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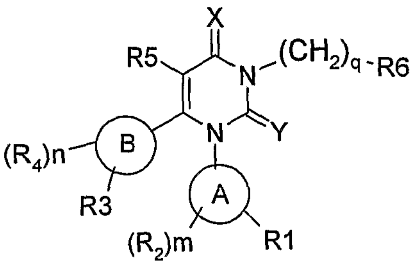
(54) Title: NOVEL BIO-ACTIVE DERIVATIVES



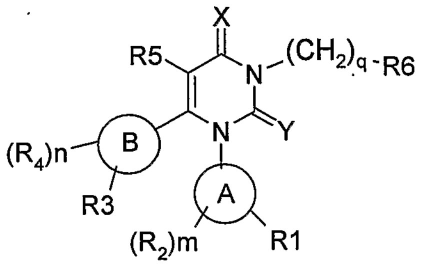
(I)

(57) Abstract: The present invention relates to novel compounds of the general formula (I), their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their hydrates, their solvates, their pharmaceutically acceptable salts and pharmaceutically acceptable compositions containing them. The present invention more particularly provides novel compounds of the general formula (I).

NOVEL BIO-ACTIVE DERIVATIVES

Field of the Invention

The present invention relates to novel compounds of the general formula (I), their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their hydrates, their solvates, their pharmaceutically acceptable salts and pharmaceutically acceptable compositions containing them. The present invention more particularly provides novel compounds of the general formula (I).



(I)

The present invention also provides a process for the preparation of the above said novel compounds of the formula (I), their pharmaceutically acceptable salts, their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their hydrates, their solvates, their pharmaceutically acceptable salts, and pharmaceutical compositions containing them.

The novel compounds 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-1, IL-6, IL-1β, IL-8, IL-12 and cyclooxygenase's 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-1; HIV-2; HIV-3; cytomegalovirus (CMV); influenza; adenovirus; the herpes viruses (including HSV-1, 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 provide the necessary "help" for T cell stimulation and proliferation. Most importantly macrophages make IL-1, 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 cells, and a large number of chronic and acute conditions have been recognized to be associated with perturbation of the inflammatory response. A large number of cytokines participate in this response, including IL-1, IL-6, IL-8 and TNF. It appears that the activity of these cytokines in the regulation of inflammation rely at least in part on the activation 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-1 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 extra vascular 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), were recently approved by the U.S. 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-1 over basal levels have been implicated in mediating or exacerbating a number of disease states including rheumatoid arthritis; osteoporosis; multiple myeloma; uveitis; 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-1, HIV-2, HIV-3, cytomegalovirus (CMV), influenza, adenovirus, the herpes viruses (including HSV-1, HSV-2), and herpes zoster are also exacerbated by TNF-α.

It 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 prostaglandins 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-1β is associated with numerous disease conditions, it is desirable to develop compounds that inhibit the production or activity of IL-1β.

In rheumatoid arthritis models in animals, multiple intra-articular injections of IL-1 have led to an acute and destructive form of arthritis (Chandrasekhar et al., Clinical Immunol Immunopathol. 55, 382, 1990). In studies using cultured rheumatoid synovial cells, IL-1 is a more potent inducer of stromelysin than 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).

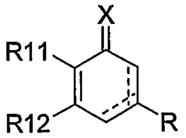
In rheumatoid arthritis, both IL-1 and TNF-α induce synoviocytes and chondrocytes to produce collagenase and neutral proteases, which leads to tissue destruction within the arthritic joints. In a model of arthritis (collagen-induced arthritis (CIA) in rats and mice) intra-articular administration of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

IL-8 has been implicated in exacerbating and/or causing many disease states in which massive neutrophil infiltration into sites of inflammation or injury (e.g., ischemia) is mediated. Chemotactic nature of IL-8, includes, but is 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 also has the 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-1, COX-2 and COX-3. COX-1 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-1 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 anti-inflammatory 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-1 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 cardiovascular risks. So, inhibition of COX-2 without causing cardiovascular risks and gastric ulcers due to inhibition of COX-1 are shown to be safe and is concerned in the present invention.

Few prior art reference which disclose the closest pyrimidine compounds are given here:

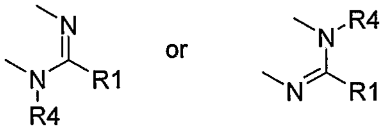
i) US patent Nos. 6,420,385 and 6,410,729 discloses novel compounds of formula (IIa)



(IIa)

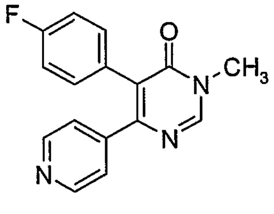
Wherein

represents



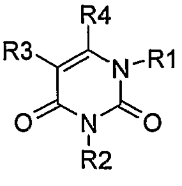
X is O, S or NR_5; R_1 and R_2 each independently represent --Y or --Z--Y, and R_3 and R_4 each independently --Z--Y or R_3 is a hydrogen radical; provided that R_4 is other than a substituted-aryl, (substituted-aryl)methyl or (substituted-aryl)ethyl radical; wherein each Z is independently optionally 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., R_{11} and R_{12} each independently represent optionally substituted aryl or heteroaryl.

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



(IIb)

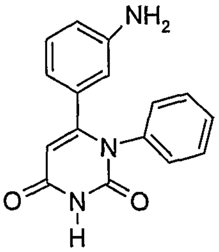
ii) DE 2142317 discloses hypnotic Uracil derivatives of formula (IIc)



(IIc)

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 (IId)



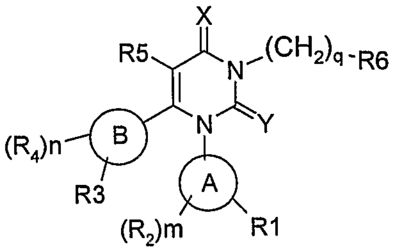
(IId)

Objective of the Invention

We have focused our research to identify cytokine inhibitors, predominantly acting through the inhibition of tumour necrosis factor - α (TNF-α) which are devoid of any side effects normally associated with 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-1, 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 compounds of the formula (I)



(I)

their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their solvates, their pharmaceutically acceptable salts and their pharmaceutically acceptable compositions, wherein X and Y may be same or different and independently represent oxygen, sulfur or NR, wherein R represents hydrogen, hydroxy, acyl, alkyl, alkoxy, aryl, amino, hydroxylamino, alkylamino, arylamino, acylamino, alkoxyamino group; the rings represented by A and B are selected from aryl or heteroaryl; R^1 and R^3 are different and represent hydrogen, alkyl, SR^7, wherein R^7 represents alkyl, aryl or acetoxy methyl group; $S(O)_pR^8$, wherein R^8 represents alkyl, hydroxy, halogen, acyloxy, hydrazine, amino or aryl group and p represents an integer of 1-2; R^2 and R^4 may be same or different and independently represent hydrogen, halogen, hydroxyl, nitro, cyano, azido, nitroso, amino, formyl, alkyl, haloalkyl, acyl, alkoxy, monoalkylamino, dialkylamino, acylamino, alkoxycarbonyl, sulfamoyl, alkylsulfonyl, alkylsulfinyl, alkylsulfanyl, alkoxyalkyl groups or carboxylic acids or its derivatives; R^5 represent hydrogen, halogen, hydroxyl or COR^9, wherein R^9 represents hydroxy, amino, halogen, alkoxy, aryloxy, monoalkylamino, dialkylamino, arylamino, groups;

R^6 is selected from hydroxy, cyano, halogen, amino, alkyl, alkoxy, alkenyl, alkanyl, aryl, monoalkylamino, dialkylamino, acylamino, arylamino, heterocyclyl, heteroaryl or selected from the formula $-COR^{10}$, $-(C\text{-}OR^{18})R^{19}$, $-(C\text{-}OR^{18})(CH_2)_qR^{19}$, $-Z\text{-}(CH_2)_r\text{-}R^{12}$; $-CO(-NR^{13})OR^{14}$, $-C(=NR^{15})R^{16}$, $-C(=NR^{15})NHR^{17}$; wherein suitable groups represented by R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19} are selected from substituted or unsubstituted groups, independently selected from hydrogen, hydroxy, halogen, amino, monoalkylamino, dialkylamino, alkoxyalkylamino, arylamino, arylalkyamino, heteroarylamino, heterocyclyl cycloalkylamino, azido, alkanol, alkyl, alkoxy, alkyloxy, aryloxy, acyloxy, acyl, aryl and heteroaryl; wherein Z is selected from O, NR^{11}, and S; when R^{12} is alkyl, then Z is not oxygen; m and n are integers, which may be same or different and are independently represented by 0-2. p is an integer ranging from 1-2. q and r are integers ranging from 1-10.

Detailed Description of the Invention

X and Y may be same or different and independently represent oxygen, sulfur or NR, wherein R represents hydrogen, hydroxy, acyl, alkyl, alkoxy, aryl, amino, hydroxylamino, alkylamino, arylamino, acylamino, and alkoxyamino group.

Suitable ring systems represented by A and B are selected from aryl and heteroaryl rings such as phenyl, naphthyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, piperidinyl, piperazinyl, pyridyl, thienyl, furyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyrimidinyl, benzopyranyl, benzofuranyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, benzopyrolyl, benzoxadiazolyl, benzothiadiazolyl, quinolinyl, isoquinolinyl, benzothienyl, benzofuranyl, indolyl and the like, which may be optionally substituted.

Suitable groups represented by R^1 and R^3 are selected from substituted and unsubstituted groups represented by hydrogen, alkyl (which may be substituted or unsubstituted and are selected from linear or branched (C_1-C_6)alkyl groups, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, n-pentyl, isopentyl, hexyl and the like), SR^7 or $S(O)_pR^8$.

Suitable groups represented by R^2 and R^4 which may be substituted or unsubstituted are selected from hydrogen, halogen atom such as fluorine, chlorine, bromine, iodine; hydroxyl, nitro, cyano, azido, nitroso, amino, formyl, linear or branched (C_1-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 chloromethane, chloroethane, trifluoromethane, trifluoroethane, dichloromethane, dichloroethane and the like; acyl group such as $-C(=O)CH_3$, $-C(=O)C_2H_5$, $-C(=O)C_3H_7$, $-C(=O)C_6H_{13}$, $-C(=S)CH_3$, $-C(=S)C_2H_5$, $-C(=S)C_3H_7$, $-C(=S)C_6H_{13}$, benzoyl; linear or branched (C_1-C_6) alkoxy group, such as methoxy, ethoxy, n-propoxy, isopropoxy and the like; monoalkylamino group such as $NHCH_3$, NHC_2H_5, NHC_3H_7, NHC_6H_{13}, and the like; dialkylamino group such as $N(CH_3)_2$, $NCH_3(C_2H_5)$, $N(C_2H_5)_2$ and the like; acylamino group such as $NHC(=O)CH_3$, $NHC(=O)C_2H_5$, $NHC(=O)C_3H_7$,

$NHC(=O)C_6H_{13}$, and the like; alkoxycarbonyl group such as methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, isopropoxycarbonyl and the like; alkylsulfonyl group such as methylsulfonyl, ethylsulfonyl, n-propylsulfonyl, iso-propylsulfonyl and the like; sulfamoyl, alkylsulfinyl group such as methylsulfinyl, ethylsulfinyl, n-propylsulfinyl, iso-propylsulfinyl and the like; alkylthio group such as methylthio, ethylthio, n-propylthio, iso-propylthio and the like; sulfamoyl, alkoxyalkyl group such as methoxymethyl, ethoxymethyl, methoxyethyl, ethoxyethyl and the like; carboxylic acid or its derivatives such as esters, amides and acid halides.

Suitable groups represented by R^5 are selected from substituted and unsubstituted groups represented by hydrogen, halogen atom such as chlorine, fluorine, bromine or iodine; hydroxyl, or $COR^{9.}$

R^6 is selected from substituted and unsubstituted groups represented by hydroxy, cyano, halogen atom such as chlorine, fluorine, bromine or iodine; amino, alkyl, alkoxy, alkenyl (such as ethylene and the like), alkynyl (such as acetylene and the like), aryl (such as phenyl, napthyl and the like which may be substituted by one or more groups selected from nitro, cyano, carboximidamide, alkoxy groups such as methoxy, ethoxy and the like, halogens such as fluorine, chlorine, iodine, bromine, haloalkyl groups such as $–CHF_2$, $-CH_2F$, $-CF_3$ and the like, monoalkylamino group such as $-NHCH_3$, $-NHC_2H_5$, $-NHC_3H_7$, $-NHC_6H_{13}$, and the like; dialkylamino group such as $-N(CH_3)_2$, $-NCH_3(C_2H_5)$, $-N(C_2H_5)_2$ and the like; acylamino group such as $-NHC(=O)CH_3$, $-NHC(=O)C_2H_5$, $-NHC(=O)C_3H_7$, $-NHC(=O)C_6H_{13}$, and the like; arylamino such as phenyl amino, naphthyl amino and the like; heterocyclyl groups such as pyrrolidinyl, morpholinyl, thiomorpholinyl, piperidinyl, piperazinyl, tetrazolyl, oxiranyl, benzodioxinyl, dioxalanyl, oxazolidinyl, 1,2,4-oxadiazolyl, 1,3 indanedionyl and the like which may be further substituted, heteroaryl groups such as pyridyl, thienyl, furyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyrimidinyl benzopyranyl, benzofuranyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, benzopyrrolyl, benzoxadiazolyl, benzothiadiazolyl, quinolinyl, isoquinolinyl, benzothienyl, benzofuranyl, indolyl and the like which may be further substituted; or is selected from the formula $-COR^{10}$, $-(C-OR^{18})R^{19}$, $-(C-OR^{18})(CH_2)_qR^{19}$, $-Z-(CH_2)_r-R^{12}$; $-CO(-NR^{13})OR^{14}$, $-C(=NR^{15})R^{16}$, $-C(=NR^{15})NHR^{17}$; wherein suitable groups represented by R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19} are selected from substituted or unsubstituted groups, independently selected from hydrogen, hydroxy, halogen, amino, monoalkylamino, dialkylamino, alkoxyalkylamino, arylamino, heteroarylamino such as thienylamino, pyridylamino, pyrimidyl amino group; cycloalkylamino group such as cyclopropylamino, cyclopentylamino, cyclohexylamino and the like; azido, alkanol, alkyl, alkoxy group such as methoxy, ethoxy, propoxy, butyloxy and the like; aryloxy group such as phenyloxy, napthyloxy and the like; acyloxy group such as $-OC(=O)CH_3$, $-OC(=O)C_2H_5$, $-OC(=O)C_3H_7$ and the like; acyl groups such as $C(=O)CH_3$, $-C(=O)C_2H_5$, $-C(=O)C_3H_7$, $-C(=O)C_6H_{13}$, $-C(=S)CH_3$, $-C(=S)C_2H_5$, $-C(=S)C_3H_7$, $-C(=S)C_6H_{13}$, benzoyl; aryl group such phenyl, napthyl and the like; heteroaryl group such as pyridyl, thienyl, furyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyrimidinyl benzopyranyl, benzofuranyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, benzopyrrolyl, benzoxadiazolyl, benzothiadiazolyl, quinolinyl, isoquinolinyl, benzothienyl, benzofuranyl, indolyl and the like; heterocyclyl groups such as pyrrolidinyl, morpholinyl, thiomorpholinyl, piperidinyl, piperazinyl and the like which may be optionally substituted by one or more groups such as formyl, alkyl, aryl, aralkyl, heteroaryl, heterocyclyl and the like; wherein Z is selected from O, NR^{11}, S; when R^{12} is alkyl, then Z is not oxygen.

Suitable groups represented by R^9 which may be substituted or unsubstituted are selected from hydroxy, amino, halogen, linear or branched (C_1-C_6) alkoxy group, such as methoxy, ethoxy, n-propoxy, isopropoxy and the like; monoalkylamino group such as $NHCH_3$, NHC_2H_5, NHC_3H_7, NHC_6H_{13}, and the like, which may be substituted; dialkylamino group such as $N(CH_3)_2$, $NCH_3(C_2H_5)$, $N(C_2H_5)_2$ and the like; aryloxy group such as phenoxy, napthoxy and the like; arylamino such as phenyl amino, naphthyl amino and the like.

Suitable groups represented by R^7 which may be substituted or unsubstituted are selected from linear or branched (C_1-C_6)alkyl groups, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, n-pentyl, isopentyl, hexyl and the like; aryl groups such as phenyl or naphthyl and the like, or the acetoxy methyl group.

Suitable groups represented by R^8 which may be substituted or unsubstituted are selected from hydroxy, halogen, acyloxy, hydrazine, amino, linear or branched $(C_1-$

C_6)alkyl group, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, n-pentyl, isopentyl, hexyl and the like; aryl group such as phenyl or naphthyl.

Suitable groups represented by R which may be substituted or unsubstituted are selected from hydrogen, hydroxy, amino, hydroxylamino, linear or branched (C_1-C_6)alkyl group, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, n-pentyl, isopentyl, hexyl and the like; linear or branched (C_1-C_6) alkoxy group, such as methoxy, ethoxy, n-propoxy, isopropoxy and the like; aryl group such as phenyl, naphthyl and the like; acyl group such as $-C(=O)CH_3$, $-C(=O)C_2H_5$, $-C(=O)C_3H_7$, $-C(=O)C_6H_{13}$, $-C(=S)CH_3$, $-C(=S)C_2H_5$, $-C(=S)C_3H_7$, $-C(=S)C_6H_{13}$, benzoyl; aryl group such as phenyl or naphthyl; alkylamino group such as $NHCH_3$, NHC_2H_5, NHC_3H_7, NHC_6H_{13}, $N(CH_3)_2$, $NCH_3(C_2H_5)$, $N(C_2H_5)_2$ and the like; acylamino group such as $NHC(=O)CH_3$, $NHC(=O)C_2H_5$, $NHC(=O)C_3H_7$, $NHC(=O)C_6H_{13}$, and the like; arylamino such as phenyl amino, naphthyl amino and the like; alkoxyamino such as methoxyamino, ethoxyamino, propoxyamino and the like.

m and n are integers, which may be same or different and are independently represented by 0-2. p is an integer ranging from 1-2. q and r are integers ranging from 1-10.

When the aryl and heteroaryl, heterocyclyl groups representing A, B and R^6 are substituted by one or more substituents which may be same or different, the substituents may be selected from halogens (fluorine, chlorine, bromine, iodine), hydroxy, nitro, cyano, carboximidamide, azido, nitroso, amino, amide, hydrazine, formyl, alkyl, haloalkyl (such as haloalkoxy, cycloalkyl, aryl (may be further substituted), alkoxy (such as methoxy, ethoxy and the like), aryloxy, acyl, acyloxy, acyloxyacyl, methylene dioxy, heterocyclyl, heteroaryl (may be further substituted), monoalkylamino, dialkylamino, acylamino, alkoxycarbonyl, aryloxycarbonyl, alkylsulfonyl, arylsulfonyl, alkylsulfinyl, arylsulfinyl, alkylthio, arylthio, sulfamoyl, alkoxyalkyl groups and carboxylic acids or its derivatives and these substituents are as defined above.

Furthermore whenever the groups A, B and R^6 represent substituted (-mono, -di, -tri, -tetra) or unsubstituted 5 to 10 membered ring systems, the rings may be monocyclic or bicyclic, saturated or partially saturated or aromatic containing 1 to 4 hetero atoms selected from O, S, N and the like.

Pharmaceutically acceptable salts of the present invention include alkali metal salts like Li, Na, and K salts, alkaline earth metal salts like Ca and Mg salts, salts of organic bases such as diethanolamine, α-phenylethylamine, benzylamine, piperidine, morpholine, pyridine, hydroxyethylpyrrolidine, hydroxyethylpiperidine, choline and the like, ammonium or substituted ammonium salts, aluminum salts. Salts also include amino acid salts such as glycine, alanine, cystine, cysteine, lysine, arginine, phenylalanine, guanidine etc. Salts may include acid addition salts where appropriate which are, sulphates, nitrates, phosphates, perchlorates, borates, hydrohalides, acetates, tartrates, maleates, citrates, succinates, palmoates, methanesulphonates, tosylates, benzoates, salicylates, hydroxynaphthoates, benzenesulfonates, ascorbates, glycerophosphates, ketoglutarates and the like. Pharmaceutically acceptable solvates may be hydrates or comprising other solvents of crystallization such as alcohols.

Representative compounds according to the present invention include:

1 methyl [4-(4-methylphenyl)-3-[4-(methylthio)phenyl]-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl]acetate;

2 [4-(4-methylphenyl)-3-[4-(methylthio)phenyl]-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl]acetic acid;

3 [4-(4-methylphenyl)-3-[4-(methylthio)phenyl]-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl]acetonitrile;

4 6-(4-methylphenyl)-1-[4-(methylthio)phenyl]-3-(2-oxopropyl) pyrimidine-2,4(1*H*,3*H*)-dione;

5 3-[(2*E*)-2-(hydroxyimino)propyl]-6-(4-methylphenyl)-1-[4-(methylthio)phenyl]pyrimidine-2,4(1*H*,3*H*)-dione;

6 3-(3-hydroxypropyl)-6-(4-methylphenyl)-1-[4-(methylthio) phenyl]pyrimidine-2,4(1*H*,3*H*)-dione;

7 3-[3-(dimethylamino)propyl]-6-(4-methylphenyl)-1-[4-(methylthio) phenyl]pyrimidine-2,4(1*H*,3*H*)-dione;

8 1-[4-(methylthio)phenyl]-6-phenyl-3-(1*H*-tetrazol-5-ylmethyl) pyrimidine-2,4(1*H*,3*H*)-dione;

9 6-(4-methylphenyl)-1-[4-(methylthio)phenyl]-3-(1*H*-tetrazol-5-ylmethyl) pyrimidine-2,4(1*H*,3*H*)-dione;

10 2-[4-(4-methylphenyl)-3-[4-(methylthio)phenyl]-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl]acetamide;

11 3-ethyl-6-(4-methylphenyl)-1-[4-(methylthio)phenyl]pyrimidine-2,4(1*H*,3*H*)-dione;

12 6-(4-methylphenyl)-1-[4-(methylthio)phenyl]-3-(4-nitrobenzyl)pyrimidine-2,4(1*H*,3*H*)-dione;

13 3-(4-fluorobenzyl)-6-(4-methylphenyl)-1-[4-(methylthio)phenyl]pyrimidine-2,4(1*H*,3*H*)-dione ;

14 4-{[4-(4-methylphenyl)-3-[4-(methylthio)phenyl]-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl]methyl}benzonitrile;

15 6-(4-methylphenyl)-1-[4-(methylthio)phenyl]-3-(oxiran-2-ylmethyl) pyrimidine-2,4(1*H*,3*H*)-dione;

16 3-(4-methoxybenzyl)-6-(4-methylphenyl)-1-[4-(methylthio) phenyl] pyrimidine-2,4(1*H*,3*H*)-dione;

17 3-(3-methoxybenzyl)-6-(4-methylphenyl)-1-[4-(methylthio) phenyl]pyrimidine-2,4(1*H*,3*H*)-dione;

18 3-(2,3-dihydro-1,4-benzodioxin-2-ylmethyl)-6-(4-methylphenyl)-1-[4-(methylthio)phenyl]pyrimidine-2,4(1*H*,3*H*)-dione;

19 3-(1,3-dioxolan-2-ylmethyl)-6-(4-methylphenyl)-1-[4-(methylthio) phenyl]pyrimidine-2,4(1*H*,3*H*)-dione;

20 6-(4-methylphenyl)-1-[4-(methylthio)phenyl]-3-[(2-oxo-1,3-oxazolidin-5-yl)methyl]pyrimidine-2,4(1*H*,3*H*)-dione;

21 6-(4-methylphenyl)-1-[4-(methylthio)phenyl]-3-[(2-oxo-1,3-dioxolan-4-yl)methyl]pyrimidine-2,4(1*H*,3*H*)-dione;

22 6-(4-methylphenyl)-1-[4-(methylthio)phenyl]-3-[4-(trifluoromethyl) benzyl]pyrimidine-2,4(1*H*,3*H*)-dione;

23 6-(4-methylphenyl)-1-[4-(methylthio)phenyl]-3-(2-piperidin-1-ylethyl)pyrimidine-2,4(1*H*,3*H*)-dione;

24 3-but-3-enyl-6-(4-methylphenyl)-1-[4-(methylthio)phenyl]pyrimidine-2,4(1*H*,3*H*)-dione;

25 6-(4-methylphenyl)-1-[4-(methylthio)phenyl]-3-prop-2-ynylpyrimidine -2,4(1*H*,3*H*)-dione;

26 6-(4-methylphenyl)-1-[4-(methylthio)phenyl]-3-(pyridin-2-ylmethyl) pyrimidine-2,4(1*H*,3*H*)-dione;

27 2-[4-(3-(4-methylphenyl)-4-(4-methylthiophenyl)-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl)butyl]-1*H*-isoindole-1,3(2*H*)-dione;

28 6-(4-methylphenyl)-1-[4-(methylthio)phenyl]-3-(quinolin-2-ylmethyl) pyrimidine-2,4(1*H*,3*H*)-dione;

29 6-(4-methylphenyl)-3-[(methylthio)methyl]-1-[4-(methylthio) phenyl] pyrimidine-2,4(1*H*,3*H*)-dione ;

30 6-(4-methylphenyl)-1-[4-(methylthio)phenyl]-3-(1-naphthylmethyl) pyrimidine-2,4(1*H*,3*H*)-dione;

31 3-[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]-1-(4-methylthio phenyl)-6-(4-methylphenyl)pyrimidine-2,4(1*H*,3*H*)-dione

32 3-(2-ethoxyethyl)-6-(4-methylphenyl)-1-[4-(methylthio) phenyl] pyrimidine-2,4(1*H*,3*H*)-dione;

33 3-(2-hydroxyethyl)-1-[4-(methylthio)phenyl]-6-phenylpyrimidine-2,4(1*H*,3*H*)-dione;

34 3-allyl-1-[4-(methylthio)phenyl]-6-phenylpyrimidine-2,4(1*H*,3*H*)-dione

35 1-[4-(methylthio)phenyl-6-(4-methylphenyl)]-3-(2-morpholin-4-ylethyl) pyrimidine-2,4(1*H*,3*H*)-dione;

36 5-[4-(4-methylphenyl)-3-[4-(methylthio)phenyl]-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl]pentanenitrile;

37 3-allyl-6-(4-methylphenyl)-1-[4-(methylthio)phenyl]pyrimidine-2,4(1*H*,3*H*)-dione;

38 [4-[4-(methylthio)phenyl]-2,6-dioxo-3-(4-tert.butyl phenyl)-3,6-dihydropyrimidin-1(2*H*)-yl]acetonitrile;

39 [3-(3,4-dimethylphenyl)-4-[4-(methylthio)phenyl]-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl]acetonitrile;

40 [3-[3-fluoro-4-(methylthio)phenyl]-4-(4-methylphenyl)-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl]acetonitrile;

41 [4-(4-fluorophenyl)-3-[4-(methylthio)phenyl]-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl]acetonitrile;

42 ({4-[3-(cyanomethyl)-6-(4-methylphenyl)-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl]phenyl}thio)methyl acetate;

43 [4-(4-methylphenyl)-3-[4-(methylsulfinyl)phenyl]-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl]acetonitrile;

44 [4-(4-methylphenyl)-3-[4-(methylsulfonyl)phenyl]-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl]acetonitrile;

45 [3-(4-methoxyphenyl)-4-[4-(methylthio)phenyl]-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl]acetonitrile;

46 3-[(2*E*)-2-(hydroxyimino)propyl]-6-(4-methylphenyl)-1-[4-(methylthio)phenyl]pyrimidine-2,4(1*H*,3*H*)-dione

47 6-(4-methylphenyl)-3-[(2*E*)-2-(methylhydrazono)propyl]-1-[4-(methylthio)phenyl]pyrimidine-2,4(1*H*,3*H*)-dione;

48 3-[2-hydroxy-3-(2,4-dimethoxybenzylamino)propyl]-6-(4-methylphenyl)-1-[4-(methylthio)phenyl]pyrimidine-2,4(1*H*,3*H*)-dione;

49 3-(2-hydroxy-3-morpholin-4-ylpropyl)-1-(4-methylthiophenyl)-6-(4-methylphenyl)pyrimidine-2,4(1*H*,3*H*)-dione ;

50 3-[3-(dimethylamino)-2-hydroxypropyl]-6-(4-methylphenyl)-1-[4-(methylthio)phenyl]pyrimidine-2,4(1*H*,3*H*)-dione;

51 4-[3-(3-(4-methylthiophenyl)-4-(4-methylphenyl)-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl)-2-hydroxypropyl]piperazine-1-carbaldehyde;

52 3-[2-hydroxy-3-(benzylamino)propyl]-6-(methylphenyl)-1-[4-(methylthio)phenyl]pyrimidine-2,4(1*H*,3*H*)-dione;

53 3-[2-hydroxy-3-(4-methylpiperazin-1-yl)propyl]-1-(4-methylthiophenyl)-6-(4-methylphenyl)pyrimidine-2,4(1*H*,3*H*)-dione;

54 3-[2-hydroxy-3-(4-(pyridin-2-yl)piperazin-1-yl)propyl]-1-(4-methylthiophenyl)-6-(4-methylphenyl)pyrimidine-2,4(1*H*,3*H*)-dione;

55 3-[2-hydroxy-3-(4-methylpiperazin-1-yl)propyl]-1-(4-methyl thiophenyl)-6-(4-methylphenyl)pyrimidine-2,4(1*H*,3*H*)-dione;

56 3-[2-hydroxy-3-(4--(1,2-benzisothiazol-3-yl)piperazin-1-yl]propyl]-1(-4-methylthiophenyl)-6-(4-methylphenyl)pyrimidine-2,4(1*H*,3*H*)-dione;

57 4-[3-(3-(4-methylthiophenyl)-4-(4-methylphenyl)-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl)-2-hydroxypropyl]-*N*-(4-chloro-3-trifluoromethylphenyl)lpiperazine-1-carboxamide;

58 3-[2-hydroxy-3-(4-(4-nitrophenyl)piperazin-1-yl)propyl]-1-(4-methylthiophenyl),6-(4-methylphenyl) pyrimidine-2,4(1*H*,3*H*)-dione;

59 3-[2-hydroxy-3-(4-pyrimidin-2-ylpiperazin-1-yl)propyl]-1-(4-methylthiophenyl)-6-(4-methylphenyl) pyrimidine-2,4(1*H*,3*H*)-dione;

60 3-(3-chloro-2-hydroxypropyl)-6-(4-methylphenyl)-1-[4-(methylthio) phenyl]pyrimidine-2,4(1*H*,3*H*)-dione;

61 3-[2-hydroxy-3-(2,4-dimethoxybenzylamino)propyl]-6-(4-methylphenyl)-1-[4-(methylthio)phenyl]pyrimidine-2,4(1*H*,3*H*)-dione;

62 3-[3-(4-trifluoromethylbenzylamino)-2-hydroxypropyl]-6-(4-methylphenyl)-1-(4-methylthiophenyl)pyrimidine-2,4(1*H*,3*H*)-dione;

63 3-[3-(4-methoxybenzylamino)-2-hydroxypropyl]-6-(4-methylphenyl)-1-(4-methyl thiophenyl)-pyrimidine-2,4(3*H*)-dione;

64 3-(2,3-dihydroxypropyl)-6-(4-methylphenyl)-1-[4-(methylthio) phenyl] pyrimidine-2,4(1*H*,3*H*)-dione;

65 *N*-{(1*Z*)-*N*-hydroxy-2-[4-(4-methylphenyl)-3-[4-(methylthio)phenyl]-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl]ethanimidoyl}-4-(trifluoromethyl)benzamide;

66 3,5-dichloro-*N*-{(1*Z*)-*N*-hydroxy-2-[4-(4-methylphenyl)-3-(4-methylthiophenyl)-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl]ethanimidoyl} benzamide;

67 3-{[5-(3,5-dichlorophenyl)-1,2,4-oxadiazol-3-yl]methyl}-6-(4-methylphenyl)-1-(4-methylthiophenyl)-pyrimidine-2,4(3*H*)-dione;

68 6-(4-methylphenyl)-1-[4-(methylthio)phenyl]-3-{[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]methyl}pyrimidine-2,4(1*H*,3*H*)-dione;

69 6-(4-methylphenyl)-1-(4-methylthiophenyl)-3-[(5-(3,4-dimethoxyphenyl)phenyl-1,2,4-oxadiazol-3-yl)methyl]pyrimidine-2,4(3*H*)-dione;

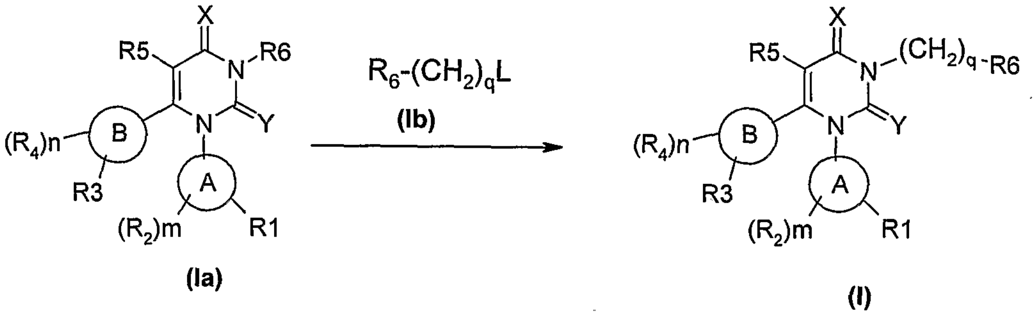
70 *N*-hydroxy-2-[4-(4-methylphenyl)-3-[4-(methylthio)phenyl]-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl]ethanimidamide;

71 *N*-hydroxy-4-{[4-(4-methylphenyl)-3-[4-(methylthio)phenyl]-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl]methyl} benzenecarboximidamide and

72 2-(3-(4-methylthiophenyl)-4-(4-methylphenyl)-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl)ethyl 2,5-dichlorophenylcarbamate.

73 [3-[4-(methylthio)phenyl]-2,6-dioxo-4-phenyl-3,6-dihydropyrimidin-1(2*H*)-yl]acetonitrile

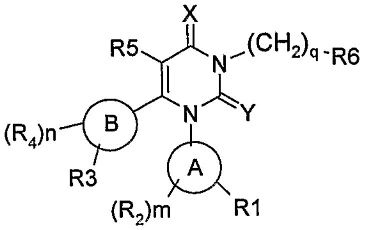
According to yet another embodiment of the present invention, there is provided a process for the preparation of novel compounds of the formula (I) wherein all symbols are as defined above, as shown in scheme I below:



Scheme-1

The reaction of compound of formula (Ia) (prepared according to the procedure disclosed in our patent WO 2003/084937) with (Ib) where L can be halogen or any other leaving group, to produce the compound of formula (I); may be carried out in the presence of solvents such as toluene, xylene, tetrahydrofuran, dioxane, chloroform, dichloromethane, dichloroethane, o-dichlorobenzene, acetone, ethyl acetate, acetonitrile, N,N-dimethylformamide, dimethylsulfoxide, ethanol, methanol, isopropylalcohol, tert-butylalcohol, acetic acid, propionic acid and the like or a mixture thereof. The condensation reaction is carried out under acidic conditions using mineral or organic acids or basic conditions using carbonates, bicarbonates, hydrides, hydroxides, alkyls and alkoxides of alkali metals and alkaline earth metals. The reaction is carried out by using phase transfer catalysts viz. triethylbenzylammonium chloride, tetrabutylammonium bromide, tetrabutylammonium hydrogensulphate, tricaprylylmethylammonium chloride (aliquat 336) and the like. The reaction is carried out at a temperature in the range of 0°C to reflux temperature for period in the range of 1 to 12 hours.

In yet another embodiment of the present invention, there is provided a process for the preparation of novel compounds of the formula (I) wherein either of R^1 and R^3 represent $S(O)_pR^8$, wherein R^8 represents amino group and p represents an integer of 1-2 and all other symbols are as defined earlier, which comprises reacting compound of formula (Ic) wherein all symbols are as defined earlier



(Ic)

with chlorosulfonic acid and ammonia.

The reaction of compound of formula (Ic) with chlorosulfonic acid and ammonia may be carried out in the presence of solvents such as acetic acid, dichloromethane, acetone, tetrahydrofuran, dioxane, ethyl acetate, chloroform, water, an alcohol and the like or a mixture thereof. The reaction is carried out at a temperature in the range of 50 °C to reflux temperature for period in the range of 2 to 12 hours.

According to yet another embodiment of the present invention there is provided a process for the conversion of novel compounds of the formula (I) wherein any of the groups R^1 or R^3 represent SR^7, wherein R^7 represents alkyl or aryl to novel compounds of the formula (I) wherein any of the groups R^1 or R^3 represent $S(O)_pR^8$, where p represents 1 or 2 and R^8 represents alkyl or aryl; by using suitable oxidizing agent. The oxidizing agent may be selected from potassium peroxymonosulfate (Oxone), hydrogen peroxide, tert-butylperoxide, Jones reagent, peracid [e.g peracetic acid, perbenzoic acid, m-chloroperbenzoic acid etc], chromic acid, potassium permanganate, alkali metal periodate [e.g sodium periodate, etc], magnesium mono peroxypthalate, osmium tetroxide/N-methylmorpholine-N-oxide, sodium tungstate, and the like. The oxidation is usually carried out in a solvent which does not adversely influence the reaction such as acetic acid, dichloromethane, acetone, ethyl acetate, chloroform, water, alcohol [eg.

methanol, ethanol, etc.], a mixture thereof or the like. The reaction temperature is usually carried out under cooling to refluxing conditions.

According to yet another embodiment of the present invention there is provided a process for the conversion of novel compounds of the formula (I) wherein R^1 or R^3 represent $S(O)_pR^8$, where p is 1-2, R^8 represents alkyl or aryl to novel compounds of the formula (I) wherein R^1 or R^3 represent $S(O)_pR^8$, where p is 1 or 2, R^8 represents amino by using the procedure described in the literature (Huang et.al. Tetrahedron Lett. 1994, 39, 7201).

According to yet another embodiment of the present invention there is provided a process for the conversion of novel compounds of the formula (I) wherein any of the groups R^6 represent cyano, acetyl, vicinyl diols, esters, aryl cyanides and the like to novel compounds of the formula (I) wherein the groups are as described in the detailed description.

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 pharmaceutically acceptable salts are prepared by reacting the compound of formula (I) with 1 to 4 equivalents of a base such as sodium hydroxide, sodium methoxide, sodium hydride, potassium t-butoxide, calcium hydroxide, magnesium hydroxide and the like, in solvents like ether, tetrahydrofuran, methanol, t-butanol, dioxane, isopropanol, ethanol etc. Mixture of solvents may be used. Organic bases such as diethanolamine, α-phenylethylamine, benzylamine, piperidine, morpholine, pyridine, hydroxyethylpyrrolidine, hydroxyethylpiperidine, choline and the like, ammonium or substituted ammonium salts, aluminum salts. Amino acid such as glycine, alanine, cysteine, lysine, arginine, phenylalanine, guanidine etc may be used for the preparation of amino acid salts. Alternatively, acid addition salts wherever applicable are prepared by the treatment with acids such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, p-toluenesulphonic acid, methanesulfonic acid, acetic acid, citric acid, maleic acid, salicylic acid, hydroxynaphthoic acid, ascorbic acid, palmitic acid, succinic acid, benzoic acid, benzenesulfonic acid, tartaric acid and in solvents like ethyl acetate, ether, alcohols, acetone, tetrahydrofuran, dioxane etc. Mixture of solvents may also be used.

The stereoisomers of the compounds forming part of this invention may be prepared by using reactants in their single enantiomeric form in the process wherever possible or by conducting the reaction in the presence of reagents or catalysts in their single enantiomer form or by resolving the mixture of stereoisomers by conventional methods. Some of the preferred methods include use of microbial resolution, resolving the diastereomeric salts formed with chiral acids such as mandelic acid, camphorsulfonic acid, tartaric acid, lactic acid, and the like wherever applicable or with chiral bases such as brucine, cinchona alkaloids and their derivatives and the like. Commonly used methods are compiled by Jaques et al in "Enantiomers, Racemates and Resolution" (Wiley Interscience, 1981). More specifically the compound of formula (I) may be converted to a 1:1 mixture of diastereomeric amides by treating with chiral amines, aminoacids, aminoalcohols derived from aminoacids; conventional reaction conditions may be employed to convert acids into an amide; the diastereomers may be separated either by fractional crystallization or chromatography and the stereoisomers of the compound of formula (I) may be prepared by hydrolysing the pure diastereomeric amide.

Various polymorphs of the compound of general formula (I) forming part of this invention may be prepared by crystallization of the compound of formula (I) under different conditions. For example, using different solvents commonly used or their mixtures for recrystallization; crystallizations at different temperatures; various modes of cooling, ranging from very fast to very slow cooling during crystallizations. Polymorphs may also be obtained by heating or melting the compound followed by gradual or fast cooling. The presence of polymorphs may be determined by solid probe NMR spectroscopy, IR spectroscopy, differential scanning calorimetry, and powder X-ray diffraction or such other techniques.

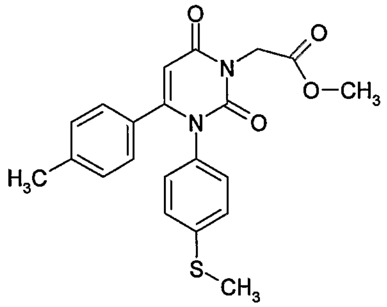
Pharmaceutically acceptable solvates of the compounds of formula (I) forming part of this invention may be prepared by conventional methods such as dissolving the compounds of the formula (I) in solvents such as water, methanol, ethanol, mixture of solvents such as acetone:water, dioxane:water, N,N-dimethylformamide:water and the like, preferably water and recrystallizing by using different crystallization techniques.

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 reactions and schemes described above in detail and 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 methyl [4-(4-methylphenyl)-3-[4-(methylthio)phenyl]-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl]acetate

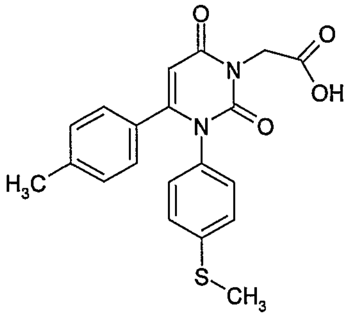


To a solution of 6-(4-methylphenyl)-1-(4-methylsulfanyl-phenyl)-pyrimidin-2,4-(1H)-dione (0.9 g, 2 mmol, prepared according to the procedure disclosed in our patent WO 2003/084937) in tetrahydrofuran (20 ml) was added previously wax removed, sodium hydride (0.14 g, 5.5 mmol) under stirring. Then after 20 minutes of stirring at ambient temperature methyl bromoacetate (1.27 g, 8.3 mmol) was added slowly under vigorous stirring. The stirring was continued for 4 hours and the completion of the reaction was confirmed by TLC. Then the resulted reaction mass was filtered to remove solid material and the filtrate was treated with water. The solid thus obtained was extracted with ethyl acetate and dried over anhydrous sodium sulphate and distilled off the solvent under vacuo and further purified by column chromatography to yield the title compound (0.86 g, 78.81 %, mp 68 – 70 °C, purity

98.7% by HPLC). ^{1}H-NMR (DMSO-d_6): δ 2.21 (s, 3H), 2.41 (s, 3H), 3.49 (s, 3H), 4.63 (s, 2H), 5.85 (s, 1H), 7.05 – 7.07 (d, 2H), 7.13 – 7.16 (m, 6H). IR (KBr) cm^{-1}: 3483, 2952, 2921, 1755, 1713, and 1666. MS m/z: 397.1 (M$^+$).

Example 2

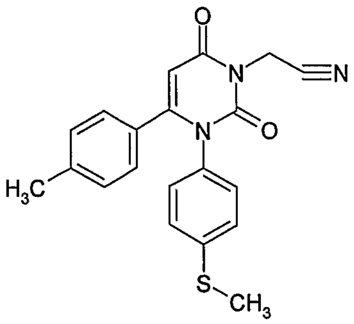
Synthesis of [4-(4-methylphenyl)-3-[4-(methylthio)phenyl]-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl]acetic acid



To a solution of methyl [4-(4-methylphenyl)-3-[4-(methylthio)phenyl]-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl]acetate (1.2 g, 3 mmol, obtained according to the procedure described in example 1) in tetrahydrofuran (5ml) a solution of lithium hydroxide (0.072g, 3mmol) in water (3ml) was added slowly under stirring. The resulted reaction mass was stirred for 8 hours until completion of reaction confirmed by TLC. The resultant reaction mixture was poured onto ice and acidified with dilute hydrochloric acid to pH 6.8. The crude material thus obtained was extracted with ethyl acetate (50 ml), dried the organic layer over anhydrous sodium sulphate and distilled off the solvent under vacuo to yield the crude product, which was purified by column chromatography, using a gradient of ethyl acetate in hexane to yield the title compound (0.165 g, 13.3%, mp 131 – 134 °C, purity 91.83% by HPLC). ^{1}H-NMR (DMSO-d_6): δ 2.21 (s, 3H), 2.41 (s, 3H), 4.49 (s, 2H), 5.8 (s, 1H), 7.05 – 7.07 (d, 2H), 7.13 – 7.16 (m, 6H). IR (KBr) cm^{-1}: 3435 (broad peak), 2923, 1708, and 1663. MS m/z: 382.9 (M$^+$).

Example 3

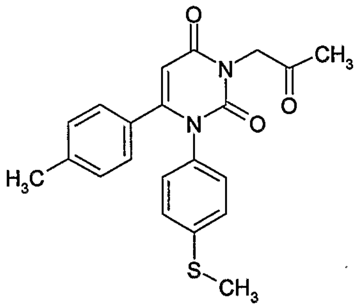
Synthesis of [4-(4-methylphenyl)-3-[4-(methylthio)phenyl]-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl]acetonitrile



To a solution of 6-(4-methylphenyl)-1-(4-methylsulfanyl-phenyl)-pyrimidin-2,4-(1H)-dione (0.15 g, 0.46 mmoles, prepared according to the procedure disclosed in our patent WO 2003/084937) in dimethylformamide (5 ml) was added cesium carbonate (0.225 g, 0.69 mmoles) and bromoacetonitrile (0.83 g, 0.69 mmoles) under stirring. Then the resulting slurry was refluxed at 80 °C under stirring, till complete conversion was confirmed by TLC. The reaction mixture was cooled to room temperature and poured into water (25ml) and the resulted organic layer was extracted with ethyl acetate (20 ml), dried over anhydrous sodium sulfate and evaporated at reduced pressure to yield a brown residue. The resultant residue was then purified by column chromatography, using a gradient of ethyl acetate in hexane to yield the title compound (0.14 g, 83.5%, purity 97.2% by HPLC). ^{1}H-NMR ($CDCl_3$): δ 7.12 (d, 2H), 7.04 - 6.97 (m, 6H), 5.90 (s, 1H), 4.90 (s, 2H), 2.43 (s, 3H), and 2.28 (s, 3H). MS m/z: 363.9(M^+).

Example 4

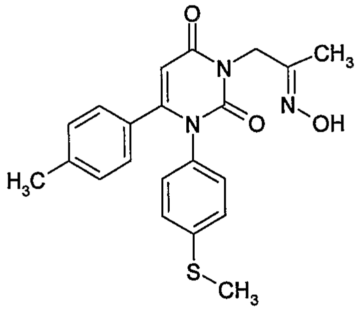
Synthesis of 6-(4-methylphenyl)-1-[4-(methylthio)phenyl]-3-(2-oxopropyl)pyrimidine-2,4(1*H*,3*H*)-dione



To a solution of 6-(4-methylphenyl)-1-(4-methylsulfanyl-phenyl)-pyrimidin-2,4-(1H)-dione (0.125 g, 0.38 mmoles, prepared according to the procedure disclosed in our patent WO 2003/084937) in dimethylformamide (5 ml) was added cesium carbonate (0.188 g, 0.57 mmoles) and 1-bromo-2,2-dimethoxy propane (0.106 g, 0.58 mmoles) under stirring. Following the remaining procedure described in example 3 the desired product was obtained (yield 0.075 g, 51.8 %, mp 156-159 °C purity 94% by HPLC). ^{1}H-NMR ($CDCl_3$): δ 7.10 - 7.06 (m, 3H), 5.87 (s, 1H), 4.82 (s, 2H), 2.41 (s, 3H), and 2.28 (s, 6H). IR (KBr) cm^{-1}: 3435, 2924, 1739, 1707, 1675, 1420, and 1400. MS m/z: 381 (M^+).

Example 5

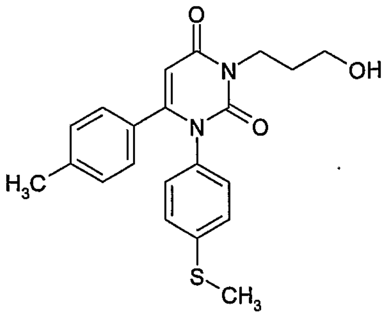
Synthesis of 3-[(2*E*)-2-(hydroxyimino)propyl]-6-(4-methylphenyl)-1-[4-(methylthio)phenyl]pyrimidine-2,4(1*H*,3*H*)-dione



Hydroxylamine hydrochloride (0.109 g, 1.57 mmoles) was added under stirring to a solution of 6-(4-methylphenyl)-1-[4-(methylthio)phenyl]-3-(2-oxopropyl)pyrimidine-2,4(1*H*,3*H*)-dione (0.2 g, 0.52 mmol, obtained according to the procedure described in example 5) in a mixture of pyridine:methanol (5ml, 1:4). The resultant reaction mass was stirred at 80° C for 24 hours. Following the remaining procedure as described in example 3 the desired product was obtained (yield 0.15 g, 72.0%, mp 176-179 °C, purity 96.8% by HPLC). ^{1}H-NMR ($CDCl_3$): δ 7.10 - 7.06 (m, 3H), 5.87 (s, 1H), 4.72 (s, 2H), 2.42 (s, 3H), 2.28 (s, 6H), and 1.95 (s, 3H). IR (KBr) cm^{-1}: 3409, 2916, 1711, 1707, 1665, 1423, and 1394. MS m/z: 396 (M^+).

Example 6

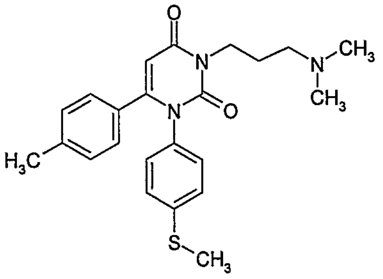
Synthesis of 3-(3-hydroxypropyl)-6-(4-methylphenyl)-1-[4-(methylthio)phenyl]pyrimidine-2,4(1*H*,3*H*)-dione



To a solution of 6-(4-methylphenyl)-1-(4-methylsulfanyl-phenyl)-pyrimidin-2,4-(1H)-dione (0.15 g, 0.46 mmoles, prepared according to the procedure disclosed in our patent WO 2003/084937) in dimethylformamide (5 ml) was added cesium carbonate (225 mg, 0.69 mmoles) and bromopropanol (62 mg, 0.69 mmoles) under stirring. Then the resultant reaction mass was refluxed at 80 °C, until complete conversion was confirmed by TLC. Following the remaining procedure as described in example 3 the desired product was obtained (yield 0.14 g, 33.9 %, purity 94.3% by HPLC). ^{1}H-NMR ($CDCl_3$): δ 7.12 – 7.10 (d, 2H), 7.00 - 6.92 (m, 6H), 5.92 (s, 1H), 4.47-4.40 (t, 2H), 4.20 - 4.17 (m, 2H), 2.43 (s, 3H), 2.28 (s, 3H), 2.22 (s, 3H), and 2.16 - 2.09 (m, 2H). MS m/z: 383.1 (M^+).

Example 7

Synthesis of 3-[3-(dimethylamino)propyl]-1-[4-(methylthio)phenyl]-6-(4-methylphenyl)-pyrimidine-2,4(1*H*,3*H*)-dione

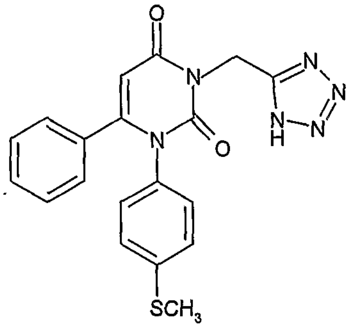


To a solution of 6-(4-methylphenyl)-1-(4-methylsulfanyl-phenyl)-pyrimidin-2,4-(1H)-dione (0.2 g, 0.62 mmoles, prepared according to the procedure disclosed in our patent WO 2003/084937) in dimethylformamide (5 ml) was added cesium carbonate (0.301 g, 0.92 mmoles) and 3-dimethylaminopropylchloride hydrochloride (0.154 g, 0.92 mmoles) under stirring. The resultant reaction mass was refluxed at 80 °C for 24 hours under continuous stirring. Following the remaining procedure as described in example 3, the desired product was obtained (yield 0.1 g, 31.7%, purity

90.5% by HPLC). ^{1}H-NMR ($CDCl_3$): δ 7.13 – 7.09 (d, 2H), 7.03 - 6.97 (m, 6H), 5.82 (s, 1H), 4.08 - 4.04 (m, 2H), 2.56 - 2.52 (m, 2H), 2.43 (s, 3H), 2.35 (s, 6H), 2.28 (s, 3H), and 1.98-1.95 (m, 2H)). MS m/z: 410.2 (M^+).

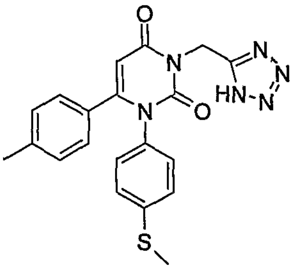
Example 8

Synthesis of [4-(methylthio)phenyl]-6-phenyl-3-(1H-tetrazol-5-ylmethyl)pyrimidine-2,4(1H,3H)-dione



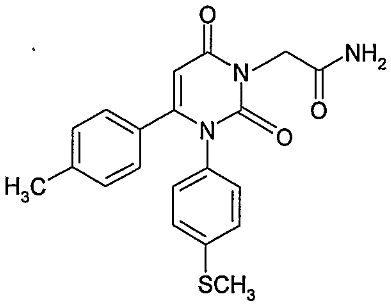
{3-[4-(methylthio)phenyl]-2,6-dioxo-4-phenyl-3,6-dihydropyrimidin-1(2H)-yl}acetonitrile, example 3 (0.7gm, 2mM), 0.84gm of triethylamine hydrochloride (6.10mM), sodium azide (0.4gm, 6.15mM) and toluene (5mL) was heated to reflux for 15 hours. Subsequently the reaction mixture was poured into cold water, then acidified with dilute hydrochloric acid and extracted with ethylacetate (100mL). The organic layer was evaporated and the crude material was triturated with isopropyl alcohol (10 mL). The solid obtained was filtered to yield the title compound. (0.18gm, 23.1%). ^{1}H-NMR ($CDCl_3$) δ: 2.406 (s, 3H), 5.557 (s, 2H), 5.96 (s, 1H), 6.96-6.98 (m, 2H), 7.065-7.091 (m, 4H), 7.10-7.28 (m, 3H), 13.51 (s, 1H). MS m/z: 393.0(M^++1).

The following compounds are prepared according to the procedure given in the example 8.

Exp.	Structure	Analytical data
9		^{1}H-NMR ($CDCl_3$) δ: 2.22 (s, 3H), 2.75 (s, 3H), 4.95 (s, 2H), 5.99 (s, 1H), 6.9 (dd, 2H), 7.03 (2H, dd), 7.21-7.24 (dd, 4H), MS m/z: 407.0 (M^++1).

Example 10

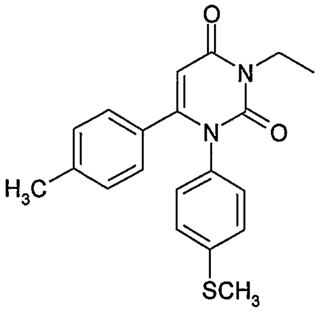
Synthesis of 2-[4-(4-methylphenyl)-3-[4-(methylthio)phenyl]-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl]acetamide



6-(4-methylphenyl)-1-[4-(methylthio)phenyl]pyrimidine-2,4(1H,3H)-dione (0.47gm, 1.45mM) was taken in a solution of ethanol (5mL) containing 0.035gm (1.52mM) of sodium and stirred for 5 minutes, then evaporated to obtain the crude product. The above crude material was dissolved in THF (5mL) and iodoacetamide (0.28gm, 1.51mM) was added, subsequently stirring was continued for 1 hour. Later on the reaction mixture was concentrated and triturated with isopropyl alcohol (15 mL); washed the solid obtained with hexane (15 mL) to obtain the title compound (0.14gm, 25.45%). ^{1}H-NMR (CDCl$_3$) δ: 2.208 (s, 3H), 2.402 (s, 3H), 4.395 (s, 2H), 5.78 (s, 1H), 7.02-7.129 (m, 8H), and 7.579 (s, 2H D2O exchangeable protons). MS m/z: 382.0 (M$^+$+1).

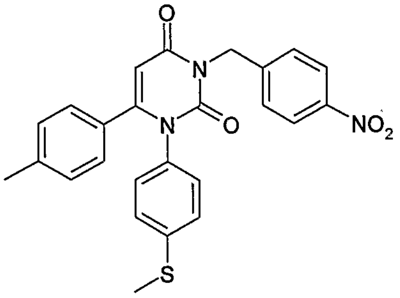
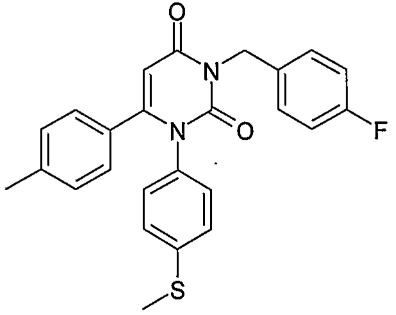
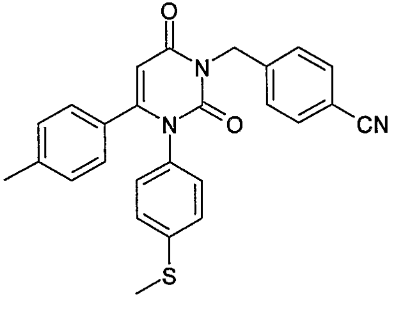
Example 11

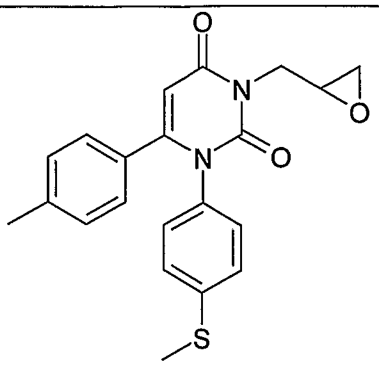
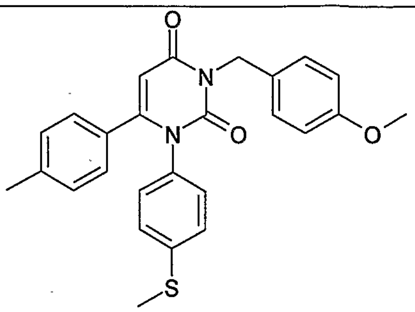
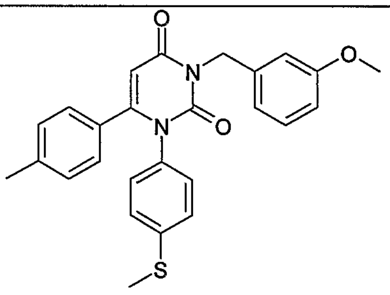
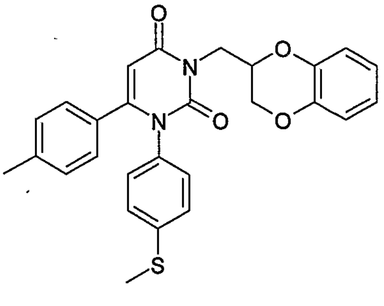
Synthesis of 3-ethyl-6-(4-methylphenyl)-1-[4-(methylthio) phenyl] pyrimidine-2,4(1H,3H)-dione

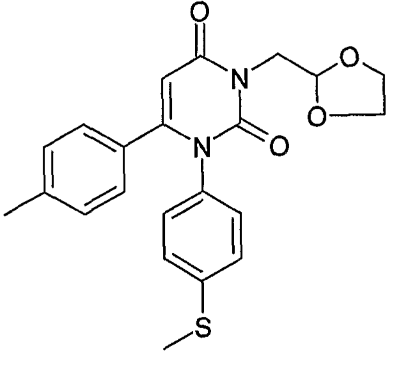
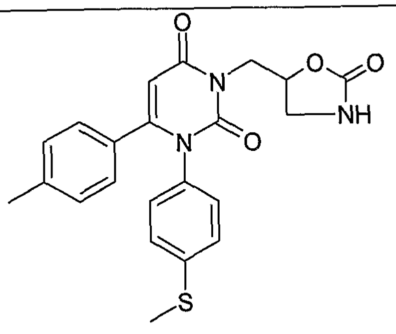
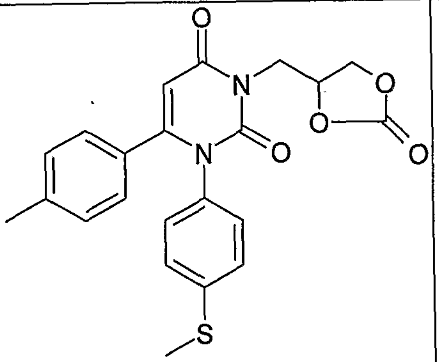
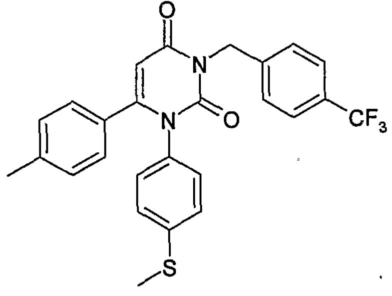


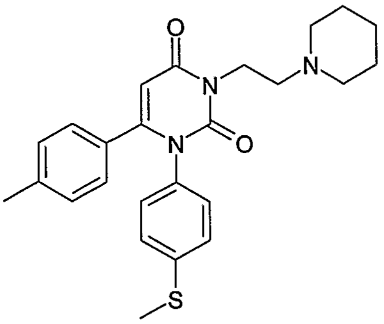
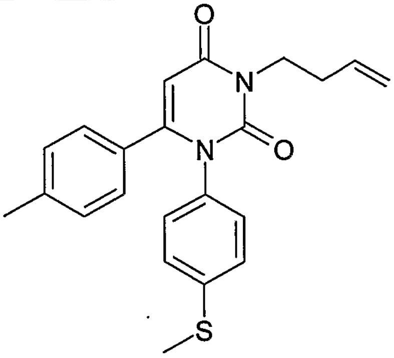
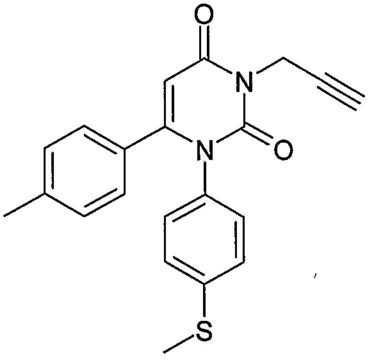
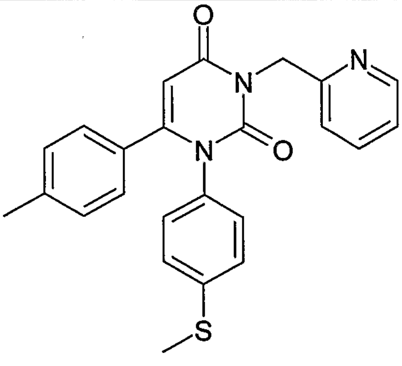
6-(4-methylphenyl)-1-[4-(methylthio)phenyl]pyrimidine-2,4(1H,3H)-dione (0.2gm, 0.62mM) was heated with bromoethane (0.1gm, 0.93 mM) and cesium carbonate (0.3gm, 0.93 mM) in dimethylformamide (5mL) for 3 hours at 80°C. The reaction mixture was poured into ice-cold water (50mL) and the solid separated out was filtered to obtain the title compound (0.09gm, 44.9%). ^{1}H-NMR ($CDCl_3$) δ: 1.257-1.320 (t, 3H), 2.275 (s, 3H), 2.405 (s, 3H), 4.05- 4.1048 (q, 2H), 5.840 (s, 1H), 6.96-7.01(m, 6H), and 7.09-7.11 (dd, 2H). MS m/z: 353.2 (M$^+$+1).

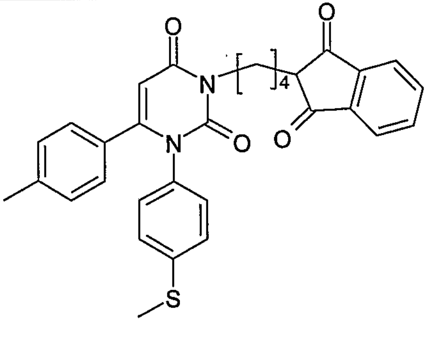
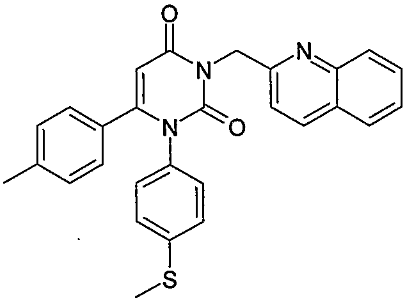
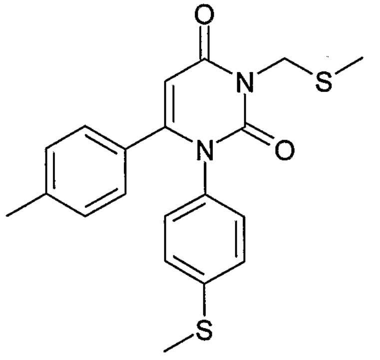
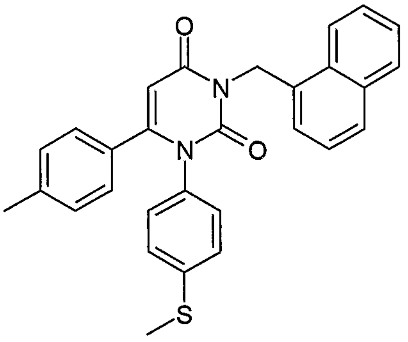
The following compounds are prepared according to the procedure given in the example 11.

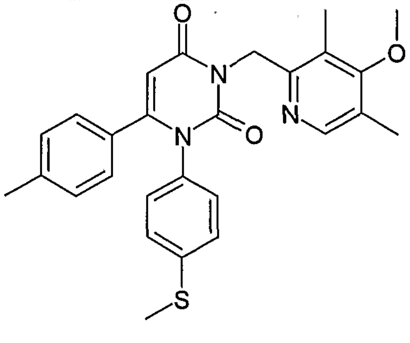
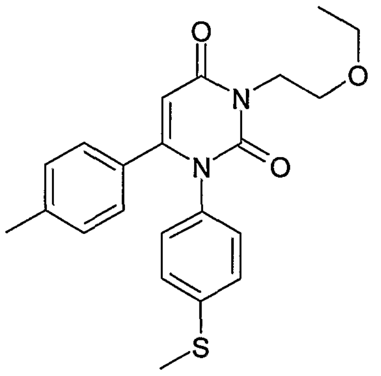
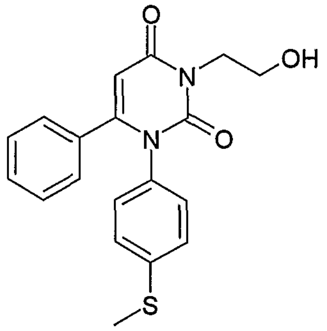
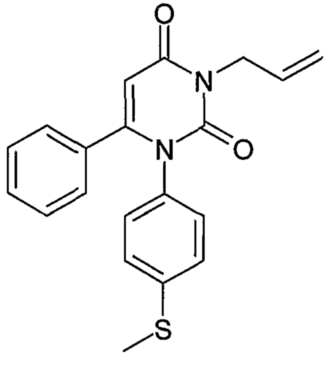
Exp.	Structure	Analytical data
12		^{1}H-NMR ($CDCl_3$) *δ*: 2.27 (s, 3H), 2.41 (s, 3H), 5.25 (s, 2H), 5.89 (s, 1H), 6.94-7.01 (m, 6H), 7.09 (d, 2H), 7.71 (d, 2H), 8.17 (d, 2H); HPLC (purity): 95.3 %; Mass calculated for $C_{25}H_{21}N_3O_4S$ – 459.52, observed 460.1; R_f 0.80 (Ethylacetate: Hexanes (1:1); m.p – 154-157 °C
13		^{1}H-NMR ($CDCl_3$) *δ*: 2.26 (s, 3H), 2.41 (s, 3H), 5.13 (s, 2H), 5.85 (s, 1H), 6.94-7.01 (m, 10H), 7.56-7.59 (d, 2H); HPLC (purity): 91.6 %; Mass calculated for $C_{25}H_{21}FN_2O_2S$ – 432.51, observed 433.1; R_f 0.78 (Ethylacetate: Hexanes (1:1).
14		^{1}H-NMR ($CDCl_3$) *δ*: 2.27 (s, 3H), 2.41 (s, 3H), 5.20 (s, 2H), 5.88 (s, 1H), 6.94-7.01 (m, 6H), 7.08-7.10 (m, 2H), 7.65-7.71 (d, 4H); HPLC (purity): 88.3 %; Mass calculated for $C_{26}H_{21}N_3O_2S$ – 439.53, observed 440.1; R_f 0.80 (Ethylacetate: Hexanes (1:1); m.p – 132-140 °C

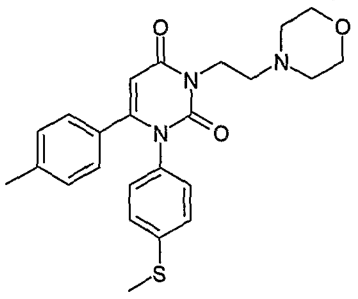
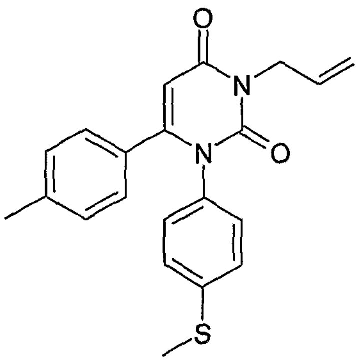
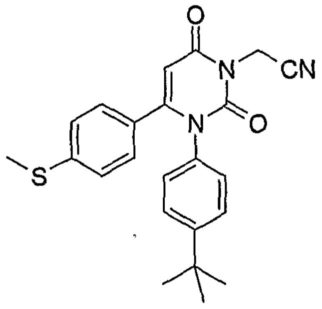
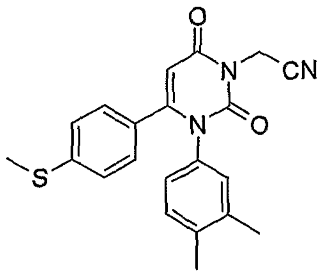
15		^{1}H-NMR ($CDCl_3$) δ: 2.27 (s, 3H), 2.42 (s, 3H), 2.77 (d, 1H), 2.81-2.83 (m, 1H), 3.31-3.34 (m, 1H), 4.02-4.07 (m, 1H), 4.34-4.38 (m, 1H), 5.86 (s, 1H), 6.97-7.00 (m, 6H), 7.11 (d, 2H); HPLC (purity): 84.0 %; R_f 0.60 (Ethylacetate: Hexanes (1:1); m.p – 147-152 °C
16		^{1}H-NMR ($CDCl_3$) δ: 2.26 (s, 3H), 2.41 (s, 3H), 3.78 (s, 3H), 5.12 (s, 2H), 5.84 (s, 1H), 6.83-6.85 (m, 2H), 6.93-6.99 (m, 6H), 7.08 (d, 2H), 7.55 (d, 2H); HPLC (purity): 91.1 %; Mass calculated for $C_{26}H_{24}N_2O_3S$ – 444.55, observed 445.2; R_f 0.46 (Ethylacetate: Hexanes (3:7); m.p – 130-134 °C
17		^{1}H-NMR ($CDCl_3$) δ: 2.26 (s, 3H), 2.39 (s, 3H), 3.79 (s, 3H), 5.16 (s, 2H), 5.86 (s, 1H), 6.83 (d, 2H), 6.93-7.00 (m, 6H), 7.08 (d, 2H), 7.22 (d, 1H); HPLC (purity): 90.8 %; Mass calculated for $C_{26}H_{24}N_2O_3S$ –444.55, observed 445.1; R_f 0.8 (Ethylacetate: Hexanes (1:1).
18		^{1}H-NMR ($CDCl_3$) δ: 2.28 (s, 3H), 2.42 (s, 3H), 4.10-4.12 (m, 1H), 4.19-4.20 (m, 1H), 4.30-4.33 (m, 1H), 4.54-4.57 (m, 2H), 5.86 (s, 1H), 6.82-6.90 (m, 5H), 6.99-7.02 (m, 5H), 7.11 (d, 2H); HPLC (purity): 93.2 %; Mass calculated for $C_{27}H_{24}N_2O_4S$ – 472.55, observed 473.1; R_f 0.78 (Ethylacetate: Hexane (1:1).

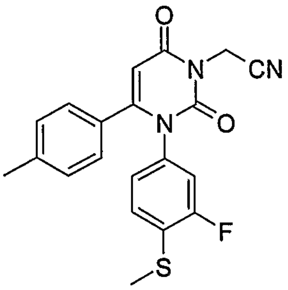
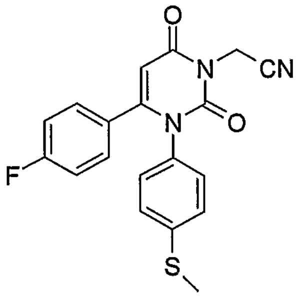
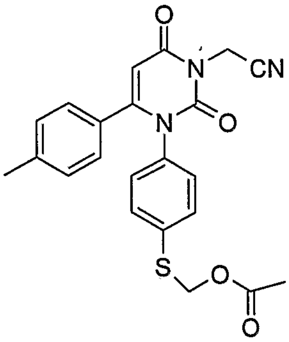
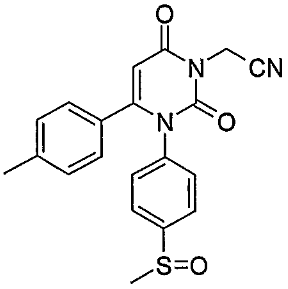
19		^{1}H-NMR (CDCl$_3$) δ: 2.27 (s, 3H), 2.41 (s, 3H), 3.90-3.93 (m, 2H), 4.07-4.10 (m, 2H), 4.16-4.18 (m, 2H), 5.47 (t, 1H), 5.85 (s, 1H), 6.91-7.01 (m, 6H), 7.11 (d, 2H); HPLC (purity): 93.2 %; Mass calculated for $C_{22}H_{22}N_2O_4S$ – 410.48, observed 411.1; R$_f$ 0.72 (Ethylacetate:Hexane (7:3).
20		^{1}H-NMR (CDCl$_3$) δ: 2.28 (s, 3H), 2.42 (s, 3H), 3.46-3.49 (m, 1H), 3.73 (t, 1H), 4.09-4.14 (m, 1H), 4.55-4.60 (m, 1H), 5.00 (bs, 1H), 5.09 (t, 1H), 5.85 (s, 1H), 6.96-7.02 (m, 6H), 7.10 (d, 2H); HPLC (purity): 89.7 %; Mass calculated for $C_{22}H_{21}N_3O_4S$ – 423.48, observed 424.1; R$_f$ 0.20 (Ethylacetate:Hexanes (8:2), m.p- 96-99 °C.
21		^{1}H-NMR (CDCl$_3$) δ: 2.28 (s, 3H), 2.43 (s, 3H), 4.07-4.10 (m, 2H), 4.13-4.18 (m, 1H), 4.37-4.41 (m, 1H), 4.56-4.63 (s, 2H), 5.87 (s, 1H) 6.92-7.01 (m, 6H), 7.11 (d, 2H); HPLC (purity): 92.0 %; Mass calculated for $C_{22}H_{20}N_2O_5S$ – 424.47, observed 425.0; R$_f$ 0.36 (Ethylacetate:Hexanes (1:1).
22		^{1}H-NMR (CDCl$_3$) δ: 2.27 (s, 3H), 2.41 (s, 3H), 5.21 (s, 2H), 5.88 (s, 1H), 6.95-7.01 (m, 6H), 7.09 (d, 2H), 7.43-7.52 (m, 1H), 7.76 (d, 1H), 7.83 (d, 2H); HPLC (purity): 93.3 %; Mass calculated for $C_{26}H_{21}F_3N_2O_2S$ – 482.51, observed 483.1; R$_f$ 0.40 (Ethylacetate:Hexanes (3:7).

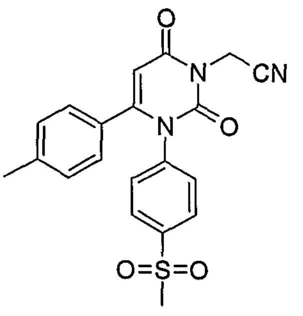
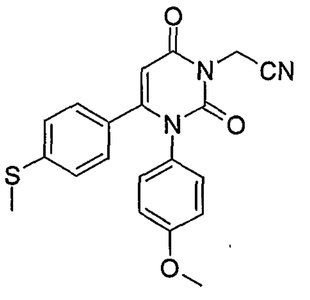
23		^{1}H-NMR ($CDCl_3$) δ: 1.28-1.33 (m, 2H), 1.61-1.71 (m, 4H), 2.26 (s, 3H), 2.42 (s, 3H), 2.53-2.59 (m, 4H), 2.67-2.72 (m, 2H), 4.19 (t, 2H), 5.82 (s, 1H), 6.99-7.02 (m, 6H), 7.10 (d, 2H); HPLC (purity): 96.2 %; Mass calculated for $C_{25}H_{29}N_3O_2S$ – 435.58, observed 436.1; R_f 0.60 (Dichloromethane:Methanol (9:1).
24		^{1}H-NMR ($CDCl_3$) δ: 2.27 (s, 3H), 2.42 (s, 3H), 2.45-2.50 (m, 2H), 4.06-4.10 (m, 2H), 5.03-5.13 (m, 1H), 4.56-4.63 (s, 2H), 5.85 (s, 1H) 6.96-6.99 (m, 6H), 7.10 (d, 2H); HPLC (purity): 95.6%; Mass calculated for $C_{22}H_{22}N_2O_5S$ – 378.49, observed 379.1; R_f 0.35 (Ethylacetate:Hexane (3:7), m.p- 138-140 °C
25		^{1}H-NMR ($CDCl_3$) δ: 2.20 (t, 1H), 2.27 (s, 3H), 2.42 (s, 3H), 4.78 (s, 2H), 5.88 (s, 1H), 6.96-7.02 (m, 6H), 7.10 (d, 2H); HPLC (purity): 95.0 %; Mass calculated for $C_{21}H_{18}N_2O_2S$ – 362.44, observed 363.0; R_f 0.33 (Ethylacetate:Hexanes (3:7).
26		^{1}H-NMR ($CDCl_3$) δ: 2.27 (s, 3H), 2.40 (s, 3H), 5.34 (s, 2H), 5.93 (s, 1H), 6.98-7.01 (m, 2H), 7.07-7.09 (d, 4H), 7.15-7.17 (m, 2H), 7.29-7.31 (m, 2H), 7.63 (d, 1H), 8.56 (d, 1H); HPLC (purity): 98.4 %; Mass calculated for $C_{24}H_{21}N_3O_2S$ – 415.5, observed 416.1; R_f 0.67 (Chloroform:Methanol (9:1).

27		^{1}H-NMR (CDCl$_3$) δ: 1.72-1.79 (m, 4H), 2.27 (s, 3H), 2.42 (s, 3H), 3.72-3.76 (m, 2H), 4.01-4.07 (m, 2H), 5.85 (s, 1H) 6.96-6.99 (m, 6H), 7.10 (d, 2H), 7.69 (t, 2H), 7.81-7.83 (m, 2H); HPLC (purity): 88.0%; Mass calculated for $C_{30}H_{27}N_3O_4S$ – 525.61, observed 526.1; R$_f$ 0.36 (Ethylacetate:Hexanes (3:7), m.p- 144-146 °C
28		^{1}H-NMR (CDCl$_3$) δ: 2.29 (s, 3H), 2.42 (s, 3H), 5.52 (s, 2H), 5.96 (s, 1H), 6.99-7.09 (m, 8H), 7.39 (d, 1H), 7.49 (d, 1H), 7.66 (m, 1H), 7.77 (d, 1H), 8.04-8.11 (d, 2H); HPLC (purity): 96.0 %; Mass calculated for $C_{28}H_{23}N_3O_2S$ – 465.57, observed 466.1; R$_f$ 0.31 (Ethylacetate:Hexane (3:7).
29		^{1}H-NMR (CDCl$_3$) δ: 2.27 (s, 3H), 2.35 (s, 3H), 2.42 (s, 3H), 5.11 (s, 2H), 5.66 (s, 1H), 6.98-7.00 (t, 6H), 7.02 (d, 2H); HPLC (purity): 96.6 %; Mass calculated for $C_{20}H_{20}N_2O_2S_2$ – 384.42, observed 385.0; R$_f$ 0.53 (Ethylacetate:Hexane (3:7).
30		^{1}H-NMR (CDCl$_3$) δ: 2.29 (s, 3H), 2.39 (s, 3H), 5.52 (s, 2H), 5.85 (s, 1H) 6.99-7.09 (m, 9H), 7.39 (d, 1H), 7.49 (d, 1H), 7.66-7.70 (m, 1H), 7.77 (d, 1H), 8.04-8.09 (m, 2H); HPLC (purity): 96.3%; Mass calculated for $C_{29}H_{24}N_2O_2S$ – 464.57, observed465.1; Rf 0.41 (Ethylacetate:Hexanes (3:7).

31		^{1}H-NMR ($CDCl_3$) δ: 2.01 (s, 3H), 2.19 (s, 3H), 2.28 (s, 3H), 2.42 (s, 3H), 3.73 (s, 3H), 5.23 (s, 2H), 5.94 (s, 1H), 7.00-7.08 (m, 8H), 8.14 (s, 1H); HPLC (purity): 96.2 %; Mass calculated for $C_{27}H_{27}N_3O_3S$ – 473.59, observed 474.1; R*f* 0.69 (Chloroform:Methanol (9.5:0.5).
32		^{1}H-NMR ($CDCl_3$) δ: 1.20 (t, 3H), 2.27 (s, 3H), 2.42 (s, 3H), 3.56-3.61 (m, 2H), 3.74 (t, 2H), 4.24 (t, 2H), 5.84 (s, 1H), 6.96-6.99 (m, 6H), 7.10 (d, 2H); HPLC (purity): 99.7%; Mass calculated for $C_{22}H_{24}N_2O_3S$ – 396.5, observed 397.1; R*f* 0.48 (Ethylacetate: Hexanes (1:1).
33		^{1}H-NMR ($CDCl_3$) δ: 2.42 (s, 3H), 3.94-3.95 (m, 2H), 4.30-4.32 (t, 2H), 5.91 (s, 1H) 6.98 (d, 2H), 7.09-7.11 (m, 4H), 7.20-7.27 (m, 3H); HPLC (purity): 94.0%; Mass calculated for $C_{19}H_{18}N_2O_3S$ – 354.5, observed 355.0; R*f* 0.2 (Ethylacetate:Hexanes (1:1).
34		^{1}H-NMR ($CDCl_3$) δ: 2.40 (s, 3H), 4.61 (d, 2H), 5.24 (d, 1H), 5.36 (d, 1H), 5.88 (s, 1H), 5.92-5.99 (m, 1H), 6.97 (d, 2H), 7.10 (t, 4H), 7.11-7.26 (m, 3H); HPLC (purity): 93.9 %; Mass calculated for $C_{20}H_{18}N_2O_2S$ – 350.44, observed 351.0; R*f* 0.30 (Ethylacetate:Hexanes (3:7).

35		^{1}H-NMR (CDCl$_3$) δ: 2.27 (s, 3H), 2.42 (s, 3H), 2.58-2.68 (m, 6H), 3.65-3.70 (m, 4H), 4.15-4.28 (m, 2H), 5.83 (s, 1H), 6.97-6.99 (d, 6H), 7.11 (d, 2H); HPLC (purity): 97.9 %; Mass calculated for $C_{24}H_{27}N_3O_3S$ – 437.56, observed 438.2; R_f 0.18 (Ethylacetate: Hexane (1:1).
37		^{1}H-NMR (CDCl$_3$) δ: 2.27 (s, 3H), 2.42 (s, 3H), 4.62 (s, 2H), 5.23 (d, 1H), 5.36 (d, 1H), 5.85 (s, 1H), 5.91-6.01 (m, 1H), 6.97-7.01 (m, 6H), 7.10 (d, 2H); HPLC (purity): 99.8 %; Mass calculated for $C_{21}H_{20}N_2O_2S$ – 364.46, observed 365.1; R_f 0.47 (Ethylacetate: Hexane (3:7).
38		^{1}H-NMR (CDCl$_3$) δ: 1.258 (s, 9H), 2.417 (s, 3H), 4.924 (s, 2H), 5.915 (s, 1H), 6.98-7.04 (dd, 2H), 7.25-7.31 (dd, 2H), 7.53-7.544 (dd, 2H), and 7.69-7.71 (dd, 2H); MS m/z: 406.4 (M^++1).
39		^{1}H-NMR (CDCl$_3$) δ: 2.196 (s, 6H), 2.434 (s, 3H), 4.904 (s, 2H), 5.88 (s, 1H), 6.76-6.788 (d, 1H), 6.890 (s, 1H), and 7.01-7.05 (m, 5H); MS m/z: 378.3 (M^++1).

40		^{1}H-NMR (CDCl$_3$) δ: 2.28 (s, 3H), 2.60 (s, 3H), 4.923 (s, 2H), 5.96 (s, 1H), 6.91 (s, 1H), and 6.98-7.13 (m, 7H); MS m/z: 382.42 (M$^+$+1).
41		^{1}H-NMR (CDCl$_3$) δ: 2.623 (s, 3H), 4.93 (s, 2H), 5.89 (s, 1H), 7.05-7.12 (m, 2H), and 7.21-7.68(m, 6H); MS m/z: 368.4 (M$^+$+1).
42		^{1}H-NMR (CDCl$_3$) δ: 2.09 (s, 3H), 2.28 (s, 3H), 4.923 (s, 2H), 5.301 (s, 2H), 5.90 (s, 1H), 7.03 (2H, dd), 7.21(dd, 2H), and 7.43-7.65 (m, 4H); MS m/z: 422.0 (M$^+$+1).
43		^{1}H-NMR (CDCl$_3$) δ: 2.22 (s, 3H), 2.75 (s, 3H), 4.95 (s, 2H), 5.99 (s, 1H), 6.9 (dd, 2H), 7.03 (2H, dd), 7.21-7.24 (dd, 4H); MS m/z: 380.4 (M$^+$+1).

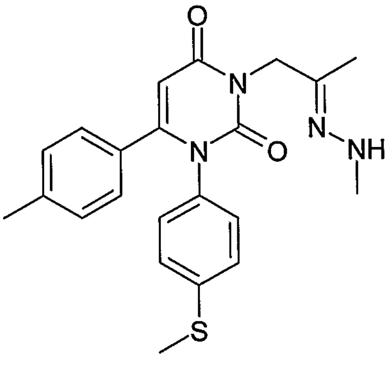
44		^{1}H-NMR (CDCl$_3$) δ: 2.232 (s, 3H), 2.95 (s, 3H), 4.965 (s, 2H), 5.88 (s, 1H), 6.912 (dd, 2H), 7.015-7.043 (2H, dd), 7.30 (dd, 4H), 7.80 (dd, 2H); MS m/z: 396.0 (M$^+$+1).
45		^{1}H-NMR (CDCl$_3$) δ: 2.409 (s, 3H), 3.698 (s, 3H), 4.890 (s, 2H), 5.89 (s, 1H), 6.82-6.84 (dd, 1H), 7.1053 (dd, 2H), 7.150 (dd, 2H), and 7.199-7.22 (dd, 2H); MS m/z: 380.1 (M$^+$+1).

Example 46

Synthesis of 3-[(2*E*)-2-(hydroxyimino)propyl]-6-(4-methylphenyl)-1-[4-(methylthio)phenyl]pyrimidine-2,4(1*H*,3*H*)-dione

To a stirred solution of Example 4 (200 mg, 0.52 mmoles) in ethanol: pyridine mixture (5ml, 4:1) was added hydroxylamine hydrochloride (109 mg, 0.15 mmoles) and the reaction was allowed to stir at room temperature for 30 minutes, followed by refluxing at 60 °C for 8 hours. To the reaction mixture was added, ice-cold water and was subsequently filtered to yield the desired compound. ^{1}H-NMR (CDCl$_3$) δ: 1.95 (s, 3H), 2.27 (s, 3H), 2.41 (s, 3H), 4.72 (s, 2H), 4.98 (bs, 1H), 5.88 (s, 1H), 6.97-7.01 (m, 6H), 7.08-7.11 (m, 2H); HPLC (purity): 96.8 %; Mass calculated for $C_{21}H_{21}N_3O_3S$ – 395.48, observed 396.0; R_f 0.40 (Ethylacetate:Hexanes (1:1); m.p – 176-179 °C.

The following compounds are prepared according to the procedure given in the example 46

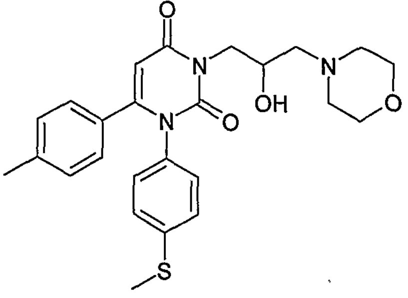
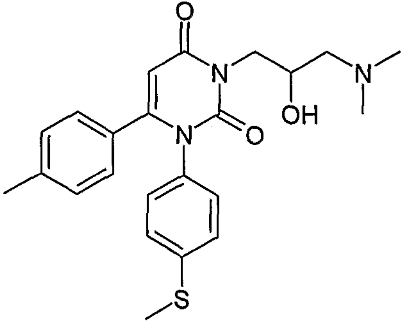
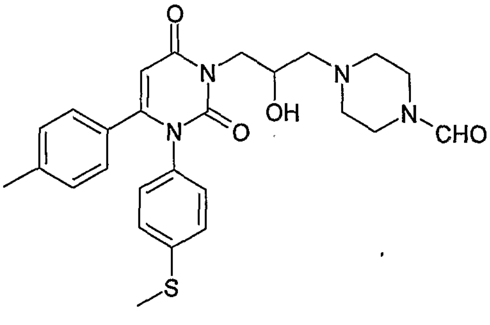
No	Structure	Analytical Data
47		^{1}H-NMR (CDCl$_3$) δ: 2.27 (s, 6H), 2.41 (s, 3H), 2.66 (s, 3H), 4.81 (s, 2H), 5.87 (s, 2H), 6.93-7.01 (m, 6H), 7.08-7.11 (m, 2H); HPLC (purity): 93.6 %; Mass calculated for $C_{22}H_{24}N_4O_2S$ – 408.52, observed 409.0; R$_f$ 0.51 (Ethylacetate: Hexanes (1:1).

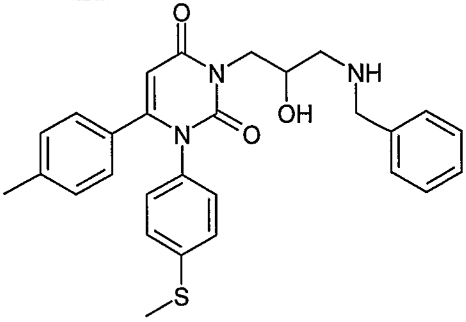
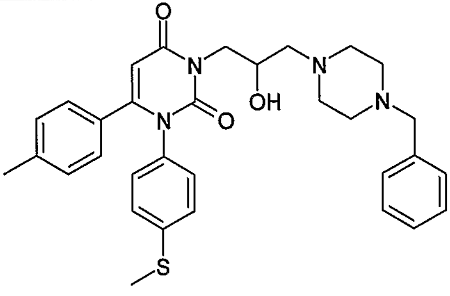
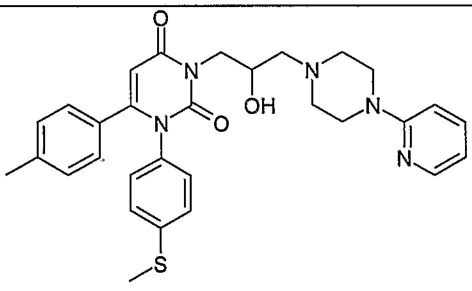
Example 48

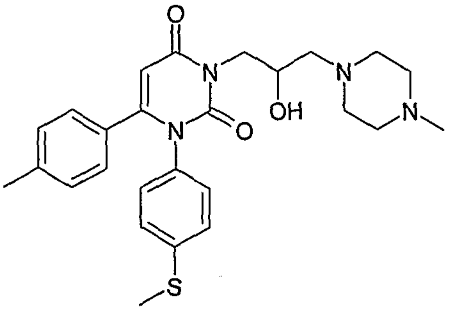
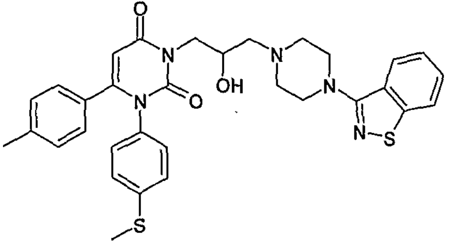
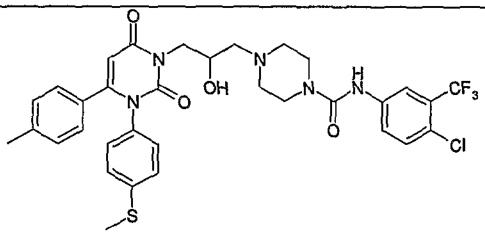
Synthesis of 3-[2-hydroxy-3-(2,4-dimethoxybenzylamino)propyl]-6-(4-methylphenyl)-1-[4-(methylthio)phenyl]pyrimidine-2,4(1*H*,3*H*)-dione

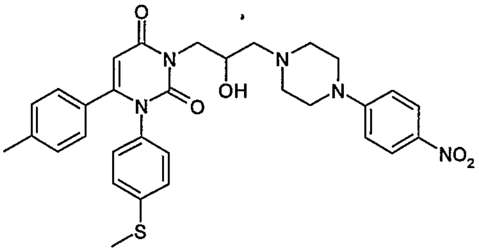
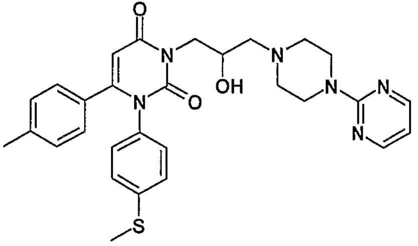
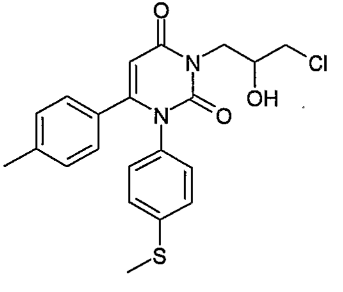
To a solution of Example 15 (150 mg, 0.39 mmoles) in THF (4 ml) was added lithium perchlorate (41.9 mg, 0.39 mmoles) at ice-cold temperature (0-5°C) and stirred. After 10 minutes, 2,4-dimethoxy benzylamine (98.9 mg, 0.59 mmoles) was added and the resulting slurry was stirred at room temperature until complete conversion. To the reaction mixture was added, saturated aqueous ammonium chloride (25 ml) solution and the organic layer was extracted with dichloromethane (20 ml x 3), dried over anhydrous sodium sulfate and evaporated at reduced pressure to yield a brown residue. The resulting residue was then subjected to silica gel column chromatography, using a gradient of ethyl acetate in hexanes. R$_f$ 0.23 (9:1, chloroform:methanol). ^{1}H-NMR (CDCl$_3$) δ: 2.27 (s, 3H), 2.39 (s, 3H), 2.74-2.77 (m, 2H), 2.95-2.99 (m, 1H), 3.79 (s, 3H), 3.80 (s, 3H), 3.86-3.90 (m, 1H), 4.02-4.06 (m, 2H), 4.08-4.09 (m, 1H), 4.15-4.17 (m, 1H), 5.79 (s, 1H), 6.41-6.43 (m, 2H), 6.97-7.06 (m, 8H), 7.16 (d, 2H); HPLC (purity): 88 %; Mass calculated for $C_{30}H_{33}N_3O_5S$ – 547.67, observed 548.2; R$_f$ 0.23 (Chloroform:Methanol (9:1)

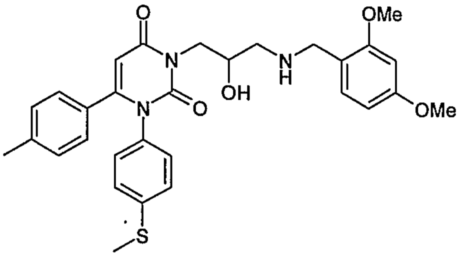
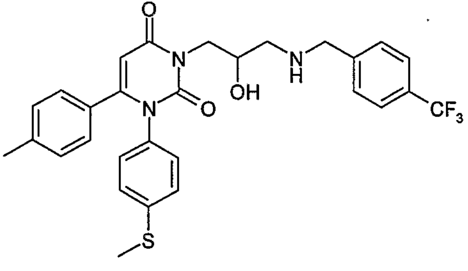
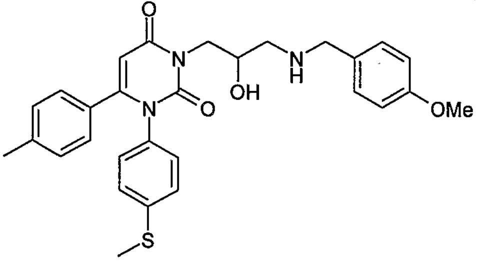
The following compounds are prepared according to the procedure given in the example 49

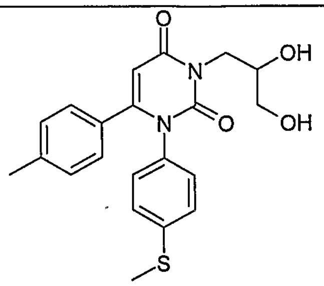
Exp.	Structure	Analytical Data
49		^{1}H-NMR (CDCl$_3$) δ: 2.27 (s, 3H), 2.42 (s, 3H), 2.59-2.62 (m, 4H), 2.72-2.76 (m, 2H), 3.70-3.74 (m, 4H), 4.07-4.11 (m, 1H), 4.16 (d, 1H), 4.22-4.27 (m, 1H), 5.87 (s, 1H), 6.96-7.02 (m, 6H), 7.10 (d, 2H); HPLC (purity): 97.3 %; Mass calculated for $C_{25}H_{29}N_3O_4S$ – 467.58, observed 468.1; R$_f$ 0.37 (Chloroform:Methanol (9:1).
50		^{1}H-NMR (CDCl$_3$) δ: 2.24 (s, 3H), 2.39 (s, 3H), 2.42 (s, 6H), 2.48-2.51 (m, 1H), 2.59-2.62 (m, 2H), 3.72-3.76 (m, 1H), 4.02-4.05 (m, 1H), 4.22-4.25 (m, 1H), 5.87 (s, 1H), 6.99-7.02 (m, 6H), 7.10 (d, 2H); HPLC (purity): 88.6 %; Mass calculated for $C_{23}H_{27}N_3O_3S$ – 425.55, observed 426.1; R$_f$ 0.28 (Chloroform:Methanol (9:1).
51		^{1}H-NMR (CDCl$_3$) δ: 2.27 (s, 3H), 2.42 (s, 3H), 2.54-2.61 (m, 6H), 3.39-3.43 (m, 2H), 3.49-3.58 (m, 2H), 4.13-4.24 (m, 3H), 5.88 (s, 1H), 6.96-7.02 (m, 6H), 7.11 (d, 2H), 8.11 (s, 1H); HPLC (purity): 97.4 %; Mass calculated for $C_{26}H_{30}N_4O_4S$ – 494.61, observed 495.1; R$_f$ 0.36 (Chloroform:Methanol (9:1).

52		^{1}H-NMR (CDCl$_3$) δ: 2.26 (s, 3H), 2.40 (s, 3H), 2.52-2.62 (m, 2H), 2.72-2.79 (m, 1H), 2.89-2.92 (m, 1H), 3.87-3.96 (m, 2H), 4.10-4.16 (m, 2H), 5.83 (s, 1H), 6.96-7.09 (m, 9H), 7.32-7.36 (d, 4H); HPLC (purity): 92.7 %; Mass calculated for $C_{28}H_{29}N_3O_3S$ – 487.61, observed 488.1; R$_f$ 0.52 (Chloroform:Methanol (85:15).
53		^{1}H-NMR (CDCl$_3$) δ: 2.27 (s, 3H), 2.42 (s, 3H), 2.49-2.52 (m, 7H), 2.62-2.65 (m, 3H), 3.49 (s, 2H), 4.00-4.04 (m, 2H), 4.21-4.26 (m, 1H), 5.88 (s, 1H), 6.96-7.01 (m, 7H), 7.10 (t, 2H), 7.24-7.31 (m, 4H); HPLC (purity): 97.6%; Mass calculated for $C_{32}H_{36}N_4O_3S$ – 556.72, observed 557.2; R$_f$ 0.45 (Chloroform:Methanol (9:1).
54		^{1}H-NMR (CDCl$_3$) δ: 2.27 (s, 3H), 2.42 (s, 3H), 2.56-2.62 (m, 4H), 2.74-2.76 (m, 2H), 3.07-3.10 (m, 1H), 3.52-3.62 (m, 4H), 4.11 (d, 1H), 4.24-4.28 (m, 2H), 5.87 (s, 1H), 6.60-6.65 (m, 2H), 6.99 (d, 6H), 7.10 (d, 2H), 7.47-7.52 (d, 1H), 8.18 (d, 1H); HPLC (purity): 92.9 %; Mass calculated for $C_{30}H_{33}N_5O_3S$ – 543.68, observed 544.2; R$_f$ 0.56 (Chloroform:Methanol (9:1).

55		^{1}H-NMR ($CDCl_3$) δ: 2.27 (s, 3H), 2.31 (s, 3H), 2.42 (s, 3H), 2.50-2.55 (m, 6H), 2.62-2.67 (m, 2H), 4.03-4.07 (m, 1H), 4.13-4.15 (m, 1H), 4.15-4.24 (m, 1H), 5.87 (s, 1H), 6.96-7.02 (m, 6H), 7.11 (d, 2H); HPLC (purity): 94.1 %; Mass calculated for $C_{26}H_{32}N_4O_3S$ – 480.62, observed 481.2; R_f 0.15 (Chloroform:Methanol (9:1).
56		^{1}H-NMR ($CDCl_3$) δ: 2.28 (s, 3H), 2.42 (s, 3H), 2.69-2.73 (m, 2H), 2.82-2.85 (m, 2H), 3.56-3.61 (m, 6H), 4.08-4.12 (m, 1H), 4.26-4.30 (m, 2H), 5.89 (s, 1H), 6.96-7.02 (m, 6H), 7.10 (d, 2H), 7.35 (t, 1H), 7.46 (t, 1H), 7.81 (d, 1H), 7.99 (d, 1H); HPLC (purity): 95.5%; Mass calculated for $C_{32}H_{33}N_5O_3S_2$ – 599.7, observed 600.1; R_f 0.62 (Chloroform:Methanol (9:1).
57		^{1}H-NMR ($CDCl_3$) δ: 2.27 (s, 3H), 2.41 (s, 3H), 2.58-2.67 (m, 6H), 3.37-3.52 (m, 4H), 4.13-4.25 (m, 3H), 5.87 (s, 1H), 6.93-7.00 (d, 6H), 7.09 (d, 2H), 7.38 (d, 1H), 7.56 (d, 1H), 7.69 (d, 1H); HPLC (purity): 89.4 %; Mass calculated for $C_{33}H_{33}ClF_3N_5O_4S$ – 688.16, observed 690.1; R_f 0.32 (Chloroform:Methanol (95:5).

58		^{1}H-NMR ($CDCl_3$) *δ*: 2.28 (s, 3H), 2.42 (s, 3H), 2.58-2.67 (m, 5H), 3.43-3.50 (m, 6H), 4.18-4.26 (m, 3H), 5.89 (s, 1H), 6.81 (d, 2H), 6.97-7.02 (m, 6H), 7.11 (d, 2H), 8.12 (d, 2H); HPLC (purity): 95.5 %; Mass calculated for $C_{31}H_{33}N_5O_5S$ – 587.69, observed 588.2; R*f* 0.44 (Chloroform:Methanol (9:1).
59		^{1}H-NMR ($CDCl_3$) *δ*: 2.27 (s, 3H), 2.42 (s, 3H), 2.69-2.73 (m, 4H), 2.82-2.85 (m, 2H), 3.72-3.75 (m, 1H), 3.88-3.94 (m, 4H), 4.11-4.14 (m, 1H), 4.26-4.30 (m, 2H), 5.88 (s, 1H), 6.52 (t, 1H), 6.96-7.02 (m, 6H), 7.10 (d, 2H), 8.28-8.33 (m, 2H); HPLC (purity): 92.7%; Mass calculated for $C_{29}H_{32}N_6O_3S$ – 544.67, observed 545.2; R*f* 0.57 (Chloroform:Methanol (9:1).
60		^{1}H-NMR ($CDCl_3$) *δ*: 2.28 (s, 3H), 2.42 (s, 3H), 3.36 (d, 1H), 3.67-3.70 (m, 2H), 4.25-4.28 (m, 2H), 4.35-4.37 (m, 1H), 5.89 (s, 1H), 6.97-7.03 (d, 6H), 7.11 (d, 2H); HPLC (purity): 99.7 %; Mass calculated for $C_{21}H_{21}ClN_2O_3S$ – 416.92, observed 417.0; R*f* 0.67 (Chloroform:Methanol (9:1).

61		^{1}H-NMR ($CDCl_3$) δ: 2.27 (s, 3H), 2.39 (s, 3H), 2.74-2.77 (m, 2H), 2.95-2.99 (m, 1H), 3.79 (s, 3H), 3.80 (s, 3H), 3.86-3.90 (m, 1H), 4.02-4.06 (m, 2H), 4.08-4.09 (m, 1H), 4.15-4.17 (m, 1H), 5.79 (s, 1H), 6.41-6.43 (m, 2H), 6.97-7.06 (m, 8H), 7.16 (d, 2H); HPLC (purity): 88 %; Mass calculated for $C_{30}H_{33}N_3O_5S$ – 547.67, observed 548.2; R*f* 0.23 (Chloroform:Methanol (9:1).
62		^{1}H-NMR ($CDCl_3$) δ: 2.28 (s, 3H), 2.41 (s, 3H), 2.72-2.77 (m, 2H), 3.88-3.89 (m, 2H), 4.11-4.22 (m, 3H), 5.87 (s, 1H), 6.95-7.03 (m, 6H), 7.10 (d, 2H), 7.44 (d, 2H), 7.56 (d, 2H); HPLC (purity): 82.11%; Mass calculated for $C_{29}H_{28}F_3N_3O_3S$ – 555.61, observed 556.1; R*f* 0.37 (Chloroform:Methanol (9.5:0.5).
63		^{1}H-NMR ($CDCl_3$) δ: 2.28 (s, 3H), 2.41 (s, 3H), 2.72-2.77 (m, 2H), 3.79 (s, 3H), 3.88-3.89 (m, 2H), 4.11-4.22 (m, 3H), 5.85 (s, 1H), 6.85 (d, 2H), 6.96-7.01 (m, 6H), 7.11 (d, 2H), 7.56 (d, 2H); HPLC (purity): 94.9 %; Mass calculated for $C_{29}H_{31}N_3O_4S$ – 517.64, observed 518.1; R*f* 0.47 (Chloroform:Methanol (9:1).

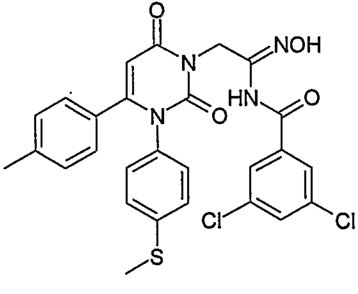
64		^{1}H-NMR (CDCl$_3$) δ: 2.28 (s, 3H), 2.43 (s, 3H), 2.88 (bs, 1H), 3.30 (d, 1H), 3.58-3.62 (m, 2H), 4.07 (d, 1H), 4.27-4.30 (m, 2H), 5.91 (s, 1H), 6.96-6.99 (m, 6H), 7.10-7.13 (d, 2H); HPLC (purity): 97.3%; Mass calculated for $C_{21}H_{22}N_2O_4S$ – 398.48, observed 398.9; R*f* 0.50 (Dichloromethane: Methanol (9:1).

Example 65.

Synthesis of *N*-{(1*Z*)-*N*-hydroxy-2-[4-(4-methylphenyl)-3-[4-(methylthio)phenyl]-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl]ethanimidoyl}-4-(trifluoromethyl)benzamide

To a solution of example 71 (100 mg, 0.25 mmoles) in DCM (3 ml) was added DIPEA (0.087ml, 0.50 mmoles) at ice-cold condition (0-5° C). After 10 min, 4-(trifluoromethyl)benzoylchloride (63.mg, 0.31 mmoles) was added to the above solution and allowed to stir at room temperature for 24 h. To the reaction mixture was added water (20 ml) and filtered. The resulting solid was washed with dichloromethane to yield an off white solid. ^{1}H-NMR (CDCl$_3$) δ: 2.28 (s, 3H), 2.42 (s, 3H), 4.94 (s, 2H), 5.93 (s, 1H), 6.97-7.01 (m, 6H), 7.11 (d, 2H), 7.72 (d, 2H), 8.13 (d, 2H); HPLC (purity): 88.5 %; Mass calculated for $C_{28}H_{23}F_3N_4O_4S$ – 568.57, observed 569.1; R*f* 0.24 (Ethylacetate: Hexane (1:1)

The following compounds are prepared according to the procedure given in the example 65

Exp	Structure	Analytical Data
66		^{1}H-NMR (CDCl$_3$) δ: 2.28 (s, 3H), 2.42 (s, 3H), 4.93 (m, 2H), 5.92 (s, 1H), 6.98-7.03 (m, 6H), 7.10 (d, 2H), 7.55 (s, 1H), 7.88 (s, 2H); HPLC (purity): 84.8%; Mass calculated for $C_{27}H_{22}Cl_2N_4O_4S$ – 569.46, observed 569.4; R*f* 0.71 (Chloroform:Methanol (95:5).

Example 67

Synthesis of 3-{[5-(3,5-dichlorophenyl)-1,2,4-oxadiazol-3-yl]methyl}-6-(4 methylphenyl)-1-(4-methylthiophenyl)-pyrimidine-2,4(3*H*)-dione

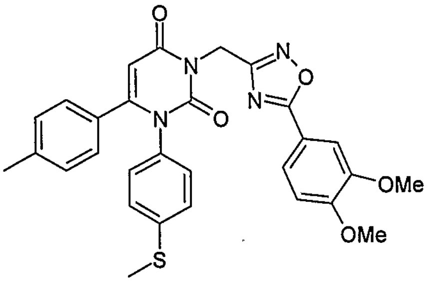
A solution of 3,5-Dichlorobenzoic acid (73 mg, 0.38 mmoles), EDCI (72.5 mg, 0.38 mmoles) and hydroxybenzotriazole (51 mg, 0.38 moles) in DMF (4 ml) was stirred for 30 min, followed by the addition of example 71 (150 mg, 0.38 moles). The resulting solution was stirred and refluxed for 48 h. To the reaction mixture was added, water (20 ml) and the organic layer was extracted with dichloromethane (25 ml x 3 times). The organic layer was dried over anhydrous sodium sulfate and evaporated at reduced pressure to yield a residue, which was subjected to column chromatography using a gradient of ethyl acetates in hexanes (0 –15 %). ^{1}H-NMR ($CDCl_3$) δ: 2.29 (s, 3H), 2.41 (s, 3H), 4.91-5.01 (m, 2H), 5.42 (s, 1H), 7.00-7.03 (m, 6H), 7.10 (d, 2H), 7.56 (d, 1H), 7.95-8.00 (2H); HPLC (purity): 92.1%; Mass calculated for $C_{27}H_{20}Cl_2N_4O_3S$ – 551.44, observed 553.0; R_f 0.53 (Ethylacetate: Hexane (3:7).

Example 68

Synthesis of 6-(4-methylphenyl)-1-[4-(methylthio)phenyl]-3-{[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]methyl}pyrimidine-2,4(1*H*,3*H*)-dione

To a solution of example 71 (76 mg, 0.19 mmoles) in DCM (3 ml) was added DIPEA (0.07ml, 0.38 moles) at ice-cold temperature (0-5° C). After 10 minutes, trifluoroacetic anhydride (48.mg, 0.23 mmoles) was added to the above solution and was allowed to stir at room temperature for 24 hours. To the reaction mixture was added, aqueous saturated $NaHCO_3$ (20 ml) and the organic layer was extracted with dichloromethane (25 ml x 3 times). The organic layer was dried over anhydrous sodium sulfate and evaporated at reduced pressure to yield a residue, which was subjected to column chromatography using a gradient of ethyl acetates in hexanes (0 –15 %). ^{1}H-NMR ($CDCl_3$) δ: 2.28 (s, 3H), 2.41 (s, 3H), 5.44 (s, 2H), 5.94 (s, 1H), 6.98-7.02 (m, 6H), and 7.10 (d, 2H); HPLC (purity): 89.7 %; Mass calculated for $C_{22}H_{17}F_3N_4O_3S$ – 474.46, observed 475.0; R_f 0.77 (Ethylacetate: Hexane (1:1).

The following compounds are prepared according to the procedure given in the example 67 or 68.

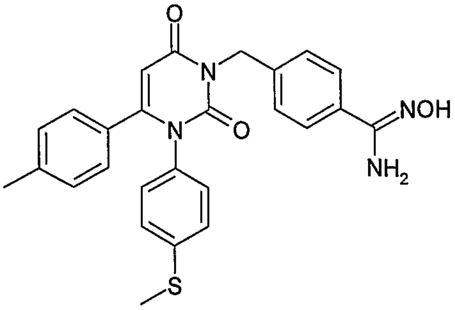
Exp	Structure	Analytical Data
69		^{1}H-NMR (CDCl$_3$) δ: 2.28 (s, 3H), 2.41 (s, 3H), 3.96 (s, 3H), 3.97 (s, 3H), 5.40 (s, 2H), 5.94 (s, 1H), 6.95-7.02 (m, 6H), 7.09 (d, 2H), 7.57 (s, 1H), 7.72-7.75 (m, 2H); HPLC (purity): 93.8 %; Mass calculated for $C_{29}H_{26}N_4O_5S$ – 542.61, observed 543.1; R$_f$ 0.51 (Ethylacetate: Hexane (8:2).

Example 70

Synthesis of N-hydroxy-2-[4-(4-methylphenyl)-3-[4-(methylthio)phenyl]-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl]ethanimidamide

Hydroxylamine hydrochloride (104 mg, 0.14 mmoles) was taken in ethanol (4 ml) and to this slurry was added aqueous NaOH (1ml of 1.4M soln). To the above solution was added example 3 (170 mg, 0.47 mmoles) and refluxed at 60° C until complete conversion. To the reaction mixture was added, water (20 ml) and the organic layer was extracted with dichloromethane (25 ml x 3 times). The organic layer was dried over anhydrous sodium sulfate and evaporated at reduced pressure to yield the desired compound. ^{1}H-NMR (CDCl$_3$) δ: 2.27 (s, 3H), 2.41 (s, 3H), 4.72 (s, 2H), 5.13 (bs, 2H), 5.89 (s, 1H), 6.96-7.01 (m, 6H), 7.02-7.11 (m, 2H); HPLC (purity): 92.6 %; Mass calculated for $C_{20}H_{20}N_4O_3S$ – 396.46, observed 397.0; R$_f$ 0.30 (Ethylacetate: Hexanes (1:1); m.p – 212-215 °C.

The following compounds are prepared according to the procedure given in the example 71 from example 14 or 69

Exp	Structure	Analytical Data
71		^{1}H-NMR (CDCl$_3$) δ: 2.25 (s, 3H), 2.41 (s, 3H), 4.17-4.20 (m, 2H), 5.14 (s, 1H), 5.86 (s, 2H), 6.94-7.00 (m, 8H), 7.09 (d, 2H), 7.52 (s, 2H); HPLC (purity): 88.9 %; Mass calculated for $C_{26}H_{24}N_4O_3S$ –

		472.56, observed 472.9; R_f 0.25 (Ethylacetate: Hexanes (1:1); m.p – 193-194 °C.

Example 72

Synthesis of 2-(3-(4-methylthiophenyl)-4-(4-methylphenyl)-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl)ethyl 2,5-dichlorophenylcarbamate

To a solution of example 6 (100 mg, 0.27 mmoles) in DCM (3 ml) was added TEA (0.05ml, 0.32 mmoles) at ice-cold temperature (0-5° C). After 10 minutes, 2,5-dichlorophenylisocyanate (51.1 mg, 0.27 mmoles) was added to the above solution and was allowed to stir at room temperature for 24 hours. To the reaction mixture was added, water (20 ml) and the organic layer was extracted with dichloromethane (25 ml x 3 times). The organic layer was dried over anhydrous sodium sulfate and evaporated at reduced pressure to yield a residue, which was subjected to column chromatography using a gradient of ethyl acetates in hexanes (0 –30 %). ^{1}H-NMR ($CDCl_3$) δ: 2.27 (s, 3H), 2.42 (s, 3H), 4.39 (t, 2H), 4.53 (t, 2H), 5.84 (s, 1H), 6.96-7.00 (m, 8H), 7.08 (d, 3H), 8.25 (bs, 1H); HPLC (purity): 79.6%; Mass calculated for $C_{27}H_{23}Cl_2N_3O_4S$ – 556.46, observed 557.0; R_f 0.54 (Ethylacetate:Hexanes (1:1).

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 cyclooxygenase-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 should not haven 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-1 for 6 hours. Then test compounds (at various concentrations) or vehicle were added to blood. After that the blood was stimulated with LPS B4 (10 μg/ml) and incubated for another 18 hours at 37 °C water bath. After which the blood was centrifuged, plasma was separated and stored at -80°C (J. Pharmacol. Exp.Ther, 271, 1705, 1994; Proc. Natl. Acad. Sci. USA. 96, 7563, 1999). The plasma was assayed for PGE_2 using Cayman ELISA kit as per the procedure outlined by the manufacturer (Cayman Chemicals, Ann Arbor, USA).

COX-1 and COX-2 enzyme based assay

COX-1 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-1/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-1 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 PGH_2 (Intermediate product) by COX1/COX-2 in presence or absence of the test compound. The reaction was carried out at 37°C and after 2 minutes it was stopped by adding 1M HCl. Intermediate product PGH_2 was converted to a stable prostanoid product $PGF_{2\alpha}$ by $SnCl_2$ reduction. The amount of $PGF_{2\alpha}$ 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).

Example	COX1 % Inhibition at 10μM	COX2 % Inhibition at 10μM
3	44.82	21.16
40	58.33	31.49
73	30.29	31.14

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

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 (0.5 million/incubation well) for 15 minutes at 37° C and then stimulated with Lipopolysaccharide (*Escherichia coli*: B4; 1 μg/ml) for 18 h at 37 ° C in 5% CO_2. The levels of TNF-α 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 I.

Table I

Example No.	TNF-α Inhibition (%)	
	Conc. (μM)	
	1	10
1	30.25	45.53
3	31.43	76.72
6	37.85	61.97
37	18.44	65.32

40	36.48	57.55
46	9.66	22.54
61	23.72	49.19
63	29.06	46.09
64	17.03	52.11
65	20.04	52.11
73	43.17	81.64

***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^{TM} 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^{0} C and then stimulated with Lipopolysaccharide (*Escherichia coli*: B4; 1 µg/ml) for 18 h at 37 ^{0} 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 II.

Table II

Example No.	**IL-6 Inhibition (%)**	
	Conc. (µM)	
	1	**10**
1	11.38	22.18
6	19.19	7.62
26	9.46	18.52
28	19.62	11.19
29	16.68	27.14
37	18.33	30.68

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)].

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 rats 200gm) were fasted for 18 hours, with 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 hours of oral administration of test compounds, all the animals were sacrificed by cervical dislocation. The stomach was dissected carefully and filled up with a sterile saline solution and embedded in 6% formalin solution. Finally the stomach was cut longitudinally and the ulcer lesions were observed with computerized stereomicroscope. Compared 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.)

Inhibitory Action on Adjuvant Arthritis in rats

Compounds were assayed for their activity on rat adjuvant induced arthritis model according to Theisen-Popp et al., (Agents Actions, 42, 50-55,1994). Six to seven weeks old, Wister 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 0.1ml of *Mycobacterium butyricum* (Difco) suspended in mineral oil (5mg/ml) into the sub-plantar region of the right hind paw (J.Pharmacol.Exp.Ther., 284, 714, 1998). Body weight, paw volumes were measured at various days (0, 4, 14, 21) for all the groups. The test compound or vehicle was administered orally beginning post injection of adjuvant ('0'day) and continued for 21 days (pretreatment group). In post treatment group, the test compound or vehicle was administered starting from day 14th to 21st day. On the day 21, the body weight and paw volume of both right and left hind paw were taken. Spleen, and thymus weights were determined. In addition, the radiographs of both hind paws were taken to assess the tibio-tarsal joint integrity. Hind limb below the stifle joint was removed and fixed in 1% formalin saline for the histopathological assessment. At the end of the experiment, serum samples were analysed for inflammatory mediators. The presence or absence of lesions in the stomach was also observed.

Two-factor (`treatment` and `time`) analysis of variance with repeated measures on `time` was applied to the percentage (%) changes for body weight and foot volumes. A post hoc Dunnett's test was conducted to compare the effect of treatments to vehicle control. 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 percentage inhibition in foot volumes on days 4, 14 and 21 were fitted by a 4-parameter logistic function using a nonlinear least Squares' regression. IC_{50} was defined as the dose corresponding to a 50% reduction compared to vehicle control 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 minutes of LPS administration, the mice were bled via retro-orbital sinus puncture. Blood samples were stored overnight at 4°C. Serum samples were collected by centrifuging the samples at 4000 rpm for 15 minutes at 4°C. Immediately the serum samples were analysed for TNF-α levels using commercially available mouse TNF-α ELISA kit (Amersham Biosciences) and assay was performed by the manufacturer instruction.

Example	**TNF alpha % Inhibition in mice**
3	68.36
73	59.40

Anti-cancer screen:

Experimental drugs are screened for anti-cancer activity in three cell lines for their GI_{50}, TGI and LC_{50} values (using five concentrations for each compound). The cell lines are maintained in DMEM containing 10% fetal bovine serum. 96 well microtiter plates are inoculated with cells in 100 □L for 24 hours at 37°C, 5% CO_2, 95% air and 100% relative humidity. 5000 HCT116 cells/well, 5000 NCIH460 cells/well, 10000 U251 cells/well and 5000 MDAMB231 cells/well are plated. A separate plate with these cell lines is also inoculated to determine cell viability before the addition of the compounds (T_0).

Addition of experimental drugs:

Following 24-hour incubation, experimental drugs are added to the 96 well plates. Each plate contains one of the above cell lines and the following in triplicate: five different concentrations (0.01, 0.1, 1, 10 and 100 □M) of four different compounds, appropriate dilutions of a cytotoxic standard and control (untreated) wells. Compounds are dissolved in dimethylsulfoxide (DMSO) to make 20 mM stock solutions on the day of drug addition and frozen at –20°C. Serial dilutions of these 20 mM stock solutions are made in complete growth medium such that 100 □L of these drug solutions in medium, of final concentrations equaling 0.01, 0.1, 1, 10 and 100 □M can be added to the cells in triplicate. Standard drugs whose anti-cancer activity has been well documented and which are regularly used are doxorubicin and SAHA.

End-point measurement:

Cells are incubated with compounds for 48 hours, followed by the addition of 10 □L 3-(4,5-Dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium (MTT) solution per well and a subsequent incubation at 37°C, 5% CO_2, 95% air and 100% relative humidity, protected from light. After 4 hours, well contents are aspirated carefully followed by addition of 150 □L DMSO per well. Plates are agitated to ensure solution of the formazan crystals in DMSO and absorbance read at 570 nm.

Calculation of GI_{50}, TGI and LC_{50}:

Percent growth is calculated for each compound's concentration relative to the control and zero measurement wells (T_0; viability right before compound addition).

If a test well's O.D. value is greater than the T_0 measurement for that cell line

% Growth = (test - zero) / (control – zero) X 100

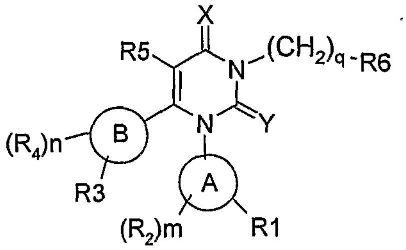
If a test well's O.D. value is lower than the T_0 measurement for that cell line, then

% Growth = (test - zero) / zero X 100

Plotting % growth versus experimental drug concentration, GI_{50} is the concentration required to decrease % growth by 50%; TGI is the concentration required to decrease % growth by 100% and LC_{50} is the concentration required to decrease % growth by 150%.

We claim:

1. Novel compounds of the formula (I),



(I)

their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their solvates, their pharmaceutically acceptable salts and their pharmaceutically acceptable compositions, X and Y may be same or different and independently represent oxygen, sulfur or NR, wherein R represents hydrogen, hydroxy, acyl, alkyl, alkoxy, aryl, amino, hydroxylamino, alkylamino, arylamino, acylamino, and alkoxyamino group.

Suitable ring systems represented by A and B are selected from aryl and heteroaryl rings such as phenyl, naphthyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, piperidinyl, piperazinyl, pyridyl, thienyl, furyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyrimidinyl, benzopyranyl, benzofuranyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, benzopyrolyl, benzoxadiazolyl, benzothiadiazolyl, quinolinyl, isoquinolinyl, benzothienyl, benzofuranyl, indolyl and the like, which may be optionally substituted.

Suitable groups represented by R^1 and R^3 are selected from substituted and unsubstituted groups represented by hydrogen, alkyl (which may be substituted or unsubstituted and are selected from linear or branched $(C_1\text{-}C_6)$alkyl groups, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, n-pentyl, isopentyl, hexyl and the like), SR^7 or $S(O)_pR^8$.

Suitable groups represented by R^2 and R^4 which may be substituted or unsubstituted are selected from hydrogen, halogen atom such as fluorine, chlorine, bromine, iodine; hydroxyl, nitro, cyano, azido, nitroso, amino, formyl, linear or branched $(C_1\text{-}C_6)$alkyl group, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, n-pentyl, isopentyl, hexyl and the like; haloalkyl such as chloromethane, chloroethane, trifluoromethane, trifluoroethane, dichloromethane, dichloroethane and the like; acyl group such as -C(=O)CH_3, -C(=O)C_2H_5, -C(=O)C_3H_7, -C(=O)C_6H_{13}, -C(=S)CH_3, -C(=S)C_2H_5, -C(=S)C_3H_7, -C(=S)C_6H_{13}, benzoyl; linear or branched (C_1-C_6) alkoxy group, such as methoxy, ethoxy, n-propoxy, isopropoxy and the like; monoalkylamino group such as $NHCH_3$, NHC_2H_5, NHC_3H_7, NHC_6H_{13}, and the like; dialkylamino group such as $N(CH_3)_2$, $NCH_3(C_2H_5)$, $N(C_2H_5)_2$ and the like; acylamino group such as NHC(=O)CH_3, NHC(=O)C_2H_5, NHC(=O)C_3H_7, NHC(=O)C_6H_{13}, and the like; alkoxycarbonyl group such as methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, isopropoxycarbonyl and the like; alkylsulfonyl group such as methylsulfonyl, ethylsulfonyl, n-propylsulfonyl, iso-propylsulfonyl and the like; sulfamoyl, alkylsulfinyl group such as methylsulfinyl, ethylsulfinyl, n-propylsulfinyl, iso-propylsulfinyl and the like; alkylthio group such as methylthio, ethylthio, n-propylthio, iso-propylthio and the like; sulfamoyl, alkoxyalkyl group such as methoxymethyl, ethoxymethyl, methoxyethyl, ethoxyethyl and the like; carboxylic acid or its derivatives such as esters, amides and acid halides.

Suitable groups represented by R^5 are selected from substituted and unsubstituted groups represented by hydrogen, halogen atom such as chlorine, fluorine, bromine or iodine; hydroxyl, or COR^9.

R^6 is selected from substituted and unsubstituted groups represented by hydroxy, cyano, halogen atom such as chlorine, fluorine, bromine or iodine; amino, alkyl, alkoxy, alkenyl (such as ethylene and the like), alkynyl (such as acetylene and the like), aryl (such as phenyl, napthyl and the like which may be substituted by one or more groups selected from nitro, cyano, carboximidamide, alkoxy groups such as methoxy, ethoxy and the like, halogens such as fluorine, chlorine, iodine, bromine, haloalkyl groups such as –CHF_2, -CH_2F, -CF_3 and the like, monoalkylamino group such as -$NHCH_3$, -NHC_2H_5, -NHC_3H_7, -NHC_6H_{13}, and the like; dialkylamino group such as -$N(CH_3)_2$, -$NCH_3(C_2H_5)$, -$N(C_2H_5)_2$ and the like; acylamino group such as -NHC(=O)CH_3, -NHC(=O)C_2H_5, -NHC(=O)C_3H_7, -NHC(=O)C_6H_{13}, and the like; arylamino such as phenyl amino, naphthyl amino and the like; heterocyclyl groups such as pyrrolidinyl, morpholinyl, thiomorpholinyl, piperidinyl, piperazinyl, tetrazolyl, oxiranyl, benzodioxinyl, dioxalanyl, oxazolidinyl, 1,2,4-oxadiazolyl, 1,3 indanedionyl and the like which may be further substituted, heteroaryl groups such as pyridyl, thienyl, furyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyrimidinyl benzopyranyl, benzofuranyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, benzopyrrolyl, benzoxadiazolyl, benzothiadiazolyl, quinolinyl, isoquinolinyl, benzothienyl, benzofuranyl, indolyl and the like which may be further substituted; or is selected from the formula $-COR^{10}$, $-(C-OR^{18})R^{19}$, $-(C-OR^{18})(CH_2)_qR^{19}$, $-Z-(CH_2)_r-R^{12}$; $-CO(-NR^{13})OR^{14}$, $-C(=NR^{15})R^{16}$, $-C(=NR^{15})NHR^{17}$; wherein suitable groups represented by R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19} are selected from substituted or unsubstituted groups, independently selected from hydrogen, hydroxy, halogen, amino, monoalkylamino, dialkylamino, alkoxyalkylamino, arylamino, heteroarylamino such as thienylamino, pyridylamino, pyrimidyl amino group; cycloalkylamino group such as cyclopropylamino, cyclopentylamino, cyclohexylamino and the like; azido, alkanol, alkyl, alkoxy group such as methoxy, ethoxy, propoxy, butyloxy and the like; aryloxy group such as phenyloxy, napthyloxy and the like; acyloxy group such as $-OC(=O)CH_3$, $-OC(=O)C_2H_5$, $-OC(=O)C_3H_7$ and the like; acyl groups such as $C(=O)CH_3$, $-C(=O)C_2H_5$, $-C(=O)C_3H_7$, $-C(=O)C_6H_{13}$, $-C(=S)CH_3$, $-C(=S)C_2H_5$, $-C(=S)C_3H_7$, $-C(=S)C_6H_{13}$, benzoyl; aryl group such phenyl, napthyl and the like; heteroaryl group such as pyridyl, thienyl, furyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyrimidinyl benzopyranyl, benzofuranyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, benzopyrrolyl, benzoxadiazolyl, benzothiadiazolyl, quinolinyl, isoquinolinyl, benzothienyl, benzofuranyl, indolyl and the like; heterocyclyl groups such as pyrrolidinyl, morpholinyl, thiomorpholinyl, piperidinyl, piperazinyl and the like which may be optionally substituted by one or more groups such as formyl, alkyl, aryl, aralkyl, heteroaryl, heterocyclyl and the like; wherein Z is selected from O, NR^{11}, S; when R^{12} is alkyl, then Z is not oxygen.

Suitable groups represented by R^9 which may be substituted or unsubstituted are selected from hydroxy, amino, halogen, linear or branched (C_1-C_6) alkoxy group, such as methoxy, ethoxy, n-propoxy, isopropoxy and the like; monoalkylamino group such as $NHCH_3$, NHC_2H_5, NHC_3H_7, NHC_6H_{13}, and the like, which may be substituted; dialkylamino group such as $N(CH_3)_2$, $NCH_3(C_2H_5)$, $N(C_2H_5)_2$ and the like; aryloxy group such as phenoxy, napthoxy and the like; arylamino such as phenyl amino, naphthyl amino and the like.

Suitable groups represented by R^7 which may be substituted or unsubstituted are selected from linear or branched (C_1-C_6)alkyl groups, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, n-pentyl, isopentyl, hexyl and the like; aryl groups such as phenyl or naphthyl and the like, or the acetoxy methyl group.

Suitable groups represented by R^8 which may be substituted or unsubstituted are selected from hydroxy, halogen, acyloxy, hydrazine, amino, linear or branched (C_1-C_6)alkyl group, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, n-pentyl, isopentyl, hexyl and the like; aryl group such as phenyl or naphthyl.

Suitable groups represented by R which may be substituted or unsubstituted are selected from hydrogen, hydroxy, amino, hydroxylamino, linear or branched (C_1-C_6)alkyl group, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, n-pentyl, isopentyl, hexyl and the like; linear or branched (C_1-C_6) alkoxy group, such as methoxy, ethoxy, n-propoxy, isopropoxy and the like; aryl group such as phenyl, naphthyl and the like; acyl group such as $-C(=O)CH_3$, $-C(=O)C_2H_5$, $-C(=O)C_3H_7$, $-C(=O)C_6H_{13}$, $-C(=S)CH_3$, $-C(=S)C_2H_5$, $-C(=S)C_3H_7$, $-C(=S)C_6H_{13}$, benzoyl; aryl group such as phenyl or naphthyl; alkylamino group such as $NHCH_3$, NHC_2H_5, NHC_3H_7, NHC_6H_{13}, $N(CH_3)_2$, $NCH_3(C_2H_5)$, $N(C_2H_5)_2$ and the like; acylamino group such as $NHC(=O)CH_3$, $NHC(=O)C_2H_5$, $NHC(=O)C_3H_7$, $NHC(=O)C_6H_{13}$, and the like; arylamino such as phenyl amino, naphthyl amino and the like; alkoxyamino such as methoxyamino, ethoxyamino, propoxyamino and the like.

m and n are integers, which may be same or different and are independently represented by 0-2. p is an integer ranging from 1-2. q and r are integers ranging from 1-10.

When the aryl and heteroaryl, heterocyclyl groups representing A, B and R^6 are substituted by one or more substituents which may be same or different, the substituents may be selected from halogens (fluorine, chlorine, bromine, iodine), hydroxy, nitro, cyano, carboximidamide, azido, nitroso, amino, amide, hydrazine, formyl, alkyl, haloalkyl (such as haloalkoxy, cycloalkyl, aryl (may be further substituted), alkoxy (such as methoxy, ethoxy and the like), aryloxy, acyl, acyloxy, acyloxyacyl, methylene dioxy, heterocyclyl, heteroaryl (may be further substituted), monoalkylamino, dialkylamino, acylamino, alkoxycarbonyl, aryloxycarbonyl, alkylsulfonyl, arylsulfonyl, alkylsulfinyl, arylsulfinyl, alkylthio, arylthio, sulfamoyl, alkoxyalkyl groups and carboxylic acids or its derivatives and these substituents are as defined above.

Furthermore whenever the groups A, B and R^6 represent substituted (-mono, -di, -tri, -tetra) or unsubstituted 5 to 10 membered ring systems, the rings may be monocyclic or bicyclic, saturated or partially saturated or aromatic containing 1 to 4 hetero atoms selected from O, S, N and the like.

2. Novel compounds as claimed in the claim 1, derivatives, analogs, stereoisomers, polymorphs, hydrates, solvates, pharmaceutically acceptable salts, and compositions thereof.

3. Novel compounds as mentioned below.

1 methyl [4-(4-methylphenyl)-3-[4-(methylthio)phenyl]-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl]acetate;

2 [4-(4-methylphenyl)-3-[4-(methylthio)phenyl]-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl]acetic acid;

3 [4-(4-methylphenyl)-3-[4-(methylthio)phenyl]-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl]acetonitrile;

4 6-(4-methylphenyl)-1-[4-(methylthio)phenyl]-3-(2-oxopropyl) pyrimidine-2,4(1*H*,3*H*)-dione;

5 3-[(2*E*)-2-(hydroxyimino)propyl]-6-(4-methylphenyl)-1-[4-(methylthio)phenyl]pyrimidine-2,4(1*H*,3*H*)-dione;

6 3-(3-hydroxypropyl)-6-(4-methylphenyl)-1-[4-(methylthio) phenyl] pyrimidine-2,4(1*H*,3*H*)-dione;

7 3-[3-(dimethylamino)propyl]-6-(4-methylphenyl)-1-[4-(methylthio) phenyl]pyrimidine-2,4(1*H*,3*H*)-dione;

8 1-[4-(methylthio)phenyl]-6-phenyl-3-(1*H*-tetrazol-5-ylmethyl) pyrimidine-2,4(1*H*,3*H*)-dione;

9 6-(4-methylphenyl)-1-[4-(methylthio)phenyl]-3-(1*H*-tetrazol-5-ylmethyl) pyrimidine-2,4(1*H*,3*H*)-dione;

10 2-[4-(4-methylphenyl)-3-[4-(methylthio)phenyl]-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl]acetamide;

11 3-ethyl-6-(4-methylphenyl)-1-[4-(methylthio)phenyl]pyrimidine-2,4(1*H*,3*H*)-dione;

12 6-(4-methylphenyl)-1-[4-(methylthio)phenyl]-3-(4-nitrobenzyl)pyrimidine-2,4(1*H*,3*H*)-dione;

13 3-(4-fluorobenzyl)-6-(4-methylphenyl)-1-[4-(methylthio)phenyl]pyrimidine-2,4(1*H*,3*H*)-dione ;

14 4-{[4-(4-methylphenyl)-3-[4-(methylthio)phenyl]-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl]methyl}benzonitrile;

15 6-(4-methylphenyl)-1-[4-(methylthio)phenyl]-3-(oxiran-2-ylmethyl) pyrimidine-2,4(1*H*,3*H*)-dione;

16 3-(4-methoxybenzyl)-6-(4-methylphenyl)-1-[4-(methylthio) phenyl] pyrimidine-2,4(1*H*,3*H*)-dione;

17 3-(3-methoxybenzyl)-6-(4-methylphenyl)-1-[4-(methylthio) phenyl] pyrimidine-2,4(1*H*,3*H*)-dione;

18 3-(2,3-dihydro-1,4-benzodioxin-2-ylmethyl)-6-(4-methylphenyl)-1-[4-(methylthio)phenyl]pyrimidine-2,4(1*H*,3*H*)-dione;

19 3-(1,3-dioxolan-2-ylmethyl)-6-(4-methylphenyl)-1-[4-(methylthio) phenyl]pyrimidine-2,4(1*H*,3*H*)-dione;

20 6-(4-methylphenyl)-1-[4-(methylthio)phenyl]-3-[(2-oxo-1,3-oxazolidin-5-yl)methyl]pyrimidine-2,4(1*H*,3*H*)-dione;

21 6-(4-methylphenyl)-1-[4-(methylthio)phenyl]-3-[(2-oxo-1,3-dioxolan-4-yl)methyl]pyrimidine-2,4(1*H*,3*H*)-dione;

22 6-(4-methylphenyl)-1-[4-(methylthio)phenyl]-3-[4-(trifluoromethyl) benzyl]pyrimidine-2,4(1*H*,3*H*)-dione;

23 6-(4-methylphenyl)-1-[4-(methylthio)phenyl]-3-(2-piperidin-1-ylethyl) pyrimidine-2,4(1*H*,3*H*)-dione;

24 3-but-3-enyl-6-(4-methylphenyl)-1-[4-(methylthio)phenyl]pyrimidine-2,4(1*H*,3*H*)-dione;

25 6-(4-methylphenyl)-1-[4-(methylthio)phenyl]-3-prop-2-ynylpyrimidine - 2,4(1*H*,3*H*)-dione;

26 6-(4-methylphenyl)-1-[4-(methylthio)phenyl]-3-(pyridin-2-ylmethyl) pyrimidine-2,4(1*H*,3*H*)-dione;

27 2-[4-(3-(4-methylphenyl)-4-(4-methylthiophenyl)-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl)butyl]-1*H*-isoindole-1,3(2*H*)-dione;

28 6-(4-methylphenyl)-1-[4-(methylthio)phenyl]-3-(quinolin-2-ylmethyl) pyrimidine-2,4(1*H*,3*H*)-dione;

29 6-(4-methylphenyl)-3-[(methylthio)methyl]-1-[4-(methylthio) phenyl] pyrimidine-2,4(1*H*,3*H*)-dione ;

30 6-(4-methylphenyl)-1-[4-(methylthio)phenyl]-3-(1-naphthylmethyl) pyrimidine-2,4(1*H*,3*H*)-dione;

31 3-[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]-1-(4-methylthio phenyl)-6-(4-methylphenyl)pyrimidine-2,4(1*H*,3*H*)-dione

32 3-(2-ethoxyethyl)-6-(4-methylphenyl)-1-[4-(methylthio) phenyl] pyrimidine-2,4(1*H*,3*H*)-dione;

33 3-(2-hydroxyethyl)-1-[4-(methylthio)phenyl]-6-phenylpyrimidine-2,4(1*H*,3*H*)-dione;

34 3-allyl-1-[4-(methylthio)phenyl]-6-phenylpyrimidine-2,4(1*H*,3*H*)-dione

35 1-[4-(methylthio)phenyl-6-(4-methylphenyl)]-3-(2-morpholin-4-ylethyl) pyrimidine-2,4(1*H*,3*H*)-dione;

36 5-[4-(4-methylphenyl)-3-[4-(methylthio)phenyl]-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl]pentanenitrile;

37 3-allyl-6-(4-methylphenyl)-1-[4-(methylthio)phenyl]pyrimidine-2,4(1*H*,3*H*)-dione;

38 [4-[4-(methylthio)phenyl]-2,6-dioxo-3-(4-tert.butyl phenyl)-3,6-dihydropyrimidin-1(2*H*)-yl]acetonitrile;

39 [3-(3,4-dimethylphenyl)-4-[4-(methylthio)phenyl]-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl]acetonitrile;

40 [3-[3-fluoro-4-(methylthio)phenyl]-4-(4-methylphenyl)-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl]acetonitrile;

41 [4-(4-fluorophenyl)-3-[4-(methylthio)phenyl]-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl]acetonitrile;

42 ({4-[3-(cyanomethyl)-6-(4-methylphenyl)-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl]phenyl}thio)methyl acetate;

43 [4-(4-methylphenyl)-3-[4-(methylsulfinyl)phenyl]-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl]acetonitrile;

44 [4-(4-methylphenyl)-3-[4-(methylsulfonyl)phenyl]-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl]acetonitrile;

45 [3-(4-methoxyphenyl)-4-[4-(methylthio)phenyl]-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl]acetonitrile;

46 3-[(2*E*)-2-(hydroxyimino)propyl]-6-(4-methylphenyl)-1-[4-(methylthio) phenyl]pyrimidine-2,4(1*H*,3*H*)-dione

47 6-(4-methylphenyl)-3-[(2*E*)-2-(methylhydrazono)propyl]-1-[4-(methylthio) phenyl]pyrimidine-2,4(1*H*,3*H*)-dione;

48 3-[2-hydroxy-3-(2,4-dimethoxybenzylamino)propyl]-6-(4-methylphenyl)-1-[4-(methylthio)phenyl]pyrimidine-2,4(1*H*,3*H*)-dione;

49 3-(2-hydroxy-3-morpholin-4-ylpropyl)-1-(4-methylthiophenyl)-6-(4-methylphenyl)pyrimidine-2,4(1*H*,3*H*)-dione ;

50 3-[3-(dimethylamino)-2-hydroxypropyl]-6-(4-methylphenyl)-1-[4-(methylthio)phenyl]pyrimidine-2,4(1*H*,3*H*)-dione;

51 4-[3-(3-(4-methylthiophenyl)-4-(4-methylphenyl)-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl)-2-hydroxypropyl]piperazine-1-carbaldehyde;

52 3-[2-hydroxy-3-(benzylamino)propyl]-6-(methylphenyl)-1-[4-(methylthio)phenyl]pyrimidine-2,4(1*H*,3*H*)-dione;

53 3-[2-hydroxy-3-(4-methylpiperazin-1-yl)propyl]-1-(4-methylthiophenyl)-6-(4-methylphenyl)pyrimidine-2,4(1*H*,3*H*)-dione;

54 3-[2-hydroxy-3-(4-(pyridin-2-yl)piperazin-1-yl)propyl]-1-(4-methylthiophenyl)-6-(4-methylphenyl)pyrimidine-2,4(1*H*,3*H*)-dione;

55 3-[2-hydroxy-3-(4-methylpiperazin-1-yl)propyl]-1-(4-methyl thiophenyl)-6-(4-methylphenyl)pyrimidine-2,4(1*H*,3*H*)-dione;

56 3-[2-hydroxy-3-(4--(1,2-benzisothiazol-3-yl)piperazin-1-yl]propyl]-1(-4-methylthiophenyl)-6-(4-methylphenyl)pyrimidine-2,4(1*H*,3*H*)-dione;

57 4-[3-(3-(4-methylthiophenyl)-4-(4-methylphenyl)-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl)-2-hydroxypropyl]-*N*-(4-chloro-3-trifluoromethylphenyl)lpiperazine-1-carboxamide;

58 3-[2-hydroxy-3-(4-(4-nitrophenyl)piperazin-1-yl)propyl]-1-(4-methylthiophenyl),6-(4-methylphenyl) pyrimidine-2,4(1*H*,3*H*)-dione;

59. 3-[2-hydroxy-3-(4-pyrimidin-2-ylpiperazin-1-yl)propyl]-1-(4-methylthiophenyl)-6-(4-methylphenyl) pyrimidine-2,4(1*H*,3*H*)-dione;

60 3-(3-chloro-2-hydroxypropyl)-6-(4-methylphenyl)-1-[4-(methylthio) phenyl]pyrimidine-2,4(1*H*,3*H*)-dione;

61 3-[2-hydroxy-3-(2,4-dimethoxybenzylamino)propyl]-6-(4-methylphenyl)-1-[4-(methylthio)phenyl]pyrimidine-2,4(1*H*,3*H*)-dione;

62 3-[3-(4-trifluoromethylbenzylamino)-2-hydroxypropyl]-6-(4-methylphenyl)-1-(4-methylthiophenyl)pyrimidine-2,4(1*H*,3*H*)-dione;

63 3-[3-(4-methoxybenzylamino)-2-hydroxypropyl]-6-(4-methylphenyl)-1-(4-methyl thiophenyl)-pyrimidine-2,4(3*H*)-dione;

64 3-(2,3-dihydroxypropyl)-6-(4-methylphenyl)-1-[4-(methylthio) phenyl]pyrimidine-2,4(1*H*,3*H*)-dione;

65 *N*-{(1*Z*)-*N*-hydroxy-2-[4-(4-methylphenyl)-3-[4-(methylthio)phenyl]-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl]ethanimidoyl}-4-(trifluoromethyl)benzamide;

66 3,5-dichloro-*N*-{(1*Z*)-*N*-hydroxy-2-[4-(4-methylphenyl)-3-(4-methylthiophenyl)-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl]ethanimidoyl}benzamide;

67 3-{[5-(3,5-dichlorophenyl)-1,2,4-oxadiazol-3-yl]methyl}-6-(4-methylphenyl)-1-(4-methylthiophenyl)-pyrimidine-2,4(3*H*)-dione;

68 6-(4-methylphenyl)-1-[4-(methylthio)phenyl]-3-{[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]methyl}pyrimidine-2,4(1*H*,3*H*)-dione;

69 6-(4-methylphenyl)-1-(4-methylthiophenyl)-3-[(5-(3,4-dimethoxyphenyl)phenyl-1,2,4-oxadiazol-3-yl)methyl]pyrimidine-2,4(3*H*)-dione;

70 *N*-hydroxy-2-[4-(4-methylphenyl)-3-[4-(methylthio)phenyl]-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl]ethanimidamide;

71 *N*-hydroxy-4-{[4-(4-methylphenyl)-3-[4-(methylthio)phenyl]-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl]methyl} benzenecarboximidamide and

72 2-(3-(4-methylthiophenyl)-4-(4-methylphenyl)-2,6-dioxo-3,6-

dihydropyrimidin-1(2*H*)-yl)ethyl 2,5-dichlorophenylcarbamate.

73 [3-[4-(methylthio)phenyl]-2,6-dioxo-4-phenyl-3,6-dihydropyrimidin-1(2*H*)-yl]acetonitrile.

4. A pharmaceutical composition, which comprises a compound of formula (I) as defined in the claim 1 and a pharmaceutically acceptable carrier, diluent, excipient or solvate.

5. A pharmaceutical composition as claimed in the claim 1, in the form of a tablet, capsule, powder, syrup, solution or suspension.

6. A pharmaceutical composition as claimed in claim 4, wherein the amount of the compound of claim 1 in the composition is less than 60%by weight.

7. A method of prophylaxis or treatment of rheumatoid arthritis; osteoporosis; multiple myeloma; uveititis; acute and chronic myelogenous leukemia; ischemic heart disease; atherosclerosis; cancer; ischemic-induced cell damage; pancreatic beta 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; muscle degeneration; cachexia; asthma; COPD; psychotic diseases; nausea and vomiting; treatment of alcohol dependency; type I and type II diabetes; bone resorption diseases; ischemia reperfusion injury; brain trauma; multiple sclerosis; cerebral malaria; sepsis; septic shock; toxic shock syndrome; fever, and myalgias due to infection, HW-1, HIV-2, HIV-3, cytomegalovirus(CMV), influenza, adenovirus, the herpes viruses(including HSV-1, HSV-2), and herpes zoster infection in a mammal comprising administering an effective amount of, a compound: as claimed in the claim 1or claim 2, or a composition of the claim 3, to the mammal in need thereof.

8. A method of lowering plasma concentrations of either or both TNF-α and IL-1 comprising administering an effective amount of, a compound: as claimed in the claim 1 or claim 2, or a composition of the claim 3, to the mammal in need thereof.

9. A method of lowering plasma concentrations of either or both IL-6 and IL-8 comprising administering an effective amount of, a compound: as claimed in the claim 1 or claim 2, or a composition of the claim 3, to the mammal in need thereof.

10. A method of lowering plasma concentrations of anyone or a combination or all of TNF-α and IL (1, 1β, 2, 4,5, 6, 8, 10, 12, 13, 15, 18, 23) comprising administering an effective amount of a compound, a compound: as claimed in the claim 1 or claim 2, or a composition of the claim 3, to the mammal in need thereof.

11. A method of prophylaxis or treatment of a pain disorder in a mammal comprising administering an effective amount of, a compound: as claimed in the claim 1 or claim 2, or a composition of the claim 3, to the mammal in need thereof.

12. A method of decreasing prostaglandin production in a mammal comprising administering an effective amount of, a compound: as claimed in the claim 1 or claim 2, or a composition of the claim 3, to the mammal in need thereof.