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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
9 November 2006 (09.11.2006)

PCT

(10) International Publication Number
WO 2006/117657 A1

(51) International Patent Classification:
C07D 401/04 (2006.01) *A61K 31/4196* (2006.01)
C07D 249/12 (2006.01) *A61P 29/00* (2006.01)

(21) International Application Number:
PCT/IB2006/001143

(22) International Filing Date: 3 May 2006 (03.05.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
1098/DEL/2005 3 May 2005 (03.05.2005) IN

(71) Applicant *(for all designated States except US)*: **RANBAXY LABORATORIES LIMITED** [IN/IN]; Plot No.90, Sector - 32, 122 001 Gurgaon, Haryana (IN).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **PALLE, Venkata, P.** [IN/IN]; G901, Sylvan Heights, Sanewadi, Aundh,, Pune, 411007 Maharashtra (IN). **VERMA, Ashwani, Kumar** [IN/IN]; 24 , Charak Sadan (AIIMS Doctor's Society), E-Block, Vikas Puri, 110018 Delhi (IN). **MALHOTRA, Sanjay** [IN/IN]; 422, Plot No.8, Sector- 10, Dwarka, Phase- I, 110075 New Delhi (IN). **RAY, Abhijit** [IN/IN]; Sector C-I, Flat No . 1408 , Vasant Kun, Flat No.1408, Vasant Kunj, 110070 New Delhi (IN). **SHARMA, Geeta** [IN/IN]; A-654, Sarita Vihar, 110044 New Delhi (IN).

(74) Common Representative: **RANBAXY LABORATORIES LIMITED**; c/o DESHMUKH, Jay, R., 600 College Road East, Suite 2100, Princeton, NJ 08540 (US).

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

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

Published:
— *with international search report*

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

WO 2006/117657 A1

(54) Title: TRIAZOLONE DERIVATIVES AS ANTI-INFLAMMATORY AGENTS

(57) Abstract: The present invention relates to novel triazolone derivatives as anti-inflammatory agents. The compounds described herein can be useful for inhibition and prevention of inflammation and associated pathologies including inflammatory and autoimmune diseases such as sepsis, rheumatoid arthritis, inflammatory bowel disease, type-1 diabetes, asthma, chronic obstructive pulmonary disorder, organ transplant rejection and psoriasis. This invention also relates to pharmacological compositions containing compounds described herein and the methods of treating sepsis, rheumatoid arthritis, inflammatory bowel disease, type-1 diabetes, asthma, chronic obstructive pulmonary disorder, organ transplant rejection and psoriasis, and other inflammatory and/or autoimmune disorders, using the compounds.

TRIAZOLONE DERIVATIVES AS ANTI-INFLAMMATORY AGENTS

Field of the Invention

The present invention relates to novel triazolone derivatives as anti-inflammatory agents. The compounds described herein can be useful for inhibition and prevention of inflammation and associated pathologies including inflammatory and autoimmune diseases such as sepsis, rheumatoid arthritis, inflammatory bowel disease, type-1 diabetes, asthma, chronic obstructive pulmonary disorder, organ transplant rejection and psoriasis. This invention also relates to pharmacological compositions containing compounds described herein and the methods of treating sepsis, rheumatoid arthritis, inflammatory bowel disease, type-1 diabetes, asthma, chronic obstructive pulmonary disorder, organ transplant rejection and psoriasis, and other inflammatory and/or autoimmune disorders, using the compounds.

Background of the Invention

During the last decade, numerous studies have focused on the roles played by cytokines, a unique class of ontracellular regulatory proteins, in the pathogenesis of many diseases. Cytokines play a crucial role in initiating, maintaining, and regulating immunological and inflammatory processes. Advances in our understanding of their role in immune and inflammatory disorders have led to the development of cytokine-based therapies-that is, therapies that aim to inhibit or restore the activity of specific cytokines. Today, drugs that block inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), are among the most successful agents being introduced to the market.

Elevated levels of proinflammatory cytokines viz TNF-α and IL-1β are associated with the pathogenesis of many immune mediated inflammatory disorders like sepsis, rheumatoid arthritis, inflammatory bowel disease, type-1 diabetes, asthma, chronic obstructive pulmonary disease, organ transplant rejection and psoriasis. Inflammation is regulated by a large number of pro- and anti-inflammatory mediators, which include cytokines, eicosanoids, nitric oxide, and reactive oxygen species. The central role of these inflammatory mediators in the pathogenesis of both chronic and acute inflammatory diseases is well documented. Until a few years ago, inflammatory disorders were treated primarily with relatively non-selective anti-inflammatory agents, such as corticosteroids

and various non-steroidal anti-inflammatory drugs. In recent years, novel therapies have been developed that specifically interfere with the action of selected pro-inflammatory mediators, such as TNF-α and PGE-2. These specific anti-inflammatory therapies have already proven to be very successful in the treatment of rheumatoid arthritis, inflammatory bowel disease, and several other inflammatory diseases.

The development of protein-based therapies that inhibit the activities of tumor necrosis factor-alpha (TNF-α), including etanercept (Enbrel; Amgen/Wyeth), infliximab (Remicade; Centocor), and adalimumab (Humira; Abbott), has been an important advancement in the treatment of autoimmune diseases such as rheumatoid arthritis. The approval of Kineret - an interleukin-1 (IL-1beta) receptor antagonist - further indicates the clinical activity of protein-based therapies that regulate cytokine activities. However, current injectable therapies have associated limitations and risks, including the potential for increased malignancies and infections and increased congestive heart failure. Studies in rodent models have provided evidence that targeting specific pathways involved in TNF-α activities are effective approaches to interrupting the pro-inflammatory process. Oral small molecules that regulate these pathways represent an advancement in the treatment of chronic inflammatory diseases when used either as a monotherapy or in combination with the current injectables.

Numerous studies have now clearly established that the pathogenesis of inflammatory diseases requires cytokine-mediated communication between endothelial cells, infiltrating leukocytes, resident macrophages, mast cells, epithelial cells and osteoclasts. The p38 mitogen activated protein kinase (p38 MAPK) regulates cytokine levels and therefore plays a central role in both the cellular infiltration and activation responses associated with inflammatory diseases.

The p38 MAPK is a member of a large family of MAPK's, the signalling pathways of which also include the extracellular regulated kinases (ERK) and the c-jun N terminal kinases (JNK). MAP kinases are Serine Threonine Kinases that transduce environmental stimuli to the nucleus. They are activated by upstream MAPK kinases by phosphorylation on both tyrosine and threonine residues. The MAPK pathways are involved in alterations in cell physiology resulting from a variety of stimuli and control cell death, cell cycle machinery, gene transcription and protein translation. p38α MAPK was first identified as

a tyrosine phosphorylated protein in LPS (Lipopolysaccharide) stimulated macrophages. The human p38α MAPK was identified as the target of pyridinyl imidazole compounds (cytokine suppressive anti-inflammatory drugs) that were known to block TNF-α and IL-1 release from LPS stimulated monocytes. After the cloning of first p38 MAPK (p38α), additional members of the p38 MAPK family were cloned by homology, including the p38α, p38β and p38γ.

The p38 pathway controls the activity of multiple transcription factors and the expression of many genes. There is ample evidence implicating a pivotal role for p38 in inflammatory processes mediated by IL-1 and TNF-α. p38 inhibitors have been shown to effectively block both TNF-α and IL-1 biosynthesis by LPS stimulated human monocytes. In addition, p38 MAPK also plays a role in the production of IL-4, IL-6, IL-8 and IL-12. p38 MAPK is also critical for cell response to certain cytokines. Treatment of human neutrophils with GM-CSF, TNF-α or TGF-α results in p38 activation. GM-CSF and TNF-α are potent enhancers of neutrophil respiratory activity suggesting a role for p38 MAPK in respiratory burst.

p38 has also been implicated in the induction of cyclooxygenase-2 (COX-2) in LPS induced monocytes. COX-2 enzyme is the key enzyme in the production of prostaglandins from arachidonic acid. Inhibitors of p38 MAP kinase are also expected to inhibit COX-2 expression. Accordingly inhibitors of cytokine synthesis would be expected to be effective in disorders currently treated with NSAID's. These disorders include acute and chronic pain as well as symptoms of inflammation and cardiovascular disease.

Compounds which modulate release of one or more of the aforementioned inflammatory cytokines can be useful in treating diseases associated with the release of these cytokines.

U.S. Patent No. 5,681,841 discloses cyclic urea derivatives, pharmaceutical compositions containing these compounds and process for preparing them. U.S. Patent No. 6,528,957 discloses N-aryl-1,2,4-triazolin-5-one derivatives. WO 94/11357 discloses process for the preparation of triazolone compounds. WO 00/59506 discloses heterocyclic containing biphenyl derivatives said to be useful for the treatment of diabetes and related disorders and method of preparing them. WO 97/03067 discloses piperazine derivatives as

therapeutic agents. Canadian Patent No. 2,197,789 discloses cyclic urea derivatives, pharmaceutical compositions containing these compounds and process for preparing them.

Summary of the Invention

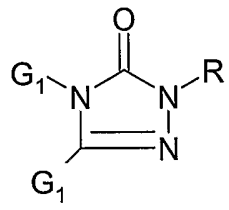
The present invention provides triazolone derivatives, which can be used for the inhibition and prevention of inflammation and associated pathologies such as sepsis, rheumatoid arthritis, inflammatory bowel disease, type-1 diabetes, asthma, chronic obstructive pulmonary disorder, organ transplant rejection and psoriasis.

Pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers or N-oxides of these compounds having the same type of activity are also provided.

Pharmaceutical compositions containing the compounds, and which may also contain pharmaceutically acceptable carriers or diluents, which may be used for the treatment of inflammatory and autoimmune diseases such as sepsis, rheumatoid arthritis, inflammatory bowel disease, type-1 diabetes, asthma, chronic obstructive pulmonary disorder, organ transplant rejection and psoriasis.

Other aspects will be set forth in accompanying description which follows and in part will be apparent from the description or may be learnt by the practice of the invention.

In accordance with one aspect, there is provided a compound having the structure of Formula I



Formula I

and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers diastereomers, N-oxides, polymorphs, metabolites;

wherein

each G_1 can be selected from aryl or heteroaryl;

R can be alkyl, cycloalkyl, heteroaryl, heterocyclyl, aryl, cycloalkylalkyl, heterocyclylalkyl, heteroarylalkyl, or $-(CH_2)_gCONR_xR_y$ [wherein R_x and R_y can be independently selected from hydrogen, alkyl, cycloalkyl, aryl, aralkyl, $-SO_nR_1$ (wherein n is 0, 1 or 2), heteroaryl, heterocyclyl, heteroarylalkyl or heterocyclylalkyl (wherein R_1 can be hydrogen, alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, heterocyclylalkyl or heteroarylalkyl)]; and

g is an integer selected from 1-3;

In accordance with second aspect, there is provided a method for the treatment of mammal suffering from inflammation and associated pathologies.

In accordance with third aspect, there is provided a method for the treatment of mammal suffering from inflammatory diseases and associated pathologies including sepsis, rheumatoid arthritis, inflammatory bowel disease, type-1 diabetes, asthma, chronic obstructive pulmonary disorder, organ transplant rejection and psoriasis.

In accordance with fourth aspect, there are provided a pharmaceutical compositions containing the compounds, and which may also contain pharmaceutically acceptable carriers or diluents, which may be used for the treatment of inflammatory and autoimmune diseases such as sepsis, rheumatoid arthritis, inflammatory bowel disease, type-1 diabetes, asthma, chronic obstructive pulmonary disorder, organ transplant rejection and psoriasis.

In accordance with fifth aspect, there is provided a process for the preparation of compounds disclosed herein.

In accordance with sixth aspect, the compounds described herein may be screened as p38 MAP Kinase inhibitors.

The following definitions apply to terms as used herein:

The term "alkyl," unless otherwise specified, refers to a monoradical branched or unbranched saturated hydrocarbon chain having from 1 to 20 carbon atoms. Alkyl groups can be optionally interrupted by atom(s) or group(s) independently selected from oxygen,

sulfur, a phenylene, sulphinyl, sulphonyl group or –NR_a-, wherein R_a can be hydrogen, alkyl, alkenyl, alkynyl cycloalkyl or aryl. This term can be exemplified by groups such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, t-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, n-decyl, tetradecyl, and the like. Alkyl groups may be substituted further (referred herein as "substituted alkyl") with one or more substituents selected from alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkenyl, acyl, acylamino, acyloxy, alkoxycarbonylamino, azido, cyano, halogen, hydroxy, keto, oxo, thiocarbonyl, carboxy, carboxyalkyl, aryl, heterocyclyl, heteroaryl, (heterocyclyl)alkyl, cycloalkoxy, -CH=N-O(C_{1-6}alkyl), -CH=N-NH(C_{1-6}alkyl), -CH=N-NH(C_{1-6}alkyl)-C_{1-6}alkyl, arylthio, thiol, alkylthio, aryloxy, nitro, aminosulfonyl, aminocarbonylamino, -NHC(=O)R_p, -NR_pR_q, -C(=O)NR_pR_q, -NHC(=O)NR_pR_q, -C(=O)heteroaryl, C(=O)heterocyclyl, -O-C(=O)NR_pR_q {wherein R_p and R_q are independently selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, alkoxy, cycloalkenyl, aryl, aralkyl, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl}, nitro, hydroxyamino, alkoxyamino or $S(O)_mR_{66}$ (wherein m is an integer from 0-2 and R_{66} is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aralkyl, aryl, heterocyclyl, heteroaryl, heteroarylalkyl or heterocyclylalkyl). Unless otherwise constrained by the definition, alkyl substituents may be further substituted by 1-3 substituents selected from alkyl, alkenyl, alkynyl, carboxy, -NR_pR_q, -C(=O)NR_pR_q, -OC(=O)NR_pR_q, -NHC(=O)NR_pR_q (wherein R_p and R_q are the same as defined earlier), hydroxy, alkoxy, halogen, CF_3, cyano, and $S(O)_mR_{66}$ (wherein m is an integer from 0-2 and R_{66} are the same as defined earlier); or an alkyl group also may be interrupted by 1-5 atoms of groups independently selected from oxygen, sulfur or -NR_a- {wherein R_a is selected from hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, acyl, aralkyl,-C(=O)OR_p (wherein R_p is the same as defined earlier), $S(O)_mR_{66}$ (wherein m is an integer from 0-2 and R_{66} is as defined earlier), or -C(=O)NR_pR_q (wherein R_p and R_q are as defined earlier)}. Unless otherwise constrained by the definition, all substituents may be substituted further by 1-3 substituents selected from alkyl, carboxy, carboxyalkyl, -NR_pR_q, -C(=O)NR_pR_q, -O-C(=O)NR_pR_q (wherein R_p and R_q are the same as defined earlier) hydroxy, alkoxy, halogen, CF_3, cyano, and $S(O)_mR_{66}$ (wherein m is an integer from 0-2 and R_{66} is same as defined earlier); or an alkyl group as defined above that has both substituents as defined above and is also interrupted by 1-5 atoms or groups as defined above.

The term "alkenyl," unless otherwise specified, refers to a monoradical of a branched or unbranched unsaturated hydrocarbon group having from 2 to 20 carbon atoms with cis, trans, or geminal geometry. It can be optionally interrupted by atom(s) or group(s) independently chosen from oxygen, sulfur, phenylene, sulphinyl, sulphonyl and –NR_a-, wherein R_a can be hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl or aryl. In the event that alkenyl is attached to a heteroatom, the double bond cannot be alpha to the heteroatom. Alkenyl groups may be substituted further (referred to herein as "substituted alkenyl") with one or more substituents selected from alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkenyl, acyl, acylamino, acyloxy, $-NHC(=O)R_p$, $-NR_pR_q$, $-C(=O)NR_pR_q$, $-NHC(=O)NR_pR_q$, $-O-C(=O)NR_pR_q$ (wherein R_p and R_q are the same as defined earlier), alkoxycarbonylamino, azido, cyano, halogen, hydroxy, oxo, keto, carboxyalkyl, thiocarbonyl, carboxy, arylthio, thiol, alkylthio, aryl, aralkyl, aryloxy, heterocyclyl, heteroaryl, heterocyclyl alkyl, heteroaryl alkyl, aminosulfonyl, aminocarbonylamino, alkoxyamino, hydroxyamino, alkoxyamino, nitro, or SO_2R_{66} (wherein R_{66} are is same as defined earlier). Unless otherwise constrained by the definition, alkenyl substituents optionally may be substituted further by 1-3 substituents selected from alkyl, carboxy, hydroxy, alkoxy, halogen, $-CF_3$, cyano, $-NR_pR_q$, $-C(=O)NR_pR_q$, $-O-C(=O)NR_pR_q$ (wherein R_p and R_q are the same as defined earlier) and $-SO_2R_{66}$ (wherein R_{66} is same as defined earlier). Groups, such as ethenyl or vinyl ($CH=CH_2$), 1-propylene or allyl ($-CH_2CH=CH_2$), iso-propylene ($-C(CH_3)=CH_2$), bicyclo[2.2.1]heptene, and the like, exemplify this term.

The term "alkynyl," unless otherwise specified, refers to a monoradical of an unsaturated hydrocarbon, having from 2 to 20 carbon atoms. It can be optionally interrupted by atom(s) or group(s) independently chosen from oxygen, sulfur, phenylene, sulphinyl, sulphonyl and –NR_a-, wherein R_a can be hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl or aryl. In the event that alkynyl is attached to a heteroatom, the triple bond cannot be alpha to the heteroatom. Alkynyl groups may be substituted further (referred to herein as "substituted alkynyl") with one or more substituents selected from alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkenyl, acyl, acylamino, acyloxy, alkoxycarbonylamino, azido, cyano, halogen, hydroxy, keto, oxo, thiocarbonyl, carboxy, carboxyalkyl, arylthio, thiol, alkylthio, aryl, aralkyl, aryloxy, aminosulfonyl, aminocarbonylamino, hydroxyamino, alkoxyamino, nitro, heterocyclyl, heteroaryl,

heterocyclylalkyl, heteroarylalkyl, -NHC(=O)R_p, -NR_pR_q, -NHC(=O)NR_pR_q, -C(=O)NR_pR_q, -O-C(=O)NR_pR_q (wherein R_p and R_q are the same as defined earlier), $S(O)_mR_{66}$ (wherein m is an integer from 0-2 and R_{66} is as defined earlier). Unless otherwise constrained by the definition, alkynyl substituents optionally may be substituted further by 1-3 substituents selected from alkyl, carboxy, carboxyalkyl, hydroxy, alkoxy, halogen, CF_3, -NR_pR_q, -C(=O)NR_pR_q, -NHC(=O)NR_pR_q, -C(=O)NR_pR_q (wherein R_p and R_q are the same as defined earlier), cyano, or $S(O)_mR_{66}$ (wherein m is an integer from 0-2 and R_{66} is same as defined earlier). Groups such as ethynyl, (-C≡CH), propargyl (or propynyl, -CH_2C≡CH), and the like exemplify this term.

The term "cycloalkyl," unless otherwise specified, refers to cyclic alkyl groups of from 3 to 20 carbon atoms having a single cyclic ring or multiple condensed rings, which may optionally contain one or more olefinic bonds, unless otherwise constrained by the definition. Such cycloalkyl groups can include, for example, single ring structures, including cyclopropyl, cyclobutyl, cyclooctyl, cyclopentenyl, and the like, or multiple ring structures, including adamantanyl, tricyclo[3.3.1.1]decane, bicyclo[2.2.2]octane, bicyclo[4.4.0]decane, bicylco[4.3.0]nonane, bicyclo[3.3.0]octane, bicyclo [2.2.1] heptane and the like, or cyclic alkyl groups to which is fused an aryl group, for example, indane, and the like. Spiro and fused ring structures can also be included. Cycloalkyl groups may be substituted further with one or more substituents selected from alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkenyl, acyl, acylamino, acyloxy, alkoxycarbonylamino, azido, cyano, halogen, hydroxy, oxo, thiocarbonyl, carboxy, carboxyalkyl, arylthio, thiol, alkylthio, aryl, aralkyl, aryloxy, aminosulfonyl, aminocarbonylamino, -NR_pR_q, -NHC(=O)NR_pR_q, -NHC(=O)R_p, -C(=O)NR_pR_q, -O-C(=O)NR_pR_q (wherein R_p and R_q are the same as defined earlier), nitro, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl, or $S(O)_mR_{66}$ (wherein m is an integer from 0-2 and R_{66} is same as defined earlier). Unless otherwise constrained by the definition, cycloalkyl substituents optionally may be substituted further by 1-3 substituents selected from alkyl, carboxy, hydroxy, alkoxy, halogen, CF_3, -NR_pR_q, -C(=O)NR_pR_q, -NHC(=O)NR_pR_q, -O-C(=O)NR_pR_q (wherein R_p and R_q are the same as defined earlier), cyano or $S(O)_mR_{66}$ (wherein m is an integer from 0-2 and R_{66} is same as defined earlier).

The term "alkoxy" denotes the group O-alkyl, wherein alkyl is the same as defined above.

The term "aryl" herein refers to aromatic system having 6 to 14 carbon atoms, wherein the ring system can be mono-, bi- or tricyclic and are carbocyclic aromatic groups. For example, aryl groups include, but are not limited to, phenyl, biphenyl, anthryl or naphthyl ring and the like, optionally substituted with 1 to 3 substituents selected from halogen (*e.g.*, F, Cl, Br, I), hydroxy, alkyl, alkenyl, alkynyl, cycloalkyl, alkoxy, acyl, aryloxy, CF_3, cyano, nitro, $COOR_s$ (wherein R_s is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aralkyl, heterocyclylalkyl, heteroarylalkyl), $NHC(=O)R_p$, $-NR_pR_q$, $-C(=O)NR_pR_q$, $-NHC(=O)NR_pR_q$, $-O-C(=O)NR_pR_q$, $S(O)_mR_{66}$ (wherein m is an integer from 0-2 and R_{66} is same as defined earlier), carboxy, optionally substituted heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl, amino carbonyl amino, mercapto, haloalkyl, optionally substituted aryl, optionally substituted heterocyclylalkyl, thioalkyl, $-CONHR_p$, $-OCOR_p$, $-COR_p$, $-NHSO_2R_p$, or $-SO_2NHR_p$ (wherein R_p and R_q are the same as defined earlier). The aryl group optionally may be fused with a cycloalkyl group, wherein the cycloalkyl group may optionally contain heteroatoms selected from O, N or S. Groups such as phenyl, naphthyl, anthryl, biphenyl, and the like exemplify this term.

The term "aralkyl," unless otherwise specified, refers to alkyl-aryl linked through an alkyl portion (wherein alkyl is as defined above) and the alkyl portion contains 1-6 carbon atoms and aryl is as defined below. Examples of aralkyl groups include benzyl, ethylphenyl, propylphenyl, naphthylmethyl and the like.

The term "aralkenyl," unless otherwise specified, refers to alkenyl-aryl linked through alkenyl (wherein alkenyl is as defined above) portion and the alkenyl portion contains 1 to 6 carbon atoms and aryl is as defined below.

The term "aryloxy" denotes the group O-aryl, wherein aryl is as defined above.

The term "carboxy," as defined herein, refers to $-C(=O)OH$.

The term "heteroaryl," unless otherwise specified, refers to an aromatic ring structure containing 5 or 6 ring atoms, or a bicyclic or tricyclic aromatic group having from 8 to 14 ring atoms, with one or more heteroatom(s) independently selected from N, O or S. Heteroaryl groups can be optionally substituted with 1 to 8 substituent(s) (referred herein as "substituted heteroaryl") selected from halogen (*e.g.*, F, Cl, Br, I), hydroxy, alkyl, alkenyl, alkynyl, cycloalkyl, acyl, carboxy, aryl, alkoxy, aralkyl, cyano, nitro,

heterocyclyl, heteroaryl, -NR_pR_q, CH=NOH, –$(CH_2)_wC(=O)R_t$ {wherein w is an integer from 0-4 and R_t is hydrogen, hydroxy, OR_p, NR_pR_q, -$NHOR_z$ or –NHOH}, -$C(=O)NR_pR_q$ and–$NHC(=O)NR_pR_q$, $S(O)_mR_{66}$, -O-$C(=O)NR_pR_q$, -O-$C(=O)R_p$, -O-$C(=O)OR_p$ (wherein m, R_{66}, R_p and R_q are as defined earlier, and R_z is alkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, heteroarylalkyl or heterocyclylalkyl). Unless otherwise constrained by the definition, the substituents are attached to a ring atom, *i.e.*, carbon or heteroatom in the ring. Examples of heteroaryl groups include oxazolyl, imidazolyl, pyrrolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, thiazolyl, oxadiazolyl, benzoimidazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, thienyl, isoxazolyl, triazinyl, furanyl, benzofuranyl, indolyl, benzothiazolyl, or benzoxazolyl, benzthiazinyl, benzthiazinonyl, benzoxazinyl, benzoxazinonyl, quinazonyl, carbazolyl phenothiazinyl, phenoxazinyl and the like.

The term 'heterocyclyl," unless otherwise specified, refers to a non-aromatic monocyclic or bicyclic cycloalkyl group having 5 to 10 atoms wherein 1 to 8 carbon atoms in a ring are replaced by heteroatoms selected from O, S or N, and optionally are benzofused or fused heteroaryl having 5-6 ring members and/or optionally are substituted, wherein the substituents are selected from halogen (*e.g.*, F, Cl, Br, I), hydroxy, alkyl, alkenyl, alkynyl, cycloalkyl, acyl, optionally substituted aryl, alkoxy, alkaryl, cyano, nitro, oxo, carboxy, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, -O-$C(=O)R_p$, -O-$C(=O)OR_p$, -$C(=O)NR_pR_q$, $S(O)_mR_{66}$, -O-$C(=O)NR_pR_q$, -$NHC(=O)NR_pR_q$, -NR_pR_q, NR_pR_q, mercapto, haloalkyl, thioalkyl, -$COOR_p$, -COONH R_p, -CO R_p, -$NHSO_2$ R_p, SO_2NH R_p (wherein m, R_{66}, R_p and R_q are as defined earlier) or guanidine. Such ring systems can be mono-, bi- or tricyclic. Carbonyl or sulfonyl group can replace carbon atom(s) of heterocyclyl. Unless otherwise constrained by the definition, the substituents are attached to the ring atom, *i.e.*, carbon or heteroatom in the ring. Also, unless otherwise constrained by the definition, the heterocyclyl ring optionally may contain one or more olefinic bond(s). Examples of heterocyclyl groups include oxazolidinyl, tetrahydrofuranyl, dihydrofuranyl, benzoxazinyl, benzthiazinyl, imidazolyl, benzimidazolyl, tetrazolyl, carbaxolyl, indolyl, phenoxazinyl, phenothiazinyl, dihydropyridinyl, dihydroisoxazolyl, dihydrobenzofuryl, azabicyclohexyl, thiazolidinyl, dihydroindolyl, pyridinyl, isoindole 1,3-dione, piperidinyl,

tetrahydropyranyl, piperazinyl, 3H-imidazo[4,5-b]pyridine, isoquinolinyl, 1H-pyrrolo[2,3-b]pyridine, and the like.

"Heteroarylalkyl" refers to alkyl-heteroaryl group linked through alkyl portion, wherein the alkyl and heteroaryl are as defined earlier.

"Heterocyclylalkyl" refers to alkyl-heterocyclyl group linked through alkyl portion, wherein the alkyl and heterocyclyl are as defined earlier.

"Acyl" refers to –C(=O)R″ wherein R″ is selected from hydrogen, alkyl, cycloalkyl, aryl, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl or heterocyclylalkyl.

"Alkylcarbonyl" refers to –C(=O)R″, wherein R″ is selected from alkyl, cycloalkyl, aryl, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl or heterocyclylalkyl.

"Alkylcarboxy" refers to –O–C(=O)R″, wherein R″ is selected from alkyl, cycloalkyl, aryl, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl or heterocyclylalkyl.

"Amine," unless otherwise specified, refers to $–NH_2$. "Substituted amine," unless otherwise specified, refers to $–N(R_v)_2$, wherein each R_v independently is selected from hydrogen {provided that both R_v groups are not hydrogen (defined as "amino")}, alkyl, alkenyl, alkynyl, aralkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, heterocyclylalkyl, heteroarylalkyl, acyl, $S(O)_mR_{66}$ (wherein m is an integer from 0-2 and R_{66} is as defined above), $-C(=O)NR_pR_q$, $NHC(=O)NR_pR_q$, or $-NHC(=O)OR_p$ (wherein R_p and R_q are as defined earlier).

"Thiocarbonyl" refers to –C(=S)H. "Substituted thiocarbonyl" refers to–C(=S)R″, wherein R″ is selected from alkyl, cycloalkyl, aryl, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl or heterocyclylalkyl, amine or substituted amine.

The term *"thioacyl"* refers to –C(=S)R″ wherein R″ is the same as defined above;

Unless otherwise constrained by the definition, all substituents optionally may be substituted further by 1-3 substituents selected from alkyl, aralkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, carboxy, carboxyalkyl, hydroxy, alkoxy, halogen, CF_3, cyano, $-C(=T)NR_pR_q$, $-O(C=O)NR_pR_q$ (wherein R_p, R_q and T are the same as defined earlier) and $-OC(=T)NR_pR_q$,, $S(O)_mR_{66}$ (wherein m is an integer from 0-2 and R_{66} is the same as defined earlier).

The term "leaving group" refers to groups that exhibit or potentially exhibit the properties of being labile under the synthetic conditions and also, of being readily separated from synthetic products under defined conditions. Examples of leaving groups include, but are not limited to, halogen (*e.g.*, F, Cl, Br, I), triflates, tosylate, mesylates, alkoxy, thioalkoxy, or hydroxy radicals and the like.

The term "protecting groups" refers to moieties that prevent chemical reaction at a location of a molecule intended to be left unaffected during chemical modification of such molecule. Unless otherwise specified, protecting groups may be used on groups, such as hydroxy, amino, or carboxy. Examples of protecting groups are found in T.W. Greene and P.G.M. Wuts, "Protective Groups in Organic Synthesis", 2nd Ed., John Wiley and Sons, New York, N.Y., which is incorporated herein by reference. The species of the carboxylic protecting groups, amino protecting groups or hydroxy protecting groups employed are not critical, as long as the derivatised moieties/moiety is/are stable to conditions of subsequent reactions and can be removed without disrupting the remainder of the molecule.

The term "pharmaceutically acceptable salts" refers to derivatives of compounds that can be modified by forming their corresponding acid or base salts. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acids salts of basic residues (such as amines), or alkali or organic salts of acidic residues (such as carboxylic acids), and the like.

As used herein, the term "cycloalkenyl" refers to unsaturated carbocyclic ring having three to seven carbon atoms. One or more hydrogen of said alkenyl or alkynyl can be replaced by halogen, hydroxy, cyano, or $-NR_{44}R_{55}$, wherein R_{44} and R_{55} are selected from hydrogen and alkyl. Examples of cycloalkenyl include, but are not limited to, cyclopropenyl and cyclobutenyl, and the like. Multiple cyclic structures are also included.

As used herein, the term "halogen" refers to fluorine, chlorine, bromine or iodine.

The term "pharmaceutically acceptable solvates" refers to solvates with water (*i.e.*, hydrates, hemihydrate or sesquihydrate) or pharmaceutically acceptable solvents, for example solvates with common organic solvents as ethanol and the like. Such solvates are also encompassed within the scope of the disclosure.

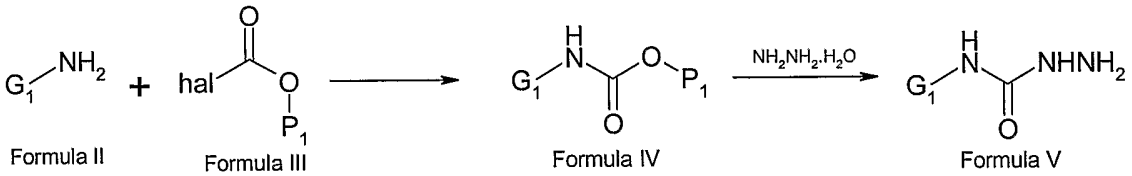
The term "alkylene," unless specified otherwise, refers to a diradical of the branched or unbranched saturated hydrocarbon chain as defined above for the term "alkyl." This term is exemplified by groups such as methylene, ethylene, propylene isomers (*e.g.*, $-CH_2CH_2CH_2$ and $-CH(CH_3)CH_2$) and the like. Alkylene groups may further be substituted with one or more substituents selected from alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, acyl, thioacyl, acyloxy, cycloalkyloxy, heterocyclyloxy, azido, cyano, halogen, hydroxy, thiol, aryloxy, heteroaryloxy, aminosulfonyl, $-COOR_5$ (wherein R_{55} is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl or heterocyclylalkyl), $-NHR_z$, $-NR_xR_y$, $-C(=O)NR_xR_y$, $-OC(=O)NR_xR_y$ (wherein R_z, R_x and R_y are the same as defined herein), nitro, $-S(O)_mR_{66}$ (wherein m and R_{66} is the same as defined earlier). Unless otherwise constrained, all substituents may be further substituted by 1-3 substituents chosen from alkyl, $-COOR_5$, $-NHR_z$, $-NR_xR_y$, $-C(=O)NR_xR_y$, $-OC(=O)NR_xR_y$, hydroxy, alkoxy, halogen, $-CF_3$, cyano and $-S(O)_mR_{66}$. Alkylene groups as defined above may also be interrupted by 1-5 atoms of groups independently chosen from oxygen, sulfur and $-NR_a$ (wherein R_a is chosen from hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, acyl, aralkyl, $-COOR_5$, $-SO_2R_{66}$, $-C(=O)NR_xR_y$).

The term "alkenylene," unless specified otherwise, refers to a diradical of a branched or unbranched unsaturated hydrocarbon group as defined above for the term "alkenyl." In the event that alkenylene is attached to the heteroatom, the double bond cannot be alpha to the heteroatom. Alkenylene groups are connected by two bonds to the rest of the structure of compound of Formula I. Alkenylene groups may further be substituted with one or more substituents selected from the group consisting of alkyl, alkynyl, alkoxy, cycloalkyl, acyl, thioacyl, acyloxy, $-COOR_{55}$ (wherein R_{55} is the same as defined earlier), $-NHR_z$, $-NR_xR_y$, $-C(=O)NR_xR_y$, $-OC(=O)NR_xR_y$ (wherein R_z, R_x and R_y are the same as defined earlier), azido, cyano, halogen, hydroxy, thiol, aryl, aralkyl, aryloxy, heterocyclyl, heteroaryl, heterocyclyloxy, heteroaryloxy, cycloalkyloxy, heterocyclylalkyl, heteroarylalkyl, aminosulfonyl, alkoxyamino, nitro, $-S(O)_mR_{66}$ (wherein R_{66} and m are the same as defined earlier). Unless otherwise constrained, all substituents may optionally be further substituted by 1-3 substituents chosen from alkyl, $-COOR_{55}$, hydroxy, alkoxy, halogen, $-CF_3$, cyano, $-NHR_z$, $-NR_xR_y$, $-C(=O)NR_xR_y$, $-OC(=O)NR_xR_y$ and $-S(O)_mR_{66}$.

Detailed Description of the Invention

The compounds described herein may be prepared by techniques well known in the art and familiar to a practitioner skilled in art of this invention. In addition, although the compounds of the present invention may be prepared by the processes described herein, those processes are not the only means by which the compounds described may be synthesised. Further, the various synthetic steps described herein may be performed in an alternate sequence in order to give the desired compounds.

Scheme I



Formula II Formula III Formula IV Formula V

The compounds of Formulae IV and V can be prepared by, for example, following the procedure as depicted in Scheme I. Thus a compound of Formula II (G_1 is the same as defined earlier) can be reacted with a compound of Formula III [hal is Cl, Br or I and P_1 is aryl (such as phenyl or p-nitrophenyl)] to give a compound of Formula IV, which can be reacted with hydrazine monohydrate to give a compound of Formula V.

The reaction of a compound of Formula II with a compound of Formula III to give a compound of Formula IV can be carried out in an organic solvent, for example, dichloroethane, dichloromethane, chloroform or carbon tetrachloride in the presence of a base, for example, pyridine, N-methylmorpholine, triethylamine or diisopropylethylamine.

The reaction of a compound of Formula IV with hydrazine monohydrate to give a compound of Formula V can be carried out in an organic solvent, for example, dioxane, ethanol, tetrahydrofuran, diethylether or dimethylformamide.

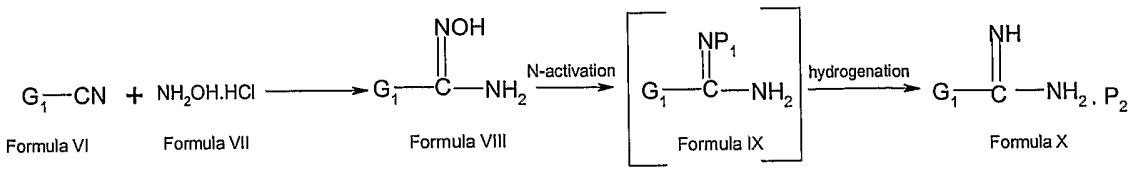
Alternatively, one may also use hydrazine sulphate or hydrazine in place of hydrazine monohydrate.

Particular illustrative compounds which may be prepared by following Scheme I, for example, include:

Phenyl (4-fluorophenyl)carbamate

N-(4-Fluorophenyl)hydrazinecarboxamide

Scheme II



The compounds of Formulae VIII and X can be prepared by following, for example, the reaction sequence as depicted in Scheme II. Thus a compound of Formula VI (wherein G_1 is the same as defined earlier) can be reacted with a compound of Formula VII to give a compound of Formula VIII, which can undergo N-activation to give a compound of Formula IX (*in-situ*) (wherein P_1 represents N-activating groups selected form acetyl, propionyl or trifluoro acetyl), which can undergo hydrogenation to give a salt of Formula X (wherein P_2 is acetic acid, propionic acid or trifluoroacetic acid).

The reaction of a compound of Formula VI with a compound of Formula VII to give compound of Formula VIII can be carried out in presence of a base, for example, sodium carbonate, lithium carbonate or potassium carbonate in water and in an organic solvent, for example, ethanol, methanol, propanol or isopropylalcohol.

The N-activation of compounds of Formula VIII to give a compound of Formula IX (*in–situ*) can be carried out with N-activating agents, for example, acetic acid, propionic acid or trifluoroacetic acid in the presence of a corresponding anhydride, for example, acetic anhydride, propionic anhydride or trifluoroacetic anhydride.

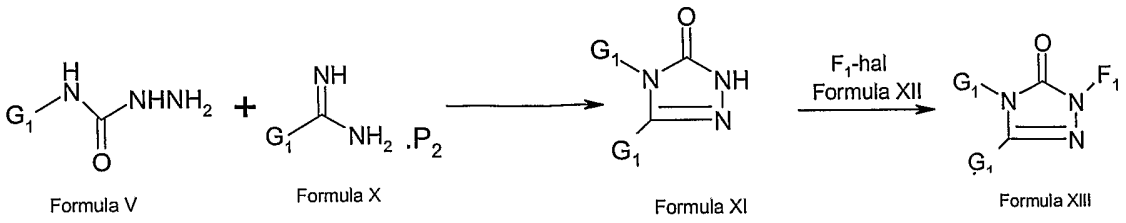
The hydrogenation of a compound of Formula IX to give a compound of Formula X can be carried out under hydrogenating conditions, for example, palladium on carbon or, for example, under catalytic transfer hydrogenation conditions such as ammonium formate and palladium on carbon.

Some illustrative compounds which may be prepared following, for example, Scheme II include:

N'-Hydroxypyridine-4-carboximidamide

Pyridine-4-carboximidamide acetate

Scheme III



The compound of Formula XIII can be prepared by following, for example, the reaction sequence as depicted in Scheme III. Thus a compound of Formula V (wherein G_1 is the same as defined earlier) can be reacted with compound of Formula X to give compound of Formula XI, which can be reacted with a compound of Formula XII (wherein F_1 is alkyl, cycloalkyl or aryl and hal is Cl, Br or I) to give compound of Formula XIII.

The reaction of a compound of Formula V with compound of Formula X to give a compound of Formula XI can be carried out in an organic solvent, for example, dimethylformamide, dimethylsulphoxide, tetrahydrofuran, diethyl ether or dioxane in the presence of protonating agent, for example, acetic acid.

The reaction of compound of Formula XI with compound of Formula XII to give a compound of Formula XIII (when F_1 is aryl) can be carried out in an organic solvent, for example, dioxane, tetrahydrofuran, diethyl ether or dimethylformamide in the presence of a base, for example, potassium carbonate, potassium phosphate, cesium carbonate, lithium carbonate or sodium carbonate and catalyst, for example, copper iodide or palladium (0) or palladium (II) in combination with triphenylphosphine.

The reaction of compound of Formula XI with compound of Formula XII to give a compound of Formula XIII (when F_1 is alkyl or cycloalkyl) can be carried out in an organic solvent, for example, dimethylformamide, dioxane, tetrahydrofuran or diethyl ether in the presence of a base, for example, potassium carbonate, cesium carbonate, lithium carbonate or sodium carbonate.

Particular illustrative compounds which could be prepared in this way include:

4-(4-Fluorophenyl)-5-pyridin-4-yl-2-[4-(1*H*-tetrazol-5-yl)phenyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 1),

4-[4-(4-Fluorophenyl)-5-oxo-3-pyridin-4-yl-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]-*N*'-hydroxybenzenecarboximidamide (Compound No. 2),

4-[4-(4-Fluorophenyl)-5-oxo-3-pyridin-4-yl-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]benzonitrile (Compound No. 3),

4-(4-Fluorophenyl)-2-(4-methoxyphenyl)-5-pyridin-4-yl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 4),

2-(4-Chlorophenyl)-4-(4-fluorophenyl)-5-pyridin-4-yl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 5),

2-(2,4-Difluorophenyl)-4-(4-fluorophenyl)-5-pyridin-4-yl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 6),

4-(4-Fluorophenyl)-2-(4-methylphenyl)-5-pyridin-4-yl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 7),

2-Cycloheptyl-4-(4-fluorophenyl)-5-pyridin-4-yl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 8),

2-Cyclohexyl-4-(4-fluorophenyl)-5-pyridin-4-yl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 9),

2-(Cyclopropylmethyl)-4-(4-fluorophenyl)-5-pyridin-4-yl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 10),

4-(4-Fluorophenyl)-2-(2-morpholin-4-ylethyl)-5-pyridin-4-yl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 11),

2-(Cyclohexylmethyl)-4-(4-fluorophenyl)-5-pyridin-4-yl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No.12),

2-Cyclopentyl-4-(4-fluorophenyl)-5-pyridin-4-yl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 13),

4-(4-Fluorophenyl)-2-(2-piperidin-1-ylethyl)-5-pyridin-4-yl-2,4-dihydro-3*H*-1,2,4-triazol-3-on

2-[4-(4-Fluorophenyl)-5-oxo-3-pyridin-4-yl-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]acetamide (Compound No. 15),

4-[4-(4-Fluorophenyl)-5-oxo-3-phenyl-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]-2-methylbenzonitrile (Compound No. 16),

2-(4-Chlorophenyl)-4-(4-fluorophenyl)-5-phenyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 17),

(4-(4-Fluorophenyl)-2-(4-methylphenyl)-5-phenyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 18),

4-(4-Fluorophenyl)-2-(4-methoxyphenyl)-5-phenyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 19),

4-(4-Fluorophenyl)-2,5-diphenyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 20),

2-(2,4-Difluorophenyl)-4-(4-fluorophenyl)-5-phenyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 21),

4-(4-Fluorophenyl)-2-(4-nitrophenyl)-5-phenyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 22),

4-(4-Fluorophenyl)-2-(2-morpholin-4-ylethyl)-5-phenyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 23),

4-(4-Fluorophenyl)-5-phenyl-2-(2-piperidin-1-ylethyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 24), and

4-(4-Fluorophenyl)-5-phenyl-2-(3-piperidin-1-ylpropyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 25).

Examples set forth demonstrate the general synthetic procedure for the preparation of representative compounds. The examples are provided to illustrate particular aspect of the disclosure and do not limit the scope of the present invention.

EXAMPLES

Scheme I, procedure:

Example 1: Synthesis of *N*-(4-fluorophenyl)hydrazinecarboxamide (Formula V)

Step *a*: Phenyl (4-fluorophenyl)carbamate

To a cold solution of 4-fluoroaniline (11.73g, 105.56mmol) at 0°C in 1,2-dichloroethane (50ml) was added pyridine (12.5g, 158.34mmol) and stirred for 15 minutes. To the resulting reaction mixture was added phenyl chloroformate (19.87ml, 158.34mmol) dropwise and stirred at the same temperature for 2 hrs. The organic solvent was evaporated under reduced pressure followed by removal of pyridine azeotropically by addition of toluene. To the residue thus obtained was added water and stirred till a solid title compound was obtained. Yield =12.0g.

Step *b*: *N*-(4-fluorophenyl)hydrazinecarboxamide

To the solution of the compound obtained from step *a* above (12g, 51.95mmoles) in 1,4-dioxane (60ml) was added hydrazine hydrate (6.5g, 129.87mmol) and refluxed for approx. 2.5 hours. The solvent was evaporated under reduced pressure followed by addition of dichloromethane and hexane. A white solid was separated out which was filtered, washed with hexane and dried under reduced pressure to furnish the title compound. Yield = 8g.

Scheme II, procedure:

Example 2: Synthesis of pyridine-4-carboximidamide acetate (Formula IX)

Step *a*: *N'*-hydroxypyridine-4-carboximidamide

The compounds 4-pyridyl carbonitrile (commercially available) (25g, 240.13mmoles), hydroxylamine hydrochloride (61.24g, 881.28mmoles) and sodium carbonate (43.77g, 413.02mmoles) were dissolved in a solution of water (125ml) and ethanol (375ml). The reaction mixture was then stirred for 10 minutes at room temperature followed by refluxing for 17 hrs. The resulting reaction mixture was cooled to room temperature and diluted with ice-cold water. The precipitate thus obtained were collected by filtration, washed with water and dried under vacuum to furnish the title compound.

Yield = 30g.

Step *b*: Pyridine-4-carboximidamide acetate

The compound obtained from step *a* above (145.98mmoles, 20g) was dissolved in glacial acetic acid (100ml) and acetic anhydride (218.98mmoles, 20.64ml) and stirred for 5 minutes. To the resulting reaction mixture was added palladium on carbon (10g, 10%) and hydrogenated at 45-50 psi for 2hrs. The mixture was filtered through celite pad and washed with glacial acetic acid. The filtrate was concentrated under reduced pressure and excess glacial acetic acid was removed by co-evaporating the residue with n-heptane for approximately four times to furnish the title compound. Yield: 18g.

Scheme III, procedure:

Example 3: Synthesis of 4-(4-fluorophenyl)-5-pyridin-4-yl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Formula X)

To a mixture of *N*-(4-fluorophenyl)hydrazinecarboxamide (6g, 25.947mmol) and pyridine-4-carboximidamide acetate (18.8g, 103.89mmol) was added dry dimethylformamide (60ml) under nitrogen atmosphere and cooled to 0°C. To the resulting reaction mixture was added glacial acetic acid (30ml) and stirred for 30 minutes at the same temperature and then at 110°C for 5 hours under nitrogen atmosphere. The solvent was evaporated under reduced pressure followed by addition of saturated sodium bicarbonate solution. The solid thus obtained was filtered and mother liquor was extracted with ethyl acetate. The solvent was evaporated under reduced pressure and the residue thus obtained was purified by column chromatography using ethyl acetate in hexane (2:8) as eluent to furnish the title compound. Yield: 1g.

Example 4: Synthesis of 4-(4-fluorophenyl)-2-(4-methylphenyl)-5-pyridin-4-yl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 7)

To a mixture of the compound obtained from Example 3 (0.10g, 0.390mmol), potassium carbonate (0.108g, 0.78mmol) and copper iodide (0.015g, 0.07mmol) under argon atmosphere was added dry dioxane (5ml), (±)-*trans* cyclohexane diamine (10mol%) and 4-bromo toluene (0.134g, 0.78mmol) and stirred for 15 hours at 110°C. The resulting reaction mixture was cooled to room temperature followed by quenching with ethyl acetate. The mixture was filtered through celite pad. The filtrate was concentrated under

reduced pressure and the residue thus obtained was purified by column chromatography using ethyl acetate in hexane (2:8) as eluent to furnish the title compound. Yield: 0.09g.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.62 (2H, d, J=8.00Hz, Ar-*H*), 7.94 (2H, d, J=8.00Hz, Ar-*H*), 7.33-7.27 (6H, m, Ar-*H*), 7.22-7.19 (2H, m, Ar-*H*) and 2.39 (3H, s, Ar-CH_3).

Mass spectrum (*m/z,* +ve ion mode): 347[M^++1].

Following analogues were prepared similarily,

4-(4-Fluorophenyl)-5-pyridin-4-yl-2-[4-(1*H*-tetrazol-5-yl)phenyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 1)

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.64 (2H, d, J=6.00Hz, Ar-*H*), 8.17 (4H, s, Ar-*H*), 7.61-7.58 (2H, m, Ar-*H*), 7.43-7.36 (2H, m, Ar-*H*) and 7.35 (2H, d, J=1.60Hz, Ar-*H*).

Mass spectrum (*m/z* +ve ion mode): 401[M^++1].

4-[4-(4-Fluorophenyl)-5-oxo-3-pyridin-4-yl-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]-*N*'-hydroxybenzenecarboximidamide (Compound No. 2)

^{1}H NMR (400 MHz, DMSO-d_6): δ 9.69 (1H, s, N-*OH* & D_2O exchangeable), 8.64 (2H, d, J=5.60Hz, Ar-*H*), 8.03 (2H, d, J=8.80Hz, Ar-*H*), 7.83 (2H, d, J=8.80Hz, Ar-*H*), 7.62-7.56 (3H, m, Ar-*H*), 7.43-7.34 (3H, m, Ar-*H*) and 5.87 (2H, brs, NH_2 & D_2O exchangeable).

Mass spectrum (*m/z,* +ve ion mode): 391[M^++1].

4-[4-(4-Fluorophenyl)-5-oxo-3-pyridin-4-yl-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]benzonitrile (Compound No. 3)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.66 (2H, s, Ar-*H*), 8.30 (2H, d=8.80Hz, Ar-*H*), 7.80 (2H, d, J=8.80Hz, Ar-*H*), 7.76-7.30 (2H, m, Ar-*H*) and 7.33-7.21 (4H, m, Ar-*H*).

Mass spectrum (*m/z,* +ve ion mode): 358[M^++1].

IR spectrum (KBr): 3377, 2223, 1713, 1602, 1508 and 1373 cm^{-1}.

4-(4-Fluorophenyl)-2-(4-methoxyphenyl)-5-pyridin-4-yl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 4)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.62 (2H, d, J=6.00Hz, Ar-*H*), 7.95 (2H, d, J=9.20Hz, Ar-*H*), 7.33-7.02 (6H, m, Ar-*H*), 7.00 (2H, d, J=9.20Hz, Ar-*H*) and 3.86 (3H, s, Ar-OCH_3).

Mass spectrum (*m/z*, +ve ion mode): 362[M^++1].

2-(4-Chlorophenyl)-4-(4-fluorophenyl)-5-pyridin-4-yl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 5)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.64 (2H, d, J=4.00Hz, Ar-*H*), 8.06 (2H, d, J=8.00Hz, Ar-*H*), 7.44 (2H, d, J=8.00Hz, Ar-*H*) and 7.33-7.20 (6H, m, Ar-*H*).

Mass spectrum (*m/z*, +ve ion mode): 369[M^++1+2] and 367[M^++1].

IR spectrum (KBr): 3448, 1706, 1601, 1495 and 1376 cm^{-1}.

2-(2,4-Difluorophenyl)-4-(4-fluorophenyl)-5-pyridin-4-yl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 6)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66-7.60 (1H, m, Ar-*H*), 7.34-7.19 (8H, m, Ar-*H*) and 7.07-7.02 (2H, m, Ar-*H*).

Mass spectrum (*m/z*, positive ion mode): 369[M^++1].

4-[4-(4-Fluorophenyl)-5-oxo-3-phenyl-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]-2-methylbenzonitrile (Compound No. 16)

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.16-8.10 (2H, m, Ar-*H*), 7.69 (2H, d, J=9.00Hz, Ar-*H*), 7.46-7.36 (6H, m, Ar-*H*), 7.19-7.14 (2H, m, Ar-*H*) and 2.61 (3H, s, Ar-CH_3).

Mass spectrum (*m/z*, +ve ion mode): 371[M^++1]

IR spectrum (KBr): 3431, 2215, 1719, 1609, 1511 and 1365 cm^{-1}

2-(4-Chlorophenyl)-4-(4-fluorophenyl)-5-phenyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 17)

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.05 (2H, d, J=9.00Hz, Ar-*H*), 7.42-7.24 (9H, brm, Ar-*H*) and 7.15-7.10 (2H, m, Ar-*H*).

Mass spectrum (*m/z*, +ve ion mode): 368[M^++1+2] and 366[M^++1].

IR spectrum (KBr): 3456, 1709, 1491, 1375, 1231 and 1153 cm^{-1}.

(4-(4-Fluorophenyl)-2-(4-methylphenyl)-5-phenyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 18)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.94-7.91 (2H, m, Ar-*H*), 7.41-7.27 (9H, m, Ar-*H*), 7.17-7.11 (2H, m, Ar-*H*) and 2.38 (3H, s, Ar-CH_3).

Mass spectrum (*m/z*, +ve ion mode): 346[M^++1].

IR spectrum (KBr): 3450, 1706, 1515, 1379 and 1153 cm^{-1}.

4-(4-Fluorophenyl)-2-(4-methoxyphenyl)-5-phenyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 19)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.96 (2H, d, J=9.00Hz, Ar-*H*), 7.41-7.30 (4H, m, Ar-*H*), 7.17-7.11 (3H, m, Ar-*H*), 7.00 (2H, m, Ar-*H*), 7.00 (2H, d, J=6.00Hz, Ar-*H*) and 3.84 (3H, s, Ar-OCH_3).

Mass spectrum (*m/z*, +ve ion mode): 362[M^++1]

IR spectrum (KBr): 3449, 1706, 1513, 1247 and 1156 cm^{-1}.

4-(4-Fluorophenyl)-2,5-diphenyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 20)

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.10 (2H, d, J=6.00Hz, Ar-*H*), 7.49-7.37 (7H, brm, Ar-*H*), 7.35-7.18 (3H, brm, Ar-*H*) and 7.15-7.12 (2H, m, Ar-*H*).

Mass spectrum (*m/z*, +ve ion mode): 332[M^++1].

2-(2,4-Difluorophenyl)-4-(4-fluorophenyl)-5-phenyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 21)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43-7.34 (1H, brm, Ar-*H*), 7.32-7.27 (7H, brm, Ar-*H*), 7.17-7.11 (2H, brm, Ar-*H*) and 7.05-6.99 (2H, brm, Ar-*H*).

Mass spectrum (*m/z*, +ve ion mode): 368[M^++1].

4-(4-Fluorophenyl)-2-(4-nitrophenyl)-5-phenyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 22)

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.36-8.26 (4H, brm, Ar-*H*) and 7.55-7.15 (9H, brm, Ar-*H*).

Mass spectrum (*m/z*, +ve ion mode): 378[M^++1].

Example 5: Synthesis of 2-(cyclohexylmethyl)-4-(4-fluorophenyl)-5-pyridin-4-yl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No.12)

To a solution of the compound obtained from Example 3 above (0.080g, 0.312mmol) in dry dimethylformamide (2ml) was added potassium carbonate (0.130g, 0.938 mmol) and stirred for 10 minutes. To the resulting reaction mixture was added cyclohexylmethyl bromide (0.111g, 0.625mmol) and stirred at 80°C for 8-10 hours. The reaction mixture was poured into water, extracted with ethyl acetate, washed with water, dried over anhydrous sodium sulphate, filtered and evaporated under reduced pressure. The residue thus obtained was purified by column chromatography using ethyl acetate in hexane (2:3) as eluent to furnish the title compound. Yield: 0.040g.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.57 (2H, d, J=4.00Hz, Ar-*H*), 7.25-7.14 (6H, m, Ar-*H*), 3.76 (2H, d, J=4.00Hz, -NCH_2), 1.77-1.74 (1H, m, -*CH*), 1.69-1.67 (6H, m, 3× -CH_2) and 1.33-1.28 (4H, m, 2×-CH_2).

Mass spectrum (*m/z,* +ve ion mode): 353[M^++1].

Following analogues were prepared similarily,

2-Cycloheptyl-4-(4-fluorophenyl)-5-pyridin-4-yl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 8)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.57 (2H, d, J=8.00Hz, Ar-*H*), 7.27-7.15 (6H, m, Ar-*H*), 4.44-4.41 (1H, m, -N*CH*), 2.07-2.03 (4H, m, 2×-CH_2), 1.69-1.65 (2H, m, -CH_2) and 1.64-1.59 (6H, m, 3×-CH_2).

Mass spectrum (*m/z,* +ve ion mode): 353[M^++1].

2-Cyclohexyl-4-(4-fluorophenyl)-5-pyridin-4-yl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 9)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.56 (2H, d, J=8.00Hz, Ar-*H*), 7.27-7.15 (6H, m, Ar-*H*), 4.23-4.19 (1H, m, -N*CH*), 2.02-1.83 (6H, m, 3×-CH_2) and 1.46-1.25 (4H, m, 2×-CH_2).

Mass spectrum (*m/z,* +ve ion mode): 339[M^++1].

2-(Cyclopropylmethyl)-4-(4-fluorophenyl)-5-pyridin-4-yl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 10)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (2H, brs, Ar-*H*), 7.27-7.20 (6H, m, Ar-*H*), 3.75 (2H, d, J=12.00Hz, -NCH_2), 2.96 (1H, m, -*CH*) and 1.35-1.30 (4H, m, 2×-CH_2).

Mass spectrum (*m/z*, +ve ion mode): 311[M^++1].

4-(4-Fluorophenyl)-2-(2-morpholin-4-ylethyl)-5-pyridin-4-yl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 11)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.58 (2H, d, J=4.00Hz, Ar-*H*), 7.25-7.16 (6H, m, Ar-*H*), 4.08 (2H, t, J=8.00Hz, -OCH_2), 3.72-3.70 (4H, brm, -OCH_2 & -NCH_2), 2.83 (2H, t, J=8.00Hz, -NCH_2) and 2.58 (2H, brm, -NCH_2).

Mass spectrum (*m/z*, +ve ion mode): 370[M^++1].

2-Cyclopentyl-4-(4-fluorophenyl)-5-pyridin-4-yl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 13)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.56 (2H, d, J=4.00Hz, Ar-*H*), 7.25-7.15 (6H, m, Ar-*H*), 4.79-4.73 (1H, m, -*CH*), 2.12-2.01 (6H, m, 3×-CH_2) and 2.00-1.91 (2H, m, -CH_2).

Mass spectrum (*m/z*, +ve ion mode): 325[M^++1].

4-(4-Fluorophenyl)-2-(2-piperidin-1-ylethyl)-5-pyridin-4-yl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No.14)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.54 (2H, d, J=4.00Hz, Ar-*H*), 7.23-7.21 (4H, m, Ar-*H*), 7.18-7.15 (2H, m, Ar-*H*), 4.06 (2H, t, J=8.00Hz, -NCH_2), 2.80 (2H, brm, -NCH_2), 2.50 (4H, brm, 2×-NCH_2) and 1.64-1.57 (6H, brm, 3×-CH_2).

Mass spectrum (*m/z*, +ve ion mode): 368[M^++1].

2-[4-(4-Fluorophenyl)-5-oxo-3-pyridin-4-yl-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]acetamide (Compound No. 15)

^{1}H NMR (400 MHz, $CDCl_3$+MeOD): δ 8.54 (2H, d, J=8.00Hz, Ar-*H*), 7.48-7.21 (7H, m, Ar-*H* & -N*H*) and 4.66 (2H, s, -CH_2CO).

Mass spectrum (*m/z*, +ve ion mode): 314[M^++1].

IR spectrum (KBr): 3422, 1686, 1623, 1507 and 1219 cm^{-1}.

4-(4-Fluorophenyl)-2-(2-morpholin-4-ylethyl)-5-phenyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 23)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39-7.08 (9H, brm, Ar-*H*), 4.06 (2H, t, J=6.00Hz, -NCH_2), 3.72-3.69 (4H, m, 2×-OCH_2), 2.83 (2H, t, J=6.00Hz, -NCH_2) and 2.59-2.56 (4H, m, 2×-NCH_2).

Mass spectrum (*m/z,* +ve ion mode): 369[M^++1].

4-(4-Fluorophenyl)-5-phenyl-2-(2-piperidin-1-ylethyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 24)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.52-7.50 (1H, m, Ar-*H*), 7.37-7.07 (8H, m, Ar-*H*), 4.10 (2H, t, J=6.00Hz, -NCH_2), 4.05 (2H, t, J=6.00Hz, -NCH_2), 2.89-2.78 (2H, m, -NCH_2), 2.57-2.52 (4H, brm, -NCH_2&-CH_2), 2.41-2.36 (2H, brm, -CH_2) and 1.45-1.44 (2H, brm, -CH_2).

Mass spectrum (*m/z,* +ve ion mode): 367[M^++1].

4-(4-Fluorophenyl)-5-phenyl-2-(3-piperidin-1-ylpropyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 25)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38-7.21 (7H, brm, Ar-*H*), 7.17-7.08 (2H, m, Ar-*H*), 3.97 (2H, t, J=6.00Hz, -NCH_2), 2.77-2.72 (6H, brm, 3×-NCH_2), 1.74-1.71 (4H, m, 2×-CH_2), 1.52-1.50 (2H, m, -CH_2) and 1.35-1.33 (2H, m, -CH_2).

Mass spectrum (*m/z,* +ve ion mode): 381[M^++1].

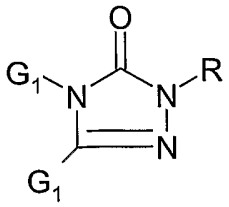
Example 6: *p38 Inhibition Assay*

p38 MAP Kinase inhibitory potential was evaluated utilizing the proprietary IQ technology (Pierce Biotechnology). The assay incorporates an iron-containing compound that binds specifically to phosphate groups present on fluorescent dye-labeled phosphorylated peptides which in this case was the Epidermal Growth Factor Receptor Peptide (KRELVEPLTPSGEAPNQALLR). Recombinant activated GST- p38MAP kinase-α was used at a concentration of 40nM. The reaction was initiated with 100μM ATP. When bound to the phosphate group, the iron-containing compound was brought into proximity to the flurophore and act as a dark quencher of the fluorescent dye. Results were quantitated by comparing the observed relative fluorescence units of test samples to blanks containing no enzyme. A dose response curve was generated with different concentrations of inhibitor and the IC_{50} was calculated using Graph Pad Prism.

Compound Nos. 1-25 were tested and showed p38 inhibitory activity in the range of from about 800μM to about 100μM, for example, from about 800μM to about 20μM, or from about 800μM to about 10μM, or from about 800μM to about 4μM..

We Claim:

1. A compound having the structure of Formula I



Formula I

and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers diastereomers, N-oxides, polymorphs, metabolites, wherein

G_1 is independently aryl or heteroaryl;

R is alkyl, cycloalkyl, heteroaryl, heterocyclyl, aryl, cycloalkylalkyl, heterocyclylalkyl, heteroarylalkyl, $-(CH_2)_gCONR_xR_y$ [wherein R_x and R_y are hydrogen, alkyl, cycloalkyl, aryl, aralkyl, $-SO_nR_1$ (wherein n is 0, 1 or 2), heteroaryl, heterocyclyl, heteroarylalkyl or heterocyclylalkyl (wherein R_1 is hydrogen, alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, heterocyclylalkyl or heteroarylalkyl).]; and

g is an integer selected from 1-3.

2. A compound selected from the group consisting of

4-(4-Fluorophenyl)-5-pyridin-4-yl-2-[4-(1*H*-tetrazol-5-yl)phenyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 1),

4-[4-(4-Fluorophenyl)-5-oxo-3-pyridin-4-yl-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]-*N*'-hydroxybenzenecarboximidamide (Compound No. 2),

4-[4-(4-Fluorophenyl)-5-oxo-3-pyridin-4-yl-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]benzonitrile (Compound No. 3),

4-(4-Fluorophenyl)-2-(4-methoxyphenyl)-5-pyridin-4-yl-2,4-dihydro-3*H*-1,2,4-triazol-3- one (Compound No. 4),

2-(4-Chlorophenyl)-4-(4-fluorophenyl)-5-pyridin-4-yl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 5),

2-(2,4-Difluorophenyl)-4-(4-fluorophenyl)-5-pyridin-4-yl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 6),

4-(4-Fluorophenyl)-2-(4-methylphenyl)-5-pyridin-4-yl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 7),

2-Cycloheptyl-4-(4-fluorophenyl)-5-pyridin-4-yl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 8),

2-Cyclohexyl-4-(4-fluorophenyl)-5-pyridin-4-yl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 9),

2-(Cyclopropylmethyl)-4-(4-fluorophenyl)-5-pyridin-4-yl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 10),

4-(4-Fluorophenyl)-2-(2-morpholin-4-ylethyl)-5-pyridin-4-yl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 11),

2-(Cyclohexylmethyl)-4-(4-fluorophenyl)-5-pyridin-4-yl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No.12),

2-Cyclopentyl-4-(4-fluorophenyl)-5-pyridin-4-yl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 13),

4-(4-Fluorophenyl)-2-(2-piperidin-1-ylethyl)-5-pyridin-4-yl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No.14),

2-[4-(4-Fluorophenyl)-5-oxo-3-pyridin-4-yl-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]acetamide (Compound No. 15),

4-[4-(4-Fluorophenyl)-5-oxo-3-phenyl-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]-2-methylbenzonitrile (Compound No. 16),

2-(4-Chlorophenyl)-4-(4-fluorophenyl)-5-phenyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 17),

(4-(4-Fluorophenyl)-2-(4-methylphenyl)-5-phenyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 18),

4-(4-Fluorophenyl)-2-(4-methoxyphenyl)-5-phenyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 19),

4-(4-Fluorophenyl)-2,5-diphenyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 20),

2-(2,4-Difluorophenyl)-4-(4-fluorophenyl)-5-phenyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 21),

4-(4-Fluorophenyl)-2-(4-nitrophenyl)-5-phenyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 22),

4-(4-Fluorophenyl)-2-(2-morpholin-4-ylethyl)-5-phenyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 23),

4-(4-Fluorophenyl)-5-phenyl-2-(2-piperidin-1-ylethyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 24), and

4-(4-Fluorophenyl)-5-phenyl-2-(3-piperidin-1-ylpropyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Compound No. 25).

3. A method for treating mammals suffering from inflammation and associated pathologies.

4. A method for treating mammals suffering from sepsis, rheumatoid arthritis, inflammatory bowel disease, type-1 diabetes, asthma, chronic obstructive pulmonary disorder, organ transplant rejection, acute coronary syndrome and psoriasis, the method comprising administration of a therapeutically effective amount of compound of claim 1.

5. A pharmaceutical composition for the treatment of inflammation and associated pathologies, the composition comprising a compound of claim 1, and a pharmaceutically acceptable carrier.

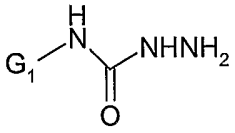
6. A pharmaceutical composition for treating mammals suffering from sepsis, rheumatoid arthritis, inflammatory bowel disease, type-1 diabetes, asthma, chronic obstructive pulmonary disorder, organ transplant rejection, acute coronary syndrome and psoriasis, the composition comprising a compound of claim 1, and a pharmaceutically acceptable carrier.

7. A method for treating mammals suffering from inflammation and associated pathologies, the method comprising administration of a composition of claim 5.

8. A method according to claim 3 wherein the disease or disorder is mediated through p38 MAP Kinase.

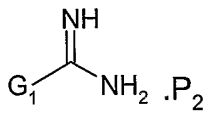
9. A method of making a compound of Formula XIII, or pharmaceutically acceptable salts or esters thereof wherein the method comprise:

a. reacting a compound of Formula V



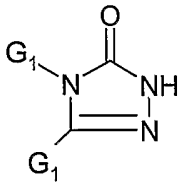
Formula V

with compound of Formula X



Formula X

to give compound of Formula XI,



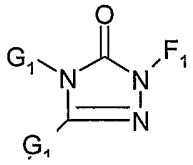
Formula XI

b. reacting a compound of Formula XI with a compound of Formula XII

F_1-hal

Formula XII

to give compound of Formula XIII



Formula XIII

wherein

P_2 is acetic acid, propionic acid or trifluoroacetic acid;

F_1 is alkyl, cycloalkyl or aryl;

hal is Cl, Br or I; and

G_1 is independently aryl or heteroaryl.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2006/001143

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/04 C07D249/12 A61K31/4196 A61P29/00

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

B. FIELDS SEARCHED

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00/59506 A (BRISTOL-MYERS SQUIBB CO) 12 October 2000 (2000-10-12) claims 1,6,14,34; examples 29,30	1,3-9
X	WO 00/71537 A (ASTRAZENECA AB; KARABELAS, KOSTAS; LEPISTOE, MATTI; SJOE, PETER) 30 November 2000 (2000-11-30) claim 1; examples 15,40	1,3-9
X	EP 0 612 741 A (DR. KARL THOMAE GMBH) 31 August 1994 (1994-08-31) page 47, line 37 page 48, line 50 page 51, line 47	1,3-9

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 August 2006	22/08/2006

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

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2006/001143

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 971 606 C (ALLGEMEINE ELEKTRICITAETS-GESELLSCHAFT) 26 February 1959 (1959-02-26) examples 2,5,23	1,5,6
X	WO 03/083063 A (TRIAD THERAPEUTICS, INC; LANG, HENGYUAN; CHANG, EDCON; CEFALO, DUSTIN;) 9 October 2003 (2003-10-09) example 13	1,5,6
X	WO 2004/099170 A (THE INSTITUTE OF PHARMACEUTICAL DISCOVERY, LLC; WHITEHOUSE, DARREN; HU) 18 November 2004 (2004-11-18) examples 91,92	1,5,6
X	DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; MALISZEWSKA-GUZ, ALICJA ET AL: "Derivatives of hydroxy-1,2,4-triazole. Part III. Reaction of hydroxy-1,2,4-triazoles with ethylene chlorohydrin" XP002393845 retrieved from STN Database accession no. 1996:511904 Compounds with RN=181425-71-8; 181418-41-7; 181425-73-0; 181425-75-2 abstract & ANNALES UNIVERSITATIS MARIAE CURIE-SKLODOWSKA, SECTIO AA: CHEMIA , VOLUME DATE 1991-1992, 46-47, 35-40 CODEN: AUMCD7; ISSN: 0137-6853, 1995,	1
A	WO 00/10563 A (SMITHKLINE BEECHAM CORPORATION; ADAMS, JERRY, L; LEE, DENNIS) 2 March 2000 (2000-03-02) claim 1	1-9

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2006/001143

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

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

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

Although claims 3,4,7,8 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

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

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

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

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

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

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

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

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

Remark on Protest

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

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

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2006/001143

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0059506 A	12-10-2000	AU 3903600 A	23-10-2000
		BG 105968 A	31-05-2002
		BR 0009563 A	15-01-2002
		CA 2366871 A1	12-10-2000
		CN 1345239 A	17-04-2002
		CZ 20013542 A3	16-01-2002
		EE 200100504 A	16-12-2002
		EP 1181014 A1	27-02-2002
		HU 0202251 A2	28-11-2002
		ID 30322 A	22-11-2001
		JP 2002541106 T	03-12-2002
		LT 2001092 A	25-02-2002
		LV 12782 A	20-01-2002
		MX PA01009984 A	24-04-2002
		NO 20014823 A	04-10-2001
		NZ 513493 A	27-02-2004
		PL 350900 A1	10-02-2003
		SK 13152001 A3	04-04-2002
		TR 200102874 T2	21-03-2002
		ZA 200106856 A	20-11-2002
WO 0071537 A	30-11-2000	AT 259798 T	15-03-2004
		AU 4968600 A	12-12-2000
		BR 0010520 A	19-02-2002
		CA 2372743 A1	30-11-2000
		CN 1351602 A	29-05-2002
		DE 60008372 D1	25-03-2004
		DE 60008372 T2	19-05-2005
		EP 1183252 A1	06-03-2002
		JP 2003500404 T	07-01-2003
		MX PA01011884 A	06-05-2002
		NO 20015664 A	21-01-2002
		NZ 515281 A	29-08-2003
		US 6492406 B1	10-12-2002
EP 0612741 A	31-08-1994	AT 167185 T	15-06-1998
		AU 673875 B2	28-11-1996
		AU 5632494 A	25-08-1994
		CA 2116068 A1	23-08-1994
		CN 1099755 A	08-03-1995
		CZ 9400374 A3	15-12-1994
		DE 4332168 A1	23-03-1995
		DK 612741 T3	29-03-1999
		ES 2118992 T3	01-10-1998
		FI 940806 A	23-08-1994
		HU 70768 A2	30-10-1995
		IL 108733 A	04-01-1998
		JP 3545446 B2	21-07-2004
		JP 6256343 A	13-09-1994
		MX 9401315 A1	31-08-1994
		NO 940595 A	23-08-1994
		NZ 250944 A	27-02-1996
		PH 30602 A	31-07-1997
		PL 178215 B1	31-03-2000
		SG 52300 A1	28-09-1998
		US 5519036 A	21-05-1996
DE 971606 C	26-02-1959	NONE	

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2006/001143

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03083063 A	09-10-2003	AU 2003230727 A1	13-10-2003
WO 2004099170 A	18-11-2004	AU 2004236248 A1	18-11-2004
		BR PI0409916 A	25-04-2006
		CA 2524235 A1	18-11-2004
		EP 1620422 A2	01-02-2006
		MX PA05011536 A	23-01-2006
WO 0010563 A	02-03-2000	AT 266399 T	15-05-2004
		CA 2341370 A1	02-03-2000
		DE 69917296 D1	17-06-2004
		DE 69917296 T2	25-05-2005
		EP 1112070 A1	04-07-2001
		ES 2221426 T3	16-12-2004
		JP 2003525201 T	26-08-2003