(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
4 January 2007 (04.01.2007)

PCT

(10) International Publication Number
WO 2007/000655 A2

(51) **International Patent Classification:**
C07D 487/04 **(2006.01)**

(21) **International Application Number:**
PCT/IB2006/001791

(22) International Filing Date: 28 June 2006 (28.06.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
813/CHE/2005 28 June 2005 (28.06.2005) IN

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(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available):* AE, AG, AL, AM, **AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN,** CO, CR, **CU, CZ, DE, DK, DM, DZ,** EC, EE, **EG,** ES, **FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA,** LC, **LK,** LR, LS, **LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT,** RO, RS, **RU,** SC, **SD,** SE, **SG, SK,** SL, **SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW**

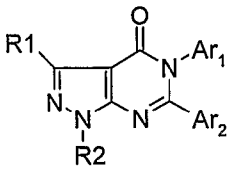
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available):* ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2007/000655 A2

(54) Title: NOVEL PYRAZOLOPYRIMIDINONE DERIVATIVES



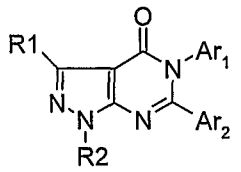
(I)

(57) **Abstract:** The present invention relates to novel pyrazolopyrimidinones of the general formula (I), their derivatives, their analogs, their pharmaceutically acceptable salts and pharmaceutically acceptable compositions containing them. The present invention more particularly provides novel pyrazolopyrimidinones derivatives of the general formula (I).

NOVEL PYRAZOLOPYRIMIDINONE DERIVATIVES

Field of the Invention

The present invention relates to novel pyrazolopyrimidinones of the general formula (I), their derivatives, their analogs, their pharmaceutically acceptable salts and pharmaceutically acceptable compositions containing them. The present invention more particularly provides novel pyrazolopyrimidinones derivatives of the general formula (I).



(I)

The present invention also provides a process for the preparation of the above said novel pyrazolopyrimidinones of the formula (I) pharmaceutically acceptable salts, their derivatives, their analogs, their pharmaceutically acceptable salts, and pharmaceutical compositions containing them.

The novel pyrazolopyrimidinones of the present invention are useful for the treatment of inflammation and immunological diseases. Particularly the compounds of the present invention are useful for the treatment of inflammation and immunological diseases those mediated by cytokines such as TNF-α, IL-I, IL-6, IL-1β, IL-8, IL-12, MAP kinase, p38 kinase and cyclooxygenase such as COX-2 and COX-3. The compounds of the present invention are also useful for the treatment of rheumatoid arthritis; osteoporosis; multiple myeloma; uveititis; acute and chronic myelogenous leukemia; ischemic heart disease, atherosclerosis, cancer, ischemic-induced cell damage, pancreatic β cell destruction; osteoarthritis; rheumatoid spondylitis; gouty arthritis; inflammatory bowel disease; adult respiratory distress syndrome (ARDS); psoriasis; Crohn's disease; allergic rhinitis; ulcerative colitis; anaphylaxis; contact dermatitis; asthma; muscle degeneration; cachexia; type I and type II diabetes; bone resorption diseases; ischemia reperfusion injury; atherosclerosis; brain trauma; multiple sclerosis; cerebral malaria; sepsis; septic shock; toxic shock syndrome; fever and myalgias due to infection; and as diuretic;

and diseases mediated by HIV-I; HIV-2; HIV-3; cytomegalovirus (CMV); influenza; adenovirus; the herpes viruses (including HSV-I, HSV-2) and herpes zoster viruses.

Background of Invention

The present invention is concerned with treatment of immunological diseases or inflammation, notably such diseases are mediated by cytokines or cyclooxygenase. The principal elements of the immune system are macrophages or antigen-presenting cells, T cells and B cells. The role of other immune cells such as NK cells, basophils, mast cells and dendritic cells are known, but their role in primary immunologic disorders is uncertain. Macrophages are important mediators of both inflammation and providing the necessary "help" for T cell stimulation and proliferation. Most importantly macrophages make IL-I, IL-6, IL-8, IL-12 and TNF-α all of which are potent pro-inflammatory molecules and also provide help for T cells. In addition, activation of macrophages results in the induction of enzymes, such as cyclooxygenase-2 (COX-2) and cyclooxygenase-3 (COX-3), inducible nitric oxide synthase (iNOS) and production of free radicals capable of damaging normal cells. Many factors activate macrophages, including bacterial products, superantigens and interferon gamma (IFNγ). It is believed that phosphotyrosine kinases (PTKs) and other undefined cellular kinases are involved in the activation process.

Cytokines are molecules secreted by immune cell large number of chronic and acute conditions have been recognized to be associated with pertrubation of the inflammatory response. A large number of cytokines participate in this response, including IL-I, IL-6, IL-8 and TNF. It appears that the activity of these cytokines in the regulatin of inflammation rely at least in part on the activatin of an enzyme on the cell signaling pathway, a member of the MAP known as CSBP and RK. This kinase is activated by dual phosphorylation after stimulation by physiochemical stress, treatment with lipopolysaccharides or with proinflammatory cytokines such as IL-I and TNF. Therefore, inhibitors of the kinase activity of p38 are useful anti¬inflammatory agents.

Cytokines are molecules secreted by immune cells that are important in mediating immune responses. Cytokine production may lead to the secretion of other

cytokines, altered cellular function, cell division or differentiation. Inflammation is the body's normal response to injury or infection. However, in inflammatory diseases such as rheumatoid arthritis, pathologic inflammatory processes can lead to morbidity and mortality. The cytokine tumor necrosis factor-alpha (TNF-α) plays a central role in the inflammatory response and has been targeted as a point of intervention in inflammatory disease. TNF-α is a polypeptide hormone released by activated macrophages and other cells. At low concentrations, TNF-α participates in the protective inflammatory response by activating leukocytes and promoting their migration to extravascular sites of inflammation (Moser et al., J Clin Invest, 83, 444-55,1989). At higher concentrations, TNF-α can act as a potent pyrogen and induce the production of other pro-inflammatory cytokines (Haworth et al., Eur J Immunol, 21, 2575-79, 1991; Brennan *et al*, Lancet, 2, 244-7, 1989). TNF-α also stimulates the synthesis of acute-phase proteins. In rheumatoid arthritis, a chronic and progressive inflammatory disease affecting about 1% of the adult U.S. population, TNF-α mediates the cytokine cascade that leads to joint damage and destruction (Arend *et al*, Arthritis Rheum, 38, 151-60, 1995). Inhibitors of TNF-α, including soluble TNF receptors (etanercept) (Goldenberg, Clin Ther, 21, 75-87, 1999) and anti-TNF-α antibody (infliximab) (Luong *et al*, Ann Pharmacother, 34, 743-60, 2000), recently approved by the U.S. Food and Drug Administration (FDA) as agents for the treatment of rheumatoid arthritis.

Elevated levels of TNF-α have also been implicated in many other disorders and disease conditions, including cachexia, septic shock syndrome, osteoarthritis, inflammatory bowel disease such as Crohn's disease and ulcerative colitis etc.

Elevated levels of TNF-α and/or IL-I over basal levels have been implicated in mediating or exacerbating a number of disease states including rheumatoid arthritis; osteoporosis; multiple myeloma; uveititis; acute and chronic myelogenous leukemia; pancreatic β cell destruction; osteoarthritis; rheumatoid spondylitis; gouty arthritis; inflammatory bowel disease; adult respiratory distress syndrome (ARDS); psoriasis; Crohn's disease; allergic rhinitis; ulcerative colitis; anaphylaxis; contact dermatitis; asthma; muscle degeneration; cachexia; type I and type II diabetes; bone resorption diseases; ischemia reperfusion injury; atherosclerosis; brain trauma;

multiple sclerosis; cerebral malaria; sepsis; septic shock; toxic shock syndrome; fever, and myalgias due to infection. HIV-I, HTV-2, HIV-3, cytomegalovirus (CMV), influenza, adenovirus, the herpes viruses (including HSV-I, HSV-2), and herpes zoster are also exacerbated by TNF-α.

It can be seen that inhibitors of TNF-α are potentially useful in the treatment of a wide variety of diseases. Compounds that inhibit TNF-α have been described in several patents.

Excessive production of IL-6 is implicated in several disease states; it is highly desirable to develop compounds that inhibit IL-6 secretion. Compounds that inhibit IL-6 have been described in U.S. Pat. Nos. 6,004,813; 5,527,546 and 5,166,137.

The cytokine IL-1β also participates in the inflammatory response. It stimulates thymocyte proliferation, fibroblast growth factor activity, and the release of prostaglandin from synovial cells. Elevated or unregulated levels of the cytokine IL-1β have been associated with a number of inflammatory diseases and other disease states, including but not limited to adult respiratory distress syndrome, allergy, Alzheimer's disease etc. Since overproduction of IL-Iβ is associated with numerous disease conditions, it is desirable to develop compounds that inhibit the production or activity of IL-Iβ.

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

In rheumatoid arthritis, both IL-I and TNF-α induce synoviocytes and chondrocytes to produce collagenase and neutral proteases, which leads to tissue destruction within the arthritic joints. In a model of arthritis (collagen-induced

arthritis (CIA) in rats and mice) intra-articular administration of TNF-α either prior to or after the induction of CIA led to an accelerated onset of arthritis and a more severe course of the disease (Brahn et al., Lymphokine Cytokine Res. 11, 253, 1992; and Cooper, Clin. Exp.Immunol. 898, 244, 1992).

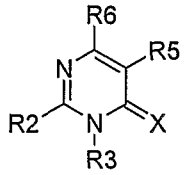
IL-8 has been implicated in exacerbating and/or causing many disease states in which massive neutrophil in filtration into sites of inlammation or injury (e.g., ischemia) is mediated chemotactic nature of IL-8, including, but not limited to, the following: asthma, inflammatory bowl disease, psoriasis,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

It has been reported that Cyclooxygenase enzyme exists in three isoforms, namely, COX-I, COX-2 and COX-3. COX-I enzyme is essential and primarily responsible for the regulation of gastric fluids whereas COX-2 enzyme is present at the basal levels and is reported to have a major role in the prostaglandin synthesis for inflammatory response. These prostaglandins are known to cause inflammation in the body. Hence, if the synthesis of these prostaglandins is stopped by way of inhibiting COX-2 enzyme, inflammation and its related disorders can be treated. COX-3 possesses glycosylation-dependent cyclooxygenase activity. Comparison of canine COX-3 activity with murine COX-I and COX-2 demonstrated that this enzyme is selectively inhibited by analgesic/antipyretic drugs such as acetaminophen, phenacetin, antipyrine, and dipyrone, and is potently inhibited by some nonsteroidal antiinflammatory drugs. Thus, inhibition of COX-3 could represent a primary central mechanism by which these drugs decrease pain and possibly fever. Earlier reports before to coxibs development show that inhibitors of COX-I enzyme causes gastric ulcers, where as selective COX-2 and COX-3 enzyme inhibitors are devoid of this function and hence are found to be safe. But, recent reports show that the selective COX-2 inhibitors (COXIBs) are associated with the cardiovascular risks. So,

inhibition of COX-2 without causing cardiovascular risks and gastric ulcers due to inhibition of COX-I are showed to be safe and is concerned in the present invention.

Few prior art references, which disclose the closest compounds, are given here:

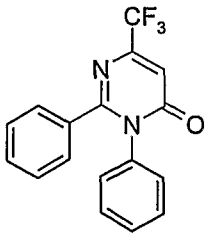
i) US patent Nos. 5,726,124 and 5,300,477 disclose novel herbicidal compounds of formula (Ha)



(IIa)

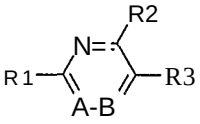
R_2 is a substituted or unsubstituted aryl group or a substituted or unsubstituted heteroaromatic group (e.g. a heteroaromatic ring structure having four to five carbon atoms and one heteroatom selected from the group consisting of nitrogen, sulfur and oxygen); R_3 is an alkyl, haloalkyl, polyhaloalkyl, haloalkenyl, polyhaloalkenyl, alkenyl, alkynyl, haloalkynyl, polyhaloalkynyl, alkoxyalkyl, dialkoxyalkyl, haloalkoxyalkyl, oxoalkyl, trimethylsilylalkynyl, cyanoalkyl or aryl group; R_5 is a hydrogen, halo, acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkoxyalkyl, alkoxyimino, alkoxycarbonylalkyl, dialkoxyalkyl, formyl, haloalkyl, haloalkenyl, haloalkynyl, haloalkoxy, hydroxyalkyl, hydroxyimino, polyhaloalkyl, polyhaloalkenyl, polyhaloalkynyl, polyhaloalkoxy, trimethylsilylalkynyl, alkoxyalkoxy, aminocarbonylalkyl, alkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, cyanoalkyl, hydroxy or cyano group; and R_6 is a hydrogen, halo, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, haloalkyl, haloalkenyl, haloalkynyl, haloalkoxy, haloalkylthio, polyhaloalkyl, polyhaloalkenyl, polyhaloalkynyl, polyhaloalkoxy, polyhaloalkylthio, cycloalkyl, aryl, aryloxy, heterocyclyl, aralkyl, alkylamino, dialkylamino, dialkylaminocarbonyl, or cyano group; and X is oxygen or sulfur.

An example of these compounds is shown in formula (lib)



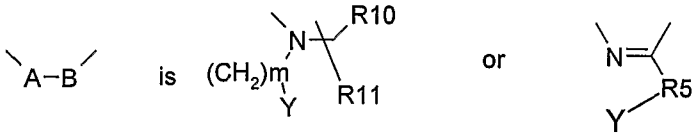
(IIb)

ii) US patent No. 5,474,996 discloses novel compounds of formula (lie)



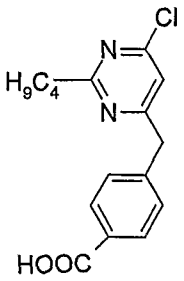
(lie)

wherein



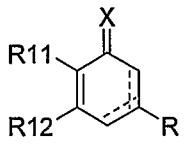
Rs is a single bond or ~$(CH_2)_m$ —, -NH-, etc., m is an integer of 0 to 4; Y is Yi-B-Y_2 is a monocyclic aryl of 5 to 6 ring member or condensed ring of 8 to 10 ring members optionally containing at least one heteroatom chosen from oxygen, nitrogen and sulfur; Rio and Rn together form oxo group; R_2 is chosen from the group consisting of hydrogen, halogen, hydroxyl, mercapto, cyano, nitro, formyl, benzoyl, acyl of 1 to 6 carbon atoms, alkyl, alkenyl, alkoxy, alkylthio of up to 10 carbon atoms, phenyl, phenoxy, naphthyl, benzyl, phenylthio, biphenyl, biphenylmethyl and indole; R_3 is alkyl substituted with carboxy or esterified carboxy.

An example of these compounds is shown in formula (Hd)



(lid)

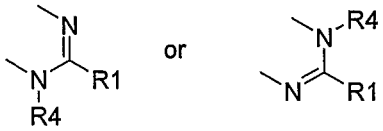
iii) US patent Nos. 6,420,385 and 6,410,729 discloses novel compounds of formula (He)



(IIe)

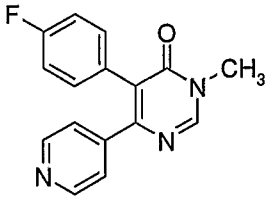
wherein

represents



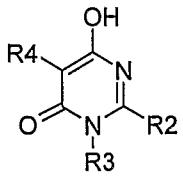
X is O, S or NR_5; R_1 and R_2 are each independently represent ~Y or --Z--Y, and R_3 and R_4 are each independently --Z--Y or R_3 is a hydrogen radical; provided that R_4 is other than a substituted-aryl, (substituted-aryl)methyl or (substituted-aryl)ethyl radical; wherein each Z is independently optionally substituted alkyl, alkenyl, alkynyl, heterocyclyl, aryl or heteroaryl; Y is independently a hydrogen; halo, cyano, nitro, etc., R_5 is independently a hydrogen, optionally substituted alkyl, alkenyl, alkynyl etc., Rn and Ri_2 each independently represent optionally substituted aryl or heteroaryl.

An example of these compounds is shown in formula (Hf)



(IIf)

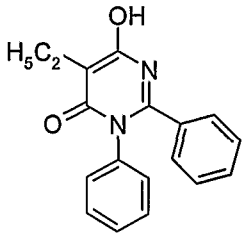
iv) US patent No. 4,771,040 discloses 6-oxopyrimidinyl(thiono)phosphate pesticide compounds and intermediate of formula (Hg)



(IIg)

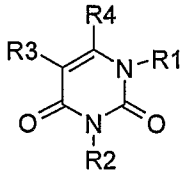
wherein R_2 represents hydrogen, optionally substituted alkyl, or alkoxy, alkylthio, dialkylamino or aryl; R_3 represents alkyl or aryl; R_4 represents hydrogen, halogen or alkyl.

An example of these compounds is shown in formula (Hh)



(IIh)

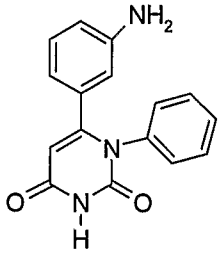
v) DE 2 1423 17 discloses hypnotic uracil derivatives of formula (Hi)



(IIi)

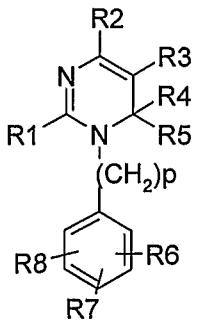
wherein R_1 is H, alkyl, alkenyl, dialkylaminoalkyl, or aralkyl; R_2 is H, alkyl, aryl, or halogen; R_3 is alkyl, alkenyl, cycloalkyl, aralkyl, aralkenyl, or aryl, R_4 is alkyl, alkenyl, cycloalkyl, aralkyl, aryl, etc.

An example of these compounds is shown in formula (Hj)



(IIj)

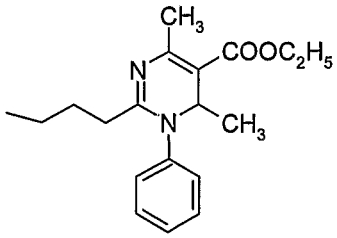
vi) US patent No. 5,470,975 discloses dihydropyrimidine derivatives of formula (Hk)



(IIk)

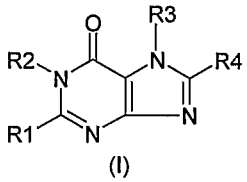
R_1 is alkyl, alkenyl, alkynyl, cycloalkyl, NR_4R_5 etc., R_2 is hydrogen, halogen, SR_4, etc., R_3 is R_4, --COOR, -$CONH_2$, CN, etc., R_4, R_5 are independently selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl etc., or R_4 and R5 together with the carbon atoms to which they are attached form a carbonyl or a thiocarbonyl group; R_6 is --CN, alkyl, acyloxy, SO_2NH_2, aryl, furyl; R_7 is H, halogen, etc., R_8 is H, halogen, alkyl, alkoxy etc.,

An example of these compounds is shown in formula (III)

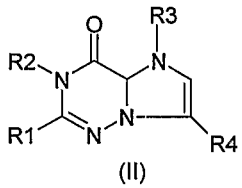


(III)

(vii) EP 1460077 A1 The present invention relates to novel pyrazolopyrimidones, compositions comprising pyrazolopyrimidones as well as to the use of compounds and the composition for the production of a medicament acting as a PDE inhibitor, such as for the treatment of erectile dysfunction.Compound, represented by one of the structural formulas:



(I)



(II)

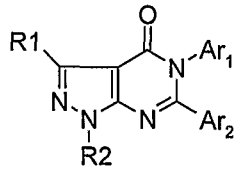
or mixtures thereof wherein R_1, R_2, R_3, and R_4 are independently hydrogen, halogen, hydroxyl, amino, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, haloalkyl, alkylaryl, aryl, aralkyl, alkoxy, carboxy or heterocyclyl, all of these substituents being substituted or unsubstituted, with the exception of formula (XI), wherein R_1 being hydrogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, piperidinomethyl, methoxymethyl, N-methylpiperazino methyl, carbethoxy, p-chlorophenoxymethyl or Ar-(CH_2)n-, wherein n is 0-4;

Objective of the Invention

We have focused our research to identify cytokine inhibitors with predominantly acting through the inhibition of tumour necrosis factor - α (TNF-α) which are devoid of any side effects normally associated with tumour necrosis factor -α (TNF-α) inhibitors. Our sustained efforts have resulted in novel compounds of the formula (I). The derivatives may be useful in the treatment of inflammation and immunological diseases. Particularly the compounds of the present invention are useful for the treatment of immunological diseases those mediated by cytokines such as TNF-α, IL-I, IL-6, IL-1β, IL-8, IL-12 and inflammation. The compounds of the present invention are also useful in the treatment of rheumatoid arthritis; osteoporosis; multiple myeloma; uveititis; acute and chronic myelogenous leukemia; ischemic heart disease; atherosclerosis; cancer; ischemic-induced cell damage; pancreatic β-cell destruction; osteoarthritis; rheumatoid spondylitis; gouty arthritis; inflammatory bowel disease; adult respiratory distress syndrome (ARDS); psoriasis; Crohn's disease; allergic rhinitis; ulcerative colitis; anaphylaxis; contact dermatitis; asthma; muscle degeneration; cachexia; bone resorption diseases; ischemia reperfusion injury; atherosclerosis; brain trauma; multiple sclerosis; sepsis; septic shock; toxic shock syndrome; fever, and myalgias due to infection.

Summary of the Invention

The present invention relates to novel pyrazolopyrimidinone derivatives of the formula (I)



(I)

their derivatives, their pharmaceutically acceptable salts and their pharmaceutically acceptable compositions, wherein Ar_1 and Ar_2 may be same or different and independently represent substituted or unsubstituted groups selected from aryl, heteroaryl, heterocyclyl group; R_1 represents hydrogen, hydroxyl, halogen, formyl, amino, hydrazine, alkylamino, arylamino, acylamino, sulfonylamino, substituted (C_1-C6)alkyl, substituted or unsubstituted groups selected from acyl, aryl, aralkyl,

heteroaryl, heteroaralkyl, heterocyclyl, -$NHCH_2CN$, - $NHCH_2C(=NH)NHOH$, $NHCONH_2$, -$NHCSNH_2$, -NHCONH-alkyl, , -NHCONH-aryl, -NHCSNH-alkyl, -NHCSNH-aryl,-NHCO-aryl, -NHCO-heteroaryl, NHCO-piperzine, -NHCS-piperzine; R_2 represents hydrogen, hydroxy, nitro, nitroso, alkyl, azido, halogen, -$C(=NH)NH_2$, formyl, substituted or unsubstituted groups selected from haloalkyl, alkoxy, aryloxy, aralkyl, aralkoxy, heteroaryl, heterocyclyl, acyl, acyloxy, cycloalkyl, amino, monoalkylamino, dialkylamino, acylamino, alkylsufonyl, arylsulfonyl, alkylsulfinyl, arylsulfinyl, alkylthio, arylthio, alkoxycarbonyl, aryloxycarbonyl, alkoxyalkyl, sulfamoyl, carboxylic acid and its derivatives.

Detailed Description of the Invention

Suitable groups represented by Ar_1 and Ar_2 are selected from aryl group such as phenyl or naphthyl, the aryl group may be substituted; heteroaryl group may be mono or fused system such as pyridyl, thienyl, furyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyrimidinyl, pyrazine, piperazine, benzopyranyl, benzofuranyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, benzopyrrolyl, benzoxadiazolyl, benzothiadiazolyl and the like, the heteroaryl group may be substituted; heterocyclyl group such as pyrrolidinyl, thiazolidinyl, oxazolidinyl, morpholinyl, thiomorpholinyl, piperidinyl, piperazinyl, and the like, the heterocyclyl group may be substituted.

The substituents on the groups represented by Ar_1 and Ar_2 are selected from hydroxy, nitro, nitroso, formyl, azido, halo or substituted or unsubstituted groups selected from alkyl, haloalkyl, alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heteroaryl, heterocyclyl, acyl, acyloxy, cycloalkyl, amino, hydrazine, monoalkylamino, dialkylamino, acylamino, alkylsulfonyl, arylsulfonyl, alkylsulfinyl, arylsulfinyl, alkylthio, arylthio, alkoxycarbonyl, aryloxycarbonyl, alkoxyalkyl, sulfamoyl, -SO_2N_3, -SO_2NHNH_2, -SO_2NHR_3, -SO_2NHCOR_3, -$SO_2NHNHCOR_3$, R_3 may be alkyl, haloalkyl, aryl, heteroaryl, -carboxylic. acid and its derivatives;

Suitable groups represented by R_1 are selected from hydrogen, hydroxyl, amino, alkylamino, arylamino, acylamino, sulfonylamino, hydrazine, halogen atom such as fluorine, chlorine, bromine or iodine; formyl, substituted or unsubstituted linear or branched (Ci-C_6) alkyl group, such as methyl, ethyl, n-propyl, isopropyl, n-

butyl, isobutyl, t-butyl, n-pentyl, isopentyl, hexyl and the like; acyl group such as -C(=O)CH_3, -CC=O)C_2H_5, -CC=O)C_3H_7, -C(=O)C_6H_{13}, -C(=S)CH_3, -CC=S)C_2H_5, -C(=S)C_3H_7, -C(=S)C_6H_{13}, benzoyl and the like, which may be substituted; -$NHCH_2CN$, -$NHCH_2C$(=NH)NHOH,$NHCONH_2$, -$NHCSNH_2$, -NHCONH-alkyl, , -NHCONH-aryl, -NHCSNH-alkyl, -NHCSNH-aryl, -NHCO-aryl, -NHCO-heteroaryl, -NHCO-piperzine, -NHCS-piperzine; aryl group such as phenyl or naphthyl, the aryl group may be substituted; aralkyl group such as benzyl, phenylethyl, phenyl propyl and the like, which may be substituted; heteroaryl group may be mono or fused system such as pyridyl, thienyl, furyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyrimidinyl, pyrazine, piperazine, benzopyranyl, benzofuranyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, benzopyrrolyl, benzoxadiazolyl, benzothiadiazolyl and the like, the heteroaryl group may be substituted; heterocyclyl group such as pyrrolidinyl, thiazolidinyl, oxazolidinyl, moϕ holinyl, thiomorpholinyl, piperidinyl, piperazinyl, and the like, the heterocyclyl group may be substituted; heteroaralkyl wherein the heteroaryl group is as defined above.

Suitable groups represented by R_2 are selected from hydrogen, hydroxy, nitro, nitroso, formyl, azido, -C(=NH)NH_2, halogen atom such as fluorine, chlorine, bromine or iodine; or substituted or unsubstituted linear or branched (Ci-C_6) alkyl group, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, n-pentyl, isopentyl, hexyl and the like; haloalkyl such as chloromethyl, chloroethyl, trifiuoromethyl, trifluoroethyl, dichloromethyl, dichloroethyl and the like, which may be substituted; aryl group such as phenyl or naphthyl, the aryl group may be substituted; cyclo (C_3-Ce) alkyl group such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like, the cycloalkyl group may be substituted; acyl group such as -CC=O)CH_3, -CC=O)C_2H_5, -CC=O)C_3H_7, -C(=O)C_6H_{13}, -C(=S)CH_3, -CC=S)C_2H_5, -CC=S)C_3H_7, -C(=S)C_6H_{13}, benzoyl and the like, which may be substituted; linear or branched (Ci-C_6) alkoxy group, such as methoxy, ethoxy, n-propoxy, isopropoxy and the like; aryloxy group such as phenoxy, napthoxy, the aryloxy group may be substituted; aralkoxy group such as benzyloxy, phenethyloxy and the like, which may be substituted; acyloxy group such as MeCOO-, EtCOO-, PhCOO- and the like, which may be substituted; heterocyclyl groups such as pyrrolidinyl, morpholinyl,

thiomorpholinyl, piperidinyl, piperazinyl, and the like, the heterocyclyl group may be substituted; heteroaryl group may be mono or fused system such as pyridyl, thienyl, furyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyrimidinyl, pyrazine, piperazine, benzopyranyl, benzofuranyl, benzimjdazolyl, benzoxazolyl, benzothiazolyl, benzopyrrolyl, benzoxadiazolyl, benzothiadiazolyl and the like, the heteroaryl group may be substituted; aralkyl group such as benzyl, phenylethyl, phenyl propyl and the like, which may be substituted; amino, which may be substituted; hydrazine, which may be substituted; monoalkylamino group such as -NHCH$_3$, -NHC$_2$H$_5$, -NHC$_3$H$_7$, -NHC$_6$Hi$_3$, and the like, which may be substituted; dialkylamino group such as -N(CH$_3$)$_2$, -NCH$_3$(C$_2$H$_5$), -N(C$_2$Hs)$_2$ and the like, which may be substituted; acylamino group such as -NHC(=O)CH$_3$, -NHC(=O)C$_2$H$_5$, -NHC(=O)C$_3$H$_7$, -NHC(=O)C$_6$H$_{13}$, and the like, which may be substituted; alkoxycarbonyl group such as methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, isopropoxycarbonyl and the like, the alkoxycarbonyl group may be substituted; aryloxycarbonyl group such as phenoxycarbonyl, napthoxycarbonyl, the aryloxycarbonyl group may be substituted; alkylsulfonyl group such as methylsulfonyl, ethylsulfonyl, n-propylsulfonyl, iso-propylsulfonyl and the like, the alkylsulfonyl group may be substituted; arylsulfonyl group such as phenylsulfonyl or naphthylsulfonyl, the arylsulfonyl group may be substituted; alkylsulfïnyl group such as methylsulfmyl, ethylsulfïnyl, n-propylsulfinyl, iso-propylsulfmyl and the like, the alkylsulfinyl group may be substituted; arylsulfinyl group such as phenylsulfinyl or naphthylsulfinyl, the arylsulfinyl group may be substituted; alkylthio group such as methylthio, ethylthio, n-propylthio, iso-propylthio and the like, the alkylthio group may be substituted; arylthio group such as phenylthio, or naphthylthio, the arylthio group may be substituted; alkoxyalkyl group such as methoxymethyl, ethoxymethyl, methoxyethyl, ethoxyethyl and the like, which may be substituted; sulfamoyl; carboxylic acid and its derivatives such as esters, amides and acid halides.

When the groups R_1, R_2, are substituted, the substituents are selected from halogen, hydroxy, nitro, cyano, azido, nitroso, amino, hydrazine, formyl, alkyl, aryl, cycloalkyl, alkoxy, aryloxy, acyl, acyloxyacyl, heterocyclyl, heteroaryl, monoalkylamino, dialkylamino, acylamino, alkoxycarbonyl, aryloxycarbonyl, alkylsulfonyl, arylsulfonyl, alkylsulfinyl, arylsulfinyl, alkylthio, arylthio, sulfamoyl,

alkoxyalkyl groups or carboxylic acids and its derivatives and these substituents are as defined above.

Representative compounds according to the present invention include:

3-Amino-5-(4-methylphenyl)-6-[4-(methylthio)phenyl] -1,5-dihydro-4H-pyrazolo[3,4-cdpyrimidin-4-one;

3-Amino-5-**(3**,4-dimethylphenyl)-6-[4-(methylthio)phenyl] -1**,5**-dihydro-4H-pyrazolo[3,4-*d*f]pyrimidin-4-one;

3-Amino-5-(4-fluorophenyl)-6-[4-(methylthio)phenyl]-l,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

3-Amino-5-[(4-methylthio)phenyl]-6-(4-fluorophenyI)-1**,5**-dihydro-4H-pyrazolo**[3**,4-d]pyrimidin-4-one;

3-Amino-5-(4-tert-butylphenyl)-6-[4-(methylthio)phenyl]-l,5-dihydro-4H-pyrazolo[3,4-cfIpyrimidin-4-one;

3-Amino-5-(4-isopropylphenyl)-6-[(4-methylthio)phenyl]-l ,5-dihydro-4H-pyrazolo[3,4-<f]pyrimidin-4-one;

3-Amino-5-[(4-methylthio)phenyl]-6-(4-chlorophenyl)-l,5-dihydro-4H-pyrazolo[3,4-cf]pyrimidin-4-one;

3-Amino-5-(4-chlorophenyl)-6-[(4-methylthio)phenyl]- l,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

3-Amino-5-(4-ethylphenyl)-6-[(4-methylthio)phenyl]- l,5-dihydro-4H-pyrazolo[3,4-*d*]pyrimidin-4-one;

3-Amino-5-[(4-methylthio)phenyl]- 6-phenyl-l,5-dihydro-4H-pyrazolo[3,4-</jpyrimidin-4-one;

3-Amino-5-(4-fluorophenyl)-6-phenyl-l,5-dihydro-4H-pyrazolo[3,4-J]pyrimidin-4-one;

3-Amino-5-[(4-methylthio)phenyl]-6-(4-methylphenyl)-l,5-dihydro-4H-pyrazolo[3,4-cf]pyrimidin-4-one;

3-Amino-5-(4-methylphenyl)-6-[(4-methylsulfonyl)phenyl]-l,5-dihydro-4H-pyrazolo[3,4-cf]pyrimidin-4-one;

3-Amino-5-(4-ethoxyphenyl)-6-[(4-methylthio)phenyl]-l,5-dihydro-4H-pyrazolo[3,4-c(]pyrimidin-4-one;

3-Amino-5-(4-methylphenyl)-6-phenyl-l,5-dihydro-4H-pyrazolo[3,4-c(]pyrimidin-4-one;

3-Amino-5-[(4-methylthio)phenyl]- 6-(4-trifluoromethylphenyl)-l,5-dihydro-4H-pyrazolo[3,4-<^]pyrimidin-4-one;

4-[3-Amino-5-(4-methylphenyl)-4-oxo-4,5-dihydro-lH-pyrazolo[3,4-c(]pyrimidin-6-yl]benzenesulfonamide;

3-Amino-5-(4-bromophenyl)-6-[(4-methylthio)phenyl]-l,5-dihydro-4H-pyrazolo[3,4-cT]pyrimidin-4-one;

3-Amino-5-(3,4-dimethylphenyl)-l-methyl-6-[4-(methylthio)phenyl]-l,5-dihydro-4H-pyrazolo[3,4-*a*(]pyrimidin-4-one;

3-Amino-5-(4-ethoxyphenyl)-l-methyl-6-[4-(methylthio)phenyl]-l,5-dihydro-4H-pyrazolo[3,4-if]pyrimidin-4-one;

3-Amino-5-(4-isopropylphenyl)-l-methyl-6-[4-(methylthio)phenyl]-l,5-dihydro-4H-pyrazolo[3,4-c(]pyrimidin-4-one;

3-Amino-5-(2,4-dimethylphenyl)-l-methyl-6-[4-(methylthio)phenyl]-l,5-dihydro-4H-pyrazolo[3,4-<f]pyriniidin-4-one;

3-Amino-5-(4-chlorophenyl)-l-methyl-6-[4-(methylthio)phenyl]-l,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin~4~one;

3-Amino-5-(4-fluorophenyl)-l-methyl-6-[4-(methylthio)phenyl]-l,5-dihydro-4H-pyrazolo[3,4-fif]pyrimidin-4-one;

3-Amino-5-(4-methoxyphenyl)-l-methyl-6-[4-(methylthio)phenyl]-l,5-dihydro-4H-pyrazolo[3,4-<i]pyrimidin-4-one;

3-Amino-5-(4-methoxyphenyl)- 1-methyl-6-pyridin-4-yl- 1,**5**-dihydro-4*H*-pyrazolo[3,4-*a*f]pyrimidin-4-one;

3-Amino-5-(4-ethoxyphenyl)- 1-methyl-6-pyridin-3-yl-1,5-dihydro-4*H*-pyrazolo[3,4-cf]pyrimidin-4-one;

3-Amino-5-(4-methoxyphenyl)-l-methyl-6-pyridin-3-yl-l,5-dihydro-4 *H*-pyrazolo[3,4-*a*(Ipyrimidin-4-one;

3-Amino-5-(4-bromophenyl)-l-methyl-6-[4-(methylthio)phenyl]-l,5-dihydro-4 *H*-pyrazolo[3,4-£f]pyrimidin-4-one;

3-Amino-6-[4-(dimethylamino)phenyl]-5-(4-methoxyphenyl)-l-methyl-l,5-dihydro-4*H*-pyrazolo[3,4-cf]pyrimidin-4-one;

3-Amino-5-(2,4-dimethylphenyl)-l-(2-hydroxyethyl)- 6-[4-(methylthio)phenyl]-l,5-dihydro-4*H*-pyrazolo[3,4-fi(]pyriniidin-4-one;

3-Amino- 1-(2-hydroxyethyl)-5-(4-methoxyphenyl)-6-pyridin-3 -yl- 1,5-dihydro-4*H*-pyrazolo[3,4-fidpyrimidin-4-one;

3-Amino-6-[4-(dimethylamino)phenyl]-l-methyl-5-[(4-methylthio)phenyl]-l,5-dihydro-4*H*-pyrazolo[3,4-<f]pyrimidin-4-one;

N-[5-(3,4-Dimethylphenyl)-4-oxo-6-[(4-methylthio)phenyl]-4,5-dihydro-l H-pyrazolo[3,4-c0pyrimidin-3-yl]acetamide;

l-Acetyl-3-amino-5-(3,4-dimethylphenyl)-6-[(4-methylthio)phenyl]-l,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

3-Amino-5-(4-methoxyphenyl)-6-[4-(methylthio)phenyl]-l,5-dihydro-4 *H*-pyrazolo[3,4-fif]pyrimidin-4-one;

N-(4-Oxo-5-(2,4-dimethylphenyl)-l-methyl-6-[(4-methylthio)phenyl]-4,5-dihydro-1*H*-pyrazolo[3**,4**-J]pyrimidin-3 -yl)-4-(trifluoromethyl)benzamide;

N-{5-(2,4-Dimethylphenyl)-l-methyl-6-[4-(methylthio)phenyl]-4-oxo-4,5-dihydro-l*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}acetamide;

2,2,2-trifluoro-*N*-{5-(2,4-dimethylphenyl)-l-methyl-6-[4-(methylthio)phenyl]-4-oxo-4,5-dihydro-l *H*-pyrazolo[3,4-*a*(]pyrimidin-3-yl}acetaniide;

2,2,2-trifluoro-*N*-[5-(4-methoxyphenyl)-l-methyl-4-oxo-6-pyridin-3-yl-4,5-dihydro-l*H*-pyrazolo[3,4-d]pyrimidin-3-yl]acetamide;

N-(4-Oxo-5-(4-chlorophenyl)-l-methyl-6-[(4-methylthio)phenyl]-4,5-dihydro-l *H*-pyrazolo**[3**,4-*a*(]pyrimidin-3-yl)-3-fluorobenzamide;

3-Amino-5-(4-methoxy ρhenyl)-6-[4-methylphenyl]-l,5-dihydro-4 *H*-pyrazolo[3,4-J]pyrimidin-4-one;

3-Amino-5-(4-methoxyphenyl)-6-[4-methoxyphenyl]-l,5-dihydro-4 *H*-pyrazolo[3,4-d]pyrimidin-4-one;

3-Amino-5-(4-methoxyphenyl)-6-[4-chlorophenyl]-l,5-dihydro-4 *H*-pyrazolo[3,4-6(]pyrimidin-4-one;

3-Amino-5-(4-chlorophenyl)-6-[4-chlorophenyl]-l,5-dihydro-4 *H*-pyrazolo[3,4-</|pyrimidin-4-one;

3-Araino-5-(4-chlorophenyl)-6-[4-methoxyphenyl]-l,5-dihydro-4 *H*-pyrazolo[3,4-£f|pyrimidin-4-one;

3-Amino-5-(4-chlorophenyl)-6-[4-methylphenyl]-l,5-dihydro-4 *H*-pyrazolo[3,4-c(]pyrimidin-4-one;

3-Amino-5-(4-fluorophenyl)-6-[4-chlorophenyl]-l,5-dihydro-4 *H*-pyrazolo[3,4-^/]pyrimidin-4-one;

3-Amino-5-(4-fluorophenyl)-6- [4-methoxyphenyl]-1,5-dihydro-4*H*-pyrazolo[3,4-<f|pyrimidin-4-one;

3-Amino-5-(4-fluorophenyl)-6-[4-methylphenyl]-l,5-dihydro-4 *H*-pyrazolo[3,4-d]pyrimidin-4-one;

3-Amino-5-(4-trifluoromethylphenyl)-6-[4-chlorophenyl]-l 5-dihydro-4*H*-pyrazolo[3,4-e(]pyrimidin-4-one;

3-Amino-5-(4-trifluoromethylphenyl)-6- [4-methoxyphenyl]-1,5-dihydro-4*H*-pyrazolo[3,4-<f]pyrimidin-4-one;

3-Amino-5-(4-trifluoromethylphenyl)-6-[4-methylphenyl]-l,5-dihydro-4 *H*-pyrazolo[3,4-<f]pyrimidin-4-one;

3-Amino-5-(4-trifluoromethylphenyl)-6-[4-(methylthio)phenyl]-l,5-dihydro-4 *H*-pyrazolo[3,4-J]pyrimidin-4-one;

3-Amino-5-(4-methylsulphonyl)-6-[4-chlorophenyl]-l,5-dihydro-4 *H*-pyrazolo[3,4-J]pyrimidin-4-one;

3-Amino-5-(4-methylsulphonyl)-6-[4-methoxyphenyl] -1,5-dihydro-4*H*-pyrazolo[3,4-cf]pyrimidin-4-one;

3-Amino-5-(4-methylsulphonyl)-6-[4-methylphenyl] -1,5-dihydro-4*H*-pyrazolo[3,4-*a*(]pyrimidin-4-one;

3-Amino-5-(4-methylsulphonyl)-6-[4-(methylthio)phenyl]-l,5-dihydro-4 *H*-pyrazolo[3,4-</|pyrimidin-4-one;

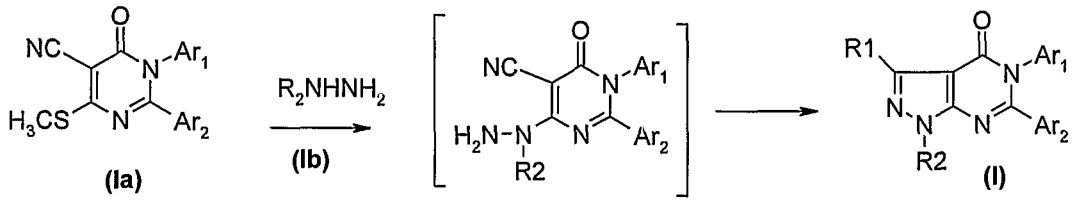
3-Amino-5-[4-(methylthio)phenyl]-6-pyridin-4-yl- 1,5-dihydro-4H-pyrazolo[3,4-if]pyrimidin-4-one;

3-Amino-5-(4-ethoxyphenyl)- 1-methyl-6-pyridin-4-yl- 1,5-dihydro-4*H*-pyrazolo[3,*A*-£/]pyrimidin-4-one;

l-{l-Methyl-5-[4-(methylthio)phenyl]-4-oxo-6-phenyl-4,5-dihydro-l *H*-pyrazolo[3,4-c(]pyrimidin-3-yl}urea and

l-{5-[4-(Methylthio)phenyl]-4-oxo-6-phenyl-4,5-dihydro-l *H*-pyrazolo[3,4-</|pyrimidin-3-yl}urea.

According to another embodiment of the present invention, there is provided a process for the preparation of novel pyrazolo[3,4-</]pyrimidin-4-one derivatives of the formula (I) wherein R_1 represents amino and all other symbols are as defined earlier as shown in scheme **I** given below:



Scheme - 1

The reaction of compound of formula (Ia) with compound of formula (Ib) may be carried out using solvents like toluene, xylene, tetrahydrofuran, dioxane, chloroform, dichloromethane, dichloroethane, o-dichlorobenzene, acetone, ethylacetate, acetonitrile, N,N-dimethylformamide, dimethylsulfoxide, ethanol, methanol, isopropylalcohol, tert-butylalcohol, acetic acid, propionic acid etc., a mixture thereof or the like in the presence of base such as carbonates, bicarbonates, hydrides, hydroxides, alkoxides of alkali metals and alkaline earth metals or by neat reaction. The reaction may be carried out at a temperature in the range of 20 ^{0}C to 150 ^{0}C for period in the range of 1 to 12 h.

It is appreciated that in any of the above-mentioned reactions, any reactive group in the substrate molecule may be protected according to conventional chemical practice. Suitable protecting groups in any of the above-mentioned reactions are those used conventionally in the art. The methods of formation and removal of such protecting groups are those conventional methods appropriate to the molecule being protected.

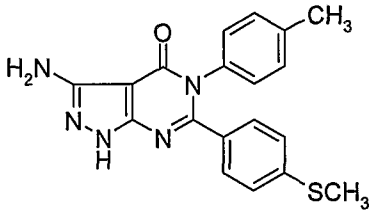
The pharmaceutical composition may be in the forms normally employed, such as tablets, capsules, powders, syrups, solutions, aerosols, suspensions and the like, may contain flavoring agents, sweeteners etc. in suitable solid or liquid carriers or diluents, or in suitable sterile media to form injectable solutions or suspensions.

Such compositions typically contain from 1 to 20 %, preferably 1 to 10 % by weight of the active compound, the remainder of the composition being the pharmaceutically acceptable carriers, diluents or solvents.

The present invention is provided by the examples given below, which are provided by way of illustration only and should not be considered to limit the scope of the invention.

Example 1

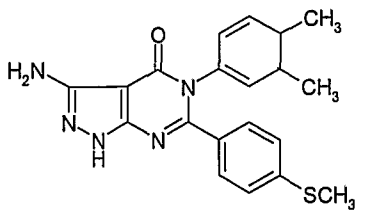
Synthesis **of** 3-amino-5-(4-methylphenyI)-6-[4-(methyIthio)phenyl]-l,5-dihydro-4*H*-pyrazolo[3,4-tf]pyrimidin-4-one



Hydrazine hydrate (0.658g, 13mmol) was added to a suspension of 5-cyano-l-(4-methylphenyl)-4-methylthio-2-(4-methylthiophenyl)-l,6-dihydro-pyrimidin-6-one (5.0g, 13mmol) (prepared according to the procedure disclosed in our PCT publication No. 03/84938) in toluene (70ml) under stirring at room temperature. Anhydrous potassium carbonate (O.lg, OJmmol) was added to the reaction mass and heated to $7O^0$C for 3 h. The solid separated was filtered, washed with toluene, water and dried to yield the title compound (2.08g, 43.5%, mp>285°C, purity 98.4% by HPLC). ^{1}H-NMR (DMSOd $_6$): δ 2.25 (s, 3H), 2.41 (s, 3H), 5.31 (bs, 2H, D_2O exchangeable), 7.04 - 7.09 (m, 6H), 7.23 -7.25 (d, 2H), 12.5 (bs, IH, D_2O exchangeable). IR (KBr) cm^{-1}: 3379,3296,3164,1701. MS m/z: 364 (M^++!).

Example 2

Synthesis **of** 3-amino-5-(3,4-dimethylphenyI)-6-[4-(methylthio)phenyI]-l,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



Hydrazine hydrate (1.02g, 20.3mmol) was added to a suspension of 5-cyano-l-(3,4-dimethylphenyl)-4-methylthio-2-(4-methylthiophenyl)- 1,6-dihydro-pyrimidin-6-one (prepared according to the procedure disclosed in our PCT publication No. 03/84938) (4.Og, lO.lmmol) in toluene (70ml) under stirring at room temperature. Anhydrous potassium carbonate (O.lg, 0.7mmol) was added to the reaction mass and heated to $7O^0$C for 3 hours. The solid separated was filtered, washed with water and dried. The crude product thus obtained was purified by column chromatography (silica gel 60-120 mesh) using ethylacetate and hexane mixture as eluent to yield the title compound (1.Og, 26.3%, mp 263 - 266 ^{0}C, purity 98.6% by HPLC). ^{1}H-NMR ($CDCl_3$): δ 1.75 (bs, 2H, D_2O exchangeable), (2.15 - 2.19 (d, 6H), 2.41 (s, 3H), 5.5 (bs, IH, D_2O exchangeable), 6.89 - 6.9 (d, IH), 6.99 - 7.0 (d, IH), 7.01 - 7.02 (m, 3H), 7.20 - 7.22 (d, 2H). IR (KBr) cm^{-1}: 3306, 3193, 2918,1693. MS m/z: 378.3 (M^++!).

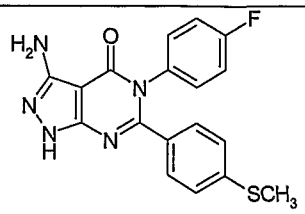
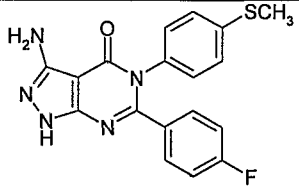
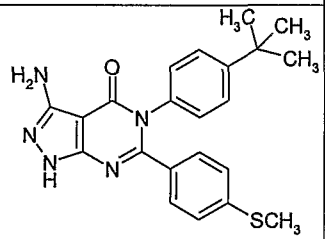
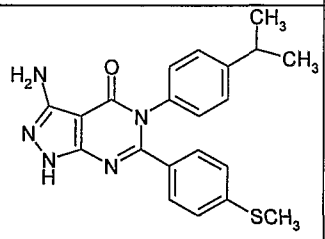
Example 3

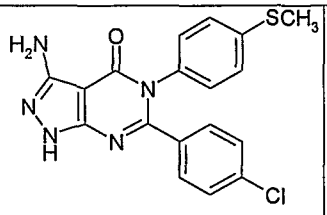
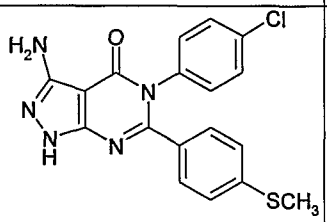
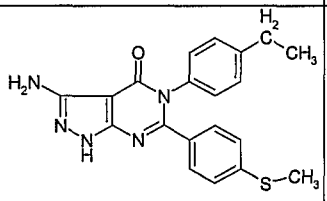
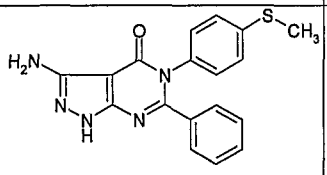
General Procedure:

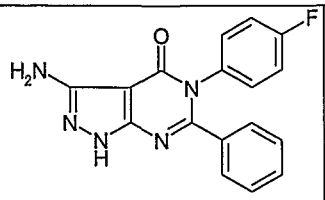
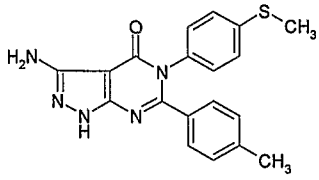
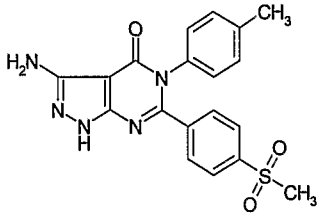
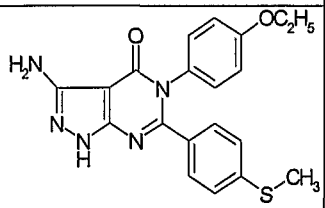
The equimolar or more than eq. molar quantities of the l,2-diaryl-5-cyano-4-methylthio-l,6-dihydro-pyrimidin-6-one (prepared according to the procedure disclosed in our PCT publication No. 03/84938) and hydrazine hydrate or substitiuted or unsubstituted alkyl hydrazine were heated at 60 - 70^0C in toluene in the presence of half molar quantity of anhydrous potassium carbonate for 3-4 hrs. The resulted solid separated was filtered, washed with toluene, water and dried to yield the title compound. Purified by the column chromatography or by recrystallization techniques.

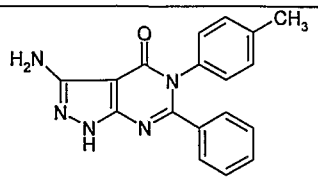
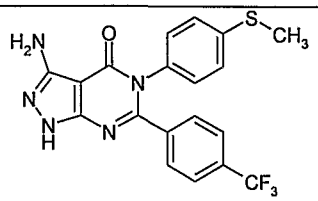
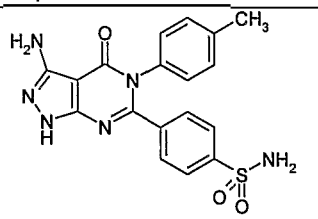
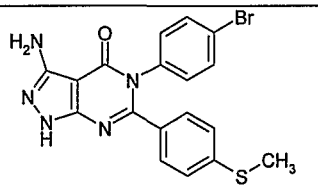
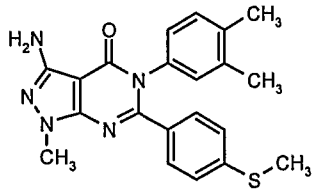
The following compounds listed in table-I are prepared by **the general procedure given in Example 3**

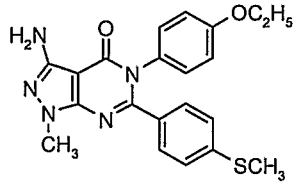
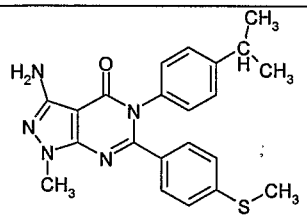
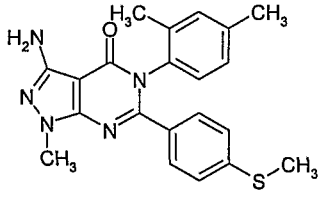
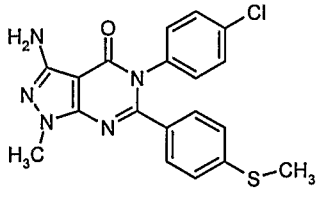
TABLE-I

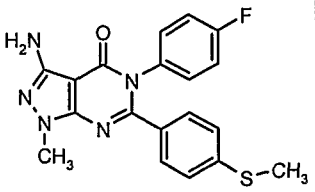
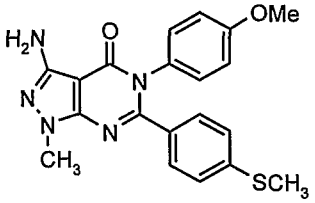
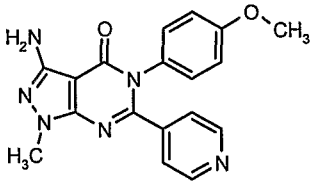
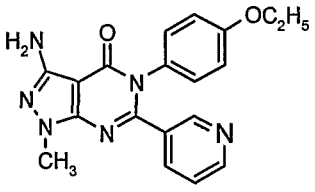
EXP.	STRUCTURE	ANALYTICAL DATA
4	 Mp: >285°C.	Purity (HPLC): 99.85%, ^{1}H-NMR (DMSO-d_6): δ 2.41(s, 3H), 5.2 (s, 2H, D_2O exchangeable), 7.05 – 7.14 (m, 4H), 7.21 – 7.28 (m, 4H), 12.5 (s, 1H, D_2O exchangeable). IR (KBr) cm^{-1}: 3451, 3292, 3131, 2918, 1694. MS m/z: 368.1 (M^++1).
5	 Mp: 278 - 280°C.	Purity (HPLC): 96.58%, ^{1}H-NMR (DMSO-d_6): δ 2.42 (s, 3H), 5.3 (s, 2H, D_2O exchangeable), 7.05 – 7.15 (m, 6H), 7.37 – 7.40 (m, 2H), 12.5 (s, 1H, D_2O exchangeable). IR (KBr) cm^{-1}: 3405, 3172, 2920, 1676. MS m/z: 368.1 (M^++1).
6	 Mp: 284 – 287°C.	Purity (HPLC): 99.8%, ^{1}H-NMR ($CDCl_3$): δ 1.28 (s, 9H), 2.41 (s, 3H), 5.3 (s, 2H, D_2O exchangeable), 7.03 - 7.05 (d, 2H), 7.12 - 7.14 (d, 2H), 7.21 – 7.23 (d, 2H), 7.30 – 7.32 (d, 2H), 12.45 (s, 1H, D_2O exchangeable). IR (KBr) cm^{-1}: 3451, 3318, 3200, 2961, 1700. MS m/z: 406.4 (M^++1).
7	 Mp: 232 – 235°C.	Purity (HPLC): 99.83% ^{1}H-NMR ($CDCl_3$): δ 1.20 - 1.22 (d, 6H), 2.17 (bs, 3H, D_2O exchangeable), 2.41 (s, 3H), 2.9 – 3.1 (m, 1H), 7.0 - 7.03 (d, 4H), 7.16 – 7.21 (m, 4H). IR (KBr) cm^{-1}: 3451, 3320, 3205, 2960, 1700. MS m/z: 392.1 (M^++1).

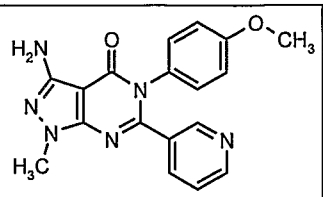
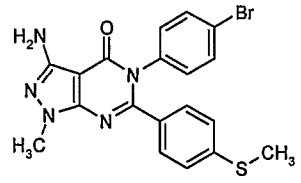
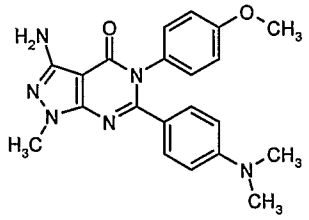
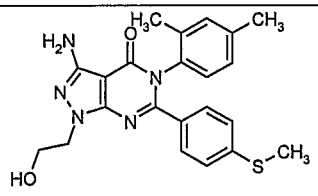
8	 Mp: 282 – 285°C,	Purity (HPLC): 99.89%, ^{1}H-NMR (DMSO-d_6): δ 2.08 (s, 3H), 5.34 (bs, 2H, D_2O exchangeable), 7.13 – 7.16 (m, 4H), 7.30 - 7.37 (m, 4H), 12.5 (1H, D_2O exchangeable). IR (KBr) cm^{-1}: 3495, 3405, 3303, 3174, 2920, 1671. MS m/z: 384 (M^++1).
9	 Mp: >285°C.	Purity (HPLC): 99.88%. ^{1}H-NMR (DMSO-d_6): δ 2.43 (s, 3H), 5.34 (s, 2H, D_2O exchangeable), 7.08 – 7.10 (m, 2H), 7.24 – 7.26 (m, 2H), 7.31 – 7.38 (m, 4H), 12.48 (s, 1H, D_2O exchangeable). IR (KBr) cm^{-1}: 3448, 3092, 2920, 1694. MS m/z: 384 (M^++1).
10	 Mp: 271 – 272°C.	Purity (HPLC): 91.83%, ^{1}H-NMR (DMSO-d_6): δ 1.1 – 1.17 (t, 3H), 2.40 (s, 3H), 2.49 – 2.58 (m, 2H), 5.30 (s, 2H, D_2O exchangeable), 7.04 – 7.06 (d, 2H), 7.12 – 7.24 (m, 4H), 7.35 – 7.38 (d, 2H), 12.44 (s, 1H, D_2O exchangeable). IR (KBr) cm^{-1}: 3377, 3294, 3182, 2964, 2917, 1698. MS m/z: 378.2 (M^++1).
11	 Mp: >285°C.	Purity (HPLC): 99.51%, ^{1}H-NMR (DMSO-d_6): δ 2.41 (s, 3H), 5.32 (s, 2H, D_2O exchangeable), 7.10 – 7.15 (m, 4H), 7.18 – 7.24 (m, 3H), 7.32 – 7.34 (m, 2H), 12.46 (s, 1H, D_2O exchangeable). IR (KBr) cm^{-1}: 3462, 3315, 3197, 2916, 1693. MS m/z: 350.2 (M^++1).

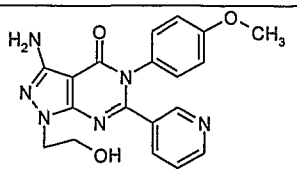
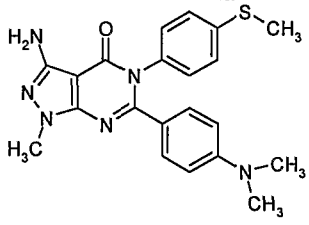
12	 Mp: 260 – 264°C.	Purity (HPLC): 98.98%, ^{1}H-NMR (DMSO-d_6): δ 5.34 (s, 2H, D_2O exchangeable), 7.11 – 7.13 (m, 2H), 7.22 – 7.30 (m, 7H), 12.49 (s, 1H, D_2O exchangeable). IR (KBr) cm^{-1}: 3455, 3144, 3090, 2921, 1694. MS m/z: 322.2 (M^++1).
13	 Mp: >285°C.	Purity (HPLC): 99.87%, ^{1}H-NMR (DMSO-d_6): δ 2.22 (s, 3H), 2.42 (s, 3H), 5.31 (bs, 2H, D_2O exchangeable), 7.02 – 7.04 (d, 2H), 7.13 – 7.22 (m, 4H), 7.32 – 7.34 (m, 2H), 12.44 (s, 1H, D_2O exchangeable). IR (KBr) cm^{-1}: 3443, 3090, 2918, 1697. MS m/z: 364 (M^++1).
14	 Mp: 192 – 195 °C.	Purity (HPLC): 97.98%, ^{1}H-NMR (DMSO-d_6): δ 2.23 (s, 3H), 3.23 (s, 3H), 5.31 (bs, 2H, D_2O exchangeable), 7.01 – 7.03 (d, 2H), 7.49 – 7.51 (d, 2H), 8.0 – 8.02 (d, 2H), 8.19 – 8.2 (d, 2H), 11.08 (bs, 1H, D_2O exchangeable), 12.5 (bs, 2H, D_2O exchangeable). IR (KBr) cm^{-1}: 3208, 2919, 1625, 1585, 1560. MS m/z: 396 (M^++1).
15	 Mp: 254 – 256°C.	Purity (HPLC): 99.77%, ^{1}H-NMR (DMSO-d_6): δ 1.27 – 1.3 (t, 3H), 2.41 (s, 3H), 3.93 – 3.98 (q, 2H), 5.56 (bs, 2H, D_2O exchangeable), 6.79 – 6.82 (d, 2H), 7.05 – 7.11(m, 4H), 7.23 – 7.25 (d, 2H). IR (KBr) cm^{-1}: 3447, 3091, 2978, 2916, 1693. MS m/z: 394.1 (M^++1).

16	 Mp: 241 – 244°C.	Purity (HPLC): 99.17%, ^{1}H-NMR (DMSO-d_6): δ 2.22 (s, 3H), 5.31(bs, 2H, D_2O exchangeable), 7.06 (bs, 4H), 7.19 – 7.25 (m, 3H), 7.30 – 7.31 (m, 2H), 12.45 (bs, 1H, D_2O exchangeable). IR (KBr) cm^{-1}: 3450, 3091, 2918, 1696. MS m/z: 318.2 (M^++1).
17	 Mp: 255 – 258°C.	Purity (HPLC): 99.68 %, ^{1}H-NMR (DMSO-d_6): δ 2.41(s, 3H), 5.35 (bs, 2H, D_2O exchangeable), 7.13 – 715 (m, 4H), 7.59 – 7.62 (m, 4H), 12.53 (bs, 1H, D_2O exchangeable). IR (KBr) cm^{-1}: 3333, 3217, 2923, 1694. MS m/z: 418.1 (M^++1).
18	 Mp: 245 – 247°C.	Purity (HPLC): 98.6%, ^{1}H-NMR (DMSO-d_6): δ 2.5 (s, 3H), 7.19 – 7.20 (m, 1H), 7.35 – 7.44 (m, 4H, 1H D_2O exchangeable), 7.76 – 7.78 (m, 1H), 7.99 – 8.11 (m, 3H), 11.55 (s, 1H, D_2O exchangeable), 12.34 (s, 1H, D_2O exchangeable). IR (KBr) cm^{-1}: 3278, 2165, 1609, 1562. MS m/z: 397.1 (M^++1).
19	 Mp: >285°C.	Purity (HPLC): 97.6%, ^{1}H-NMR (DMSO-d_6): δ 2.42 (s, 3H), 5.33 (s, 2H, D_2O exchangeable), 7.08 – 7.1 (m, 2H), 7.24 (bs, 1H), 7.5 - 7.52 (m, 2H), 12.48 (s, 1H, D_2O exchangeable). IR (KBr) cm^{-1}: 3450, 3093, 2920, 1693. MS m/z: 429.9 (M^++1).
20	 Mp: 210 - 212°C.	Purity (HPLC): 99.7%, ^{1}H-NMR ($CDCl_3$): δ 2.18 – 2.21 (d, 6H), 2.43 (s, 3H), 3.81 (s, 3H), 4.5 (s, 2H, D_2O exchangeable), 7.76 – 6.78 (d, 1H), 6.89 (s, 1H), 7.03 – 7.05 (d, 3H), 7.23 – 7.26 (d, 2H).

		IR (KBr) cm^{-1}: 3414, 3309, 3217, 1700. MS m/z: 392.1 (M^++1).
21	 Mp: 222 - 226°C.	Purity (HPLC): 95.4%, ^{1}H-NMR ($CDCl_3$): δ 1.38 – 1.41 (t, 3H), 2.43 (s, 3H), 3.38 (s, 3H), 3.96 – 4.02 (q, 2H), 4.55 (s, 2H, D_2O exchangeable), 6.79 – 6.80 (d, 2H), 6.97 – 6.99 (d, 2H), 7.04 – 7.06 (d, 2H), 7.21 – 7.23 (d, 2H). IR (KBr) cm^{-1}: 3416, 3307, 1701. MS m/z: 408.3 (M^++1).
22	 Mp: 241 – 243°C.	Purity (HPLC): 99.5%, ^{1}H-NMR (DMSO-d_6): δ 1.13 - 1.15 (d, 6H), 2.4 (s, 3H), 2.81 – 2.88 (m, 1H), 3.67 (s, 3H), 5.42 (s, 2H, D_2O exchangeable), 7.05 – 7.07 (d, 2H), 7.11 – 7.18 (m, 4H), 7.23 – 7.25 (d, 2H). IR (KBr) cm^{-1}: 3408, 3300, 3184, 2959, 1699. MS m/z: 406.5 (M^++1).
23	 Mp: 230 – 232°C,	Purity (HPLC): 99.8%, ^{1}H-NMR (DMSO-d_6): δ 1.96 (s, 3H), 2.22 (s, 3H), 2.41 (s, 3H), 3.67 (s, 3H), 5.44 (s, 2H, D_2O exchangeable), 6.93 – 6.95 (d, 1H), 7.0 (s, 1H), 7.07 – 7.1 (m, 3H), 7.24 – 7.26 (d, 2H). 7.05 – 7.07 (d, 2H), 7.11 – 7.18 (m, 4H), 7.23 – 7.25 (d, 2H). IR (KBr) cm^{-1}: 3410, 3303, 3186, 2922, 1701, 1636. MS m/z: 392.2 (M^++1).
24	 Mp: 240 – 242°C.	Purity (HPLC): 98.5%, ^{1}H-NMR ($CDCl_3$): δ 2.44 (s, 3H), 3.8 (s, 3H), 4.5 (s, 2H, D_2O exchangeable), 7.03 – 7.07 (m, 4H), 7.19 - 7.21 (d, 2H), 7.28 – 7.30 (m, 2H). IR (KBr) cm^{-1}: 3416, 3313, 3218, 2920, 1701. MS m/z: 398.1 (M^++1).

25	 Mp: 252 – 255°C.	Purity (HPLC): 97.9%, ^{1}H-NMR (DMSO-d_6): δ 2.42 (s, 3H), 3.6 (s, 3H), 5.45 (s, 2H, D_2O exchangeable), 7.08 – 7.13 (m, 2H), 7.15 - 7.17 (m, 2H), 7.25 – 7.33 (m, 4H). IR (KBr) cm^{-1}: 3414, 3304, 3184, 2921, 1699. MS m/z: 382.2 (M^++1).
26	 Mp: 230 – 232°C.	Purity (HPLC): 96.8%, ^{1}H-NMR ($CDCl_3$): δ 2.43 (s, 3H), 3.78 (s, 3H), 3.82 (s, 3H), 4.56 (s, 2H, D_2O exchangeable), 6.81 – 6.83 (d, 2H), 6.99 – 7.01 (d, 2H), 7.04 – 7.06 (d, 2H), 7.21 - 7.23 (d, 2H). IR (KBr) cm^{-1}: 3397, 3299, 3182, 1698. MS m/z: 394.1 (M^++1).
27	 Mp: 254 - 256°C.	Purity (HPLC): 99.4%, ^{1}H-NMR ($CDCl_3$): δ 3.68 (s, 3H0, 3.69 (s, 3H), 5.47 (s, 2H, D_2O exchangeable), 6.81 – 6.83 (q, 2H), 7.18 - 7.20 (d, 2H), 7.33 – 7.35 (d, 2H), 8.46 – 8.47 (d, 2H). IR (KBr) cm^{-1}: 3396, 3303, 3216, 1677. MS m/z: 349.2 (M^++1).
28	 Mp: 236 - 240°C.	Purity (HPLC): 99.76%, ^{1}H-NMR (DMSO-d_6): δ 1.26 – 1.29 (t, 3H), 2.5 (s, 3H), 3.68 (s, 3H), 3.92 – 3.97 (q, 2H), 5.45 (s, 2H, D_2O exchangeable), 6.80 – 6.82 (d, 2H), 7.16 – 7.18 (d, 2H), 7.27 – 7.29 (m, 1H), 7.72 – 7.74 (d, 1H), 8.42 – 8.44 (d, 1H), 8.53 – 8.54 (d, 1H). IR (KBr) cm^{-1}: 3422, 3362, 3211,1709. MS m/z: 363.2 (M^++1).

29	 Mp: 264 - 266°C.	Purity (HPLC): 99.5%, ^{1}H-NMR (DMSO-d_6): δ 2.5 (s, 3H), 3.68 (s, 3H), 3.69 (s, 3H), 5.45 (s, 2H, D_2O exchangeable), 6.82 – 6.84 (d, 2H), 7.18 – 7.20 (d, 2H), 7.27 – 7.29 (m, 1H), 7.72 – 7.74 (d, 1H), 8.42 – 8.44 (d, 1H), 8.53 – 8.54 (d, 1H). IR (KBr) cm^{-1}: 3414, 3339, 1693. MS m/z: 349.2 (M^++1).
30	 Mp: 244 - 246°C.	Purity (HPLC): 99.5%, ^{1}H-NMR (DMSO-d_6): δ 2.50 (s, 3H), 3.68 (s, 3H), 5.44 (bs, 2H, D_2O exchangeable), 7.10- 7.12 (d, 2H), 7.22 – 7.28 (m, 4H), 7.51 – 7.53 (d, 2H). IR (KBr) cm^{-1}: 3384, 2922, 1691.7. MS m/z: 443 (M^++1).
31	 Mp: 200 - 203°C.	Purity (HPLC): 94.6%, ^{1}H-NMR ($CDCl_3$): δ 2.93 (s, 6H), 3.79 (s, 3H), 3.82 (s, 3H), 4.54 (bs, 2H, D_2O exchangeable), (6.46 - 6.48 (d, 2H), 6.84 – 6.86 (m, 2H), 7.02 – 7.05 (m, 2H), 7.2 – 7.23 (m, 2H). IR (KBr) cm^{-1}: 3443, 3312.6, 3216.8, 2919, 2797, 1695. MS m/z: 391.1(M^++1).
32	 Mp: 155 - 159°C.	Purity (HPLC): 96.8%, ^{1}H-NMR ($CDCl_3$): δ 2.04 (s, 3H), 2.29 (s, 3H), 2.43 (s, 3H), 3.76 (bs, 1H, D_2O exchangeable), 4.02 (m, 2H), 4.32 – 4.35 (m, 2H), 4.61 (bs, 2H, D_2O exchangeable), 6.9- 7.04 (m, 5H), 7.2 - 7.22 (m, 2H). IR (KBr) cm^{-1}: 3394, 3223.7, 2924.4, 2881.9, 1705, 1678.2. MS m/z: 422.1(M^++1).

33	 Mp: 237 - 240°C.	Purity (HPLC): 95.1%, ^{1}H-NMR (DMSO-d_6): δ 3.7 (s, 3H), 3.73 - 3.77 (m, 2H), 4.09 - 4.12 (t, 2H), 4.83 - 4.86 (t, 2H), 5.47 (bs, 2H, D_2O exchangeable), 6.83 – 6.85 (m, 2H), 7.18 - 7.2 (m, 2H), 7.26 – 7.29 (m, 1H), 7.71 – 7.74 (m,1H), 8.43 – 8.45 (m, 1H), 8.54 – 8.55 (m, 1H). IR (KBr) cm^{-1}: 3466.4, 3361.7, 3256, 2948.5, 2839.6, 1697.5. MS m/z: 379 (M^++1).
34	 Mp: 243 - 247°C.	Purity (HPLC): 96.9%, ^{1}H-NMR ($CDCl_3$): δ 2.47 (s, 3H), 2.94 (s, 6H), 3.82 (s, 3H), 4.53 (bs, 2H, D_2O exchangeable), 6.46 - 6.48 (d, 2H), 7.04 - 7.06 (d, 2H), 7.18 - 7.26 (m, 4H). IR (KBr) cm^{-1}: 3467.9, 3390, 3374, 2914, 2856, 1686 MS m/z: 407.1(M^++1).

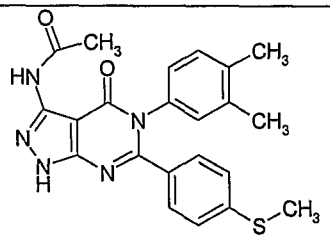
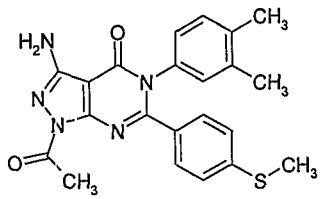
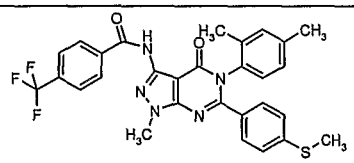
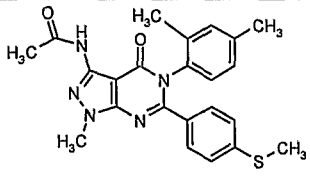
Example 35

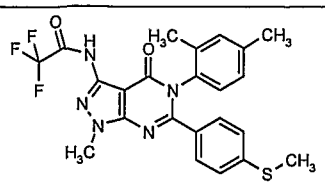
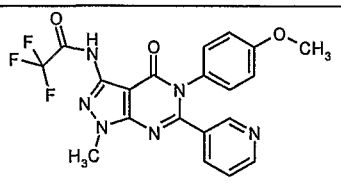
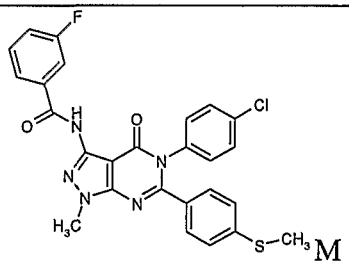
General Procedure:

The compounds synthesized were further converted to the acyl derivatives using acetyl chloride or acetic anhydride in appropriate solvents according to the conventional procedures reported, to yield the title compounds. Purified by the recrystallization techniques.

The following compounds listed in table-II are prepared by **the general procedure given in Example 35**

TABLE-π

EXP.	STRUCTURE	ANALYTICAL DATA
36	 Mp: 254 – 256°C.	Purity (HPLC): 96.7%, ^{1}H-NMR (DMSO-d_6): δ 2.08 – 2.15 (d, 6H) 2.40 (s, 3H), 2.61 (s, 3H), 6.89 – 6.91 (m, 1H), 7.02 – 7.07 (m, 4H), 7.26 – 7.28 (d, 2H), 7.77 (bs, 2H, D_2O exchangeable). IR (KBr) cm^{-1}: 3458, 3363, 2920, 1723, 1684. MS m/z: 420.1 (M^+).
37	 Mp: 210 – 213°C.	Purity (HPLC): 95.99%, ^{1}H-NMR (DMSO-d_6): δ 2.14 – 2.17 (d, 6H), 2.5 (s, 3H), 2.62 (s, 3H), 6.02 (s, 2H, D_2O exchangeable), 6.96 – 6.98 (d, 1H), 7.07 – 7.09 (m, 4H), 7.3 – 7.32 (d, 2H). IR (KBr) cm^{-1}: 3481, 1702, 1623. MS m/z: 420.2 (M^++1).
38		Purity (HPLC): 94.7%, ^{1}H-NMR ($CDCl_3$): δ 2.03 (s, 3H), 2.31 (s, 3H), 2.45 (s, 3H), 4.07 (s, 3H), 6.98-7.07 (m, 4H), 7.21- 7.30 (m, 3H), 7.69 – 7.71 (m, 2H), 8.07 – 8.09 (d, 2H), 9.30 (bs, 1H, D_2O exchangeable). MS m/z: 564.1 (M^++1).
39	 Mp: 248 - 250°C.	Purity (HPLC): 100%, ^{1}H-NMR ($CDCl_3$): δ 2.02 (s, 3H), 2.30 (s, 3H), 2.44 (s, 3H), 4.00 (s, 3H), 6.91 – 7.06 (m, 5H), 7.25 - 7.26 (m, 2H), 8.37 (bs, 1H, D_2O exchangeable). IR (KBr) cm^{-1}: 3438, 2921.5, 1703, 1550.7. MS m/z: 434.1(M^++1).

40	 Mp: 215 - 219°C.	Purity (HPLC): 94.3%, ^{1}H-NMR ($CDCl_3$): δ 2.01 (s, 3H), 2.29 (s, 3H), 2.44 (s, 3H), 4.05 (s, 3H), 6.93- 6.95 (m, 1H), 7.00 – 7.07 (m, 4H), 7.28 (m, 1H), 9.11(bs, 1H, D_2O exchangeable) IR (KBr) cm^{-1}: 3432, 2924, 2854, 2364, 1752, 1699.8. MS m/z: 488.1(M^++1).
41		Purity (HPLC): 99.7%, ^{1}H-NMR ($CDCl_3$): δ 3.79 (s, 3H), 4.06 (s, 3H), 6.86 – 6.88 (m, 2H), 7.01 – 7.03 (m, 2H), 7.2 – 7.22 (m, 1H), 7.6 – 7.62 (m, 1H), 8.54 – 8.56 (m, 1H), 8.64 - 8.65 (d, 1H), 9.1 (bs, 1H, D_2O exchangeable). MS m/z: 445.1(M^++1).
42	 p: 217 - 220°C.	Purity (HPLC): 97.1%, ^{1}H-NMR ($CDCl_3$): δ 2.46 (s, 3H), 4.06 (s, 3H), 7.07 - 7.10 (m, 4H), 7.24 – 7.36 (m, 6H), 7.69 – 7.71 (d,2H), 9.15 (bs, 2H, D_2O exchangeable). IR (KBr) cm^{-1}: 3402, 3277, 3066, 2922, 1698.2. MS m/z: 520.1(M^++1).

Described below are the examples of pharmacological assays used for finding out the efficacy of the compounds of the present invention wherein their protocols and results are provided.

***In vitro* evaluation of cycIooxygenase-2 (COX-2) inhibition activity**

. The compounds of this invention exhibited *in vitro* inhibition of COX-2. The COX-2 inhibition activities of the compounds illustrated in the examples were determined by the following method.

Human Whole Blood Assay;

Human whole blood provides a protein and cell rich milieu appropriate for the study of biochemical efficacy of anti-inflammatory compounds such as selective

COX-2 inhibitors. Studies have shown that normal human blood does not contain COX-2 enzyme. This is correlating with the observation that COX-2 inhibitors have no effect on prostaglandin E_2 (PGE_2) production in normal blood. These inhibitors were active only after incubation of human blood with lipopolysaccharide (LPS), which induces COX-2 production in the blood.

Fresh blood was collected in tubes containing sodium heparin by vein puncture from healthy male volunteers. The subjects should have no apparent inflammatory conditions and not taken NSAIDs for at least 7 days prior to blood collection. Blood was preincubated with aspirin *in vitro* (12μg/ml, at time zero) to inactivate COX-I for 6 hours. Then test compounds (at various concentrations) or vehicle were added to blood. After that blood was stimulated with LPS B:4 (10 μg/ml) and incubated for another 18 h at 37 ^{0}C water bath. After which the blood was centrifuged, plasma was separated and stored at -8O^{0}C (J. Pharmacol. Exp.Ther, 271, 1705, 1994; Proc. Natl. Acad. Sci. USA, 96, 7563, 1999). The plasma was assayed for PGE2 using Cayman ELISA kit as per the procedure outlined by the manufacturer (Cayman Chemicals, Ann Arbor, USA). Representative results of PGE2 inhibition are shown in Table I.

TABLE I

Example No	% PGE2 Inhibition	
	0.25μM	10μM
1	20.33	41.58
2	21.92	16.83
5	-	31.81
6	18.59	37.69
8	28.27	-
9	-	27.13
11	-	29.19
12	26.2	-
13	26.84	-
14	19.28	23
15	20.22	-
16	31.4	-
17	19.36	36.51

COX-I and COX-2 enzyme based assay

COX-I and COX-2 enzyme based assays were carried out to check the inhibitory potential of test compounds on the production of prostaglandin by purified recombinant COX-l/COX-2 enzyme (Proc. Nat. Acad. Sci. USA, 88, 2692-2696, 1991; J. Clin. Immunoassay 15, 116-120, 1992) In this assay, the potential of test compound to inhibit the production of prostaglandin either by COX-I or COX-2 from arachidonic acid (substrate) was measured. This was an enzyme based in-vitro assay to evaluate selective COX inhibition with good reproducibility.

Arachidonic acid was converted to PGH2 (Intermediate product) by COXl /COX-2 in presence or absence of the test compound. The reaction was carried out at 37^0C and after 2 minutes it was stopped by adding IM HCl. Intermediate product PGH2 was converted to a stable prostanoid product PGF2α by SnC12 reduction. The amount of PGF2α produced in the reaction was inversely proportional to the COX inhibitory potential of the test compound. The prostanoid product was quantified via enzyme immunoassay (EIA) using a broadly specific antibody that binds to all the major forms of prostaglandin, using Cayman ELISA kit as per the procedure outlined by the manufacturer (Cayman Chemicals, Ann Arbor, USA). Representative results of inhbition are shown in Table II.

Table II

Example No.	Conc. (μM)	COX-1 Inhibition (%)	COX-2 Inhibition (%)
23	1	51.62	Not Active
40	10	3.11	15.54

***In vitro* measurement of Tumor Necrosis Factor Alpha** (TNF- *a)*

This assay determines the effect of test compounds on the production of TNF α in human Peripheral Blood Mononuclear Cells (PBMC). Compounds were tested for their ability to inhibit the activity of TNF α in human PBMC. PBMC were isolated from blood (from healthy volunteers) using BD Vacutainer CPT™ (Cell preparation tube, BD Bio Science) and suspended in RPMI medium (Physiol. Res.

52: 593-598, 2003). The test compounds were pre-incubated with PBMC (0.5million/incubation well) for 15 minutes at 37° C and then stimulated with Lipopolysaccharide *{Escherichia colt* B4; 1 μg/ml) for 18 h at 37 ° C in 5% CO_2. The levels of TNFα in cell culture medium were estimated using enzyme linked Immunosorbent assay performed in a 96 well format as per the procedure of the manufacturer (Cayman Chemical, Ann Arbor, USA). Representative results of TNF-α inhibition are shown in Table III.

Table III

Example No	% TNF-α Inhibition
	10μM
2	53.42
19	64.79
21	75.13
22	53.97
23	86.34
24	87.88
25	52.85
30	86.57
31	87.86
36	29.91
37	29.85
40	78.04

***In vitro* measurement of** Interleukin-6 **(IL-6)**

This assay determines the effect of test compounds on the production of IL-6 in human PBMC (Physiol. Res. 52: 593-598, 2003). Compounds were tested for their ability to inhibit the activity of IL-6 in human PBMC. PBMC were isolated from blood using BD Vacutainer CPT™ Cell preparation tube (BD Bio Science) and suspended in RPMI medium. The test compounds were pre-incubated with PBMC (0.5million/incubation well) for 15 minutes at 37° C and then stimulated with Lipopolysaccharide *{Escherichia colt* B4; 1 μg/ml) for 18 h at 37 ° C in 5% CO_2. The levels of IL-6 in cell culture medium were estimated using enzyme linked Immunosorbent assay performed in a 96 well format as per the procedure of the

manufacturer (Cayman Chemical, Ann Arbor, **USA).** Representative results of **IL-6** inhibition are shown in Table **IV.**

Table IV

Example No	% IL-6 Inhibition (1μM)
19	15.93
22	12
36	12.67

Carrageenan induced Paw Edema test in Rat

The carrageenan paw edema test was performed as described by Winter et al (Proc.Soc.Exp.Biol.Med, 111, 544, 1962). Male wistar rats were selected with body weights equivalent within each group. The rats were fasted for eighteen hours with free access to water. The rats were dosed orally with the test compound suspended in vehicle containing 0.25% carboxymethylcellulose and 0.5% Tween 80. The control rats were administered with vehicle alone. After an hour, the rats were injected with 0.1 ml of 1% Carrageenan solution in 0.9% saline into the sub-plantar surface of the right hind paw. Paw volume was measured using digital plethysmograph before and after 3 hours of carrageenan injection. The average of foot swelling in drug treated animals was compared with that of control animals. Anti-inflammatory activity was expressed as the percentage inhibition of edema compared with control group [Arzneim-Forsch/Drug Res., 43 (I), 1,44-50,1993; Otterness and Bliven, Laboratory Models for Testing NSAIDs, In Non-Steroidal Anti-Inflammatory Drugs, (J. Lombardino, ed.1985)]. Representative results of edema inhibition are shown in Table V.

Ulcerogenic potential

In order to evaluate compound's role on the ulcer formation, the animals were sacrificed and the stomach was taken out and flushed with 1% formalin. Animals (male wistar 200gm) were fasted for 18hrs free access to water and the test compounds were suspended in 0.5% Tween 80 and 0.25% CMC

(carboxymethylcellulose) solution to make a uniform suspension. After 4 hrs of oral administration of test compounds, all the animals were sacrificed by cervical dislocation. Dissect the stomach carefully and filled up with a sterile saline solution and embedded in 6% formalin solution. Finally cut the stomach longnitudinaly and ulcer lesions were observed with computerized stereomicroscope. Compare the test compound treated groups with the vehicle treated groups. Dose selected: 50, 100, 200mg/kg (Marco Romano et al, Journal of clinical Investigation, 1992; 2409-2421). Representative results of ulcer incidence are shown in Table V.

TABLE-V

Example No	Rat Paw Edema model % Inhibition (5mg/kg b.wt.,p.o.)	Ulcer Incidence (Number of animals/Total number of animals)
2	30.52+10.3	No ulcer

Inhibitory Action on Adjuvant Arthritis

Compounds were assayed for their activity on rat adjuvant induced arthritis according to Theisen-Popp et al., (Agents Actions, 42, 50-55,1994). Six to seven weeks old, Wistar rats were weighed, marked and assigned to groups [a negative control group in which arthritis was not induced (non-adjuvant control), a vehicle-treated arthritis control group, test substance treated arthritis group]. Adjuvant induced arthritis was induced by an injection of *Mycobacterium butyricum* (Difco) suspended in liquid paraffin into the sub-plantar region of the right hind paw (J.Pharmacol.Exp.Ther., 284, 714, 1998). Body weight, contra-lateral paw volumes were determined at various days (0, 4, 14, 21) for all the groups. The test compound or vehicle was administered orally beginning post injection of adjuvant and continued for 21 days. On day 21, body weight and paw volume of both right and left hind paw, spleen, and thymus weights were determined. In addition, the radiograph of both hind paws was taken to assess the tibio-tarsal joint integrity. Hind limb below the stifle joint was removed and fixed in 1% formalin saline. At the end of the experiment, plasma samples were analysed for cytokines, interleukin and

prostaglandin. The presence or absence of lesions in the stomachs was also observed.

Two-factor ("treatment" and "time") Analysis of Variance with repeated measures on `time` were applied to the % changes for body weight and foot volumes. A post hoc Dunnett's test was conducted to compare the effect of treatments to vehicle. A one-way Analysis of Variance was applied to the thymus and spleen weights followed by the Dunnett's test to compare the effect of treatments to vehicle. Dose-response curves for % inhibition in foot volumes on days 4, 14 and 21 were fitted by a 4-parameter logistic function using a nonlinear Least Squares' regression. ID_{50} was defined as the dose corresponding to a 50% reduction from the vehicle and was derived by interpolation from the fitted 4-parameter equation.

LPS induced sepsis for measurement of TNF-α inhibition in mice

The LPS induced sepsis model in mice was performed as described by Les sekut et al (J Lab Clin Med 1994; 124:813-20). Female Swiss albino mice were selected and the body weights were equivalent within each group. The mice were fasted for 20 hours with free access to water. The mice were dosed orally with the test compound suspended in vehicle containing 0.5% Tween 80 in 0.25% Carboxy-methylcellulose sodium salt. The control mice were administered the vehicle alone. After 30 min of oral dosing, mice were injected with 500µg of Lipopolysaccharide *(Escherichia coli,* LPS: B4 from Sigma) in phosphate buffer saline solution into the intraperitoneal cavity of the mice. After 90 min of LPS administration mice were bled via retro-orbital sinus puncture. Blood samples were stored overnight at 4^0C. Serum samples were collected by centrifuging the samples at 4000rpm for 15min at 4°C. Immediately the serum samples were analysed for TNFα levels using commercially available mouse TNF-α ELISA kit (Amersham Biosciences) and assay was performed by the manufacturer instruction. Representative results of TNF-α inhibition are shown in Table **VI.**

Table VI

Example No.	TNF-α Inhibition (%)
2	34.29 (at 50mg/kg)
21	75.15 (at 50mg/kg)

23	92.02 (at 5mg/kg)
24	91.99 (at 50mg/kg)

DTP Human Tumor Cell Line Screen

Methodology Of The *In Vitro* Cancer Screen

The three cell line, one-dose prescreen carried out which identifies a large proportion of the compounds that would be inactive in multi-dose 60 cell line screening. The current assay utilizes a 384 well plate format and fluorescent staining technologies resulting in greater screening capacity for testing of synthetic samples.

Cell **Lines**

The cell lines of the cancer-screening panel are grown in RPMI 1640 medium containing 5% fetal bovine serum and 2 mM L-glutamine. For a typical screening experiment, cells are inoculated into 96 well microtiter plates in 100 µL. After cell inoculation, the micro-titer plates are incubated at 37° C, 5 % CO_2, 95 % air and 100 % relative humidity for 24 h prior to addition of experimental drugs. The cells are plated a densities of 5000 cells/well (MCF7), 1000 cells/well (NCI-H460), and 7500 cells/well (SF-268) to allow for varying doubling time of the cell lines. Each plate contains all three-cell lines, a series of dilutions of standard agents, total kill wells and appropriate controls. Plates are incubated under standard conditions for 24 hours prior to addition of experimental compounds or extracts.

Addition of Experimental Agents (Pure Compounds)

Experimental compounds are solubilized in dimethyl sulfoxide (DMSO) at 400-times the desired maximum test concentration (maximum final DMSO concentration of 0.25%) and stored frozen. Compounds are then diluted with complete media with 0.1% gentamicin sulfate (5 µl of test sample in 100% DMSO is added to 565 µl of complete medium). 20 µl of this solution is then dispensed into test wells containing 50 µl of cell suspension to yield a test concentration of 1.00E-04M.

Two standard drugs, meaning that their activities against the cell lines are well documented, are tested against each cell line: NSC 19893 (5-FU) and NSC 123127 (Adriamycin).

Endpoint Measurement

After compound addition, plates are incubated at standard conditions for 48 hours, 10 µl/well Alamar Blue is added and the plates are incubated for an additional 4 hours. Fluorescence is measured using an excitation wavelength of 530 nm and an emission wavelength of 590 nm.

Calculation of Percent Test Cell Growth/Control (untreated) Cell Growth (T/C)

Calculation of Percent Test Cell Growth/Control (untreated) Cell Growth (T/C)

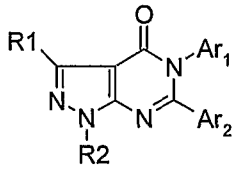
Percent growth is calculated on a plate-by-plate basis for test wells relative to control wells. Percent Growth is expressed as the ratio of fluorescence of the test well to the average fluorescence of the control wells x 100. Representative results of T/C are shown in Table VII.

Table VII

Example No.	%T/C (100µM)		
	Lung (NCI-H460)	Breast (MCF-7)	CNS (SF-268)
2	7	31	39
6	0	0	1
8	2	26	36
9	4	9	31
10	4	22	10
17	25	0	0

We claim:

1. Novel pyrazolopyrimidinones of formula (I)



their derivatives, their pharmaceutically acceptable salts and their pharmaceutically acceptable compositions, wherein Ar_1 and Ar_2 may be same or different and independently represent substituted or unsubstituted groups selected from aryl, heteroaryl, heterocyclyl group; Ri represents hydrogen, hydroxyl, halogen, formyl, amino, hydrazine, alkylamino, arylamino, acylamino, sulfonylamino, substituted (Ci-Ce)alkyl, substituted or unsubstituted .groups selected from acyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocyclyl, $-NHCH_2CN$, $-NHCH_2C(=NH)NHOH$, $-NHCONH_2$, $-NHCSNH_2$, -NHCONH-alkyl, , -NHCONH-aryl, -NHCSNH-alkyl, -NHCSNH-aryl, -NHCO-piperzine, -NHCS-piperzine, -NHCO-aryl, -NHCO-heteroaryl; R_2 represents hydrogen, hydroxy, nitro, nitroso, alkyl, azido, $-C(=NH)NH_2$, halogen, formyl or substituted or unsubstituted groups selected from haloalkyl, alkoxy, aryloxy, aralkyl, aralkoxy, heteroaryl, heterocyclyl, acyl, acyloxy, cycloalkyl, amino, monoalkylamino, dialkylamino, acylamino, alkylsufonyl, arylsulfonyl, alkylsulfinyl, arylsulfinyl, alkylthio, arylthio, alkoxycarbonyl, aryloxycarbonyl, alkoxyalkyl, sulfamoyl, carboxylic acid and its derivatives.

2. Novel pyrazolopyrimidinones as claimed in claim 1, wherein groups represented by Ar_1 and Ar_2 are selected from aryl group such as phenyl or naphthyl, the aryl group may be substituted; heteroaryl group may be mono or fused system such as pyridyl, thienyl, furyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyrimidinyl, pyrazine, piperazine, benzopyranyl, benzofuranyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, benzopyrrolyl, benzoxadiazolyl, benzothiadiazolyl and the like, the heteroaryl group may be substituted; heterocyclyl group such as

pyrrolidinyl, thiazolidinyl, oxazolidinyl, morpholinyl, thiomorpholinyl, piperidinyl, piperazinyl, and the like, the heterocyclyl group may be substituted.

3. Novel pyrazolopyrimidinones as claimed in claim 1, selected from:

1) 3-Amino-5-(4-methylphenyl)-6-[4-(methylthio)phenyl]-l,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

2) 3-Amino-5-(3,4-dimethylphenyl)-6-[4-(methylthio)phenyl]-l,5-dihydro-4H-pyrazolo[3,4-cdpyrimidin-4-one;

3) 3-Amino-5-(4-fluorophenyl)-6-[4-(methylthio)phenyl]-l,5-dihydro-4H-pyrazolo[3,4-cT]pyrimidin-4-one;

4) 3-Amino-5-[(4-methylthio)phenyl] -6-(4-fluorophenyl)- 1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

5) 3-Amino-5-(4-tert-butylphenyl)-6-[4-(methylthio)phenyl]-l,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6) 3-Amino-5-(4-isopropylphenyl)-6-[(4-methylthio)phenyl]-l,5-dihydro-4H-pyrazolo[3,4-cT|pyrimidin-4-one;

7) 3-Amino-5-[(4-methylthio)phenyl]-6-(4-chlorophenyl)-l,5-dihydro-4H-pyrazolo[3,4-cT]pyrimidin-4-one;

8) 3-Amino-5-(4-chlorophenyl)-6-[(4-methylthio)phenyl]- 1,5-dihydro-4H-pyrazolo[3,4-<f]pyrimidin-4-one;

9) 3-Amino-5-(4-ethylphenyl)-6-[(4-methylthio)phenyl]- 1,5-dihydro-4H-pyrazolo[3,4-cdpyrimidin-4-one;

10) 3-Amino-5-[(4-methylthio)phenyl]- 6-phenyl-l,5-dihydro-4H-pyrazolo[3,4-c(]pyrimidin-4-one;

11) 3-Amino-5-(4-fluorophenyl)-6-phenyl- 1,5-dihydro-4H-pyrazolo[3 ,4-cT|pyrimidin-4-one;

12) 3-Amino-5-[(4-methylthio)phenyl]-6-(4-methylphenyl)-l,5-dihydro-4H-pyrazolo[3,4-J]pyrimidin-4-one;

13) 3-Amino-5-(4-methylphenyl)-6-[(4-methylsulfonyl)phenyl]-l,5-dihydro-4H-pyrazolo[3,4-6flpyrimidin-4-one;

14) 3-Amino-5-(4-ethoxyphenyl)-6-[(4-methylthio)phenyl]-l,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

15) 3-Amino-5-(4-methylphenyl)-6-phenyl- 1,5-dihydro-4H-pyrazolo [3,4-</]pyrimidin-4-one;

16) 3-Amino-5-[(4-methylthio)phenyl] -6-(4-trifluoromethylphenyl)- 1,5-dihydro-4H-pyrazolo[3,4-<f]pyrimidin-4-one;

17) 4-[3-Amino-5-(4-memylphenyl)-4-oxo-4,5-dihydro- lH-pyrazolo[3,4-c(]pyrimidin-6-yl]benzenesulfonamide;

18) 3-Ammo-5-(4-bromophenyl)-6-[(4-methylthio)phenyl]-l,5-dihydro-4H-pyrazolo[3,4-*d*]pyrimidin-4-one;

19) 3-Amino-5-(3,4-dimethylphenyl)-l-methyl-6-[4-(methylthio)phenyl]-l,5-dihydro-4H-pyrazolo[3,4-i/]pyrimidin-4-one;

20) 3-Amino-5-(4-ethoxyphenyl)-l-methyl-6-[4-(methylthio)phenyl]-l,5-dihydro-4H-pyrazolo[3,4-J]pyrimidin-4-one;

21) 3-Amino-5-(4-isopropylphenyl)- 1-methyl-6- [4-(methylthio)phenyl] -1,5-dihydro-4H-pyrazolo [3,4-c(]pyrimidin-4-one;

22) 3-Amino-5-(2,4-dimethylphenyl)-l-methyl-6-[4-(methylthio)phenyl]-l,5-dihydro-4H-pyrazolo[3,4-cf]pyrimidin-4-one;

23) 3-Amino-5-(4-chlorophenyl)-l-methyl-6-[4-(methylthio)phenyl]-l,5-dihydro-4H-pyrazolo[3,4-cf]pyrimidin-4-one;

24) 3-Amino-5-(4-fluorophenyl)-l-methyl-6-[4-(methylthio)phenyl]-l,5-dihydro-4H-pyrazolo[3,4-<f]pyrimidin-4-one;

25) 3-Amino-5-(4-methoxyphenyl)-l-methyl-6-[4-(methylthio)phenyl]-l,5-dihydro-4H-pyrazolo[3,4-cf]pyrimidin-4-one;

26) 3-Amino-5-(4-methoxypheny I)- 1-methyl-6-pyridin-4-yl- 1,5-dihydro-4*H*-pyrazolo[3,4-</Jpyrimidin-4-one;

27) 3-Amino-5-(4-ethoxy ϋhenyl)- 1-methyl-6-pyridin-3 -yl- 1,5-dihydro-4*H*-pyrazolo[3,4-d]pyrimidin-4-one;

28) 3-Amino-5-(4-methoxypheny I)- 1-methyl-6-pyridin-3 -yl- 1,5-dihydro-4*H*-pyrazolo[3,4-c(]pyrimidin-4-one;

29) 3-Amino-5-(4-bromophenyl)-l-methyl-6-[4-(methylthio)phenyl]-l ¦5-dihydro-4*H*-pyrazolo[3,4-*a*(]pyrimidin-4-one;

30) 3-Amino-6-[4-(dimethylamino)phenyl] -5-(4-methoxyphenyl)- 1-methyl- 1,5-dihydro-4*H*-pyrazolo [3,4-<sT]pyrimidin-4-one;

31) 3-Amino-5-(2,4-dimethylphenyl)-l-(2-hydroxyethyl)- 6-[4-(methylthio)phenyl]-l,5-dihydro-4 *H*-pyrazolo[3,4-c(|pyrimidin-4-one;

32) 3-Amino- 1-(2-hydroxyethyl)-5 -(4-methoxyphenyl)-6-pyridin-3 -yl-l,5-dihydro-4 *H*-pyrazolo[3,4-c(]pyrimidin-4-one;

33) 3-Amino-6- [4-(dimethylamino)phenyl]- 1-methyl-5 -[(4-methylthio)phenyl]-l,5-dihydro-4 *H*-pyrazolo[3,4-J]pyrimidin-4-one;

34) N-[5-(3,4-Dimethylphenyl)-4-oxo-6-[(4-methylthio)phenyl]-4,5-dihydro- 1H-pyrazolo [3,4-e(]pyrimidin-3-yl] acetamide;

35) l-Acetyl-3-amino-5-(3,4-dimethylphenyl)-6-[(4-methylthio)phenyl]-l,5-dihydro-4 H-pyrazolo[3,4-c(]pyrimidin-4-one;

36) 3-Amino-5 -(4-methoxyphenyl)-6- [4-(methylthio)phenyl] -1,5-dihydro-4*H*-pyrazolo[3,4-</]pyrimidin-4-one;

37) *N*-(4-Oxo-5-(2,4-dimethylphenyl)-l-methyl-6-[(4-methylthio)phenyl]-4,5-dihydro- l*H*-pyrazolo [3,4-d]pyrimidin-3 -yl)-4-(trifluoromethyl) benzamide;

38) *N*-{5-(2,4-Dimethylphenyl)-l-methyl-6-[4-(methylthio) ρhenyl]-4-oxo-4, 5-dihydro- l*H*-pyrazolo [3,4-J]pyrimidin-3 -yl} acetamide ;

39) 2,2,2-Trifluoro- *N*-{5-(2,4-dimethylphenyl)-l-methyl-6-[4-(methylthio)phenyl]-4-oxo-4,5-dihydro-l *H*-pyrazolo[3,4-fif]pyrimidin-3-yl} acetamide;

40) 2,2,2-Trifluoro- *N*-[5-(4-methoxyphenyl)-l-methyl-4-oxo-6-pyridin-3-yl-4,5-dihydro-l *H*-pyrazolo[3,4-c(]pyrimidin-3-yl]acetamide;

41) *N*-(4-Oxo-5-(4-chlorophenyl)-l-methyl-6-[(4-methylthio)phenyl]-4,5-dihydro- 1*H*-pyrazolo [3,4-fif]pyrimidin-3-yl)-3-fluorobenzamide;

42) 3-Amino-5-(4-methoxyphenyl)-6-[4-methylphenyl]-l,5-dihydro-4 *H*-pyrazolo[3,4-d]pyrimidin-4-one;

43) 3-Amino-5-(4-methoxyphenyl)-6-[4-methoxyphenyl]-l,5-dihydro-4*H*-pyrazolo [3,*4-d*\pyrimidin-4-one;

44) 3-Amino-5-(4-methoxyphenyl)-6-[4-chlorophenyl]-l,5-dihydro-4 *H*-pyrazolo[3,4-cf]pyrimidin-4-one;

45) 3-Amino-5-(4-chlorophenyl)-6-[4-chlorophenyl]-l,5-dihydro-4 *H*-pyrazolo[3,4-<f]pyrimidin-4-one;

46) 3-Amino-5-(4-chlorophenyl)-6-[4-methoxyphenyl]-l 5-dihydro-4*H*-pyrazolo[3,4-c(]pyrimidin-4-one;

47) 3-Amino-5-(4-chlorophenyl)-6-[4-methylphenyl]-l,5-dihydro-4 *H*-pyrazolo[3,4-e(]pyrimidin-4-one;

48) 3-Amino-5-(4-fluorophenyl)-6-[4-chlorophenyl]- 1,5-dihydro-4*H*-pyrazolo[3,4-c(]pyrimidin-4-one;

49) 3-Amino-5-(4-fluorophenyl)-6-[4-methoxyphenyl]- 1,5-dihydro-4*H*-pyrazolo[3,4-cf]pyriraidin-4-one;

50) 3-Amino-5-(4-fluorophenyl)-6-[4-methylphenyl]-l,5-dihydro-4 *H*-pyrazolo[3,4-<5(]pyrimidin-4-one;

51) 3-Amino-5-(4-trifluoromethylphenyl)-6-[4-chlorophenyl]-l,5-dihydro-4*H*-pyrazolo[3,4-c(]pyriniidin-4-one;

52) 3-Amino-5-(4-trifluoromethylphenyl)-6-[4-methoxyphenyl]-l,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one;

53) 3-Amino-5-(4-trifluoromethylphenyl)-6-[4-methylphenyl]-l,5-dihydro-4*H*-pyrazolo**[3**,4-c(]pyriniidin-4-one;

54) 3-Amino-5-(4-trifluoromethylphenyl)-6-[4-(methylthio)phenyl]-l,5-dihydro-4*H*-pyrazolo[3,4-fif]pyrimidin-4-one;

55) 3-Amino-5-(4-methylsulphonyl)-6-[4-chlorophenyl]-l,5-dihydro-4 *H*-pyrazolo **[3**,4-c(]pyrimidin-4-one;

56) 3-Amino-5-(4-methylsulphonyl)-6-[4-methoxyphenyl]-l,5-dihydro-4*H*-pyrazolo[3,4-c(]pyrimidin-4-one;

57) 3-Amino-5-(4-methylsulphonyl)-6-[4-methylphenyl]-l,5-dihydro-4 *H*-pyrazolo[3,4-c(]pyrimidin-4-one;

58) 3-Amino-5-(4-methylsulphonyl)-6-[4-(methylthio)phenyl]-l,5-dihydro-4*H*-pyrazolo[3,4-J]pyrimidin-4-one;

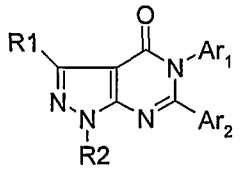
59) 3-Amino-5-[4-(methylthio)phenyl]-6-pyridin-4-yl- 1,5-dihydro-4 H-pyrazolo[3 4-d]pyrimidin-4-one;

60) 3-Amino-5-(4-ethoxyphenyl)-l-methyl-6-pyridin-4-yl-l,5-dihydro-4*H*-pyrazolo[3,4-c(]pyrimidin-4-one;

61) 1-{1-Methyl-5-[4-(methylthio)phenyl]-4-oxo-6-phenyl-4,5-dihydro-1*H*-pyrazolo [3,4-c(]pyrimidin-3-yl} urea and

62) l-{5-[4-(Methylthio)phenyl]-4-oxo-6-phenyl-4,5-dihydro-l *H*-pyrazolo [3,4-flQpyrimidin-3-yl} urea.

4. A pharmaceutical composition, which comprises a compound of formula (I)



as defined in claim 1 and a pharmaceutically acceptable carrier, diluent, excipient or solvate.

5. A pharmaceutical composition as claimed in claim 4, in the form of a tablet, capsule, powder, syrup, solution, aerosol or suspension.

6. Use of a compound of formula (I) as claimed in claim 1, for the prophylaxis or treatment of inflammation, rheumatoid arthritis, osteoporosis, uveititis, acute and chronic myelogenous leukemia, atherosclerosis, cancer, pancreatic β cell destruction, osteoarthritis, rheumatoid spondylitis, gouty arthritis, inflammatory bowel disease, psoriasis, adult respiratory distress syndrome (ARDS) and asthma.

7. Use of a compound as claimed in claim 6 for inhibiting production of cytokines as selected from TNF-α, IL-I, IL-6, IL-8 and IL-12.