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Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

E.

S.

D.

SUPERINDUSTRIA Y COMERCIO

Radicacion : 83069684 00000001

Folios: 2

Fecha (DMB): 2004-11-29 17:25:58

Tramite : 811 PCT-PATENT 379 FASE NACI 538 PETICION

Dependencia: 2829 DIVISION DE NUEVAS CREACIONES

Ref: Expediente No. 03.069.684

Solicitud de patente de invención titulada:

“NUEVOS COMPUESTOS ANTIINFLAMATORIOS DE TRIAZOLOPIRIDINAS”.

Solicitante: PFIZER PRODUCTS INC.

SOLICITUD DE EXAMEN DE PATENTABILIDAD SEGÚN
EL ARTICULO 44 DE LA DECISION 486, GACETA No. 544

CARLOS R. OLARTE, mayor de edad y vecino de Bogotá, D.C., identificado tal como aparece al pie de mi firma, en mi condición de apoderado del solicitante, respetuosamente me permito solicitar, que se examine si la invención reúne los requisitos de patentabilidad previstos en la misma. Dando cumplimiento a lo establecido en el artículo 44 de la Decisión 486 de la comisión de la Comunidad Andina de Naciones. Adjunto recibo por el monto de \$177.000 pesos para cubrir la tasa correspondiente, según la Resolución 37323 del año 2003.

Atentamente,



CARLOS R. OLARTE
C.C. 79.782.747 de Bogotá
T.P. 74.295

Anexo: Recibo por \$177.000 pesos

PTT/2004/000111 04/12/04

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NIT : 900176099-2

SUPERINDUSTRIA Y COMERCIO
Radicacion : 03869684 00000001 Folios: 2
Fecha (AMD): 2004-11-29 17:25:58
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Dependencia: 2820 DIVISION DE NUEVAS CREACIONES

RECIBO OFICIAL DE CAJA : 04 - 91,294
FECHA : NOVIEMBRE 25 DE 2004

**** CONSIGNACION ****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
JOSE SANTOS	CONSIGNACION	BANCO POPULAR	050-00110-6	29810428	24/11/2004	4,587,000.00

**** C O N C E P T O ****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	114 PTC CAP-II EXAMEN DE PATENTIBILIDAD	177,000.00
		TOTAL :	\$ 177,000.00

SON: CIENTO SETENTA Y SIETE MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

DIVISION DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 03- 69684

**EL EXTRACTO DE LA PRESENTE SOLICITUD DE PATENTE DE INVENCION –
PCT, FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No 544,
DE FECHA 30 DE SEPTIEMBRE DE 2004, EL TERMINO HABIL SEÑALADO
POR LA LEY EXPIRA EL 29 DE DICIEMBRE DE 2004.**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI

NO **X**

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US005756499A

United States Patent [19]
Adams et al.

[11] **Patent Number:** 5,756,499
[45] **Date of Patent:** May 26, 1998

[54] **SUBSTITUTED IMIDAZOLE COMPOUNDS**

[75] **Inventors:** Jerry L. Adams, Wayne; Jeffrey C. Beecham, King of Prussia; Dennis Lee Swarthmore, all of Pa.

[73] **Assignee:** SmithKline Beecham Corporation, Philadelphia, Pa.

[21] **Appl. No.:** 788,934

[22] **Filed:** Jan. 18, 1997

[51] **Int. Cl.⁶** A61K 31/445; A61K 31/535;
C07D 401/14; C07D 413/14

[52] **U.S. Cl.** 514/235.8; 514/318; 544/124;
546/194

[58] **Field of Search** 544/124; 546/194;
514/235.8

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Primary Examiner—Robert W. Ramsauer
Attorney, Agent, or Firm—Dana L. Danner; Stephen Venetianer; Edward T. Lentz

[57] **ABSTRACT**

Novel 1,4,5-substituted imidazole compounds and compositions for use in therapy as cytokine inhibitors.

39 Claims, No Drawings

SUBSTITUTED IMIDAZOLE COMPOUNDS

This application claims the benefit of provisional application Ser. Nos. 60/609,907 filed Jan. 11, 1996 and 60/814,952 filed Apr. 5, 1996.

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., DiSarelli 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 β cells.

DiSarelli, *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 sarcoidosis, bone resorption diseases, reperfusion injury, graft vs. host reaction, allograft rejection, 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 pyrexia.

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. Monokines, such as TNF, have been shown to activate HIV replication in monocytes and/or macrophages [See Poll, 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 lipopolysaccharide (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 (NAF-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 chemotactic properties for neutrophils, T-lymphocytes, and basophils. In addition it induces histamine release from basophils from both normal and atopic individuals as well as lysosomal 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 neutrophils 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 pharmaceutical compositions comprising a compound of Formula (I) and a pharmaceutically acceptable diluent or carrier.

This invention relates to a method of treating a CSBP/RK/p38 kinase mediated disease, in a mammal in need

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"C₁₋₁₀alkyl" 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, quinoxalyl, pyridine, pyrimidine, oxazole, thiazole, thiazolidine, tetrazole, 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.

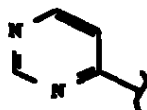
The term "alkyl" or "heteroarylalkyl" or "heterocyclylalkyl" is used herein to mean C₁₋₄ alkyl as defined above attached to an aryl, heteroaryl or heterocyclic moiety as also defined herein unless otherwise indicated.

"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 benzoyl and phenethyl.

"alkenoyl"—a C(O)C₁₋₁₀ alkyl wherein the alkyl is as defined above.

For the purposes herein the "core" 4-pyrimidinyl moiety for R₁ or R₂ 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:

- 1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-(2-phenoxy)pyrimidin-4-yl]imidazole
- 1-(4-piperidinyl)-4-(4-fluorophenyl)-5-(2-phenoxy-4-pyridinyl)imidazole

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- 1-(4-piperidinyl)-4-(4-fluorophenyl)-5-(2-(4-methoxyphenoxy)-4-pyridinyl)imidazole
- 1-(4-piperidinyl)-4-(4-fluorophenyl)-5-(2-(4-fluorophenoxy)-4-pyridinyl)imidazole
- 1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-(2-(4-methoxyphenoxy)pyrimidin-4-yl)imidazole
- 1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-(2-(4-fluorophenoxy)pyrimidin-4-yl)imidazole
- 1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-(2-(4-aminocarbonylphenoxy)pyrimidin-4-yl)imidazole
- 1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-(2-(4-ethylphenoxy)pyrimidin-4-yl)imidazole
- 1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-(2-(4-benzoyloxyphenoxy)pyrimidin-4-yl)imidazole
- 1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-(2-(4-cyanophenoxy)pyrimidin-4-yl)imidazole
- 1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-(2-(4-hydroxyphenoxy)pyrimidin-4-yl)imidazole
- 1-(4-hydroxycyclohexyl)-4-(4-fluorophenyl)-5-(2-(phenoxy)pyrimidin-4-yl)imidazole
- 1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-(2-(2,6-dimethylphenoxy)pyrimidin-4-yl)imidazole
- 1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-(2-(4-methylphenoxy)pyrimidin-4-yl)imidazole
- 1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-(2-(4-chlorophenoxy)pyrimidin-4-yl)imidazole
- 1-(3-(N-Morpholino)propyl)-4-(4-fluorophenyl)-5-(2-(phenoxy)pyrimidin-4-yl)imidazole
- 1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-(2-(3-methoxyphenoxy)pyrimidin-4-yl)imidazole
- 1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-(2-(4-phenoxyphenoxy)pyrimidin-4-yl)imidazole
- 1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-(2-(4-phenoxyphenoxy)pyrimidin-4-yl)imidazole
- 1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-(2-(3-hydroxyphenoxy)pyrimidin-4-yl)imidazole
- 1-(3-(N-Morpholino)propyl)-4-(4-fluorophenyl)-5-(2-(4-fluorophenoxy)pyrimidin-4-yl)imidazole
- 1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-(2-(2-hydroxyphenoxy)pyrimidin-4-yl)imidazole
- 1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-(2-(3,4-methylenedioxyphenoxy)pyrimidin-4-yl)imidazole
- 1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-(2-(3-fluorophenoxy)pyrimidin-4-yl)imidazole
- 1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-(2-(2-fluorophenoxy)pyrimidin-4-yl)imidazole
- 1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-(2-(2-methoxyphenoxy)pyrimidin-4-yl)imidazole
- 1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-(2-(3-trifluoromethylphenoxy)pyrimidin-4-yl)imidazole
- 1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-(2-(3,4-difluorophenoxy)pyrimidin-4-yl)imidazole
- 1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-(2-(4-methylsulfonylphenoxy)pyrimidin-4-yl)imidazole
- 1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-(2-thiophenoxy)pyrimidin-4-yl]imidazole
- 1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-(2-(1-methyltetrazol-5-ylthio)pyrimidin-4-yl)imidazole

The compounds of Formula (I) 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 R₁, R₂, and R₃ 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. While the schemes describe compounds of For-

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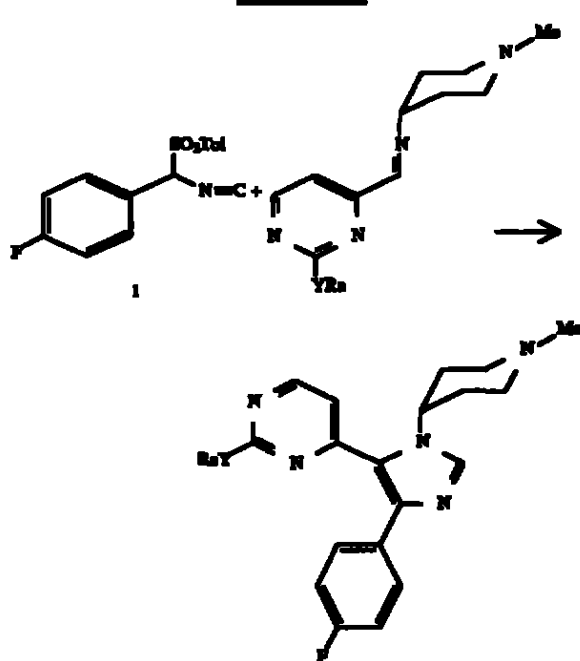
primary amine, to generate an imine, which may suitably be isolated or reacted *in situ*, with the desired isonitrile in the presence of a variety of suitable bases, and solvents as described herein to afford the 5-(4-pyrimidinyl)-substituted imidazoles, wherein R_2 and R_4 are as defined herein for 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 were hard to handle. The black color was 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*-dimethylformamide (DMF), MeCN, halogenated solvents, such as methylene chloride or chloroform, tetrahydrofuran (THF), dimethylsulfoxide (DMSO), alcohols, such as methanol or ethanol, benzene, or toluene, DMF 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.

SCHEME VII



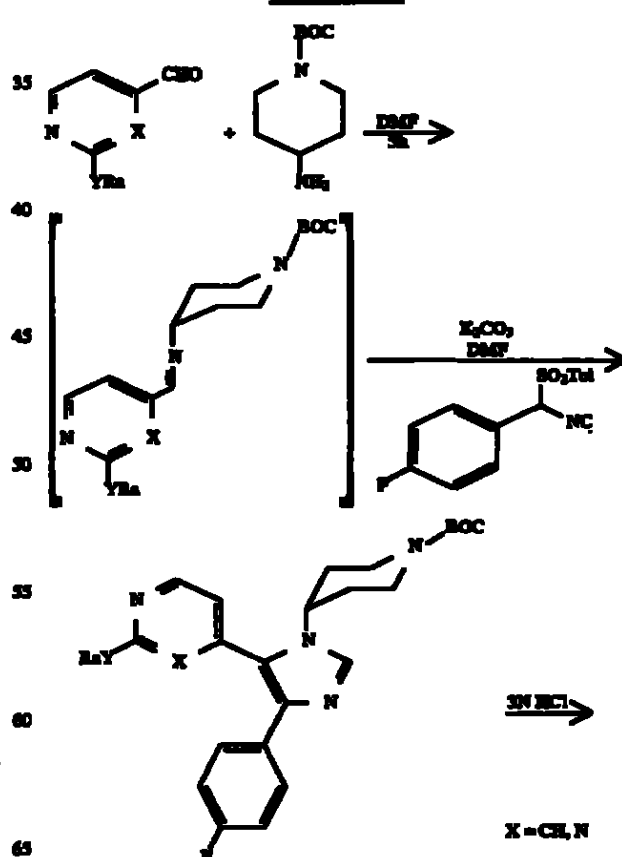
While not convenient for large scale work, addition of NaH to the isonitrile, perhaps with temperatures lower than 25° C. (in THF) are likely needed. Additionally, BuLi has also been reported to be an effective base for deprotonating tosyl benzylisonitriles at -50° C. (DiSanto, et al., *Synth. Commun.* 1993, 23, 795).

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Various temperature conditions may be utilized depending upon the preferred base. For instance, $(BuNH)_2/DME$, $K_2CO_3/MeOH$, K_2CO_3 in DMF, at temperatures above 40° C., the yields may drop to about 20% but little difference is expected between 0° C. and 25° C. Consequently, temperature ranges below 0° C., and above 80° C. are contemplated as also being within the scope of this invention. Preferably, the temperature ranges are from about 0° C. to about 25° C. For purposes herein, room temperature, is generally depicted as 25° C., but it is recognized that this may vary from 20° C. to 30° 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 $C(O)R$, 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



X = CH, N

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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 allyl ethers, such as *t*-butyldimethyl or *t*-butyldiphenyl, and alkyl ethers, such as methyl connected by an alkyl chain of variable link, (C₁₋₁₀R₂₀)_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 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) 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 a pharmaceutically acceptable salt thereof.

Compounds of Formula (I) are capable of inhibiting inducible proinflammatory proteins, such as COX-2, also referred to by many other names such as prostaglandin endoperoxide synthase-2 (PGE₂-2) 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 prostaglandins 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 admin-

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istering 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.

In particular, compounds of Formula (I) 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.

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 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 cadomula 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 β 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 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 sarcoidosis, bone resorption diseases, such as osteoporosis, reperfusion injury, graft vs. host reaction, allograft rejection, 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 pyrexia.

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). 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 a pharmaceutically acceptable salt thereof.

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c) 2-Chloro-4-pyridinecarboxaldehyde(1-*t*-butoxycarbonyl-4-aminopiperidine)imine

Following the procedure of example 1(d) except using 2-chloro-4-pyridinecarboxaldehyde afforded the title compound. ¹H NMR (CDCl₃): 8.45 (d, 1H, *J*=5.1 Hz), 8.29 (s, 1H), 7.65 (s, 1H), 7.52 (d, 1H, *J*=5.1 Hz), 4.05 (br-s, 2H), 3.48 (m, 1H), 3.03 (m, 2H), 1.73 (m, 4H), 1.48 (s, 9H).

d) 1-(1-*t*-Butoxycarbonyl-4-piperidinyl)-4-(4-fluorophenyl)-5-(2-chloro-4-pyridinyl)imidazole

Following the procedure of example 1(g) except using the compound from the previous step afforded the title compound which was purified by flash chromatography with 0-5% CH₃OH/CH₂Cl₂ and then recrystallized from ethyl acetate/hexanes to give a light yellow solid.

e) 1-(1-*t*-Butoxycarbonyl-4-piperidinyl)-4-(4-fluorophenyl)-5-(2-phenoxy-4-pyridinyl)imidazole

To a stirring suspension of NaH (120 mg, 3.0 mmol) in DMA (1.3 mL) was added phenol (0.40 g, 4.25 mmol). After the bubbling ceases, 1-(1-*t*-butoxycarbonyl-4-piperidinyl)-4-(4-fluorophenyl)-5-(2-chloro-4-pyridinyl)imidazole (0.20 g, 0.44 mmol) was added and the resulting solution was heated at 120° C. until no evidence of starting material was seen by mass spectroscopy (1-3 days). To the cooled solution was added 1M NaOH and the mixture was extracted thrice with EtOAc. The combined organic layers were washed with NaCl (sat.), dried over MgSO₄, filtered, and evaporated under reduced pressure to give a light yellow solid. The solid was then chromatographed with 50-80% EtOAc/Hex to give the title compound as a white solid (143 mg, 64% yield). HS (+) MS *m/z*=515 (MH⁺)

f) 1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-(2-phenoxy-4-pyridinyl)imidazole

To the compound from the previous step (143 mg, 0.28 mmol) was added a cooled solution of TFA (10 mL) at -10° C. The reaction was allowed to warm to room temperature, stirred 30 min at room temperature, and evaporated under reduced pressure to give an orange oil which was dissolved in water (10 mL) and add 3N HCl (0.5 mL). The water layer was washed twice with EtOAc, made basic with 50% NaOH, and extracted the aqueous layer thrice with EtOAc. The combined organic layers were washed with NaCl, dried over MgSO₄, filtered and evaporated under reduced pressure to give a white foam (80 mg, 70%). HS (+) MS *m/z*=415 (MH⁺).

Example 3

1-(4-piperidinyl)-4-(4-fluorophenyl)-5-[2-(4-methoxyphenoxy)-4-pyridinyl]imidazole

Following the procedure of examples 2a and 2f except using 4-methoxyphenol afforded the title compound as a white foam in 74% yield for the two steps. HS (+) MS *m/z*=445 (MH⁺).

Example 4

1-(4-piperidinyl)-4-(4-fluorophenyl)-5-[2-(4-fluorophenoxy)-4-pyridinyl]imidazole

Following the procedure of examples 2e and 2f except using 4-fluorophenol afforded the title compound as a white foam in 35% yield for the two steps. HS (+) MS *m/z*=433 (MH⁺).

Example 5

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(4-methoxyphenoxy)pyrimidin-4-yl]imidazole

The title compound was prepared by the method of examples 1(i) and 1(j) except using 4-methoxyphenol. mp=190°-191°.

Example 6

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(4-fluorophenoxy)pyrimidin-4-yl]imidazole

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The title compound was prepared by the method of examples 1(i) and 1(j) except using 4-fluorophenol. mp=186°-187°.

Example 7

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(4-aminocarbonylphenoxy)pyrimidin-4-yl]imidazole

The title compound was prepared by the method of examples 1(i) and 1(j) except using 4-hydroxybenzamide. mp=229°-230°.

Example 8

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(4-ethoxyphenoxy)pyrimidin-4-yl]imidazole

The title compound was prepared by the method of examples 1(i) and 1(j) except using 4-ethoxyphenol. mp=173-174.

Example 9

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(4-benzyloxyphenoxy)pyrimidin-4-yl]imidazole

The title compound was prepared by the method of examples 1(i) and 1(j) except using 4-benzyloxyphenol. mp=178°-179°.

Example 10

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(4-cyanophenoxy)pyrimidin-4-yl]imidazole

The title compound was prepared by the method of examples 1(i) and 1(j) except using 4-cyanophenol. mp=192°-193°.

Example 11

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(4-hydroxyphenoxy)pyrimidin-4-yl]imidazole

The title compound was prepared by the method of examples 1(i) and 1(j) except using hydroquinone. mp=255°-260° (dec).

Example 12

1-(4-Hydroxycyclohexyl)-4-(4-fluorophenyl)-5-[2-(4-phenoxy)pyrimidin-4-yl]imidazole

a) 1-Amino-4-(1,3-dioxycyclopentyl)cyclohexane

To a mixture of 1,4-cyclohexanedione monomethylene ketal (27.6 g, 177 mmol) and hydroxylamine hydrochloride (49.2 g, 708 mmol) in H₂O (250 mL) was added portionwise Na₂CO₃ (49.2 g, 547 mmol). After stirring 1 h, the mixture was extracted with EtOAc. The organic phase was dried (Na₂SO₄) and concentrated affording 4-(1,3-dioxycyclopentyl)-cyclohexanone oxime (27.5 g, 90% yield).

The oxime (27.5 g, 161 mmol), Raney Ni (ca 13.5 mL as a suspension in EtOH) and EtOH (200 mL) were combined and shaken at 50 psi H₂ for 4 h. The catalyst was filtered off and the filtrate was concentrated to afford the title compound as a colorless oil (23.6 g, 93% yield). ¹H NMR (CDCl₃): 82.64 (m, 1H), 1.75°-1.25 (m, 12H).

b) 2-Methylthiopyrimidine-4-carboxaldehyde(4-ethylene ketal cyclohexyl)imine

A mixture of 2-methylthiopyrimidine-4-carboxaldehyde (9.5 g, 6.9 mmol) prepared in example 1(b) and 1-amino-4-(1,3-dioxycyclopentyl)cyclohexane (10.8 g, 6.9 mmol) from the previous step were stirred in DMF (150 mL) 18 h. The title compound was used without any purification. ¹H NMR (CDCl₃): 88.51 (d, 1H), 8.21 (s, 1H), 7.53 (d, 1H), 3.93 (s, 4H), 3.40 (m, 1H), 2.35 (s, 3H), 1.94-1.70 (m, 6H), 1.61 (m, 2H).

c) 1-(4-Ethylene ketal cyclohexyl)imidazole-4-(4-fluorophenyl)-5-[2-(2-methylthio)pyrimidin-4-yl]imidazole

The title compound was prepared by the method of examples 1(i) and 1(j) except using resorcinol. MS ES+m/z=431 (MH⁺).

Example 21

1-(3-N-Morphollanyl-1-propyl)-4-(4-fluorophenyl)-5-[2-(4-fluorophenoxy)pyrimidin-4-yl]imidazole

The title compound was prepared by the method of example 16 except using 4-fluorophenol. MS ES+m/z=278 (MH⁺).

Example 22

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(2-hydroxyphenoxy)pyrimidin-4-yl]imidazole

The title compound was prepared by the method of examples 1(i) and 1(j) except using catechol. MS ES+m/z=431 (MH⁺).

Example 23

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-((3,4-methylenedioxy)phenoxy)pyrimidin-4-yl]imidazole

The title compound was prepared by the method of examples 1(i) and 1(j) except using sesamol. mp=131°-132°.

Example 24

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(3-fluorophenoxy)pyrimidin-4-yl]imidazole

The title compound was prepared by the method of examples 1(i) and 1(j) except using 3-fluorophenol. mp=155°-156°.

Example 25

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(2-fluorophenoxy)pyrimidin-4-yl]imidazole

The title compound was prepared by the method of examples 1(i) and 1(j) except using 2-fluorophenol. mp=154°-155°.

Example 26

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(2-methoxyphenoxy)pyrimidin-4-yl]imidazole

The title compound was prepared by the method of examples 1(i) and 1(j) except using 2-methoxyphenol. MS ES+m/z=446 (MH⁺).

Example 27

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(3-trifluoromethylphenoxy)pyrimidin-4-yl]imidazole

The title compound was prepared by the method of examples 1(i) and 1(j) except using 3-trifluoromethylphenol. mp=137°-138°.

Example 28

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(3,4-difluorophenoxy)pyrimidin-4-yl]imidazole

The title compound was prepared by the method of examples 1(i) and 1(j) except using 3,4-difluorophenol. MS ES+m/z=452 (MH⁺).

Example 29

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(4-methylsulfonylphenoxy)pyrimidin-4-yl]imidazole

The title compound was prepared by the method of examples 1(i) and 1(j) except using 4-methylsulfonylphenol. MS ES+m/z=494 (MH⁺).

Example 30

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[(2-phenylthio)pyridin-4-yl]imidazole

Following the procedure of examples 2(e) and 2(f) except using thiophenol afforded the title compound as a yellow foam in 36% yield for the two steps. ES (+) MS m/e=431 (MH⁺).

Example 31

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[(2-(1-methyltetrazol-5-ylthio)pyridin-4-yl]imidazole;

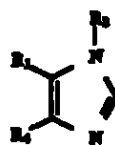
Following the procedure of examples 2(e) and 2(f) except using 5-mercapto-1-methyltetrazole afforded the title compound as a light yellow foam. The foam was further purified by reverse phase chromatography with 60-70% CH₃CN/H₂O and 0.1% TFA. The relevant fractions were combined and made basic with 1M NaOH and extracted thrice with EtOAc. The combined organic layers were dried over MgSO₄, filtered, and evaporated under reduced pressure to give an off-white foam in 13% yield for the two steps. ES (+) MS m/e=437 (MH⁺).

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

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 art 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:

What is claimed is:

1. A compound represented by the formula:



R₁ is a 4-pyridyl ring, which ring is substituted with Y—R, and optionally with an additional independent substituent selected from C₁₋₄ alkyl, halogen, hydroxyl, C₁₋₄ alkoxy, C₁₋₄ alkylthio, C₁₋₄ alkylsulfinyl, CH₂OR₁₂, amide, mono and di-C₁₋₄ alkyl substituted amino, N(R₁₀)C(O)R₈, or NHR₈;

Y is oxygen or sulfur;

R₂ 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)NR₇R₁₇, C(Z)OR₁₆, (CR₁₀R₂₀)_mCOR₁₃, SR₉, SOR₉, OR₁₃, halo-substituted-C₁₋₄ alkyl, C₁₋₄alkyl, ZC(Z)R₁₂, NR₁₀C(Z)R₁₄, or (CR₁₀R₂₀)_mNR₁₀R₂₀ and which, for other positions of substitution, is halogen cyano C(Z)NR₁₃R₁₄, C(Z)OR₇, (CR₁₀R₂₀)_mCOR₃, S(O)_mR₃, OR₃, halo-substituted-C₁₋₄ alkyl, —C₁₋₄ alkyl, (CR₁₀R₂₀)_mNR₁₀C(Z)R₃, NR₁₀S(O)_mR₄, NR₁₀S(O)_mNR₇R₁₇, ZC(Z)R₃ or (CR₁₀R₂₀)_mNR₁₃R₁₄;

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 —(CR₁₀R₂₀)_nOR_n, heterocyclyl, heterocyclylC₁₋₁₀alkyl, C₁₋₁₀alkyl, halo-substituted C₁₋₁₀alkyl, C₂₋₂₀alkenyl, C₂₋₁₀alkynyl, C₃₋₇cycloalkyl, C₃₋₇cycloalkylC₁₋₁₀alkyl, C₃₋₇cycloalkenyl, C₃₋₇cycloalkenylC₁₋₁₀alkyl, aryl, arylC₁₋₁₀alkyl, heterocaryl, heterocarylC₁₋₁₀alkyl, (CR₁₀R₂₀)OR₁₁, (CR₁₀R₂₀)S(O)_mR₁₈, (CR₁₀R₂₀)_nNHS(O)₂R₁₈, (CR₁₀R₂₀)_nNR₁₃R₁₄, (CR₁₀R₂₀)_nNO₂, (CR₁₀R₂₀)_nCN, (CR₁₀R₂₀)_nSO₂R₁₈, (CR₁₀R₂₀)_nS(O)_mNR₁₃R₁₄, (CR₁₀R₂₀)_nC(Z)R₁₁, (CR₁₀R₂₀)_nOC(Z)R₁₁, (CR₁₀R₂₀)_nC(Z)OR₁₁, (CR₁₀R₂₀)_nC(Z)NR₁₃R₁₄, (CR₁₀R₂₀)_nC(Z)NR₁₁OR_n, (CR₁₀R₂₀)_nNR₁₀C(Z)NR₁₃R₁₄, (CR₁₀R₂₀)_nNR₁₀C(Z)NR₁₃R₁₄, (CR₁₀R₂₀)_nN(OR₈)C(Z)NR₁₃R₁₄, (CR₁₀R₂₀)_nN(OR₈)C(Z)R₁₁, (CR₁₀R₂₀)_nC(=NOR₈)R₁₁, (CR₁₀R₂₀)_nNR₁₀C(=NR₁₃)NR₁₃R₁₄, (CR₁₀R₂₀)_nOC(Z)NR₁₃R₁₄, (CR₁₀R₂₀)_nNR₁₀C(Z)NR₁₃R₁₄, (CR₁₀R₂₀)_nNR₁₀C(Z)OR_n, 5-(R₁₂)-1,2,4-oxadiazol-3-yl or 4-(R₁₂)-5-(R₁₃R₂₀)-4,5-dihydro-1,2,4-oxadiazol-3-yl; wherein the aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heterocaryl, heterocarylalkyl, 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_n is aryl, aryl C_{1-6} alkyl, heterocyclic, heterocyclyl C_{1-6} alkyl, heteroaryl, heteroaryl C_{1-6} alkyl, wherein each of these moieties may be optionally substituted; 30

R₂ is hydrogen, C₁₋₄ alkyl, C₃₋₇ cycloalkyl, aryl, aryl/C₁₋₄ alkyl, heteroaryl, heteroaryl/C₁₋₄ alkyl, heterocyclyl, or heterocyclyl/C₁₋₄ alkyl;

R₁ is heterocyclyl, heterocyclylC₁₋₁₀ alkyl or R₂;

R_2 is hydrogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl or NR_7R_{17} , excluding the moieties $-SR_2$ being $-SNR_7R_{17}$ and $-SOR_2$ being $-SOH$;

R_5 is hydrogen, a pharmaceutically acceptable cation, C_{1-10} alkyl, C_{3-7} cycloalkyl, aryl, aryl(C_{1-4} alkyl, heteroaryl, heteroaryl(C_{1-4} alkyl, heterocyclic, aryl, or C_{1-10} alkynyl);

R₇ and R₁₇ is each independently selected from hydrogen or C₁₋₄ alkyl or R₇ and R₁₇ 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 NR₁₆;

R_9 is 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} cycloalkenyl, aryl, aryl- C_{1-10} alkyl, heteroaryl, heteroaryl- C_{1-10} alkyl, $(CR_{10}R_{20})_nOR_{11}$, $(CR_{10}R_{20})_nS(O)_mR_{18}$, $(CR_{10}R_{20})_nNHS(O)_2R_{19}$, $(CR_{10}R_{20})_nNR_{13}R_{14}$; wherein the aryl, arylalkyl, heteroaryl, heteroaryl alkyl may be optionally substituted;

R_2 is hydrogen, $-C(Z)R_{11}$ or optionally substituted C_{1-10} alkyl, $S(O)_2R_{12}$, 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;

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;

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-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 NR₂;

R_{13} is R_{10} or $C(Z)-C_{1-4}$ alkyl;

R₁₅ is C₁₋₄ alkyl, halo-substituted-C₁₋₄ alkyl, or C₂₋₇ cycloalkyl;

R₁₈ is C₁₋₁₀ alkyl, C₂₋₇ cycloalkyl, heterocyclyl, aryl, arylalkyl, heterocyclyl, heterocyclyl-C₁₋₂₀ alkyl, heteroaryl or heteroarylalkyl;

R₁₀ is hydrogen, cyano, C₁₋₄ alkyl, C₃₋₇ cycloalkyl or aryl;

or a pharmaceutically acceptable salt thereof.

2. The compound according to claim 1 wherein Y is oxygen.

3. The compound according to claim 3 wherein the R_m moiety is optionally substituted one or more times with halogen; C_{1-4} alkyl; halo-substituted alkyl; hydroxy; hydroxy substituted C_{1-4} alkyl; C_{1-4} alkoxy; $S(O)_n$ alkyl and $S(O)_n$ aryl (wherein n is 0, 1, or 2); $C(O)OR_{11}$; $C(O)R_{11}$; $-OC(O)R_9$; $-O-(CH_2)_3-O$; amino; mono- and di- C_{1-4} alkyl-substituted amino; $-N(R_{10})C(O)R_9$; $-C(O)NR_{10}R_{20}$; cyano; nitro; N-heterocyclyl ring which ring has from 5 to 7 members and optionally contains an additional heteroatom selected from oxygen, sulfur or NR₁₅; aryl; arylalkyl; aryloxy; or arylalkyloxy; and

wherein s is 1 to 3; and

R₁ is C₁₋₆ alkyl, C₃₋₇ cycloalkyl, aryl, arylC₁₋₄ alkyl, heteroaryl, heteroarylC₁₋₄ alkyl, heterocyclyl, or a heterocyclylC₁₋₄ alkyl moiety, all of which moieties may be optionally substituted.

4. The compound according to claim 3 wherein the substituent is halogen, halosubstituted alkyl, hydroxy, cyano, alkyl, aryl, alkoxy, aryloxy, arylalkyloxy, alkylthio, alkylsulfonyl, aminocarbonyl, methylcarbamoyl, tetrazole, methyltetrazolyl.

5. The compound according to claim 2 wherein R₄ is an optionally substituted phenyl.

6. The compound according to claim 5 wherein the phenyl is substituted one or more times independently by halogen, $-\text{SR}_2$, $-\text{S(O)R}_2$, $-\text{OR}_{12}$, halo-substituted- C_{1-4} alkyl, or C_{1-4} alkyl.

7. The compound according to claim 1 wherein R_2 is selected from optionally substituted C_{1-10} alkyl, optionally substituted heterocyclyl, optionally substituted heterocyclyl C_{1-10} alkyl, optionally substituted C_{2-7} cycloalkyl, or optionally substituted C_{2-7} cycloalkyl C_{1-10} alkyl.

8. The compound according to claim 7 wherein R₂ is an optionally substituted heterocycyl, or optionally substituted heterocycylC₁₋₁₀ alkyl.

9. The compound according to claim 8 wherein substituents are independently selected from halogen; C₁₋₆ alkyl; aryl; aryl; C(O)OR₁₁; C(O)H; C(O)C₁₋₄ alkyl; hydroxy substituted C₁₋₁₆ alkyl; C₁₋₁₆ alkoxy; S(O)_mC₁₋₄ alkyl (wherein m is 0, 1, or 2); or NR₁₀R₂₀.

10. The compound according to claim 8 wherein R₂ is morpholino propyl, piperidine, N-methylpiperidine, N-benzylpiperidine, 2,2,6,6-tetramethylpiperidine, 4-amino-piperidine, or 4-amino-2,2,6,6-tetramethyl piperidine.

11. The compound according to claim 7 wherein R_2 is an optionally substituted C_{2-7} -cycloalkyl, or optionally substituted C_{2-7} -cycloalkyl C_{1-10} alkyl.

12. The compound according to claim 11 wherein the optional substituents are independently selected from halo-

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gen; hydroxy; C₁₋₁₀ alkoxy; S(O)_m alkyl, wherein m is 0, 1, or 2; S(O)_m aryl; cyano; nitro; NR₂R₁₇ group; N(R₁₀)C(O) and X₁ is C₁₋₄ alkyl, aryl or arylC₁₋₄alkyl; C₁₋₁₀ alkyl; optionally substituted alkyl wherein the substituents are halogen, hydroxy, nitro, cyano, NR₂R₁₇ group, S(O)_m alkyl and S(O)_m aryl; optionally substituted alkylene; optionally substituted alkane; C(O)OR₁₁; the group R₉; —C(O)H; —O; —N—OR₁₁; —N(H)—OH (or substituted alkyl or aryl derivatives thereof on the nitrogen or the oxime moiety); —N(OR₉)—C(O)—R₉; optionally substituted aryl; an optionally substituted arylC₁₋₄alkyl; optionally substituted heterocycle or heterocyclic C₁₋₄alkyl;

wherein R₄ is hydrogen, a pharmaceutically acceptable cation, aryl or a C₁₋₁₀ alkanoyl;

R₆ is a 1,3-dioxyalkylene group of the formula —O—(CH₂)_s—O—, wherein s is 1 to 3;

R₇ is NR₂₁R₂₂; alkyl₁₋₆; halosubstituted alkyl₁₋₆; hydroxy substituted alkyl₁₋₆; alkenyl₂₋₆; aryl or heteroaryl optionally substituted by halogen, alkyl₁₋₆, halosubstituted alkyl₁₋₆, hydroxyl, or alkoxy₁₋₆;

R₂₁ is hydrogen, or alkyl₁₋₆;

R₂₂ is hydrogen, alkyl₁₋₆, aryl, benzyl, heteroaryl, alkyl substituted by halogen or hydroxyl, or phenyl substituted by a member selected from the group consisting of halo, cyano, alkyl₁₋₃, alkoxy₁₋₆, halosubstituted alkyl₁₋₆, alkylthio, alkylsulphonyl, or alkylsulfinyl; or R₂₁ and R₂₂ may together with the nitrogen to which they are attached form a ring having 5 to 7 members, which members may be optionally replaced by a heteroatom selected from oxygen, sulfur or nitrogen.

13. The compound according to claim 11 wherein R₂ is hydroxycyclohexyl, 4-methyl-4-hydroxycyclohexyl, 4-pyrrolidinyl-cyclohexyl, 4-methyl-4-aminocyclohexyl, 4-methyl-4-acetamidocyclohexyl, 4-keto cyclohexyl, 4-oxiranyl, or 4-hydroxy-4-(1-propenyl)cyclohexyl.

14. The compound according to claim 1 which is:

1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-(2-phenoxy-4-pyridinyl)imidazole;

1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-[2-(4-methoxyphenoxy)-4-pyridinyl]imidazole;

1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-[2-(4-fluorophenoxy)-4-pyridinyl]imidazole;

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(2,6-dimethylphenoxy)pyridin-4-yl]imidazole;

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(4-methylphenoxy)pyridin-4-yl]imidazole;

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(4-chlorophenoxy)pyridin-4-yl]imidazole; or

1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-[2-(1-methyltetrazol-5-ylthio)pyridin-4-yl]imidazole

or a pharmaceutically acceptable salt thereof.

15. A pharmaceutical composition comprising a compound according to any of claims 1 to 14 and a pharmaceutically acceptable carrier or diluent.

16. 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 (I) according to any of claims 1 to 14.

17. The method according to claim 16 wherein the mammal is afflicted with a cytokine mediated disease selected from psoriatic arthritis, Reiter's syndrome, rheumatoid arthritis, gout, traumatic arthritis, rubella arthritis and acute synovitis, rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic condition, sepsis, septic shock, endotoxic shock, gram negative sepsis,

toxic shock syndrome, Alzheimer's disease, stroke, neurotrauma, asthma, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcososis, bone resorption disease, osteoporosis, osteoarthritis, cardiac and renal reperfusion injury, thrombosis, glomerulonephritis, diabetes, graft vs. host reaction, allograft rejection, inflammatory bowel disease, Crohn's disease, ulcerative colitis, eczema, contact dermatitis, psoriasis, sunburn, and conjunctivitis.

18. The method according to claim 16 wherein the disease state is mediated by IL-1, IL-6, IL-8, or TNF.

19. The method according to claim 16 wherein the cytokine mediated disease state is asthma, osteoporosis, or arthritis.

20. 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 (I) according to claim 1.

21. A method of treating osteoporosis 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.

22. 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 (I) according to claim 1.

23. The method according to claim 22 wherein inhibition of PGHS-2 is used in the prophylaxis or therapeutic treatment of edema, fever, algolia, neuromuscular pain, headache, cancer pain, or arthritic pain.

24. A method of treating a CSBP/PRK/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.

25. The method according to claim 24 wherein the mammal is afflicted with a CSBP/PRK/p38 kinase mediated disease which is psoriatic arthritis, Reiter's syndrome, rheumatoid arthritis, gout, traumatic arthritis, rubella arthritis and acute synovitis, rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic condition, sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, Alzheimer's disease, stroke, neurotrauma, asthma, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcososis, bone resorption disease, osteoporosis, osteoarthritis, cardiac and renal reperfusion injury, thrombosis, glomerulonephritis, diabetes, graft vs. host reaction, allograft rejection, inflammatory bowel disease, Crohn's disease, ulcerative colitis, eczema, contact dermatitis, psoriasis, sunburn, or conjunctivitis.

26. The method according to claim 25 wherein the compound is:

1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-(2-phenoxy-4-pyridinyl)imidazole;

1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-[2-(4-methoxyphenoxy)-4-pyridinyl]imidazole;

1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-[2-(4-fluorophenoxy)-4-pyridinyl]imidazole;

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(2,6-dimethylphenoxy)pyridin-4-yl]imidazole;

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(4-methylphenoxy)pyridin-4-yl]imidazole;

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(4-chlorophenoxy)pyridin-4-yl]imidazole; or

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1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-[2-(1-methyltetrazol-5-ylthio)pyridin-4-yl]imidazole or a pharmaceutically acceptable salt thereof.

27. A process for preparing a compound of Formula (I) as defined in claim 1 which comprises reacting a compound of the Formula (II):



with a compound of the Formula (III):



wherein p is 0 or 2; and a base strong enough to deprotonate the isonitrile moiety of Formula (II); and R₁, R₂ and R₄ are as defined in claim 1 or are precursors of the groups R₁, R₂ and R₄ and Ar is an optionally substituted phenyl group, and thereafter if necessary, converting a precursor of R₁, R₂ and R₄ to a group R₁, R₂ and R₄.

28. The process according to claim 27 wherein the reaction, when p=0, utilizes TBD as a base.

29. The process according to claim 27 wherein the reaction, when p=2, the base is an amine, a carbonate, a hydride, or an alkyl or aryl lithium reagent.

30. The process according to claim 27 wherein the imine of Formula (III), is isolated prior to reaction with Formula (II).

31. The process according to claim 30 wherein the imine of Formula (III), is formed in situ prior to reaction with Formula (II).

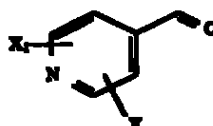
32. The process according to claim 31 wherein the imine is formed in situ by reacting an aldehyde of the formula R₁CHO, wherein R₁ is as defined for Formula (I), with a primary amine of the formula R₂NH₂, wherein R₂ is as defined for Formula (I).

33. The process according to claim 32 wherein formation of the imine in situ utilizes dehydrating conditions.

34. The process according to claim 33 wherein the solvent is N,N-dimethylformamide (DMF), halogenated solvents, tetrahydrofuran (THF), dimethylsulfoxide (DMSO), alcohols, benzene, or toluene, or DME.

35. The process according to claim 22 wherein the aldehyde R₁CHO is a pyridine aldehyde of the formula:

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(I)

wherein

10 X is YR₃, and X₁ is defined as the optional substituent group on the R₁ moiety in Formula (I) according to claim 1, to yield a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

15 36. The process according to claim 27 wherein the primary amine R₂NH₂ is is piperidine, 1-formyl-4-piperidine, 1-benzyl-4-piperidine, 1-methyl-4-piperidine, 1-ethoxycarbonyl-4-piperidine, 2,2,6,6-tetramethyl-4-piperidine, morpholine ethyl, morpholine propyl, pyrrolidinyl propyl, or piperidinyl propyl.

20 37. The process according to claim 27 wherein the compound is:

1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-[2-(phenoxy-4-pyridinyl)imidazole];

1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-[2-(4-methoxyphenoxy)-4-pyridinyl]imidazole;

1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-[2-(4-fluorophenoxy)-4-pyridinyl]imidazole;

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(2,6-dimethylphenoxy)pyridin-4-yl]imidazole;

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(4-methylphenoxy)pyridin-4-yl]imidazole;

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(4-chlorophenoxy)pyridin-4-yl]imidazole; or

1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-[2-(1-methyltetrazol-5-ylthio)pyridin-4-yl]imidazole

or a pharmaceutically acceptable salt thereof.

38. The compound according to claim 2 wherein R₃ is an optionally substituted aryl or arylalkyl.

39. The compound according to claim 3 wherein R₃ is an optionally substituted aryl or arylalkyl.

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United States Patent [19]

Adams et al.

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[54] PYRIDYL SUBSTITUTED IMIDAZOLES

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[22] PCT Filed: Jan. 13, 1993

[86] PCT No.: PCT/US93/00675

§ 371 Date: Nov. 22, 1994

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[51] Int. Cl.⁶ A61K 31/44; C07D 401/04

[52] U.S. Cl. 514/341; 546/274.1

[58] Field of Search 546/278, 274.1; 514/341

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[57] ABSTRACT

The novel compounds of Formula (I) have been found to be useful cytokine suppressive agents and therefore useful in the treatment and prophylaxis of disease states mediated thereby.

18 Claims, No Drawings

PYRIDYL SUBSTITUTED IMIDAZOLES

This application is a 371 of PCT/US93/00675 filed Jan. 13, 1993 now WO 9314,082.

FIELD OF THE INVENTION

This invention relates to novel compounds and methods of treating interleukin-1 (IL-1), interleukin-8 (IL-8), and Tumor Necrosis Factor (TNF) mediated diseases.

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., DiSarello et al., *Rev. Infect. Disease*, 6:31 (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 β cells.

DiSarello, *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 sarcoidosis, bone resorption diseases, reperfusion injury, graft vs. host reaction, allograft rejection, 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), knoid 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 proteins 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 Poll, 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 leukocytes. Its production from endothelial cells is induced by IL-1, TNF, or lipopolysaccharide (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 chemotactic properties for neutrophils, T-lymphocytes, and basophils. In addition it induces histamine release from basophils from both normal and atopic individuals as well as lysosomal 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 neutrophils 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 (hereinafter CSAID's), 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 pharmaceutical compositions comprising a com-

either by production of TNF itself, or by TNF causing another monokine to be released, such as but not limited to IL-1, or IL-6. A disease state in which IL-1, for instance is a major component, and whose production or action, is exacerbated or secreted in response to TNF, would therefore be considered a disease state mediated by TNF.

By the term "cytokine" as used herein is meant 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 but many other cells produce monokines, such as natural killer cells, fibroblasts, basophils, neutrophils, endothelial cells, brain astrocytes, bone marrow stromal cells, epidermal keratinocytes, and β -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), Tumor Necrosis Factor-alpha (TNF- α) and Tumor Necrosis Factor beta (TNF- β).

By the term "cytokine interfering or cytokine suppressive amount" is meant an effective amount of a compound of Formula (I) which will cause a decrease in the in vivo levels of the cytokine to normal or sub-normal levels, when given to the patient for the prophylaxis or therapeutic 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 an 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- β (also known as lymphotxin) 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- α and TNF- β are inhibited by the compounds of the present invention and thus are herein referred to collectively as "TNF" unless specifically delineated otherwise.

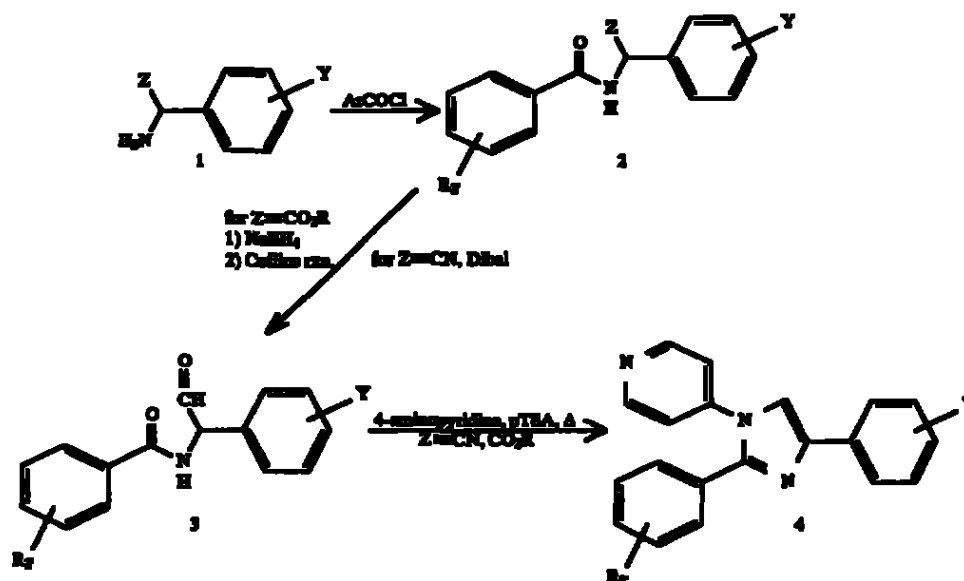
The compounds of the present invention may contain one or more asymmetric carbon atoms and may exist in racemic and optically active forms. All of these compounds are contemplated to be within the scope of the present invention. Exemplified compounds of Formula (I) are:

- 1-(4-pyridyl)-2-(4-fluorophenyl)-4-phenylimidazole;
- 1-(4-pyridyl)-2-(4-fluorophenyl)-4-(4-hydroxyphenyl)imidazole;
- 1-(4-pyridyl)-2-(4-fluorophenyl)-4-(4-thiomethylphenyl)imidazole;
- 1-(4-pyridyl)-2-(4-fluorophenyl)-4-(4-methylsulfinylphenyl)imidazole;
- 1-(4-pyridyl)-2-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)imidazole;
- 1-(4-pyridyl)-2-(4-fluorophenyl)-4-methylimidazole;
- 1-(4-pyridyl)-2-(4-N,N-dimethylaminomethylphenyl)imidazole;
- 1-(4-pyridyl)-2-(4-fluorophenyl)-4-(benzyloxy)imidazole;
- 1-(2-methyl-4-pyridyl)-4-(4-methylsulfinylphenyl)imidazole;
- 1-(2-methyl-4-pyridyl)-4-(4-thiomethylphenyl)imidazole; or
- 1-(2-methyl-4-pyridyl)-4-(3-chlorophenyl)imidazole.

METHODS OF PREPARATION

Preparation of the compounds of Formula (I) can be carried out by one of skill in the art according to the procedures outlined in the Examples, *infra*. The preparation of any remaining compounds of Formula (I) not described therein may be prepared by the analogous processes disclosed herein.

Scheme I



ity does not seem to correlate with the property of any of the compounds of Formula (I) in mediating arachidonic acid metabolism inhibition since other nonsteroidal antiinflammatory drugs with potent cyclooxygenase and/or lipooxygenase inhibitory activity do not inhibit TNF production at nontoxic doses. Furthermore, the ability of a compound to inhibit production of prostaglandin and/or leukotriene synthesis does not mean that it will necessarily also inhibit TNF production.

EXAMPLE C

Inhibitory Effect of Compounds of Formula (I) on IL-8 Production

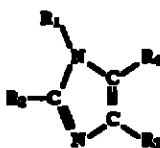
The effects of compounds of Formula (I) on the inhibition of IL-8 production from Human Umbilical Vein Endothelial cells is examined using the following protocol.

Primary human umbilical cord endothelial cells (HUVEC) are obtained from Cell Systems (Kirkland, Wash.) and maintained in culture medium supplemented with 15% fetal bovine serum and 1% CS-HBGF consisting of α FGF and heparin. Cells are then diluted 20-fold before being plated (250 μ l) into gelatin coated 96-well plates. Prior to use, culture medium is replaced with fresh medium (200 μ l). 25 μ l of either buffer or test compounds at the appropriate concentration is added to each well in quadruplicate wells. This is followed immediately by the addition of 25 μ l of the compounds of Formula (I) at concentrations between 1–10 μ M. The plates are allowed to incubate for the appropriate time, as indicated in a humidified incubator at 37° C. with 5% CO₂. 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, Minn.). All data presented is as a mean value (ng/ml) of multiple samples based on the standard curve. IC₅₀'s where appropriate are generated by non-linear regression analysis.

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 art 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.

What is claimed is:

1. A compound of the formula:



wherein

R₁ is a mono- or di- substituted 4-pyridyl wherein the substituent is independently selected from the group consisting of hydrogen, C₁₋₄ alkyl, halo, O—C₁₋₄ alkyl, S—C₁₋₄ alkyl, or N(R₅)₂;

R₂ is hydrogen, C₁₋₄ alkyl, or R₂ may form a heterocyclic ring which is pyrrolidine, piperidine, piperazine, morpholine, imidazolidine, or pyrazolidine;

R₃ is mono- or di-substituted phenyl wherein the substituents are independently selected from the group

consisting of hydrogen, halo, S(O)_nR₆, OR₆, halo substituted C₁₋₄ alkyl, C₁₋₄ alkyl, or N(R₁₂)₂;

R₄ is hydrogen, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₂₋₇ cycloalkyl, or C₂₋₇ cycloalkenyl;

R₅ is (X)_r—(Q)_r—(Y)_r;

X is hydrogen, —(C(R₁₀)₂)_n—NR₁₂—O— or S(O)_n;

r is a number having a value of 0 or 1;

m is a number having a value of 0, 1 or 2;

Q is alkenyl, alkynyl, cycloalkyl, cycloalkenyl, phenyl, naphthyl, phenyl C₁₋₁₀alkyl, or naphthyl C₁₋₁₀ alkyl;

s is a number having a value of 0 or 1;

Y is a substituent selected from the group consisting of hydrogen, C₁₋₁₀ alkyl, halo-substituted C₁₋₁₀ alkyl, halogen, —(C(R₁₀)₂)_nOR₆, —(C(R₁₀)₂)_nNO₂, —(C(R₁₀)₂)_nS(O)_nR₁₁, —(C(R₁₀)₂)_nSR₆, —(C(R₁₀)₂)_nS(O)_nOR₆, —(C(R₁₀)₂)_nS(O)_nNR₆R₆, —X_r—P(Z)—(X_rR₁₃)_s, —(C(R₁₀)₂)_nNR₆R₆, —(C(R₁₀)₂)_nCO₂R₆, —(C(R₁₀)₂)_nOC(O)—R₆, —(C(R₁₀)₂)_nCN, —(C(R₁₀)₂)_nCONR₆R₆, —(C(R₁₀)₂)_nC(S)NR₆R₆, —(C(R₁₀)₂)_nNR₆C(O)R₆, —(C(R₁₀)₂)_nNR₆C(S)R₆, —(C(R₁₀)₂)_nNR₆C(Z)NR₆R₆, —(C(R₁₀)₂)_nNR₆S(O)_nR₁₁, —(C(R₁₀)₂)_nNR₆C(=NCN)—S—R₁₁, —(C(R₁₀)₂)_nNR₆C(=NCN)—NR₆R₆, —(C(R₁₀)₂)_nNR₆C(O)C(O)—NR₆R₆, —(C(R₁₀)₂)_nNR₆C(O)C(O)—OR₁₀, —(C(R₁₀)₂)_nC(=NR₆)—NR₆R₆, —(C(R₁₀)₂)_nC(=NR₆)—Z—R₁₁, —(C(R₁₀)₂)_nOC(Z)—NR₆R₆, —(C(R₁₀)₂)_nNR₆S(O)_nCF₃, or —(C(R₁₀)₂)_nNR₆C(O)OR₁₀;

t is a number having a value of 0, 1, 2, or 3;

X_n is independently —(C(R₁₀)₂)_n—NR₆—, —O— or —S—;

Z is oxygen or sulfur;

m' is a number having a value of 1 or 2;

n is a number having a value of 0 to 10;

R₆ is hydrogen, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₂₋₇ cycloalkyl, C₂₋₇ cycloalkenyl, phenyl, naphthyl, or N(R₇)₂; provided that when m is 1 or 2 then R₆ is not hydrogen;

R₇ is hydrogen, C₁₋₄ alkyl, halo substituted C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₂₋₇ cycloalkyl, C₂₋₇ cycloalkenyl, phenyl, naphthyl, or naphthyl C₁₋₁₀ alkyl;

R₇ is hydrogen, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, phenyl, naphthyl, or may form a heterocyclic ring which is pyrrolidine, piperidine, piperazine, morpholine, imidazolidine, or pyrazolidine; provided that when R₇ is N(R₇)₂ then m is 1 or 2;

R₈ is hydrogen, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₂₋₇ cycloalkyl, C₂₋₇ cycloalkenyl, phenyl, naphthyl, phenyl C₁₋₁₀alkyl, or naphthyl C₁₋₁₀ alkyl;

R₉ is hydrogen, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₂₋₇ cycloalkyl, C₂₋₇ cycloalkenyl, phenyl, naphthyl, phenyl C₁₋₁₀ alkyl, or naphthyl C₁₋₁₀ alkyl, or R₈ and R₉ may together form a heterocyclic ring which is pyrrolidine, piperidine, piperazine, morpholine, imidazolidine, or pyrazolidine;

R₁₀ is hydrogen, or C₁₋₄ alkyl;

R₁₁ is C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₂₋₇ cycloalkyl, C₂₋₇ cyclo phenyl, naphthyl, phenyl C₁₋₁₀ alkyl, or naphthyl C₁₋₁₀ alkyl;

R₁₂ is hydrogen, C₁₋₄ alkyl, phenyl, naphthyl, or may form a heterocyclic which is pyrrolidine, piperidine, piperazine, morpholine, imidazolidine, or pyrazolidine;

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R_{13} is hydrogen, C_{1-10} alkyl, cycloalkyl; phenyl, naphthyl, phenyl C_{1-10} alkyl, or naphthyl C_{1-10} alkyl; and pharmaceutically acceptable salts thereof.
2. The compound according to claim 1 wherein s is 0.
3. The compound according to claim 2 wherein r is 0.
4. The compound according to claim 3 wherein Y is alkyl, $-(C(R_{10})_2)_nOR_9$, $-(C(R_{10})_2)_nS(O)_mR_{11}$, $-(C(R_{10})_2)_nSR_9$, $-(C(R_{10})_2)_nS(O)_mOR_9$, $-(C(R_{10})_2)_nS(O)_mNR_9R_9$, $-X_9-P(Z)-(X_9R_{13})_2$, $-(C(R_{10})_2)_nNR_9R_9$, $-(C(R_{10})_2)_nC(Z)OR_9$, $-(C(R_{10})_2)_nOC(Z)-R_9$, $-(C(R_{10})_2)_nC(O)NR_9R_9$, $-(C(R_{10})_2)_nNR_{10}C(=NCN)-NR_9R_9$, or $-(C(R_{10})_2)_nNR_{10}S(O)_mR_{11}$.
5. The compound according to claim 4 wherein Y is alkyl, $-(C(R_{10})_2)_nOR_9$, $(CH_2)_nS(O)_mR_9$, $(CH_2)_nCO_2R_9$, $-(C(R_{10})_2)_nNR_{10}C(=NCN)-NR_9R_9$, $-(C(R_{10})_2)_nNR_9R_9$, or $-X_9-P(Z)-(X_9R_{13})_2$; and n is 0 to 4.
6. The compound according to claim 1 wherein s is 1.
7. The compound according to claim 6 wherein Q is phenyl or naphthyl.
8. The compound according to claim 7 wherein Y is alkyl, $-(C(R_{10})_2)_nOR_9$, $-(C(R_{10})_2)_nS(O)_mR_{11}$, $-(C(R_{10})_2)_nSR_9$, $-(C(R_{10})_2)_nS(O)_mOR_9$, $-(C(R_{10})_2)_nS(O)_mNR_9R_9$, $-X_9-P(Z)-(X_9R_{13})_2$, $-(C(R_{10})_2)_nNR_9R_9$, $-(C(R_{10})_2)_nC(Z)OR_9$, $-(C(R_{10})_2)_nOC(Z)-R_9$, $-(C(R_{10})_2)_nC(O)NR_9R_9$, $-(C(R_{10})_2)_nNR_{10}C(=NCN)-NR_9R_9$, or $-(C(R_{10})_2)_nNR_{10}S(O)_mR_{11}$.
9. The compound according to claim 7 wherein r is 0, or r is 1 and X is $-(C(R_{10})_2)_n$.
10. The compound according to claim 7 wherein R_4 is hydrogen or alkyl.
11. The compound according to claim 1 wherein R_2 is a mono-substituted phenyl wherein the substituents are independently selected from the group consisting of hydrogen, halo, $S(O)_mR_9$, OR_9 , or C_{1-4} alkyl.
12. The compound according to claim 1 wherein R_1 is 4-pyridyl substituted in the 2-position with a C_{1-4} alkyl.
13. The compound according to claim 1 wherein R_2 is a mono-substituted phenyl wherein the substituents are independently selected from the group consisting of hydrogen, halo, $S(O)_mR_9$, OR_9 , or C_{1-4} alkyl; r is 0, s is 1, Q is aryl,

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Y is hydrogen, alkyl, $-(C(R_{10})_2)_nOR_9$, $-(C(R_{10})_2)_nS(O)_mR_{11}$, $-(C(R_{10})_2)_nSR_9$, $-(C(R_{10})_2)_nS(O)_mOR_9$, $-(C(R_{10})_2)_nS(O)_mNR_9R_9$, $-X_9-P(Z)-(X_9R_{13})_2$, $-(C(R_{10})_2)_nNR_9R_9$, $-(C(R_{10})_2)_nCO_2R_9$, $-(C(R_{10})_2)_nOC(O)-R_9$, $-(C(R_{10})_2)_nCONR_9R_9$, $-(C(R_{10})_2)_nNR_{10}C(=NCN)-NR_9R_9$, or $-(C(R_{10})_2)_nNR_{10}S(O)_mR_{11}$. R_4 is hydrogen or methyl, R_9 is hydrogen, C_{1-4} alkyl, or may optionally cyclize with R_9 to form a 5 membered heterocyclic ring together with the nitrogen to which they are attached.
14. The compound according to claim 1 which is
1-(4-pyridyl)-2-(4-fluorophenyl)-4-phenylimidazole;
1-(4-pyridyl)-2-(4-fluorophenyl)-4-(4-hydroxyphenyl)imidazole;
1-(4-pyridyl)-2-(4-fluorophenyl)-4-(4-thiomethylphenyl)imidazole;
1-(4-pyridyl)-2-(4-fluorophenyl)-4-(4-methylsulfinylphenyl)imidazole;
1-(4-pyridyl)-2-(4-fluorophenyl)-4-methylimidazole;
1-(2-methylpyrid-4-yl)-2-(4-fluorophenyl)-4-(4-thiomethylphenyl)imidazole; or
1-(2-methylpyrid-4-yl)-2-(4-fluorophenyl)-4-(4-methylsulfinylphenyl)imidazole.
15. The compound according to claim 1 wherein R_2 is a phenyl mono- or di-substituted independently by halogen.
16. A pharmaceutical or veterinary composition comprising an effective amount of a compound according to claim 1 and a pharmaceutically or veterinary acceptable carrier or diluent.
17. The pharmaceutical or veterinary composition comprising an effective amount of a compound according to claim 14 and a pharmaceutically or veterinary acceptable carrier or diluent.
18. A method of treating septic shock, endotoxic shock, gram negative sepsis, or toxic shock in a mammal in need thereof, which method comprises administering to said mammal an effective amount of a compound according to claim 1.

* * * * *

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO**DIVISION DE NUEVAS CREACIONES**

2020

Bogotá, D.C., Marzo 26 de 2007

Abogado

CARLOS R. OLARTE**ASUNTO**

Radicación No.	03 069684
Trámite	002
Evento	001
Actuación	- 430
Oficio No.	500 4342
Folios	00

Solicitante: Pfizer Products Inc.**Título de la solicitud:** NUEVOS COMPUESTOS ANTIINFLAMATORIOS DE TRIAZOLOPIRIDINAS

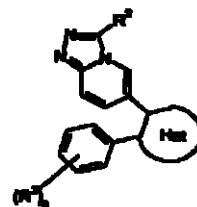
Como resultado del examen de fondo, realizado conforme a lo establecido por el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se notifica el siguiente concepto técnico:

Documentos estudiados

Para el presente estudio se tuvieron en cuenta el capítulo descriptivo comprendido en los folios 73 - 270 y el capítulo reivindicatorio de los folios 271 - 293 de la solicitud.

Objeto de la Invención

El objeto de la presente solicitud de patente de invención consiste en:



Reivindicaciones 1– 13: Un compuesto de la fórmula (I):

Reivindicación 14: Procedimiento de tratamiento que consiste en administrar un compuesto a un paciente

Reivindicación 15: Composiciones que los contienen

El problema planteado en esta solicitud es la necesidad de compuestos útiles para tratar inflamación, osteoartritis, artritis reumatoide, cáncer, repercusión ó isquemia en apoplejía ó ataque cardíaco, enfermedades inmunes.

Para resolver este problema técnico la solicitud en estudio proporciona un compuesto de la fórmula (I).

El objeto de la invención definido anteriormente se clasificó de acuerdo con la IPC: A61K31/435; A61P29/00; C07D471/04.

También se reivindica prioridad de la Solicitud de Patente de los Estados Unidos US 60 274 840 de marzo 9 de 2001, con respecto a la cual la fecha de presentación de la actual solicitud cumple el plazo máximo permitido.

Con respecto a los Art. 28 y 30 de la D 486

El artículo 28 de la Decisión 486 establece: *"La descripción deberá divulgar la invención de manera suficientemente clara y completa para su comprensión y para que una persona capacitada en la materia técnica correspondiente pueda ejecutarla. La descripción de la invención indicará el nombre de la invención e incluirá la siguiente información:*

c) una descripción de la invención en términos que permitan la comprensión del problema técnico y de la solución aportada por la invención, exponiendo las diferencias y eventuales ventajas con respecto a la tecnología anterior;

La descripción no presenta datos que ilustren la solución aportada por la invención, es decir su actividad como antiinflamatorios, ni la diferencia de estos con respecto a los compuestos del arte previo, es decir que su actividad como antiinflamatorios sea superior a la de los compuestos del arte previo.

El artículo 30 de la Decisión 486 establece: *"Las reivindicaciones definirán la materia que se desea proteger mediante la patente. Deben ser claras y concisas y estar enteramente sustentadas por la descripción.*

Los términos "heteroaril", "heterociclo" no definen el alcance de la invención. Debieran usarse términos más concretos tales como pirrol, tiazol, oxazol, imidazol, pirazol. Se solicita hacer las precisiones del caso.

Los términos "alquil", "alquenil" no definen el alcance de la invención. Deblera decirse el número de carbonos de cada cadena y su nombre químico preciso.

El término "heterociclo C1-10" no tiene sentido porque para conformar un anillo cíclico se necesitan por lo menos 3 carbonos. Debe hacerse la corrección necesaria.

Excepciones a la Patentabilidad

El artículo 20 de la Decisión 486 establece: *"No serán patentables: d) los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales"*

El Procedimiento de tratamiento de la reivindicación 14 que consiste en administrar un compuesto a un paciente, no es patentable de acuerdo con el Art 20, literal d), de la decisión 486.

Determinación del Estado de la Técnica

El artículo 16 de la decisión 486 de la comisión de la Comunidad Andina que establece que *"El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida.*

Solo para el efecto de la determinación de la novedad, también se considerará dentro del estado de la técnica, el contenido de una solicitud de patente en trámite ante la oficina nacional competente, cuya fecha de presentación o de prioridad fuese anterior a la fecha de presentación o de prioridad de la solicitud de patente que se estuviese examinando, siempre que dicho

contenido esté incluido en la solicitud de fecha anterior cuando ella se publique o hubiese transcurrido el plazo previsto en el artículo 40°.

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es Marzo 9 de 2001, se consultaron las bases de datos y los archivos con que cuenta la entidad con fecha de publicación anterior y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

No.	Documento	Título	Fecha de Publicación
D1	US 5 756 499	Substituted imidazole compounds	May 26 de 1998
D2	US 5 716 972	Pyridyl substituted imidazoles	Feb 10 de 1998

Evaluación de los requisitos de Patentabilidad

El artículo 14 de la Decisión 486 de la Comisión de la Comunidad Andina establece que *"Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial"*.

En cumplimiento del artículo 14 de la Decisión 486, se procedió a evaluar el cumplimiento de los requisitos de novedad, nivel inventivo y aplicación industrial, con el fin de establecer la patentabilidad de la invención reivindicada en la solicitud en estudio.

Evaluación del Nivel Inventivo

El artículo 18 de la Decisión 486 de la Comisión de la Comunidad Andina establece que *Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica*.

El documento del Estado de la Técnica más próximo es D1 que enseña compuestos derivados de imidazol, que tienen propiedades antiinflamatorias. La única diferencia con D1 es que esta solicitud no presenta datos que ilustren la solución aportada por la invención, es decir que su actividad como antiinflamatorios sea superior a la de los compuestos del arte previo.

El Problema Técnico planteado en esta solicitud: la necesidad de compuestos compuestos útiles para tratar inflamación, osteoartritis, artritis reumatoide, cáncer, repercusión ó isquemia en apoplejía ó ataque cardíaco, enfermedades inmunes, se había resuelto previamente mediante el mismo tipo de compuestos de fórmula (I) previamente conocidos. Por esta razón se considera que son evidentes para un experto en la materia.

Además, puesto que tanto D2 divulgaban previamente; compuestos imidazol con actividad antiinflamatoria, una persona conocedora de la materia motivada por tal sugerencia lograría los compuestos de esta solicitud. De manera que para un experto sería obvio combinar estos dos documentos. Por lo cual no hay nivel inventivo.

La composición de la reivindicación 15 no se considera inventiva porque el compuesto que la caracteriza no es inventivo.

Conclusión

En conclusión, los requisitos de patentabilidad de la presente solicitud están afectados así:

Item	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	US 5 758 499	1 - 13	Novedad y Nivel Inventivo
D2	US 5 716 972	1 - 13	Novedad y Nivel Inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de la notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No. 10 de 2001.

ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

El anterior requerimiento fue notificado por fijación en lista, de fecha

13 ABR 2007

CONCEPTO TÉCNICO No. 537	EXAMINADOR TÉCNICO Código 202007
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EXAMEN TÉCNICO DE FONDO			
Nº Solicitud	03 069684	Fecha de presentación	14-08-2003
Nº Prioridad	US 60 274 840	Fecha de prioridad	09-03-2001

Palabra clave	Triazolopiridinas
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CLASIFICACIONES INTERNACIONALES DE BÚSQUEDA
A61K31/435; A61P29/00; C07D471/04

DOCUMENTOS CORRESPONDIENTES EN OTROS PAÍSES	
Patente Original	WO02072579
Otros	EP1370559 (A1) OA12552 (A) MXPA03008144 (A) EP1370559 (A0) EE200300437 (A) CN1496366 (A) CA2440222 (A1) EP1370559 (B1) ES2260415T (T3) DE60210755T (T2)

BASES DE DATOS CONSULTADAS			
OEPM	Epollne	Espacenet	Oficina US

INFORMES DE EXÁMENES EN OTRAS OFICINAS		
Documento	Fecha	Ref. Afiliadas
WO02072579	2002-09-19	

ANTERIORIDADES ENCONTRADAS		
Documento de Patentes	Ref. Afiliadas	Referencia
US 5756 499	1 - 13	Nivel inventivo
US 5716 972	1 - 13	Nivel inventivo
LITERATURA NO PATENTES		
Documento no Patentes	Ref. Afiliadas	Referencia

Observaciones

Fecha del examen	Marzo 26 de 2007
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