

Following the procedure of example 6, step (f) except substituting isopropylamine afforded the title compound as a tan solid in 20% yield: ES (+) MS m/e = 395 (MH^+).

Example 8

5-(2-Amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(1-methyl-4-piperdinyl)imidazole

a) 2-Acetamidopyrimidine-4-carboxaldehyde monomethyl monoacetoxy acetal
A mixture of 2-aminopyrimidine-4-carboxaldehyde dimethyl acetal (9.0 g, 53 mmol) and acetic anhydride (25 mL) was heated to 60° for 18 h. Concetrated H_2SO_4 (10 drops) was added and the solution was heated to 100° for 10 h. After cooling to ambient temperature, the volatiles were evaporated and the residue was vacuum filtered through a pad of silica gel eluting with 4% MeOH in CH_2Cl_2. Evaporation of the filtrate followed by trituration of the residue with ether afforded the title compound as a white solid; yield 8.6g (68%).

b) 2-Acetamidopyrimidine-4-carboxaldehyde Sodium methoxide (0.056 g, 1.0 mmol) was added to a solution of 2-acetamido-pyrimidine-4-carboxaldehyde monomethyl monoacetoxy acetal (5.0 g, 21 mmol) in MeOH (25 mL) at ambient temperature. After stirring at this temperature for 3 h, the reaction mixture was neutralized by addition of 3N HCl. The resulting solution was concentrated and the residue was treated with CH_2Cl_2. Remaining solids were removed by filtration and the solvent was evaporated to afford the title compound as a yellow solid: yield 3.2 g (92%).

c) 2-Acetamidopyrimidine-4-carboxaldehyde (1-methylpiperdine-4-yl)imine Following the procedure of example 75 (b), as described in WO 95/02591, Adams et al., except substituting 2-acetamidopyrimidine-4-carboxaldehyde afforded the title compound as off-white solid in 75% yield.

d) 5-(2-Acetamido-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(1-methyl-4-piperdinyl)imidazole Following the procedure of example 6 (d) except substituting 2-acetamidopyrimidine-4-carboxaldehyde (1-methylpiperdine-4-yl)imine afforded the title compound as yellow solid in 51% yield.

e) 5-(2-Amino-4-pyrimidinyl)-4-4(4-fluorophenyl)-1-(1-methyl-4-piperdinyl)imidazole A solution of 5-(2-acetamido-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(1-methyl-4-piperdinyl)imidazole (4.0 g, 0.010 mol) in 40 mL of 3N HCl was heated to 75°C for 18 h. After cooling to ambient temperature, the reaction mixture was neutralized with solid sodium hydrogen carbonate. The resulting precipitate was isolated by filtration, washed with water and air dried to afford the title compound as a white solid in quatitative yield.

Example 9

5-(2-Acetamido-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(4-morpholino-3-propyl)imidazole

A solution of 5-(2-amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(4-morpholino-3-propyl)imidazole (0.50 g, 1.3 mmol) in acetic anhydride (10 mL) was heated to reflux for 18 h. After cooling to ambient temperature, excess acetic anhydride was evaporated and the residue was partitioned between saturated aqueous $NaHCO_3$ and ethyl acetate. The layers were separated and the organic phase was concentrated. The residue was dissolved in MeOH (10 mL) and 2.5N NaOH (1 mL) was added. After stirring at ambient temperature for 2 h, the solution was partially evaporated and the resulting precipitate was collected by filtration, washed with water and air-dried to afford the title compound as a white solid; yield 0.28 g (51%): ES (+) MS m/e = 425 (MH^+).

Example 10

a) α-(p-Toluenesulfonyl)-4-fluorobenzylformamide

To a stirred solution of 4-fluorobenzaldehyde (124 g, 979 mmoles) in acetonitrile (620 mL, 5 volumes) and toluene (620 mL, 5 volumes) was added formamide (110 g, 2.45 moles, 2.5 equiv.) followed by chlorotrimethylsilane (119 g, 1.07 moles, 1.1 equiv.). The reaction was heated at 50°C under nitrogen for 5 hours. To the resulting white slurry was added p-toluenesulfinic acid (230 g, 1.47 moles, 1.5 equiv.) and the reaction was heated at 50°C for an additional 5 hours then cooled to ambient temperature. Methanol (250 mL) and t-butyl methyl ether (620 mL) were added. After 15 minutes the reaction was poured into water (3 L) pre-cooled to 0°C. After stirring for 30 minutes at 0°C, the product was collected by suction filtration and rinsed with t-butyl methyl ether (250 mL).

The product, a white, crystalline solid, was dried to a constant weight at 40°C/<1 mm Hg to afford 270 g (879 mmoles) of desired product (90% yield). ^{1}H NMR (300 MHz, CD_3CN) δ 7.99 (1H, s), 7.92 (1H, m), 7.71 (2H, d, J = 8.3 Hz), 7.49 (2H, dd, J = 5.3, 8.8 Hz), 7.39 (2H, d, J = 8.1 Hz), 7.16 (2H, t, J = 8.8 Hz), 6.31 (1H, d, J = 10.6 Hz), 2.42 (3H, s).

Alternative conditions to those used above in part (a) were employed: a) toluene at about 50°C; b) acetonitrile at about 50°C; c) and using the conditions above but at temperatures of 30, 40, 50, 60 and 70°C.

b) α-(p-Toluenesulfonyl)-4-fluorobenzylisonitrile

A stirred suspension of α-(p-toluenesulfonyl)-4-fluorobenzylformamide produced in step (a) above, (100 g, 325 mmoles) in THF (650 mL, 6.5 volumes) was cooled to 0°C and $POCl_3$ (46 mL, 487 mmoles, 1.5 equiv.) was added. A 1°C exotherm was observed. After 15 minutes at 0°C, the white slurry was cooled to -5°C. Triethylamine (166 g, 1.62 moles, 5 equiv.) was added dropwise to the slurry over 45 minutes at such a rate to keep the reaction temperature below 0°C but above -5°C. Caution should be exercised at the beginning of the addition because the reaction has a tendency to exotherm quickly. After complete addition, the yellow slurry was stirred for 30 minutes at 0°C. The reaction slurry has a tendency to darken during the stirring period. The reaction was poured into a mixture of saturated aqueous sodium bicarbonate (1 L) and ethyl acetate (1 L), both pre-cooled to 0°C. The organic phase was subsequently washed with water followed by brine. The organic phase was concentrated under vacuum via rotary evaporation until about 10% of the initial volume remained. 1-Propanol (200 mL) was added and concentrated again under vacuum at 35°C until about 10% of the initial volume remained. This process was repeated with fresh 1-propanol (200 mL). A fine, yellow precipitate was observed. The precipitate was cooled to 0°C and the product was collected by suction filtration and rinsed with 1-propanol (50 mL). The off-white solid was dried to a constant weight at 40°C/<1 mm to give 65.7 g (227 mmoles) of desired product, affording a 70% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (2H, d, J = 6.7 Hz), 7.46 (4H, m), 7.08 (2H, t, J = 8.6 Hz), 5.62 (1H, s), 2.46 (3H, s).

Alternative conditions to those used above in part (b) were employed, such as: a) different solvents: DME, DME/acetonitrile(10:1) using the same reaction conditions; b) using the reaction conditions above but ranging the temperature from -30, -15, -10, and 0°C; c) using reaction temperature at 0°C, and at -10°C; d) a variety of dehydrating agents including trifluroacetic anhydride, thionyl chloride, and oxalyl chloride.

Example 11

5-(2-Acetamido-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(1-methylpiperidin-4-yl)imidazole

To a solution of the 2-acetylamido pyrimidinyl-4-carboxaldehyde (0.84 g, 5.08 mmol) and 1-methylpiperidin-4-yl-amino dihydrochloride salt (1.04 g, 5.59 mmol) in 21

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mL of DMF was added powdered K_2CO_3 (1.54 g, 11.2 mmol). After approx 6 h, the α-(p-Toluenesulfonyl)-4-fluorobenzylisonitrile, produced in step (b) Example 10 above, (1.76 g, 6.10 mmol) and powdered K_2CO_3 (0.84 g, 6.10 mmo) were added and the sides of the flask rinsed with 5 mL of DMF. After 16 h, 300 mL of H_2O were added to the reaction mixture and the solution was extracted with EtOAc (3 X 100 mL). The combined organics were washed with H_2O (3 X 50 mL), dried over Na_2SO_4 and concentrated. The pure title compound (0.75 g, 38%) was recrystallized from EtOAc as a pale yellow crystal. ^1H NMR (300 MHz, $CDCl_3$) δ 8.71 (1H, s), 8.39 (1H, d, J = 5.2 Hz), 7.81 (1H, s), 7.39 (2H, m), 7.13 (2H, t, J = 8.7 Hz), 6.81 (1H, d, J = 5.2 Hz), 4.88 (1H, m), 2.94 (2H, d, J = 10.1 Hz), 2.47 (3H, s), 2.32 (3H, s), 2.07 (6H, m).

Example 12

5-[4-(2-Methylthioamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-piperidine)imidazole

To a solution of the 2-methylthio amino-4-pyrimidine carboxaldehyde (3.4 g, 22.07 mmol) and 4-amino-1-methyl piperidine dihydrochloride salt (4.54 g, 24.3 mmol) in 44 mL of DMF was added K_2CO_3 (7.02 g, 50.8 mmol). After about 6 h, the solution was cooled to about 0°C and the isonitrile of Example 10 step (b), above, (7.68 g, 26.5 mmol) and K_2CO_3 (3.57 g, 25.38 mmol) were added and stirred with gradual warming to about 25°C. After about 16 h, the reaction mixture was diluted with 200 mL of EtOAc and washed with 200 mL of H_2O. The aqueous layer was extracted with EtOAc (2 X 100 mL) and the combined organics were washed with H_2O (3 X 100 mL). The organics were dried over Na_2SO_4 and concentrated and the titled product was recrystallized from EtOAc/Hex to give 5.12 g (61%) of a pale yellow crystal. ^1H NMR (300 MHz, $CDCl_3$) δ 8.33 (1H, d, J = 5.3 Hz), 7.79 (1H, s), 7.41 (2H, m), 7.01 (2H, t, J = 8.7 Hz), 6.77 (2H, d, J = 5.2 Hz), 4.68 (1H, m), 2.98 (2H, m), 2.59 (3H, s), 2.32 (3H, s), 2.07 (6H, m).

Example 13

5-[4-(2-Methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(1-methylpiperidin-4-yl)imidazole

To a solution of the 2-methylamino-4-pyrimidine carboxaldehyde (2.79 g, 20.37 mmol) and 4-amino-1-methyl piperidine dihydrochloride salt (4.19 g, 22.41 mmol) in 41 mL of DMF was added powdered K_2CO_3 (6.19 g, 44.82 mmol). The mixture was stired at room temperature for about 6 h. The solution was cooled to about 0°C and the isonitrile of Example 85, step (b) (7.07 g, 24.44 mmol) and powdered K_2CO_3 (3.10 g, 22.41 mmol) were added. Stir at about 0°C for about 3 h, then slowly warm to room temperature over about 2 h. Add 100 mL of H_2O and stir for about 15 min. Filter the solution and wash with 50 mL of H_2O and 50 mL of TBME. After drying, 5.56 g (74%) of the titled compound was isolated as

an off-white powder. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (1H, d, J = 4.9 Hz), 7.76 (1H, s), 7.45 (2H, m), 6.99 (2H, t, J = 8.7 Hz), 6.40 (1H, d, J = 5.1 Hz), 5.29 (1H, m), 4.65 (1H, br s), 3.04 (3H, d, J = 5.1 Hz), 2.97 (2H, m), 2.31 (3H, s), 2.13-1.98 (6H, m).

Alternatively the reaction above has been employed at room temperature.

Example 14

5-[4-(2-Aminopyrimidinyl)]-4-(4-fluorophenyl)-1-(2,2,6,6-tetramethyl-4-piperidinyl)imidazole

a) 2-Aminopyrimidine-4-carboxaldehyde 4-(2,2,6,6-tetramethylpiperidinyl) imine To the compound of example 2(b), above (0.752 g, 6.1 mmol), 4-Amino-2,2,6,6-tetramethylpiperidine (1.00 g, 6.42 g), CH_2Cl_2 (90 mL), and CH_3OH (1 mL) were combined, stirred overnight and concentrated to afford the title compound as a yellow solid.

b) 5-[4-(2-amino)pyrimidinyl]-4-(4-fluorophenyl)-1-(2,2,6,6-tetramethyl-4-piperidinyl)imidazole The product of (a), above, and the product of example 4 (b), above, (1.86 g, 6.42 mmol), K_2CO_3 (0.842 g, 6.1 mmol), and DMF (12 mL), were combined and stirred for 3 days. Poured into H_2O (25 mL) and extracted with EtOAc (4 x 25 mL) dried (Na_2SO_4) and concentrated to an oil. Flash chromatography (0-10% MeOH in CH_2Cl_2) afforded 0.837 g (35%) of the title compound. mp = 227 - 230 (dec).

Example 15

In methods analogous to those described above except using the compound of example 3 (b) as the aldehyde precursor to the imine the following compound may be prepared: 5-(2-Methylamino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(2,2,6,6-tetramethyl-4-piperidine)imidazole; mp = 184 - 185.

In methods analogous to those described in example 1 except using the product of example of example 2 (b) or the product of example 3 (b) as the aldehyde and the appropriate amine to afford the imine intermediate, the following compounds may be prepared:

Example 16

5-(2-Amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(tetrahydro-4-thiopyranyl)-imidazole mp = 228 - 230.

Example 17

5-(2-Amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(tetrahydro-4-pyranyl)imidazole mp = 222 - 223.

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Example 18

5-(2-Methylamino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(2-cyanoethyl)imidazole mp = 193 - 194.

In methods analogous to those described in example 14 of WO 95/02591, Adams et al., (Attorney Docket P50172-1) except using the product of example of example 16 as starting material, the following compounds may be prepared:

Example 19

5-(2-Amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(tetrahydro-4-sulfinylpyranyl)imidazole mp = 255 - 265 (dec).

Example 20

5-(2-Amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(tetrahydro-4-sulfonyl-pyranyl)imidazole The product of example 16, above, (213 mg, 0.6 mmol), CH_2Cl_2 (2.25 mL), CH_3OH (0.75 mL), and TFA (92 mL, 1.2 mmol) were cooled to 4° and MCPBA (ca. 80%) (387 mg) was added, warmed to 23° over 20 min, poured into EtOAc (50 mL), and washed with 5% aq Na_2CO_3, dried (Na_2SO_4), concentrated, filtered through a plug of silica (0 - 4% MeOH), afforded pure 5-(2-amino-4-pyrimidinyl}-4-(4-fluorophenyl)-1-(tetrahydro-4-sulfonylpyranyl)imidazole (80 mg, 34%). mp = 228 - 230°.

Example 21

5-(2-Methylamino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-[1-(2,2,2-trifluoroethyl)-piperidin-4-yl]imidazole

a) 2-N-Methylaminopyrimidine-4-carboxaldehyde dimethyl acetal

Pyruvic aldehyde dimethyl acetal (277 mL, 2.3 mol) and N,N-dimethyl formamide dimethyl acetal (304 mL, 2.3 mol) were stirred together at 100° for 18 h. The mixture was concentrated to a brown oil.

Sodium metal (25 g) was dissolved in EtOH (3 L). Methyl guanidine hydrochloride (112 g) was added and the mixture was stirred 5 h. The above described oil (1.15 mmol) was added and the mixture was refluxed for 24 h, cooled, filtered, and concentrated. The resulting residue was triturated with hot EtOAc and filtered over celite. The filtrate was concentrated affording the title compound as a brown oil. ^1H NMR ($CDCl_3$): δ 8.33 (d, 1H), 6.75 (d, 1H), 5.10 (s, 1H), 3.40 (s, 6H), 3.00 (s, 3H).

b) 2-N-Methylaminopyrimidine-4-carboxaldehyde

A mixture of the compound of example 21(a) was hydrolyzed by the procedure of example 26 (e) to afford the title compound as a yellow foam. ^1H NMR ($CDCl_3$): δ 9.88 (s, 1H), 7.13 (d, 1H), 7.01 (d, 1H), 2.05 (s, 3H).

c) 2-N-Methylaminopyrimidine-4-carboxaldehyde[1-[1-(2,2,2-trifluoroethyl)-4-aminopiperidine]imine

The product of example 26 (c) and the product of example 21(b) were reacted by the procedure of example 1(f) to afford the title compound as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 8.34 (d, 1), 8.14 (s, 1), 7.13 (d, 1), 5.2 (m, 1), 3.33 (m, 1), 3.05 (m, 7), 2.55 (m, 2), 1.88 (m, 2), 1.75 (m, 2).

d) 5-(2-Methylamino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-[1-(2,2,2-trifluoroethyl)-piperidin-4-yl] imidazole

The product of example 21(c), and the product of example 26(h) were reacted by the procedure of example 26(i) to afford the title compound. Crystals from acetone/ hexane. mp = 189 - 191°C.

Example 22

5-(2-Amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-[(1-trifluoroacetyl)-4-piperidinyl]imidazole

The product of example 46 (c), as described in WO 95/02591, Adams et al., (Attorney Docket P50172-1) (500 mg, 1.12 mmol)was suspended in CH_2Cl_2 (50 mL), and Et3N (585 mL, 4.2 mmol) was added and after 30 sec trifluoroacetic anhydride (160 mL, 1.12 mmol) was added. After 1 h the insoluble material was filtered off and the filtrate was concentrated. The resulting white powder was filtered through a plug of silica (1 - 2% CH_3OH in CH_2Cl_2 to afford 350 mg (72%) of the title compound. mp = 249 - 250°.

Example 23

5-(4-Pyridyl)-4-(4-fluorophenyl)-1-(4-piperidinyl) imidazole

a) Pyridine-4-carboxaldehyde(ethyl 4-amino-piperdinecarboxylate)imine

Following the procedure of example 26(c) herein, except substituting ethyl 4-amino-piperdinecarboxylate for 4-(3-aminopropyl)morpholine afforded the title compound in quantitative yield.

b) 1-[(1-Ethoxycarbonyl)piperdin-4-yl]-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole

Following the procedure of example 11 except substituting pyridine-4-carboxaldehyde(ethyl 4-amino-piperdinecarboxylate)imine for 2-N-methylamino-4-carboxaldehyde(4-ethylene ketal cyclohexyl)imine afforded the title compound as a light yellow solid in 71% yield.

c) 4-(4-Fluorophenyl)-5-(4-pyridyl)-1-(4-piperdinyl)imidazole

Concentrated hydrochloric acid (40 mL) was added to 1-[(1-ethoxycarbonyl)-piperdin-4-yl]-4-(4-fluorophenyl)-5-(4-pyridyl)imidazole (9.4 g, 24 mmol) and the mixture was heated to reflux for 18 h. The resulting yellow solution was cooled to ambient temperature and neutralized with 10% aqueous sodium hydroxide. The precipitate was collected, washed with water and air-dried to afford the title compound as a white solid in 71% yield. ESMS = 323 [M+H]: m.p. 185-187.0°C.

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Example 24

5-(4-Pyridyl)-4-(4-fluorophenyl)-1-(1-t-butoxy carbonyl-4-piperidinyl) imidazole

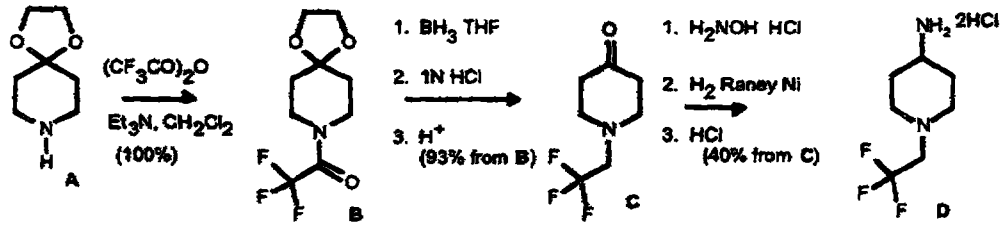
Following the procedure of example 11, except substituting pyridine-4-carboxaldehyde-(t-butoxy 4-amino-piperdinecarboxylate)imine for 2-N-methylamino-4-carboxaldehyde-(4-ethylene ketal cyclohexyl)imine afforded the title compound as a light yellow solid in 42% yield. ESMS = 423 [M+H].

Example 25

2-Methylthiopyrimidine-4-carboxaldehyde

A mixture of 2-methylthiopyrimidine-4-carboxaldehyde dimethyl acetal (3 g, 15.5 mmol) in 3N HCl (12 mL) was stirred at 40°for 18 h. After cooling to 0°C the mixture was diluted with EtOAc and neutralized by the addition of solid $NaHCO_3$. The aqueous phase was separated and extracted with EtOAc (4 x 25 mL). The combined organic extract was dried (Na_2SO_4), and concentrated. The resulting residue was purified by flash chromatography (silica gel, CH_2Cl_2) and recrystallized with hexane to afford the title compound as cream colored needles (1.12 g, 48% yield). ^1H NMR ($CDCl_3$): δ 9.95 (s, 1H), 8.77 (d, 1H), 7.43 (d, 1H), 2.63 (s, 3H).

Example 26



5-(2-Amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-[1-(2,2,2-trifluoroethyl)-4-piperidinyl] imidazole

a) 1-Trifluoroacetyl-4-(1,2-dioxyethyl)piperidine

4-(1,2-Dioxyethyl)piperidine (7.15 g, 50 mmol), CH_2Cl_2 (50 mL), Et_3N (8.35 mL, 60 mmoL), and DMAP (0.61 g, 5 mmol) were combined and trifluoroacetic anhydride (11.03 g, 52.5 mmol) in CH_2Cl_2 (50 mL) was added dropwise and kept < 30° with external cooling. After the initial reaction subsided the reaction was stirred at 23°C for 16h, washed with 1 N HCl (2 x 50 mL), dried (Na_2SO_4), and concentrated to afford 13.38g (100%) of 1-trifluoroacetyl-4-(1,2-dioxyethyl)piperidine as a white solid. IR 1693 cm^{-1}.

b) 1-(2,2,2-Trifluoroethyl)-4-piperidinone

The product of the previous step (1.19 g, 5.0 mmol) in THF (5 mL) was added to 1 M borane in THF (10 mL) at 4 - 10°, and warmed to reflux and stirred for 5 h, cooled

to 4° and 6N HCl (1.5mL) was added. The mixture was concentrated, made basic (pH > 12) with 50% aq NaOH and extracted with Et_2O (3 x 40 mL). The extract was dried (K_2CO_3) and concentrated to a colorless oil.

The above oil was dissolved in 1 N HCl (15 mL) and the solution was refluxed 1h, cooled to 23° and extracted with Et_2O (3 x 20 mL), dried (Na_2SO_4) and concentrated to afford 0.84 g (93%) of 1-trifluoroethyl-4-piperidinone as a light yellow oil. IR 1719 cm^{-1}.

c) 1-(2,2,2-Trifluoroethyl)-4-aminopiperidine hydrochloride

The product of the previous step (3.14g, 17.35 mmol), H_2O (29 mL), and H_2NOH HCl (4.82g, 69.4 mmol) were dissolved together and Na_2CO_3 (4.82g) was added in small portions. The mixture was stirred at 23° for 2h, adjusted to pH > 10 with 50% aq NaOH, extracted with Et_2O (5 x 50 mL) and concentrated to a white foam.

The above residue was dissolved in EtOH (abs) (100 mL) and Raney Ni (5 mL of a slurry in EtOH) was added and the mixture was reduced under H_2 (50 psi) for 3.5 h. The catalyst was filtered off and washed with EtOH. Etherial HCl (1 M) (40 mL) was added and the solvent was removed *in vacuo* to afford an oil. Upon addition of Et_2O (300 mL) a white solid precipitated. The solid was filtered off, washed with more Et_2O and dried invacuo to afford 1.71 g (39%) of the title compound. ^1H NMR (CD_3OD) 4.1 (m,2), 3.7 (m,2), 3.5 (m,1), 3.3 (m,2), 2.3 (m,2), 2.1 (m,2).

d) 2-Aminopyrimidine-4-carboxaldehyde dimethyl acetal

Dimethylformamide dimethyl acetal (55 mL, 0.41 mol), and pyruvic aldehyde dimethyl acetal (50 mL, 0.41 mol) were combined and heated to 100°C for 18 h. Methanol was removed *in vacuo* to afford an oil. A solution of NaOH (18 g, 0.45 mol) in H_2O (50 mL) was added to guanidine HCl (43 g, 0.45 mol) in H_2O (100 mL), and the resulting solution was added to the above described oil. The resulting mixture was stirred at 23° for 48 h. Filtration afforded 25g (50%) of the title compound.

e) 2-Aminopyrimidine-4-carboxaldehyde

The compound of the previous step (1.69 g, 10 mmol) and 3N HCl (7.3 mL, 22 mmol) were combined and heated to 48° for about 14 hours, cooled, layered with EtOAc (50 mL) and neutralized by the addition of $NaHCO_3$ (2.1g, 25 mmol) in small portions. The aqueous phase was extracted with EtOAc (5 x 50 mL) and the extracts were dried (Na_2SO_4) and concentrated to afford 0.793 g (64%) of the title compound.

f) 2-Aminopyrimidine-4-carboxaldehyde(1-trifluoroethyl-4-aminopiperidine)imine

The product of example 26(c) (1.71 g, 6.79 mmol) H_2O (16 mL), K_2CO_3 (1.21 g, 8.77 mmol), and the product of example 1(e) (0.79 g, 6.45 mmol) and CH_2Cl_2 (100 mL) were combined and stirred under Ar for 14 h. The phases were separated and the aqueous was extracted with an additional portion of CH_2Cl_2. The combined organic phases were dried (K_2CO_3) and concentrated to afford the title compound as a yellow oil.

^{1}H NMR ($CDCl_3$): δ 8.36 (d, 1), 8.13 (s, 1), 7.19 (d, 1), 5.2 (m, 2), 3.35 (m,1). 3.0 (m, 4), 2.55 (m, 2), 1.90 (m, 2), 1.75 (m, 2)

g) 4-Fluorophenyl-tolylsulfonomethylformamide

To a suspension of p-toluenesulfinic acid sodium salt (30 g) in H_2O (100 mL) was added TBME (50 mL) followed by dropwise addition of conc. HCl (15 mL). After stirring 5 min, the organic phase was removed and the aqueous phase was extracted with TBME. The organic phase was dried (Na_2SO_4) and concentrated to near dryness. Hexane was added and the free acid was filtered.

The free acid (22 g, 140.6 mmol), p-fluorobenzaldehyde (22 mL, 206 mmol), formamide (20 mL, 503 mmol) and camphorsulphonic acid (4 g, 17.3 mmol) were combined and stirred at 60° for 18 h. The resulting solid was broken up and stirred with a mixture of MeOH (35 mL) and hexane (82 mL) then filtered. The solid was resuspended in MeOH/ hexane (1:3, 200 mL) and stirred vigorously to break up remaining chunks. Filtration afforded the title compound (27 g, 62 % yield). ^{1}H NMR (400 Mhz, $CDCl_3$): δ8.13 (s, 1H), 7.71 (d, 2H), 7.43 (dd, 2H), 7.32 (d, 2H), 7.08 (t, 2H), 6.34 (d, 1H), 2.45 (s, 3H).

h) 4-Fluorophenyl-tolylsulfonomethylisocyanide

The compound of example 1(f) (2.01g, 6.25 mmol) in DME (32 mL) was cooled to -10°. $POCl_3$ (1.52 mL, 16.3 mmol) was added followed by the dropwise addition of triethylamine (4.6 mL, 32.6 mmol) in DME (3 mL) keeping the internal temperature below -5°. The mixture was gradually warmed over 1 h, quenched in H_2O and extracted with EtOAc. The organic phase was washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4), and concentrated. The resulting residue was triturated with petroleum ether and filtered to afford the title compound (1.7 g, 90% yield). ^{1}H NMR ($CDCl_3$): δ 7.63 (d, 2H), 7.33 (m, 4H), 7.10 (t, 2H), 5.60 (s, 1H), 2.50 (s, 3H).

i) 5-(2-Amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-[1-(2,2,2-trifluoroethyl)-4-piperidinyl] imidazole

The product of example 1(h) (1.96 g, 6.79 mmol), the product of example 26 (f) (<6.45 mmol), and K_2CO_3 (0.89 g, 6.45 mmol) and DMF (14 mL) were combined and stirred under Ar for 2 days. The resulting mixture was diluted with Et_2O (100 mL) and filtered. The filtrate was concentrated to a dry residue *in vacuo*. The resulting solid was triturated with Et_2O filtered and washed with Et_2O. The solid obtained was crystallized from acetone/hexane to afford 0.751g (28% from the product of example 1(e)) of 5-(2-amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-[1-(2,2,2-trifluoroethyl)-4-piperidinyl] imidazole. mp = 229 - 230°.

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Example 27

5-(2-Methylthio-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(4-piperidinyl)imidazole

a) 1-t-Butoxycarbonyl-4-aminopiperidine

1-t-Butoxycarbonyl piperidine-4-one (commercially available from Lancaster Chem) was converted to the free base of the title compound by the procedure of example 26 (c) with the ommission of the HCl treatment step.

b) 2-Methylthiopyrimidine-4-carboxaldehyde [1-t-butoxycarbonyl-4-aminopiperidinel imine

2-Methylthiopyrimidine-4-carboxaldehyde [Bredereck H. et al. Chem. Ber. 1964, 3407] (1.51g, 9.8 mmol), the product of example 27(a) (2.1 g, 10.5 mmol), $MgSO_4$ (ca 2 g) and CH_2Cl_2 (75 mL) were combined and stirred at 23° for 16 h. Filtration and concentration of the filtrate afforded the title compound as a yellow oil. ^1H NMR ($CDCl_3$): δ 8.57 (d, 1), 8.27 (s, 1), 7.58 (d, 1), 4.05 (m, 2), 3.55 (m, 1), 3.00 (m, 2), 2.60 (s, 3), 1.75 (m, 4), 1.48 (s, 9).

c) 5-(2-Methylthio-4-pyrimidinyl)-4-(4-fluorophenyl)-1-[(1-t-butoxycarbonyl)-4-piperidinyllimidazole

Following the procedure of example 26(i) except using the product of example 27(b) as the imine afforded an oil from the ether phase. Flash chromatography in 0 - 1% MeOH in CH_2Cl_2, concentration and trituration of the residue with hexane afforded 2.32g (50% from 2-methylthiopyrimidine-4-carboxaldehyde) of the title compound as a brown solid. ESP+ MS m/z = 470 (MH^+).

d) 5-(2-Methylthio-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(4-piperidinyl)imidazole

The product of the preceding example (469 mg, 1.0 mmol) was suspended in CH_3OH (2 mL), cooled to 0°C, under Ar, and 4 M HCl in dioxane was added. The resulting light yellow soln was warmed to 23°C, stirred for 4h, and diluted with Et_2O. A gummy solid separated out which solidified on Et_2O trituration for 20 min. The solid was filtered, redissolved in H_2O, washed with EtOAc, layered with a second portion of EtOAc and the aq phase was made basic by the addition of 50 % aq NaOH. Extraction with EtOAc (3X), drying of the combined extracts (K_2CO_3) and concentration afforded a solid which was triturated with Et_2O and filtered to afford 168 mg (46%) of the title compound as an off white solid. mp = 182-183°.

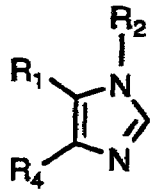
The above description fully discloses the invention including preferred embodiments thereof. Modifications and improvements of the embodiments specifically disclosed herein are within the scope of the following claims. Without further elaboration, it is believed that one skilled in the are can, using the preceding description, utilize the present invention to its fullest extent. Therefore the Examples herein are to be construed as merely illustrative and not a limitation of the scope of the

present invention in any way. The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows.

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What is Claimed is:

1. A compound of the formula:



(I)

wherein

R_1 is 4-pyridyl, pyrimidinyl, quinolyl, isoquinolinyl, quinazolin-4-yl, 1-imidazolyl or 1-benzimidazolyl, which heteroaryl ring is substituted with $N(R_{10})C(O)R_a$ or a halo substituted mono or di- C_{1-6} alkyl substituted amino and which ring is further optionally substituted with C_{1-4} alkyl, halogen, hydroxyl, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} alkylsulfinyl, CH_2OR_{12}, amino, mono and di- C_{1-6} alkyl substituted amino, or an N-heterocyclyl ring which ring has from 5 to 7 members and optionally contains an additional heteroatom selected from oxygen, sulfur or NR_{15};

R_4 is phenyl, naphth-1-yl or naphth-2-yl, or a heteroaryl, which is optionally substituted by one or two substituents, each of which is independently selected, and which, for a 4-phenyl, 4-naphth-1-yl, 5-naphth-2-yl or 6-naphth-2-yl substituent, is halogen, cyano, nitro, $-C(Z)NR_7R_{17}$, $-C(Z)OR_{16}$, $-(CR_{10}R_{20})_vCOR_{12}$, $-SR_5$, $-SOR_5$, $-OR_{12}$, halo-substituted-C_{1-4} alkyl, C_{1-4} alkyl, $-ZC(Z)R_{12}$, $-NR_{10}C(Z)R_{16}$, or $-(CR_{10}R_{20})_vNR_{10}R_{20}$ and which, for other positions of substitution, is halogen, cyano, $-C(Z)NR_{13}R_{14}$, $-C(Z)OR_3$, $-(CR_{10}R_{20})_{m''}COR_3$, $-S(O)_mR_3$, $-OR_3$, $-OR_{12}$, halo substituted C_{1-4} alkyl, C_{1-4} alkyl, $-(CR_{10}R_{20})_{m''}NR_{10}C(Z)R_3$, $-NR_{10}S(O)_{m'}R_8$, $-NR_{10}S(O)_{m'}NR_7R_{17}$, $-ZC(Z)R_3$, $-ZC(Z)R_{12}$, or $-(CR_{10}R_{20})_{m''}NR_{13}R_{14}$;

v is 0, or an integer having a value of 1 or 2;

m is 0, or the integer 1 or 2;

m' is an integer having a value of 1 or 2;

m" is 0, or an integer having a value of 1 to 5;

R_2 is C_{1-10} alkyl N_3, $-(CR_{10}R_{20})_{n'}OR_9$, heterocyclyl, heterocyclylC_{1-10} alkyl, C_{1-10}alkyl, halo-substituted C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{3-7}cycloalkylC_{1-10} alkyl, C_{5-7} cycloalkenyl, C_{5-7}cycloalkenylC_{1-10}alkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10}alkyl, $(CR_{10}R_{20})_nOR_{11}$, $(CR_{10}R_{20})_nS(O)_mR_{18}$, $(CR_{10}R_{20})_nNHS(O)_2R_{18}$, $(CR_{10}R_{20})_nNR_{13}R_{14}$, $(CR_{10}R_{20})_nNO_2$, $(CR_{10}R_{20})_nCN$, $(CR_{10}R_{20})_{n'}SO_2R_{18}$, $(CR_{10}R_{20})_nS(O)_{m'}NR_{13}R_{14}$, $(CR_{10}R_{20})_nC(Z)R_{11}$, $(CR_{10}R_{20})_nOC(Z)R_{11}$, $(CR_{10}R_{20})_nC(Z)OR_{11}$, $(CR_{10}R_{20})_nC(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nC(Z)NR_{11}OR_9$, $(CR_{10}R_{20})_nNR_{10}C(Z)R_{11}$, $(CR_{10}R_{20})_nNR_{10}C(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nN(OR_6)C(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nN(OR_6)C(Z)R_{11}$,

$(CR_{10}R_{20})_nC(=NOR_6)R_{11}$, $(CR_{10}R_{20})_nNR_{10}C(=NR_{19})NR_{13}R_{14}$, $(CR_{10}R_{20})_nOC(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nNR_{10}C(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nNR_{10}C(Z)OR_{10}$, 5-($R_{18}$)-1,2,4-oxadizaol-3-yl or 4-(R_{12})-5-($R_{18}R_{19}$)-4,5-dihydro-1,2,4-oxadiazol-3-yl; wherein the aryl, arylalkyl, heteroaryl, heteroaryl alkyl, cyclcoalkyl, cycloalkyl alkyl, heterocyclic and heterocyclic alkyl groups may be optionally substituted;

n is an integer having a value of 1 to 10;

n' is 0, or an integer having a value of 1 to 10;

Z is oxygen or sulfur;

Ra is hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, aryl, arylC_{1-4} alkyl, heteroaryl, heteroarylC_{1-4}alkyl, heterocyclyl, or heterocyclylC_{1-4} alkyl;

R_3 is heterocyclyl, heterocyclylC_{1-10} alkyl or R_8;

R_5 is hydrogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl or NR_7R_{17}, excluding the moieties -SR_5 being -SNR_7R_{17} and -$S(O)R_5$ being -SOH;

R_6 is hydrogen, a pharmaceutically acceptable cation, C_{1-10} alkyl, C_{3-7} cycloalkyl, aryl, arylC_{1-4} alkyl, heteroaryl, heteroaryl$_{1-10}$alkyl, heterocyclyl, aroyl, or C_{1-10} alkanoyl ;

R_7 and R_{17} is each independently selected from hydrogen or C_{1-4} alkyl or R_7 and R_{17} together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR_{15};

R_8 is C_{1-10} alkyl, halo-substituted C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{5-7} cycloalkenyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, $(CR_{10}R_{20})_nOR_{11}$, $(CR_{10}R_{20})_nS(O)_mR_{18}$, $(CR_{10}R_{20})_nNHS(O)_2R_{18}$, $(CR_{10}R_{20})_nNR_{13}R_{14}$; wherein the aryl, arylalkyl, heteroaryl, heteroaryl alkyl may be optionally substituted;

R_9 is hydrogen, -$C(Z)R_{11}$, optionally substituted C_{1-10} alkyl, $S(O)_2R_{18}$, optionally substituted aryl or optionally substituted aryl-C_{1-4} alkyl;

R_{10} and R_{20} is each independently selected from hydrogen or C_{1-4} alkyl;

R_{11} is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, heterocyclyl, heterocyclyl C_{1-10}alkyl, aryl, arylC_{1-10} alkyl, heteroaryl or heteroarylC_{1-10} alkyl;

R_{12} is hydrogen or R_{16};

R_{13} and R_{14} is each independently selected from hydrogen or optionally substituted C_{1-4} alkyl, optionally substituted aryl or optionally substituted aryl-C_{1-4} alkyl, or together with the nitrogen which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR9 ;

R_{15} is R_{10} or C(Z)-C_{1-4} alkyl;

R_{16} is C_{1-4} alkyl, halo-substituted-C_{1-4} alkyl, or C_{3-7} cycloalkyl;

R_{18} is C_{1-10} alkyl, C_{3-7} cycloalkyl, heterocyclyl, aryl, aryl$_{1-10}$alkyl, heterocyclyl, heterocyclyl-C_{1-10}alkyl, heteroaryl or heteroaryl$_{1-10}$alkyl;

R_{19} is hydrogen, cyano, C_{1-4} alkyl, C_{3-7} cycloalkyl or aryl;

or a pharmaceutically acceptable salt thereof.

2. The compound according to Claim 1 wherein R_1 is a 4-pyridyl or 4-pyrimindyl ring.

3. The compound according to Claim 2 wherein R_4 is an optionally substituted phenyl.

4. The compound according to Claim 3 wherein the phenyl is substituted one or more times independently by halogen,-SR_5, -$S(O)R_5$, -OR_{12}, halo-substituted-C_{1-4} alkyl, or C_{1-4} alkyl.

5. The compound according to Claim 1 wherein R_2 is selected from C_{1-10} alkyl, optionally substituted heterocylcyl, optionally substituted heterocyclylC_{1-10} alkyl, $(CR_{10}R_{20})_nNS(O)_2R_{18}$, $(CR_{10}R_{20})_nS(O)_mR_{18}$, optionally substituted arylC_{1-10} alkyl, or $(CR_{10}R_{20})_nNR_{13}R_{14}$.

6. The compound according to Claim 5 wherein R_2 is morpholino propyl, piperidine, N-methylpiperidine, N-benzylpiperidine, N-trifluoroethylpiperidine, or 2,2,6,6-tetramethylpiperidine.

7. The compound according to Claim 1 which is:

5-(2-Acetamido-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(4-morpholino-3-propyl)-imidazole;

5-(2-Acetamido-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(1-methyl-4-piperidinyl)-imidazole.

8. A pharmaceutical composition comprising a compound according to Claim 1 and a pharmaceutically acceptable carrier or diluent.

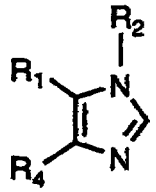
9. A method of treating a CSBP/RK/p38 kinase mediated disease, in a mammal in need thereof, which comprises administering to said mammal an effective amount of a compound of Formula (I) according to Claim 1.

10. The method according to claim 11 wherein the mammal is afflicted with a CSBP/RK/p38 kinase mediated disease which is cytokine mediated and the disease is

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selected from rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions, sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, asthma, adult respiratory distress syndrome, stroke, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcososis, bone resorption diseases, osteoporosis, reperfusion injury, graft vs. host reaction, allograft rejections, Crohn's disease, ulcerative colitis or pyresis.

11. A compound of the formula:



(II)

R_1 is 4-pyridyl, or pyrimidinyl ring substituted with a C_{1-4}alkyl amino group which ring may be further optionally substituted with C_{1-4} alkyl, halogen, hydroxyl, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} alkylsulfinyl, CH_2OR_{12}, amino, mono and di- C_{1-6} alkyl substituted amino, or an N-heterocyclyl ring which ring has from 5 to 7 members and optionally contains an additional heteroatom selected from oxygen, sulfur or NR_{15};

R_4 is phenyl, naphth-1-yl or naphth-2-yl, or a heteroaryl, which is optionally substituted by one or two substituents, each of which is independently selected, and which, for a 4-phenyl, 4-naphth-1-yl, 5-naphth-2-yl or 6-naphth-2-yl substituent, is halogen, cyano, nitro, $-C(Z)NR_7R_{17}$, $-C(Z)OR_{16}$, $-(CR_{10}R_{20})_vCOR_{12}$, $-SR_5$, $-SOR_5$, $-OR_{12}$, halo-substituted-C_{1-4} alkyl, C_{1-4} alkyl, $-ZC(Z)R_{12}$, $-NR_{10}C(Z)R_{16}$, or $-(CR_{10}R_{20})_vNR_{10}R_{20}$ and which, for other positions of substitution, is halogen, cyano, $-C(Z)NR_{13}R_{14}$, $-C(Z)OR_3$, $-(CR_{10}R_{20})_{m"}COR_3$, $-S(O)_mR_3$, $-OR_3$, $-OR_{12}$, halo substituted C_{1-4} alkyl, C_{1-4} alkyl, $-(CR_{10}R_{20})_{m"}NR_{10}C(Z)R_3$, $-NR_{10}S(O)_{m'}R_8$, $-NR_{10}S(O)_{m'}NR_7R_{17}$, $-ZC(Z)R_3$, $-ZC(Z)R_{12}$, or $-(CR_{10}R_{20})_{m"}NR_{13}R_{14}$;

v is 0, or an integer having a value of 1 or 2;

m is 0, or the integer 1 or 2;

m' is an integer having a value of 1 or 2,

m" is 0, or an integer having a value of 1 to 5;

R_2 is C_{1-10} alkyl N_3, $-(CR_{10}R_{20})_{n'}OR_9$, heterocyclyl, heterocyclylC_{1-10} alkyl, C_{1-10}alkyl, halo-substituted C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{3-7}cycloalkylC_{1-10} alkyl, C_{5-7} cycloalkenyl, C_{5-7}cycloalkenylC_{1-10}alkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10}alkyl, $(CR_{10}R_{20})_nOR_{11}$, $(CR_{10}R_{20})_nS(O)_mR_{18}$, $(CR_{10}R_{20})_nNHS(O)_2R_{18}$,

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$(CR_{10}R_{20})_nNR_{13}R_{14}$, $(CR_{10}R_{20})_nNO_2$, $(CR_{10}R_{20})_nCN$, $(CR_{10}R_{20})_{n'}SO_2R_{18}$, $(CR_{10}R_{20})_nS(O)_{m'}NR_{13}R_{14}$, $(CR_{10}R_{20})_nC(Z)R_{11}$, $(CR_{10}R_{20})_nOC(Z)R_{11}$, $(CR_{10}R_{20})_nC(Z)OR_{11}$, $(CR_{10}R_{20})_nC(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nC(Z)NR_{11}OR_9$, $(CR_{10}R_{20})_nNR_{10}C(Z)R_{11}$, $(CR_{10}R_{20})_nNR_{10}C(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nN(OR_6)C(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nN(OR_6)C(Z)R_{11}$, $(CR_{10}R_{20})_nC(=NOR_6)R_{11}$, $(CR_{10}R_{20})_nNR_{10}C(=NR_{19})NR_{13}R_{14}$, $(CR_{10}R_{20})_nOC(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nNR_{10}C(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nNR_{10}C(Z)OR_{10}$, 5-($R_{18}$)-1,2,4-oxadizaol-3-yl or 4-(R_{12})-5-($R_{18}R_{19}$)-4,5-dihydro-1,2,4-oxadiazol-3-yl; wherein the aryl, arylalkyl, heteroaryl, heteroaryl alkyl, cyclcoalkyl, cycloalkyl alkyl, heterocyclic and heterocyclic alkyl groups may be optionally substituted;

n is an integer having a value of 1 to 10;

n' is 0, or an integer having a value of 1 to 10;

Z is oxygen or sulfur;

Ra is hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, aryl, arylC_{1-4} alkyl, heteroaryl, heteroarylC_{1-4}alkyl, heterocyclyl, or heterocyclylC_{1-4} alkyl;

R3 is heterocyclyl, heterocyclylC_{1-10} alkyl or R8;

R5 is hydrogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl or NR_7R_{17}, excluding the moieties $-SR_5$ being $-SNR_7R_{17}$ and $-S(O)R_5$ being -SOH;

R6 is hydrogen, a pharmaceutically acceptable cation, C_{1-10} alkyl, C_{3-7} cycloalkyl, aryl, arylC_{1-4} alkyl, heteroaryl, heteroaryl$_{1-10}$alkyl, heterocyclyl, aroyl, or C_{1-10} alkanoyl ;

R7 and R_{17} is each independently selected from hydrogen or C_{1-4} alkyl or R7 and R_{17} together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR_{15};

R8 is C_{1-10} alkyl, halo-substituted C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{5-7} cycloalkenyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, $(CR_{10}R_{20})_nOR_{11}$, $(CR_{10}R_{20})_nS(O)_mR_{18}$, $(CR_{10}R_{20})_nNHS(O)_2R_{18}$, $(CR_{10}R_{20})_nNR_{13}R_{14}$; wherein the aryl, arylalkyl, heteroaryl, heteroaryl alkyl may be optionally substituted;

R9 is hydrogen, $-C(Z)R_{11}$, optionally substituted C_{1-10} alkyl, $S(O)_2R_{18}$, optionally substituted aryl or optionally substituted aryl-C_{1-4} alkyl;

R_{10} and R_{20} is each independently selected from hydrogen or C_{1-4} alkyl;

R_{11} is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, heterocyclyl, heterocyclyl C_{1-10}alkyl, aryl, arylC_{1-10} alkyl, heteroaryl or heteroarylC_{1-10} alkyl;

R_{12} is hydrogen or R_{16};

R_{13} and R_{14} is each independently selected from hydrogen or optionally substituted C_{1-4} alkyl, optionally substituted aryl or optionally substituted aryl-C_{1-4} alkyl, or

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together with the nitrogen which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR9 ;

R_{15} is R_{10} or C(Z)-C_{1-4} alkyl;

R_{16} is C_{1-4} alkyl, halo-substituted-C_{1-4} alkyl, or C_{3-7} cycloalkyl;

R_{18} is C_{1-10} alkyl, C_{3-7} cycloalkyl, heterocyclyl, aryl, aryl$_{1-10}$alkyl, heterocyclyl, heterocyclyl-C_{1-10}alkyl, heteroaryl or heteroaryl$_{1-10}$alkyl;

R_{19} is hydrogen, cyano, C_{1-4} alkyl, C_{3-7} cycloalkyl or aryl;

or a pharmaceutically acceptable salt thereof.

12. The compound according to Claim 11 wherein R_1 is a 4-pyrimindyl ring.

13. The compound according to Claim 11 or 12 wherein R_4 is an optionally substituted phenyl.

14. The compound according to Claim 13 wherein the phenyl is substituted one or more times independently by halogen,-SR_5, -S(O)R_5, -OR_{12}, halo-substituted-C_{1-4} alkyl, or C_{1-4} alkyl.

15. The compound according to any of Claims 11 to 13 wherein R_2 is selected from C_{1-10} alkyl, optionally substituted heterocylcyl, optionally substituted heterocyclylC_{1-10} alkyl, $(CR_{10}R_{20})_nNS(O)_2R_{18}$, $(CR_{10}R_{20})_nS(O)_mR_{18}$, optionally substituted arylC_{1-10} alkyl, or $(CR_{10}R_{20})_nNR_{13}R_{14}$.

16. The compound according to Claim 15 wherein R_2 is morpholino propyl, piperidine, N-methylpiperidine, N-benzylpiperidine, N-trifluoroethylpiperidine, N-trifluoroacetyl or 2,2,6,6-tetramethylpiperidine.

17. The compound according to Claim 11 which is:

5-[(2-Methylamino)pyrimidin-4-yl]-4-(4-fluorophenyl)-1-(4-methylpiperidin-4-yl)-imidazole;

5-[(2-Methylamino)pyrimidin-4-yl]-4-(4-fluorophenyl)-1-(4-morpholinoprop-3-yl)imidazole;

5-[(2-Methylamino)pyrimidin-4-yl]-4-(4-fluorophenyl)-1-(4-piperidinyl)imidazole;

5-[(2-Ethylamino)pyrimidin-4-yl]-4-(4-fluorophenyl)-1-(1-methylpiperdin-4-yl)-imidazole;

4-(4-Fluorophenyl)-5-[2-(isopropyl)aminopyrimidiny-4-yl]-1-(1-methylpiperdin-4-yl)imidazole;

5-[(2-Methylamino)pyrimidin-4-yl]-4-(4-fluorophenyl)-1-(2,2,6,6-tetramethyl-

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piperidin-4-yl)imidazole;
5-(2-Methylaminopyrimidin-4-yl)-4-(4-fluorophenyl)-1-(2-cyanoethyl)imidazole;
5-(2-Methylamino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-[1-(2,2,2-trifluoroethyl)-piperidin-4-yl]imidazole;
5-(2-aminopyrimidin-4-yl)-4-(4-fluorophenyl)-1-[1-(2,2,2-trifluoroethyl) piperidin-4-yl] imidazole; or
5-(2-Aminopyrimidin-4-yl)-4-(4-fluorophenyl)-1-[(1-trifluoroacetyl) piperidin-4-yl]imidazole.

18. A pharmaceutical composition comprising a compound according to any of Claims 11 to 17 and a pharmaceutically acceptable carrier or diluent.

19. A method of treating a cytokine mediated disease, in a mammal in need thereof, which comprises administering to said mammal an effective amount of a compound of Formula (II) according to Claim 11.

20. The method according to claim 11 wherein the mammal is afflicted with a cytokine mediated disease selected from rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions, sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, asthma, adult respiratory distress syndrome, stroke, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcososis, bone resorption diseases, osteoporosis, reperfusion injury, graft vs. host reaction, allograft rejections, Crohn's disease, ulcerative colitis or pyresis.

21. A method of treating inflammation in a mammal in need thereof, which comprises administering to said mammal an effective amount of a compound of Formula (II) according to Claim 11.

22. A compound which is:
5-[4-(2-Methylthio)pyrimidinyl}-4-(4-fluorophenyl)-1-(4-piperidine)imidazole:
4-(Fluorophenyl)-1-(1-methyl-4-piperidinyl)-5-(2-methylthio-4-pyrimidinyl)imidazole:
4-(Fluorophenyl)-1-(1-methyl-4-piperidinyl)-5-(2-methysulfinyl-4-pyrimidinyl)imidazole;
1-tert-Butyl-4-(4-fluorophenyl)-5-(2-methysulfinyl-4-pyrimidinyl)imidazole:
5-(2-Amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(tetrahydro-4-thiopyranyl)-imidazole ;
5-(2-Amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(tetrahydro-4-pyranyl)imidazole:
5-(2-Amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(tetrahydro-4-sulfinylpyranyl)-imidazole:

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5-(2-Amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(tetrahydro-4-sulfonylpyranyl)-imidazole:

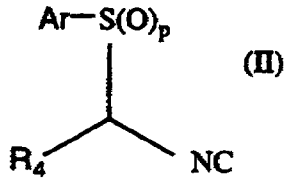
5-(2-Amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(1-trifluoroacetyl-4-piperidinyl)-imidazole;

5-(2-Amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-[1-(2,2,2-trifluoroethyl)-4-piperidinyl] imidazole;

5-(4-Pyridyl)-4-(4-fluorophenyl)-1-(4-piperidinyl) imidazole; or

5-(4-Pyridyl)-4-(4-fluorophenyl)-1-(1-t-butoxy carbonyl-4-piperidinyl) imidazole.

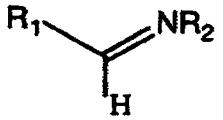
23. A process for preparing a compound of Formula (A), as defined below, which comprises reacting a compound of the Formula (IIa) :



(II)

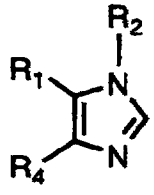
(IIa)

with a compound of the Formula (III):



(III)

wherein p is 2; and a base strong enough to deprotonate the isonitrile moiety of Formula (II); and wherein the imine of Formula (III), is formed in situ prior to reaction with Formula (IIa); and R_1, R_2 and R_4 are as defined below for Formula (A) or are precursors of the groups R_1, R_2 and R_4 and Ar is an optionally substituted phenyl group, and thereafter if necessary, converting a precursor of R_1, R_2 and R_4 to a group R_1, R_2 and R_4: wherein a compound of formula (A) is



(A)

R_1 is 4-pyridyl, pyrimidinyl, quinolyl, isoquinolinyl, quinazolin-4-yl, 1-imidazolyl or 1-benzimidazolyl, which heteroaryl ring is optionally substituted with one or two substituents each of which is independently selected from C_{1-4} alkyl, halogen, hydroxyl, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} alkylsulfinyl, CH_2OR_{12}, amino, mono or di-C_{1-6} alkyl substituted amino, $N(R_{10})C(O)R_a$ or an N-heterocyclyl ring

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which ring has from 5 to 7 members and optionally contains an additional heteroatom selected from oxygen, sulfur or NR_{15};

R_4 is phenyl, naphth-1-yl or naphth-2-yl, or a heteroaryl, which is optionally substituted by one or two substituents, each of which is independently selected, and which, for a 4-phenyl, 4-naphth-1-yl, 5-naphth-2-yl or 6-naphth-2-yl substitiuent, is halogen, cyano, nitro, $-C(Z)NR_7R_{17}$, $-C(Z)OR_{16}$, $-(CR_{10}R_{20})_vCOR_{12}$, $-SR_5$, $-SOR_5$, $-OR_{12}$, halo-substitutedC_{1-4} alkyl, C_{1-4} alkyl, $-ZC(Z)R_{12}$, $-NR_{10}C(Z)R_{16}$, or $-(CR_{10}R_{20})_vNR_{10}R_{20}$ and which, for other positions of substitution, is halogen, cyano, $-C(Z)NR_{13}R_{14}$, $-C(Z)OR_3$, $-(CR_{10}R_{20})_{m''}COR_3$, $-S(O)_mR_3$, $-OR_3$, halo-substitutedC_{1-4} alkyl, $-C_{1-4}$ alkyl, $-(CR_{10}R_{20})_{m''}NR_{10}C(Z)R_3$, $-NR_{10}S(O)_{m'}R_8$, $-NR_{10}S(O)_{m'}NR_7R_{17}$, $-ZC(Z)R_3$ or $-(CR_{10}R_{20})_{m''}NR_{13}R_{14}$;

v is 0, or an integer having a value of 1 or 2;

m is 0, or the integer 1 or 2;

m' is an integer having a value of 1 or 2,

m" is 0, or an integer having a value of 1 to 5;

R_2 is C_{1-10} alkyl N_3, $-(CR_{10}R_{20})_{n'}OR_9$, heterocyclyl, heterocyclylC_{1-10} alkyl, C_{1-10}alkyl, halo-substituted C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{3-7}cycloalkylC_{1-10} alkyl, C_{5-7} cycloalkenyl, C_{5-7}cycloalkenyl-C_{1-10}-alkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroaryl-C_{1-10}-alkyl, $(CR_{10}R_{20})_nOR_{11}$, $(CR_{10}R_{20})_nS(O)_mR_{18}$, $(CR_{10}R_{20})_nNHS(O)_2R_{18}$, $(CR_{10}R_{20})_nNR_{13}R_{14}$, $(CR_{10}R_{20})_nNO_2$, $(CR_{10}R_{20})_nCN$, $(CR_{10}R_{20})_{n'}SO_2R_{18}$, $(CR_{10}R_{20})_nS(O)_{m'}NR_{13}R_{14}$, $(CR_{10}R_{20})_nC(Z)R_{11}$, $(CR_{10}R_{20})_nOC(Z)R_{11}$, $(CR_{10}R_{20})_nC(Z)OR_{11}$, $(CR_{10}R_{20})_nC(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nC(Z)NR_{11}OR_9$, $(CR_{10}R_{20})_nNR_{10}C(Z)R_{11}$, $(CR_{10}R_{20})_nNR_{10}C(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nN(OR_6)C(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nN(OR_6)C(Z)R_{11}$, $(CR_{10}R_{20})_nC(=NOR_6)R_{11}$, $(CR_{10}R_{20})_nNR_{10}C(=NR_{19})NR_{13}R_{14}$, $(CR_{10}R_{20})_nOC(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nNR_{10}C(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nNR_{10}C(Z)OR_{10}$, 5-($R_{18}$)-1,2,4-oxadizaol-3-yl or 4-(R_{12})-5-($R_{18}R_{19}$)-4,5-dihydro-1,2.4-oxadiazol-3-yl; wherein the aryl, arylalkyl, heteroaryl, heteroaryl alkyl, heterocyclic and heterocyclic alkyl groups may be optionally substituted;

n is an integer having a value of 1 to 10;

n' is 0, or an integer having a value of 1 to 10;

Z is oxygen or sulfur;

R_a is hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, aryl, arylC_{1-4} alkyl, heteroaryl, heteroarylC_{1-4}alkyl, heterocyclyl, or heterocyclylC_{1-4} alkyl;

R_3 is heterocyclyl, heterocyclylC_{1-10} alkyl or R_8;

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R_5 is hydrogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl or NR_7R_{17}, excluding the moieties $-SR_5$ being $-SNR_7R_{17}$ and $-SOR_5$ being -SOH;

R_6 is hydrogen, a pharmaceutically acceptable cation, C_{1-10} alkyl, C_{3-7} cycloalkyl, aryl, arylC_{1-4} alkyl, heteroaryl, heteroarylalkyl, heterocyclyl, aroyl, or C_{1-10} alkanoyl;

R_7 and R_{17} is each independently selected from hydrogen or C_{1-4} alkyl or R_7 and R_{17} together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR_{15};

R_8 is C_{1-10} alkyl, halo-substituted C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{5-7} cycloalkenyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, $(CR_{10}R_{20})_nOR_{11}$, $(CR_{10}R_{20})_nS(O)_mR_{18}$, $(CR_{10}R_{20})_nNHS(O)_2R_{18}$, $(CR_{10}R_{20})_nNR_{13}R_{14}$; wherein the aryl, arylalkyl, heteroaryl, heteroaryl alkyl may be optionally substituted;

R_9 is hydrogen, $-C(Z)R_{11}$ or optionally substituted C_{1-10} alkyl, $S(O)_2R_{18}$, optionally substituted aryl or optionally substituted aryl-C_{1-4} alkyl;

R_{10} and R_{20} is each independently selected from hydrogen or C_{1-4} alkyl;

R_{11} is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, heterocyclyl, heterocyclyl C_{1-10}alkyl, aryl, arylC_{1-10} alkyl, heteroaryl or heteroarylC_{1-10} alkyl;

R_{12} is hydrogen or R_{16};

R_{13} and R_{14} is each independently selected from hydrogen or optionally substituted C_{1-4} alkyl, optionally substituted aryl or optionally substituted aryl-C_{1-4} alkyl, or together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR_9;

R_{15} is R_{10} or $C(Z)$-C_{1-4} alkyl;

R_{16} is C_{1-4} alkyl, halo-substituted-C_{1-4} alkyl, or C_{3-7} cycloalkyl;

R_{18} is C_{1-10} alkyl, C_{3-7} cycloalkyl, heterocyclyl, aryl, arylalkyl, heterocyclyl, heterocyclyl-C_{1-10}alkyl, heteroaryl or heteroarylalkyl;

R_{19} is hydrogen, cyano, C_{1-4} alkyl, C_{3-7} cycloalkyl or aryl;

or a phamaceutically acceptable salt thereof.

24. The process according to Claim 23 wherein the base is an amine, an amide, a carbonate, a hydride, or an alkyl or aryl lithium reagent, or a mono-, di- and tribasic phosphate.

25. The process according to Claim 23 wherein the imine is formed in situ by reacting an aldehyde of the formula R_1CHO, wherein R_1 is as defined for Formula (A),

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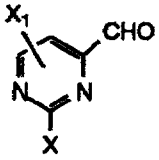
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with a primary amine of the formula R_2NH_2, wherein R_2 is as defined for Formula (A), and R_2 may be suitably protected as necessary.

26. The process according to Claim 25 wherein formation of the imine in situ utilizes dehydrating conditions.

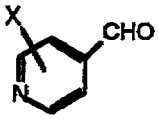
27. The process according to Claim 25 wherein the solvent is N,N-dimethyl-formamide (DMF), halogenated solvents, tetrahydrofuran (THF), dimethylsulfoxide (DMSO), alcohols, benzene, toluene, or DME.

28. The process according to Claim 25 wherein the aldehyde R_1CHO is a pyrimidine aldehyde of the formula:



wherein X and X_1 are defined as an R_1 substituent group is Formula (A) according to Claim 23, to yield a compound of Formula (A) or a pharmaceutically acceptable salt thereof.

29. The process according to Claim 25 wherein the aldehyde R_1CHO is a pyridine aldehyde of the formula:



wherein X is defined as an R_1 substituent group in Formula (A) according to Claim 23, to yield a compound of Formula (A) or a pharmaceutically acceptable salt thereof.

30. The process according to Claim 25 wherein the primary amine R_2NH_2 is an optionally substituted heterocyclic amine or a heterocyclic C_{1-10} alkyl amine.

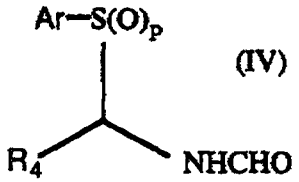
31. The process according to Claim 30 wherein the primary amine R_2NH_2 is 4-amino piperidine, 1-methyl-4-aminopiperidine, or 4-amino-2,2, 6,6-tetramethyl piperidine.

32. The process according to Claim 25 wherein the aldehyde of the formula R_1CHO, is formed in situ.

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33. The process according to Claim 32 wherein the aldehyde is formed by the hydrolysis of an acetal of the formula $R_1CH(OR_a)_2$ wherein R_1 is defined in Formula (A), and R_a is alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl.

34. A process for preparing a compound of the formula:



(IV)

wherein p is 0, or 2; Ar is an optionally substituted phenyl or naphtyl;
R_4 is as defined for Formula (A) compounds, according to Claim 23;
which process comprises reacting together an aldehyde of the formula:

R_4-CHO

wherein R_4 is as defined for Formula (A) compounds; with formamide, a dehydrating agent, an acid catalyst, p-toluenesulfinic acid, and an organic solvent.

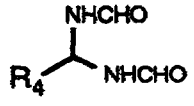
35. The process according to Claim 34 wherein the dehydrating agent and an acid catalyst are the same.

36. The process according to Claim 35 wherein the dehydrating agent and an acid catalyst is TMSCl.

37. The process according to Claim 34 wherein the acid catalyst is an anhydrous acid, TMSCl, p-toluenesulfonic acid, camphorsulfonic acid, or hydrogen chloride.

38. The process according to Claim 34 wherein the solvent is toluene or acetonitile or mixtures thereof.

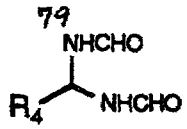
39. The process according to Claim 34 wherein the reaction forms an intermediate of the formula:



wherein R_4 is as defined for Formula (A) in Claim 23.

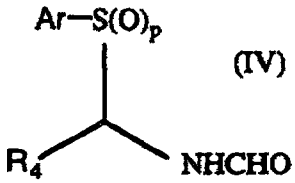
40. A compound of the formula

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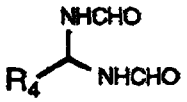
wherein R_4 is as defined for Formula (A), in Claim 23; provided that R_4 is other than an unsubstituted phenyl.

41. A process for preparing a compound of the formula:



(IV)

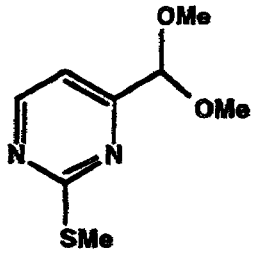
wherein p is 2; Ar is an optionally substituted phenyl or naphtyl; R_4 is as defined for Formula (A) compounds, according to Claim 23: which process comprises reacting a compound of the formula



wherein R_4 is as defined for Formula (A); with p-toluenesulfinic acid, an acid catalyst, an organic solvent.

42. The process according to Claim 41 wherein the solvent is toluene or acetonitile or mixtures thereof.

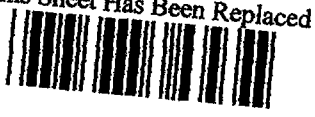
43. A process for making 2-thiomethylpyrimidine aldehyde which process comprises reacting a compound of the formula:



with acetic acid and a catalytic amount of concentrated sulfuric acid; or using aqueous hydrochloric acid.

44. A method of inhibiting the synthesis of prostaglandin endoperoxide synthase-2 (PGHS-2) in a mammal in need thereof, which comprises administering to said mammal an effective amount of a compound of Formula (A) according to Claim 23.

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45. The method according to Claim 44 wherein inhibition of PGHS-2 is used in the prophylaxis or therapeutic treatment of edema, fever, algesia, neuromuscular pain, headache, cancer pain, or arthritic pain.

46. The method according to Claim 44 wherein the compound is :
5-[4-(2-Amino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-morpholinoprop-3-yl)imidazole;
5-[4-(2-Methylamino)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-morpholinoprop-3-yl)imidazole;
5-[4-(2-Aminopyrimidinyl)-4-(4-fluorophenyl)-1-(1-benzyl-4-piperidinyl)imidazole;
5-(2-Amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(4-piperidinyl)imidazole;
5-(2-Amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(1-methylpiperidin-4-yl)-imidazole;
5-[4-(2-Methylamino)pyrimidinyl}-4-(4-fluorophenyl)-1-(1-methylpiperidin-4-yl)-imidazole;
5-(2-Aminopyrimidin-4-yl)-4-(4-fluorophenyl)-1-(2,2,6,6-tetramethylpiperidin-4-yl)imidazole;
5-[4-(2-N-Methylamino)pyrimidinyl}-4-(4-fluorophenyl)-1-(4-piperidine)imidazole;
5-(2-Methylamino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-[1-(2,2,2-trifluoroethyl)-4-piperidinyl] imidazole;
5-(2-amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-[1-(2,2,2-trifluoroethyl)-4-piperidinyl] imidazole; or a phamaceutically acceptable salt thereof.

47. A method of inhibiting the synthesis of COX-2 which comprises administering to a mammal in need thereof, an effective amount of a compound of Formula (A) as defined in Claim 23.

48. A method of inhibiting a CSBP/RK/p38 kinase, which comprises administering to a mammal in need thereof, an effective amount of a compound of Formula (A) as defined in Claim 23.

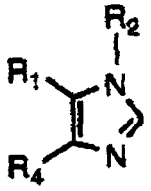
49. The method according to Claim 48 wherein the compound is a compound of Formula (II).

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What is claimed is:

1. A compound of the formula:



(II)

R_1 is a pyrimidin-4-yl ring substituted with a C_{1-4}alkyl amino group which ring may be further optionally substituted with C_{1-4} alkyl, halogen, hydroxyl, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} alkylsulfinyl, CH_2OR_{12}, amino, mono and di- C_{1-6} alkyl substituted amino, or an N-heterocyclyl ring which ring has from 5 to 7 members and optionally contains an additional heteroatom selected from oxygen, sulfur or NR_{15};

R_4 is phenyl, naphth-1-yl or naphth-2-yl, or a heteroaryl, which is optionally substituted by one or two substituents, each of which is independently selected, and which, for a 4-phenyl, 4-naphth-1-yl, 5-naphth-2-yl or 6-naphth-2-yl substituent, is halogen, cyano, nitro, $C(Z)NR_7R_{17}$, $C(Z)OR_{16}$, $(CR_{10}R_{20})_vCOR_{12}$, SR_5, SOR_5, OR_{12}, halo-substituted-C_{1-4} alkyl, C_{1-4} alkyl, $ZC(Z)R_{12}$, $NR_{10}C(Z)R_{16}$, or $(CR_{10}R_{20})_vNR_{10}R_{20}$ and which, for other positions of substitution, is halogen, cyano, $C(Z)NR_{13}R_{14}$, $C(Z)OR_3$, $(CR_{10}R_{20})_{m''}COR_3$, $S(O)_mR_3$, OR_3, OR_{12}, halo substituted C_{1-4} alkyl, C_{1-4} alkyl, $(CR_{10}R_{20})_{m''}NR_{10}C(Z)R_3$, $NR_{10}S(O)_{m'}R_8$, $NR_{10}S(O)_{m'}NR_7R_{17}$, $ZC(Z)R_3$, $ZC(Z)R_{12}$, or $(CR_{10}R_{20})_{m''}NR_{13}R_{14}$;

v is 0, or an integer having a value of 1 or 2;

m is 0, or the integer 1 or 2;

m' is an integer having a value of 1 or 2,

m" is 0, or an integer having a value of 1 to 5;

R_2 is C_{1-10} alkyl N_3, $(CR_{10}R_{20})_{n'}OR_9$, heterocyclyl, heterocyclylC_{1-10} alkyl, C_{1-10}alkyl, halo-substituted C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{3-7}cycloalkylC_{1-10} alkyl, C_{5-7} cycloalkenyl, C_{5-7}cycloalkenylC_{1-10}alkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10}alkyl, $(CR_{10}R_{20})_nOR_{11}$, $(CR_{10}R_{20})_nS(O)_mR_{18}$, $(CR_{10}R_{20})_nNHS(O)_2R_{18}$, $(CR_{10}R_{20})_nNR_{13}R_{14}$, $(CR_{10}R_{20})_nNO_2$, $(CR_{10}R_{20})_nCN$, $(CR_{10}R_{20})_{n'}SO_2R_{18}$, $(CR_{10}R_{20})_nS(O)_{m'}NR_{13}R_{14}$, $(CR_{10}R_{20})_nC(Z)R_{11}$, $(CR_{10}R_{20})_nOC(Z)R_{11}$, $(CR_{10}R_{20})_nC(Z)OR_{11}$, $(CR_{10}R_{20})_nC(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nC(Z)NR_{11}OR_9$, $(CR_{10}R_{20})_nNR_{10}C(Z)R_{11}$, $(CR_{10}R_{20})_nNR_{10}C(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nN(OR_6)C(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nN(OR_6)C(Z)R_{11}$,

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$(CR_{10}R_{20})_nC(=NOR_6)R_{11}$, $(CR_{10}R_{20})_nNR_{10}C(=NR_{19})NR_{13}R_{14}$, $(CR_{10}R_{20})_nOC(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nNR_{10}C(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nNR_{10}C(Z)OR_{10}$, 5-($R_{18}$)-1,2,4-oxadizaol-3-yl or 4-(R_{12})-5-($R_{18}R_{19}$)-4,5-dihydro-1,2,4-oxadiazol-3-yl; wherein the aryl, arylalkyl, heteroaryl, heteroaryl alkyl, cycloalkyl, cycloalkyl alkyl, heterocyclic and heterocyclic alkyl groups may be optionally substituted;

n is an integer having a value of 1 to 10;

n' is 0, or an integer having a value of 1 to 10;

Z is oxygen or sulfur;

Ra is hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, aryl, arylC_{1-4} alkyl, heteroaryl, heteroarylC_{1-4}alkyl, heterocyclyl, or heterocyclylC_{1-4} alkyl;

R_3 is heterocyclyl, heterocyclylC_{1-10} alkyl or R_8;

R_5 is hydrogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl or NR_7R_{17}, excluding the moieties -SR_5 being -SNR_7R_{17} and -$S(O)R_5$ being -SOH;

R_6 is hydrogen, a pharmaceutically acceptable cation, C_{1-10} alkyl, C_{3-7} cycloalkyl, aryl, arylC_{1-4} alkyl, heteroaryl, heteroaryl$_{1-10}$alkyl, heterocyclyl, aroyl, or C_{1-10} alkanoyl ;

R_7 and R_{17} is each independently selected from hydrogen or C_{1-4} alkyl or R_7 and R_{17} together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR_{15};

R_8 is C_{1-10} alkyl, halo-substituted C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{5-7} cycloalkenyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, $(CR_{10}R_{20})_nOR_{11}$, $(CR_{10}R_{20})_nS(O)_mR_{18}$, $(CR_{10}R_{20})_nNHS(O)_2R_{18}$, $(CR_{10}R_{20})_nNR_{13}R_{14}$; wherein the aryl, arylalkyl, heteroaryl, heteroaryl alkyl may be optionally substituted;

R_9 is hydrogen, $C(Z)R_{11}$, optionally substituted C_{1-10} alkyl, $S(O)_2R_{18}$, optionally substituted aryl or optionally substituted aryl-C_{1-4} alkyl;

R_{10} and R_{20} is each independently selected from hydrogen or C_{1-4} alkyl;

R_{11} is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, heterocyclyl, heterocyclyl C_{1-10}alkyl, aryl, arylC_{1-10} alkyl, heteroaryl or heteroarylC_{1-10} alkyl;

R_{12} is hydrogen or R_{16};

R_{13} and R_{14} is each independently selected from hydrogen or optionally substituted C_{1-4} alkyl, optionally substituted aryl or optionally substituted aryl-C_{1-4} alkyl, or together with the nitrogen which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR_9 ;

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R_{15} is R_{10} or C(Z)-C_{1-4} alkyl;
R_{16} is C_{1-4} alkyl, halo-substituted-C_{1-4} alkyl, or C_{3-7} cycloalkyl;
R_{18} is C_{1-10} alkyl, C_{3-7} cycloalkyl, heterocyclyl, aryl, aryl$_{1-10}$alkyl, heterocyclyl, heterocyclyl-C_{1-10}alkyl, heteroaryl or heteroaryl$_{1-10}$alkyl;
R_{19} is hydrogen, cyano, C_{1-4} alkyl, C_{3-7} cycloalkyl or aryl;
or a pharmaceutically acceptable salt thereof.

2. The compound according to Claim 11 wherein R_1 is a 4-pyrimindyl ring substituted in the 2-position by the C_{1-4} alkylamino group.

3. The compound according to Claim 1 or 2 wherein R_4 is an optionally substituted phenyl.

4. The compound according to Claim 3 wherein the phenyl is substituted one or more times independently by halogen, SR_5, $S(O)R_5$, OR_{12}, halo-substituted-C_{1-4} alkyl, or C_{1-4} alkyl.

5. The compound according to any of Claims 1 to 4 wherein R_2 is selected from C_{1-10} alkyl, optionally substituted heterocylcyl, optionally substituted heterocyclylC_{1-10} alkyl, $(CR_{10}R_{20})_nNS(O)_2R_{18}$, $(CR_{10}R_{20})_nS(O)_mR_{18}$, optionally substituted arylC_{1-10} alkyl, or $(CR_{10}R_{20})_nNR_{13}R_{14}$.

6. The compound according to Claim 5 wherein R_2 is morpholino propyl, piperidine, N-methylpiperidine, N-benzylpiperidine, N-trifluoroethylpiperidine, N-trifluoroacetyl or 2,2,6,6-tetramethylpiperidine.

7. The compound according to Claim 1 which is:
5-[(2-Methylamino)pyrimidin-4-yl]-4-(4-fluorophenyl)-1-(4-methylpiperidin-4-yl)-imidazole;
5-[(2-Methylamino)pyrimidin-4-yl]-4-(4-fluorophenyl)-1-(4-morpholinoprop-3-yl)imidazole;
5-[(2-Methylamino)pyrimidin-4-yl]-4-(4-fluorophenyl)-1-(4-piperidinyl)imidazole;
5-[(2-Ethylamino)pyrimidin-4-yl]-4-(4-fluorophenyl)-1-(1-methylpiperdin-4-yl)-imidazole;
4-(4-Fluorophenyl)-5-[2-(isopropyl)aminopyrimidiny-4-yl]-1-(1-methylpiperdin-4-yl)imidazole;
5-[(2-Methylamino)pyrimidin-4-yl]-4-(4-fluorophenyl)-1-(2,2,6,6-tetramethyl-piperidin-4-yl)imidazole;
5-(2-Methylaminopyrimidin-4-yl)-4-(4-fluorophenyl)-1-(2-cyanoethyl)imidazole;
5-(2-Methylamino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-[1-(2,2,2-trifluoroethyl)-piperidin-4-yl]imidazole;
5-(2-aminopyrimidin-4-yl)-4-(4-fluorophenyl)-1-[1-(2,2,2-trifluoroethyl) piperidin-4-yl] imidazole; or
5-(2-Aminopyrimidin-4-yl)-4-(4-fluorophenyl)-1-[(1-trifluoroacetyl) piperidin-4-yl]imidazole.

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8. A pharmaceutical composition comprising a compound according to any of Claims 1 to 7 and a pharmaceutically acceptable carrier or diluent.

9. A method of treating a cytokine mediated disease, in a mammal in need thereof, which comprises administering to said mammal an effective amount of a compound of Formula (II) according to Claim 1.

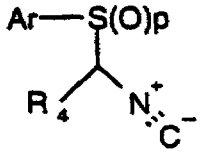
10. The method according to claim 1 wherein the mammal is afflicted with a cytokine mediated disease selected from rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions, sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, asthma, adult respiratory distress syndrome, stroke, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcososis, bone resorption diseases, osteoporosis, reperfusion injury, graft vs. host reaction, allograft rejections, Crohn's disease, ulcerative colitis or pyresis.

11. A method of treating inflammation in a mammal in need thereof, which comprises administering to said mammal an effective amount of a compound of Formula (II) according to Claim 1.

12. A compound which is:
5-[4-(2-Methylthio)pyrimidinyl]-4-(4-fluorophenyl)-1-(4-piperidine)imidazole;
4-(Fluorophenyl)-1-(1-methyl-4-piperidinyl)-5-(2-methylthio-4-pyrimidinyl)imidazole;
4-(Fluorophenyl)-1-(1-methyl-4-piperidinyl)-5-(2-methysulfinyl-4-pyrimidinyl)imidazole;
1-tert-Butyl-4-(4-fluorophenyl)-5-(2-methysulfinyl-4-pyrimidinyl)imidazole;
5-(2-Amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(tetrahydro-4-thiopyranyl)-imidazole ;
5-(2-Amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(tetrahydro-4-pyranyl)imidazole;
5-(2-Amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(tetrahydro-4-sulfinylpyranyl)-imidazole;
5-(2-Amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(tetrahydro-4-sulfonylpyranyl)-imidazole;
5-(2-Amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(1-trifluoroacetyl-4-piperidinyl)-imidazole;
5-(2-Amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-[1-(2,2,2-trifluoroethyl)-4-piperidinyl] imidazole;
5-(4-Pyridyl)-4-(4-fluorophenyl)-1-(4-piperidinyl) imidazole; or
5-(4-Pyridyl)-4-(4-fluorophenyl)-1-(1-t-butoxy carbonyl-4-piperidinyl) imidazole.

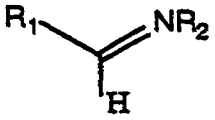
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13. A process for preparing a compound of Formula (A), as defined below, which comprises reacting a compound of the Formula (IIa) :



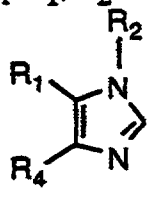
(IIa)

with a compound of the Formula (III):



(III)

wherein p is 2; and a base strong enough to deprotonate the isonitrile moiety of Formula (IIa); and wherein the imine of Formula (III), is formed in situ prior to reaction with Formula (IIa); and R_1, R_2 and R_4 are as defined below for Formula (A) or are precursors of the groups R_1, R_2 and R_4 and Ar is an optionally substituted phenyl group, and thereafter if necessary, converting a precursor of R_1, R_2 and R_4 to a group R_1, R_2 and R_4; wherein a compound of formula (A) is



(A)

R_1 is 4-pyridyl, pyrimidinyl, quinolyl, isoquinolinyl, quinazolin-4-yl, 1-imidazolyl or 1-benzimidazolyl, which heteroaryl ring is optionally substituted with one or two substituents each of which is independently selected from C_{1-4} alkyl, halogen, hydroxyl, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} alkylsulfinyl, CH_2OR_{12}, amino, mono or di-C_{1-6} alkyl substituted amino, $N(R_{10})C(O)R_a$ or an N-heterocyclyl ring which ring has from 5 to 7 members and optionally contains an additional heteroatom selected from oxygen, sulfur or NR_{15};

R_4 is phenyl, naphth-1-yl or naphth-2-yl, or a heteroaryl, which is optionally substituted by one or two substituents, each of which is independently selected, and which, for a 4-phenyl, 4-naphth-1-yl, 5-naphth-2-yl or 6-naphth-2-yl substitiuent, is halogen, cyano, nitro, $C(Z)NR_7R_{17}$, $C(Z)OR_{16}$, $(CR_{10}R_{20})_vCOR_{12}$, SR_5, SOR_5, OR_{12}, halo-substitutedC_{1-4} alkyl, C_{1-4} alkyl, $ZC(Z)R_{12}$, $NR_{10}C(Z)R_{16}$, or $(CR_{10}R_{20})_vNR_{10}R_{20}$ and which, for other positions of substitution, is halogen, cyano, $C(Z)NR_{13}R_{14}$, $C(Z)OR_3$, $(CR_{10}R_{20})_m"COR_3$, $S(O)_mR_3$, OR_3, halo-substitutedC_{1-4} alkyl, C_{1-4} alkyl, $(CR_{10}R_{20})_m"NR_{10}C(Z)R_3$, $NR_{10}S(O)_m'R_8$, $-NR_{10}S(O)_m'NR_7R_{17}$, $ZC(Z)R_3$ or $(CR_{10}R_{20})_m"NR_{13}R_{14}$;

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v is 0, or an integer having a value of 1 or 2;

m is 0, or the integer 1 or 2;

m' is an integer having a value of 1 or 2,

m" is 0, or an integer having a value of 1 to 5;

R_2 is C_{1-10} alkyl N_3, $(CR_{10}R_{20})_{n'}OR_9$, heterocyclyl, heterocyclylC_{1-10} alkyl, C_{1-10}alkyl, halo-substituted C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{3-7}cycloalkylC_{1-10} alkyl, C_{5-7} cycloalkenyl, C_{5-7}cycloalkenyl-C_{1-10}-alkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroaryl-C_{1-10}-alkyl, $(CR_{10}R_{20})_nOR_{11}$, $(CR_{10}R_{20})_nS(O)_mR_{18}$, $(CR_{10}R_{20})_nNHS(O)_2R_{18}$, $(CR_{10}R_{20})_nNR_{13}R_{14}$, $(CR_{10}R_{20})_nNO_2$, $(CR_{10}R_{20})_nCN$, $(CR_{10}R_{20})_{n'}SO_2R_{18}$, $(CR_{10}R_{20})_nS(O)_{m'}NR_{13}R_{14}$, $(CR_{10}R_{20})_nC(Z)R_{11}$, $(CR_{10}R_{20})_nOC(Z)R_{11}$, $(CR_{10}R_{20})_nC(Z)OR_{11}$, $(CR_{10}R_{20})_nC(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nC(Z)NR_{11}OR_9$, $(CR_{10}R_{20})_nNR_{10}C(Z)R_{11}$, $(CR_{10}R_{20})_nNR_{10}C(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nN(OR_6)C(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nN(OR_6)C(Z)R_{11}$, $(CR_{10}R_{20})_nC(=NOR_6)R_{11}$, $(CR_{10}R_{20})_nNR_{10}C(=NR_{19})NR_{13}R_{14}$, $(CR_{10}R_{20})_nOC(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nNR_{10}C(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nNR_{10}C(Z)OR_{10}$, 5-$(R_{18})$-1,2,4-oxadizaol-3-yl or 4-(R_{12})-5-$(R_{18}R_{19})$-4,5-dihydro-1,2,4-oxadiazol-3-yl; wherein the aryl, arylalkyl, heteroaryl, heteroaryl alkyl, heterocyclic and heterocyclic alkyl groups may be optionally substituted;

n is an integer having a value of 1 to 10;

n' is 0, or an integer having a value of 1 to 10;

Z is oxygen or sulfur;

R_a is hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, aryl, arylC_{1-4} alkyl, heteroaryl, heteroarylC_{1-4}alkyl, heterocyclyl, or heterocyclylC_{1-4} alkyl;

R_3 is heterocyclyl, heterocyclylC_{1-10} alkyl or R_8;

R_5 is hydrogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl or NR_7R_{17}, excluding the moieties SR_5 being SNR_7R_{17} and SOR_5 being SOH;

R_6 is hydrogen, a pharmaceutically acceptable cation, C_{1-10} alkyl, C_{3-7} cycloalkyl, aryl, arylC_{1-4} alkyl, heteroaryl, heteroarylalkyl, heterocyclyl, aroyl, or C_{1-10} alkanoyl;

R_7 and R_{17} is each independently selected from hydrogen or C_{1-4} alkyl or R_7 and R_{17} together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR_{15};

R_8 is C_{1-10} alkyl, halo-substituted C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{5-7} cycloalkenyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, $(CR_{10}R_{20})_nOR_{11}$, $(CR_{10}R_{20})_nS(O)_mR_{18}$, $(CR_{10}R_{20})_nNHS(O)_2R_{18}$, $(CR_{10}R_{20})_nNR_{13}R_{14}$; wherein the aryl, arylalkyl, heteroaryl, heteroaryl alkyl may be optionally substituted;

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R9 is hydrogen, C(Z)R11 or optionally substituted C1-10 alkyl, S(O)2R18, optionally substituted aryl or optionally substituted aryl-C1-4 alkyl;

R10 and R20 is each independently selected from hydrogen or C1-4 alkyl;

R11 is hydrogen, C1-10 alkyl, C3-7 cycloalkyl, heterocyclyl, heterocyclyl C1-10alkyl, aryl, arylC1-10 alkyl, heteroaryl or heteroarylC1-10 alkyl;

R12 is hydrogen or R16;

R13 and R14 is each independently selected from hydrogen or optionally substituted C1-4 alkyl, optionally substituted aryl or optionally substituted aryl-C1-4 alkyl, or together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR9;

R15 is R10 or C(Z)-C1-4 alkyl;

R16 is C1-4 alkyl, halo-substituted-C1-4 alkyl, or C3-7 cycloalkyl;

R18 is C1-10 alkyl, C3-7 cycloalkyl, heterocyclyl, aryl, arylalkyl, heterocyclyl, heterocyclyl-C1-10alkyl, heteroaryl or heteroarylalkyl;

R19 is hydrogen, cyano, C1-4 alkyl, C3-7 cycloalkyl or aryl;

or a phamaceutically acceptable salt thereof.

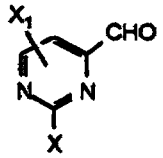
14. The process according to Claim 13 wherein the base is an amine, an amide, a carbonate, a hydride, an alkyl or aryl lithium reagent, or a mono-, di- or tribasic phosphate.

15. The process according to Claim 13 wherein the imine is formed in situ by reacting an aldehyde of the formula R1CHO, wherein R1 is as defined for Formula (A), with a primary amine of the formula R2NH2, wherein R2 is as defined for Formula (A), and R2 may be suitably protected as necessary.

16. The process according to Claim 15 wherein formation of the imine in situ utilizes dehydrating conditions.

17. The process according to Claim 15 wherein the solvent is N,N-dimethyl-formamide (DMF), halogenated solvents, tetrahydrofuran (THF), dimethylsulfoxide (DMSO), an alcohol, benzene, toluene, MeCN, or DME.

18. The process according to Claim 15 wherein the aldehyde R1CHO is a pyrimidine aldehyde of the formula:

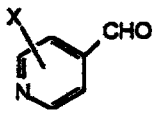


wherein X and X1 are defined as an R1 substituent group is Formula (A).

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19. The process according to Claim 15 wherein the aldehyde R_1CHO is a pyridine aldehyde of the formula:



wherein X is defined as an R_1 substituent group in Formula (A).

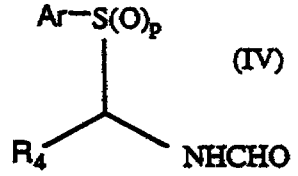
20. The process according to Claim 15 wherein the primary amine R_2NH_2 is an optionally substituted heterocyclic amine or a heterocyclic C_{1-10} alkyl amine.

21. The process according to Claim 20 wherein the primary amine R_2NH_2 is 4-amino piperidine, 1-methyl-4-aminopiperidine, or 4-amino-2,2, 6,6-tetramethyl piperidine.

22. The process according to Claim 15wherein the aldehyde of the formula R_1CHO is formed in situ.

23. The process according to Claim 22 wherein the aldehyde is formed by the hydrolysis of an acetal of the formula $R_1CH(OR_a)_2$ wherein R_1 is defined in Formula (A), and R_a is an alkyl, aryl, arylalkyl, heteroaryl, or heteroarylalkyl.

24. A process for preparing a compound of the formula:



(IV)

wherein p is 0, or 2; Ar is an optionally substituted phenyl or naphtyl;
R_4 is as defined for Formula (A) compounds, according to Claim 13;
which process comprises reacting together an aldehyde of the formula:

R_4-CHO

wherein R_4 is as defined for Formula (A) compounds; ArS(O)p H; wherein Ar and p are as defined above;
with formamide, an acid catalyst, p-toluenesulfinic acid, and optionally a dehydrating agent.

25. The process according to Claim 24 wherein the reaction process employs dehydrating agent which also provides hydrogen chloride.

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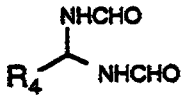
26. The process according to Claim 25 wherein the dehydrating agent and an acid catalyst are the same and are TMSCl.

27. The process according to Claim 24 wherein the acid catalyst is an anhydrous acid, TMSCl, p-toluenesulfonic acid, camphorsulfonic acid, or hydrogen chloride.

28. The process according to Claim 24 wherein the reaction process further comprises use of an organic solvent.

29. The process according to Claim 28 wherein the organic solvent is toluene, acetonitrile, or a mixture thereof.

30. A compound of the formula



wherein

R_4 is a phenyl substituted one more times independently by fluorine, SR_5, SOR_5, or halo-substitutedC_{1-4} alkyl;

R_5 is hydrogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl or NR_7R_{17}, excluding the moieties SR_5 being SNR_7R_{17} and SOR_5 being SOH;

R_7 and R_{17} is each independently selected from hydrogen or C_{1-4} alkyl or R_7 and R_{17} together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR_{15};

R_{10} is hydrogen or C_{1-4} alkyl;

R_{12} is hydrogen or R_{16};

R_{15} is R_{10} or C(Z)-C_{1-4} alkyl;

R_{16} is C_{1-4} alkyl, halo-substituted-C_{1-4} alkyl, or C_{3-7} cycloalkyl; and

Z is oxygen or sulfur.

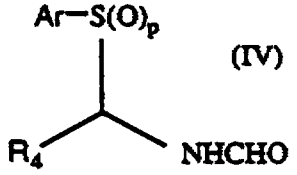
31. The compound according to Claim 30 wherein the R_4 group is phenyl substituted by fluorine.

32. A process for preparing a compound of the formula:

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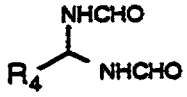
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* C L M S *



(IV)

wherein p is 2; Ar is an optionally substituted phenyl or naphtyl; R_4 is as defined for Formula (A) compounds, according to Claim 13; which process comprises reacting a compound of the formula



wherein R_4 is as defined for Formula (A); with p-toluenesulfinic acid, an acid catalyst, and an organic solvent.

33. The process according to Claim 32 wherein the solvent is toluene or acetonitile or mixtures thereof.

34. The compound which is 5-(4-Pyridyl)-4-(4-fluorophenyl)-1-(4-piperidinyl) imidazole, or a pharmaceutically acceptable salt thereof.

35. A pharmaceutical composition comprising 5-(4-Pyridyl)-4-(4-fluorophenyl)-1-(4-piperidinyl) imidazole, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent.

36. The compound which is 5-(4-Pyridyl)-4-(4-fluorophenyl)-1-(4-piperidinyl) imidazole.

37. A method of prophylaxis or treatment of a CSBP/RK/p38 kinase mediated disease in a mammal in need thereof, which method comprises adminsitering to said mammal an effective amount of 5-(4-Pyridyl)-4-(4-fluorophenyl)-1-(4-piperidinyl) imidazole, or a pharmaceutically acceptable salt thereof.

38. The method according to claim 37 wherein the mammal is afflicted with a CSBP/RK/p38 mediated disease selected from the group consisting of rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, psoriatic arthritis, traumatic arthritis, rubella arthritis, acute synovitis, gouty arthritis and other arthritic conditions.

39. The method according to claim 37 wherein the mammal is afflicted with a CSBP/RK/p38 mediated disease selected from the group consisting of sepsis, septic shock, endotoxic shock, gram negative sepsis, and toxic shock syndrome.

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40. The method according to claim 37 wherein the mammal is afflicted with a CSBP/RK/p38 mediated disease selected from the group consisting of asthma, adult respiratory distress syndrome, chronic pulmonary inflammatory disease, silicosis, and pulmonary sarcososis.

41. The method according to claim 37 wherein the mammal is afflicted with a CSBP/RK/p38 mediated disease selected from the group consisting of bone resorption diseases, osteoporosis, graft vs. host reaction, allograft rejections, or pyresis.

42. The method according to claim 37 wherein the mammal is afflicted with a CSBP/RK/p38 mediated disease selected from the group consisting of stroke, cardiac and renal reperfusion injury, thrombosis, glomerulonephritis, and cerebral malaria.

43. The method according to claim 37 wherein the mammal is afflicted with a CSBP/RK/p38 mediated disease selected from the group consisting of diabetes, and pancreatic b cells.

44. The method according to claim 37 wherein the mammal is afflicted with a CSBP/RK/p38 mediated disease selected from the group consisting of multiple sclerosis, and muscle degeneration.

45. The method according to claim 37 wherein the mammal is afflicted with a CSBP/RK/p38 mediated disease selected from the group consisting of atherosclerosis and Alzheimer's disease.

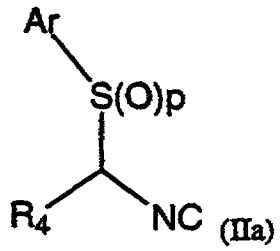
46. The method according to claim 37 wherein the mammal is afflicted with a CSBP/RK/p38 mediated disease selected from the group consisting of eczema, psoriasis, sunburn, or conjunctivitis.

47. The method according to claim 37 wherein the mammal is afflicted with a CSBP/RK/p38 mediated disease selected from the group consisting of Crohn's disease, ulcerative colitis, or inflammatory bowel disease.

48. A method of treating inflammation in a mammal in need thereof, which comprises administering to said mammal an effective amount of 5-(4-Pyridyl)-4-(4-fluorophenyl)-1-(4-piperidinyl) imidazole, or a pharmaceutically acceptable salt thereof.

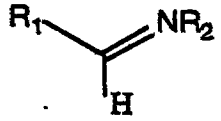
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49. A process for preparing a 5-(4-Pyridyl)-4-(4-fluorophenyl)-1-(4-piperidinyl) imidazole, or a pharmaceutically acceptable salt thereof, which comprises reacting a compound of the Formula (IIa) :



(IIa)

with a compound of the Formula (III):



(III)

wherein p is 2; and a base strong enough to deprotonate the isonitrile moiety of Formula (IIa); and wherein the imine of Formula (III), is formed in situ prior to reaction with Formula (IIa); and R_1 is 4-pyridyl, R_2 is 4-piperidinyl, and R_4 is 4-fluorophenyl or is a precursor thereof; and thereafter if necessary, converting a precursor of R_1, R_2 and R_4 to a group R_1, R_2 and R_4 as defined herein.

50. The process according to Claim 49 wherein the base is an amine, an amide, a carbonate, a hydride, an alkyl or aryl lithium reagent, or a mono-, di- or tribasic phosphate.

51. The process according to Claim 49 wherein the imine is formed in situ by reacting an aldehyde of the formula R_1CHO, wherein R_1 is a 4-pyridyl with a primary amine of the formula R_2NH_2, wherein R_2 is a 4-piperidinyl which may be suitably protected as necessary.

52. The process according to Claim 51 wherein formation of the imine in situ utilizes dehydrating conditions.

53. The process according to Claim 49 wherein the solvent is N,N-dimethyl-formamide (DMF), halogenated solvents, tetrahydrofuran (THF), dimethylsulfoxide (DMSO), an alcohol, benzene, toluene, MeCN, or DME.

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54. The process according to Claim 51 wherein the aldehyde of the formula R_1CHO is formed in situ.

55. The process according to Claim 54 wherein the aldehyde is formed by hydrolysis of an acetal of the formula $R_1CH(OR_a)_2$ wherein R_1 is 4-pyridyl, and R_a is alkyl, aryl, arylalkyl, heteroaryl,or a heteroarylalkyl.

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(57) Abstract

This invention relates to certain 5-(optionally substituted aryl or heteroaryl)-4-(optionally substituted heteroaryl)-1-(optionally substituted heterocyclyl or heterocyclylalkyl) or 1- optionally substituted alkyl or alkenyl -imidazoles and derivatives thereof. Synthetic processes for the preparation of said tri-substituted imidazoles is described. The aforementioned imidazoles are useful for treating cytokine mediated diseases. The compounds of the invention are incorporated into pharmaceutical compositions for use in treating cytokine related diseases.