

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
2 March 2006 (02.03.2006)

PCT

(10) International Publication Number
WO 2006/021848 A1

(51) International Patent Classification:
C07D 213/00 (2006.01) **A61K 31/17** (2006.01)

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

(21) International Application Number:
PCT/IB2005/002287

(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, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, 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.

(22) International Filing Date: 2 August 2005 (02.08.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/605,344 27 August 2004 (27.08.2004) US

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

(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).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **PALLE, Venkata, P.** [IN/IN]; D-011, Oakwood Estate, Akashneem Marg DLF-Phase II, Gurgaon, Haryana 122001 (IN). **VERMA, Ashwani, Kumar** [IN/IN]; 24, Charak Sadan, (AIIMS Doctor's Society), E-Block, Vikas Puri, Delhi 110018 (IN). **MALHOTRA, Sanjay** [IN/IN]; 422, Plot No. 8, Sector 10, Dwarka, Phase-I, New Delhi 110075 (IN). **WAMAN, Yogesh, Bhaskarrao** [IN/IN]; Sajjaingadh Housing Society, A-6, Jail Road, Nasik Road, Taluka and District Nasik, Maharashtra 422101 (IN). **SHARMA, Geeta** [IN/IN]; A-654, Sarita Vihar, New Delhi 110044 (IN). **RAY, Abhijit** [IN/IN]; Sector C-1, Flat No. 1408, Vasant Kunj, New Delhi 110070 (IN).

Published:

- *with international search report*
- *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

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.

(54) Title: ANTI-INFLAMMATORY AGENTS

(57) Abstract: The present invention relates to heterocyclic derivatives as anti-inflammatory agents. The compounds of this invention 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, acute coronary syndrome and psoriasis.

WO 2006/021848 A1

ANTI-INFLAMMATORY AGENTS

Field of the Invention

The present invention relates to heterocyclic derivatives as anti-inflammatory agents. The compounds of this invention 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, acute coronary syndrome and psoriasis.

This invention also relates to pharmacological compositions containing the compounds of the present invention and the methods of treating sepsis, rheumatoid arthritis, inflammatory bowel disease, type-1 diabetes, asthma, chronic obstructive pulmonary disorder, organ transplant rejection, acute coronary syndrome and psoriasis, and other inflammatory and/or autoimmune disorders, using the compounds.

Background of the Invention

During the last decade, studies have focused on the roles played by cytokines, a unique class of intercellular regulatory proteins, in the pathogenesis of many diseases. Cytokines play a crucial role in initiating, maintaining, and regulating immunological and inflammatory processes. Cytokine-based therapies that aim to inhibit or restore the activity of specific cytokines have been developed. Today, drugs that block inflammatory cytokines, such as tumor necrosis factor-alpha (TNF- α), have been introduced to the market.

Elevated levels of proinflammatory cytokines viz TNF- α and IL-1 α 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 disorder, organ transplant rejection, acute coronary syndrome 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. A particular role of these inflammatory mediators is in the pathogenesis of both chronic and acute inflammatory diseases. Inflammatory disorders have been treated primarily with relatively non-selective anti-inflammatory agents, such as corticosteroids and various

non-steroidal anti-inflammatory drugs. Other therapies have been developed that specifically interfere with the action of selected pro-inflammatory mediators, such as TNF α and PGE2. These specific anti-inflammatory therapies are useful for 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- α (TNF- α), including etanercept (Enbrel; Amgen/Wyeth), infliximab (Remicade; Centocor), and adalimumab (Humira; Abbott), has been used for the treatment of autoimmune diseases such as rheumatoid arthritis. Kineret, an interleukin-1 (IL-1) receptor antagonist, provides 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 particular approaches to interrupting the pro-inflammatory process.

The p38 MAPK is a member of a large family of MAPK's whose signaling pathways also include the extracellular regulated kinases (ERK) & the c-jun N terminal kinases (JNK). MAP kinases are Serine Threonine Kinases that transduce environmental stimuli to the nucleus and they themselves 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.

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, p38MAPk also plays a role in the production of IL-4, IL-6, IL-8 and IL-12. p38MAPk 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 p38MAPk 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 p38MAP 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.

PCT applications WO 99/58502, WO 00/17175 and WO 02/14281 disclose compounds described as p38 inhibitors. PCT application WO 01/23887 and US 6,458,789 disclose 2-aminopyridine derivatives and combinatorial libraries thereof.

Summary of the Invention

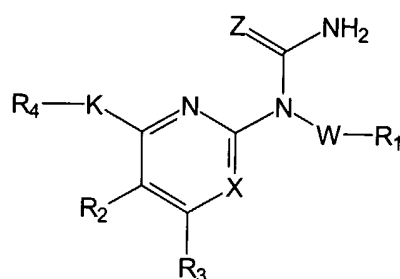
The present invention provides heterocyclic derivatives which can be used for the inhibition and prevention of inflammation and associated pathologies such as sepsis, rheumatoid arthritis, inflammatory bowel disease, type-1 diabetes, asthma, chronic obstructive pulmonary disorder, organ transplant rejection,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

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,

5



Formula I

its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers,
10 diastereomers, polymorphs or N-oxides

wherein

Z can be oxygen, sulphur, -N(CN), -N(NO₂), or -CH(NO₂).

X can be nitrogen, or carbon.

W can be alkylene, (C₃₋₆)alkenylene, or (C₃₋₆)alkynylene (wherein the double bond of the
15 alkenylene or the triple bond of the alkynylene is not attached directly to the N atom).

K can be W or a direct bond.

R₁ can be aryl, cycloalkyl, cycloheteroalkyl, heteroaryl, or heterocyclyl.

R₂ and **R₃** can be selected from hydrogen; alkyl; alkenyl; alkynyl; cycloalkyl;
cycloheteroalkyl; cycloheteroalkylalkyl; aryl; aralkyl; carboxy; -COOR₅ (wherein R₅ is
20 selected from alkyl, aryl, aralkyl, cycloalkyl, cycloheteroalkyl, cycloheteroalkylalkyl,
heterocyclyl, heteroaryl, heteroarylalkyl, heterocyclalkyl); -NR_pR_q (wherein R_p and R_q
are independently selected from hydrogen, alkyl, cycloalkyl, cycloheteroalkyl, aryl,
aralkyl, heteroaryl, heterocyclyl, cycloheteroalkylalkyl, heterocyclalkyl, heteroarylalkyl
OC(=O)NR_xR_y [wherein R_x and R_y are selected from hydrogen, hydroxy (as restricted by
25 the definition that both R_x and R_y cannot be -OH at the same time), alkyl, aryl, aralkyl, or
-SO₂R₆ (wherein R₆ is selected from alkyl, cycloalkyl, cycloheteroalkyl, -NR_pR_q (wherein
R_p and R_q are the same as defined above), aryl, aralkyl, heteroaryl, heterocyclyl,
heterocyclalkyl, or heteroarylalkyl), R_x and R_y may also together join to form, a
heterocyclyl]; -NR_jC(=O)OR_s [wherein R_s is selected from alkyl, cycloalkyl,
30 cycloheteroalkyl, aryl, aralkyl, heteroaryl, heterocyclyl, cycloheteroalkylalkyl,

heterocyclalkyl, or heteroarylalkyl and R_j is selected from the group consisting of hydrogen, lower (C_1-C_6) alkyl, lower (C_2-C_6) cycloalkyl, lower (C_1-C_3) aralkyl, aryl, heteroaryl, heteroarylalkyl, or heterocyclalkyl]; $-NR_jYR_u$ [wherein Y is $-C(=O)$, $-C(=S)$ or SO_2 , R_j is the same as defined above and R_u is selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloheteroalkyl, aryl, aralkyl, heteroaryl, heterocyclalkyl, cycloheteroalkylalkyl, heterocyclalkyl, or heteroarylalkyl]; $-NR_jC(=Z)NR_xR_y$ (wherein R_j , Z, R_x and R_y are the same as defined earlier); $-CH_2OR_5$ (wherein R_5 is the same as defined above); heteroaryl; heterocyclalkyl; heteroarylalkyl or heterocyclalkyl; with the proviso that when K is a direct bond and Z is oxygen then R_3 is hydrogen or cycloheteroalkyl group.

10 R_4 can be aryl, cycloalkyl, cycloheteroalkyl, heteroaryl or heterocyclalkyl.

In accordance with second aspect, there is provided a method for the treatment of mammal suffering from inflammation and associated pathologies the method including administration of a compound or composition disclosed herein.

15 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, acute coronary syndrome and psoriasis the method including administration of a compound or composition disclosed herein.

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

In accordance with fifth aspect, the compounds disclosed herein are screened as p38 kinase inhibitors.

The following definitions apply to terms as used herein.

25 The term "alkyl" unless otherwise specified, refers to a monoradical branched or unbranched saturated hydrocarbon chain having from 1 to 20 carbon atoms. This term can be exemplified by groups such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, t-butyl, n-hexyl, n-decyl, tetradecyl, and the like. Alkyl groups may further be substituted with one or more substituents selected from alkenyl, alkynyl, alkoxy, cycloalkyl, acyl, acylamino, acyloxy, alkoxy-carbonylamino, azido, cyano, halogen, hydroxy, oxo, 30 thiocarbonyl, carboxy, arylthio, thiol, alkylthio, aryloxy, heteroaryloxy, aminosulfonyl, -

- 6 -

COOR₅ (wherein R₅ is as defined earlier), -NHC(=O)R_x, -NR_xR_y, -C(=O)NR_xR_y, -NHC(=O)NR_xR_y, -C(=O)heteroaryl, C(=O)heterocyclyl, -OC(=O)NR_xR_y (wherein R_x and R_y are as defined earlier), nitro, -S(O)_mR₆ (wherein m is an integer from 0-2 and R₆ is as defined earlier). Unless otherwise constrained by the definition, all substituents may be further substituted by 1-3 substituents chosen from alkyl, carboxy, -COOR₅ (wherein R₅ is as defined earlier), -NR_xR_y, -C(=O)NR_xR_y, -OC(=O)NR_xR_y, -NHC(=O)NR_xR_y (wherein R_x and R_y are as defined earlier), hydroxy, alkoxy, halogen, CF₃, cyano, and -S(O)_mR₆ (where R₆ and m are as defined earlier).

Alkyl groups as defined above may also be interrupted by 1-5 atoms of groups independently chosen from oxygen, sulfur and -NR_a- (where R_a is chosen from hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, acyl, aralkyl, -C(=O)OR₅ (wherein R₅ is as defined earlier), S(O)₂R₆ (where R₆ is as defined earlier), -C(=O)NR_xR_y (wherein R_x and R_y are as defined earlier)). Unless otherwise constrained by the definition, all substituents may be further substituted by 1-3 substituents chosen from alkyl, carboxy, -NR_xR_y, -C(=O)NR_xR_y, -OC(=O)NR_xR_y (wherein R_x and R_y are the same as defined earlier), hydroxy, alkoxy, halogen, CF₃, cyano, and -S(O)_mR₆ (where m and R₆ are the same as defined earlier).

The term "alkylene," unless otherwise specified, refers to a diradical branched or unbranched saturated hydrocarbon chain having from 1 to 6 carbon atoms. This term is exemplified by groups such as methylene, ethylene, propylene isomers (e.g., -CH₂CH₂CH₂ and -CH(CH₃)CH₂) and the like. Alkylene groups may further be substituted with one or more substituents selected from alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, acyl, acylamino, acyloxy, alkoxycarbonylamino, azido, cyano, halogen, hydroxy, oxo, thiocarbonyl, carboxy, arylthio, thiol, alkylthio, aryloxy, heteroaryloxy, aminosulfonyl, -COOR₅ (wherein R₅ is as defined earlier), -NHC(=O)R_x, -NR_xR_y, -C(=O)NR_xR_y, -NHC(=O)NR_xR_y, -C(=O)heteroaryl, C(=O)heterocyclyl, -OC(=O)NR_xR_y (wherein R_x and R_y are as defined earlier), nitro, -S(O)_mR₆ (wherein m is an integer from 0-2 and R₆ is as defined earlier). Unless otherwise constrained by the definition, all substituents may be further substituted by 1-3 substituents chosen from alkyl, carboxy, -COOR₅ (wherein R₅ is as defined earlier), -NR_xR_y, -C(=O)NR_xR_y, -OC(=O)NR_xR_y, -NHC(=O)NR_xR_y (wherein R_x and R_y are as defined earlier), hydroxy, alkoxy, halogen, CF₃, cyano, and -S(O)_mR₆ (where R₆ and m are as defined earlier).

Alkylene groups as defined above may also be interrupted by 1-5 atoms of groups independently chosen from oxygen, sulfur and $-NR_a$ (where R_a is chosen from hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, acyl, aralkyl, $-C(=O)OR_5$ (wherein R_5 is as defined earlier), $S(O)_2R_6$ (where R_6 is as defined earlier), $-C(=O)NR_xR_y$ (wherein R_x and R_y are as defined earlier)). Unless otherwise constrained by the definition, all substituents may be further substituted by 1-3 substituents chosen from alkyl, carboxy, $-NR_xR_y$, $-C(=O)NR_xR_y$, $-OC(=O)NR_xR_y$ (wherein R_x and R_y are as defined earlier), hydroxy, alkoxy, halogen, CF_3 , cyano, and $-S(O)_mR_6$ (where m and R_6 are as defined earlier).

The term "alkenyl," unless otherwise specified, refers to a monoradical of a branched or unbranched unsaturated hydrocarbon group preferably having from 2 to 20 carbon atoms with cis or trans geometry. In the event that alkenyl is attached to the heteroatom, the double bond cannot be alpha to the heteroatom. Alkenyl groups may further be substituted with one or more substituents selected from alkyl, alkynyl, alkoxy, cycloalkyl, acyl, acylamino, acyloxy, $-NHC(=O)R_x$, $-NR_xR_y$, $-C(=O)NR_xR_y$, $-NHC(=O)NR_xR_y$, $-OC(=O)NR_xR_y$ (wherein R_x and R_y are as defined earlier), alkoxycarbonylamino, azido, cyano, halogen, hydroxy, oxo, thiocarbonyl, carboxy, $-COOR_5$ (wherein R_5 is as defined earlier), arylthio, thiol, alkylthio, aryl, aralkyl, aryloxy, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, aminosulfonyl, alkoxyamino, nitro, $S(O)_mR_6$ (wherein R_6 and m are as defined earlier). Unless otherwise constrained by the definition, all substituents may optionally be further substituted by 1-3 substituents chosen from alkyl, carboxy, $-COOR_5$ (wherein R_5 is as defined earlier), hydroxy, alkoxy, halogen, $-CF_3$, cyano, $-NR_xR_y$, $-C(=O)NR_xR_y$, $-OC(=O)NR_xR_y$ (wherein R_x and R_y are as defined earlier) and $-S(O)_mR_6$ (where R_6 and m are as defined earlier).

The term "alkenylene," unless and otherwise specified, refers to a diradical of a branched or unbranched unsaturated hydrocarbon group preferably having from 2 to 6 carbon atoms with cis or trans geometry. In the event that alkenylene is attached to the heteroatom, the double bond cannot be attached directly to the heteroatom. The alkenylene group is 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 alkyl, alkynyl, alkoxy, cycloalkyl, acyl, acylamino, acyloxy, $-NHC(=O)R_x$, $-$

NR_xR_y, -C(=O)NR_xR_y, -NHC(=O)NR_xR_y, -OC(=O)NR_xR_y (wherein R_x and R_y are as defined earlier), alkoxycarbonylamino, azido, cyano, halogen, hydroxy, oxo, thiocarbonyl, carboxy, -COOR₅ (wherein R₅ is as defined earlier), arylthio, thiol, alkylthio, aryl, aralkyl, aryloxy, cycloheteroalkyl, cycloheteroalkylalkyl, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl, aminosulfonyl, alkoxyamino, nitro, S(O)_mR₆ (wherein R₆ and m are the same as defined earlier). Unless otherwise constrained by the definition, all substituents may optionally be further substituted by 1-3 substituents chosen from alkyl, carboxy, -COOR₅ (wherein R₅ is as defined earlier), hydroxy, alkoxy, halogen, -CF₃, cyano, -NR_xR_y, -C(=O)NR_xR_y, -OC(=O)NR_xR_y (wherein R_x and R_y are the same as defined earlier) and -S(O)_mR₆ (where R₆ and m are as defined earlier).

The term "alkynyl," unless and otherwise specified, refers to a monoradical of an unsaturated hydrocarbon, preferably having from 2 to 20 carbon atoms. In the event that alkynyl is attached to the heteroatom, the triple bond cannot be alpha to the heteroatom. Alkynyl groups may further be substituted with one or more substituents selected from alkyl, alkenyl, alkoxy, cycloalkyl, acyl, acylamino, acyloxy, alkoxycarbonylamino, azido, cyano, halogen, hydroxy, oxo, thiocarbonyl, carboxy, arylthio, thiol, alkylthio, aryl, aralkyl, aryloxy, aminosulfonyl, nitro, cycloheteroalkyl, cycloheteroalkylalkyl, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl, -NHC(=O)R_x, -NR_xR_y, -NHC(=O)NR_xR_y, -C(=O)NR_xR_y, -OC(=O)NR_xR_y (wherein R_x and R_y are as defined earlier), -S(O)_mR₆ (wherein R₆ and m are as defined earlier). Unless otherwise constrained by the definition, all substituents may optionally be further substituted by 1-3 substituents chosen from alkyl, carboxy, -COOR₅ (wherein R₅ is as defined earlier), hydroxy, alkoxy, halogen, CF₃, -NR_xR_y, -C(=O)NR_xR_y, -NHC(=O)NR_xR_y, -C(=O)NR_xR_y (wherein R_x and R_y are the same as defined earlier cyano) and -S(O)_mR₆ (where R₆ and m are as defined earlier).

The term "alkynylene," unless and otherwise specified, refers to a diradical of an unsaturated hydrocarbon, preferably having from 2 to 6 carbon atoms. In the event that alkynylene is attached to the heteroatom, the triple bond cannot be alpha to the heteroatom. The alkenylene group is connected by two bonds to the rest of the structure of compound of Formula I. Alkynylene groups may further be substituted with one or more substituents selected from alkyl, alkenyl, alkoxy, cycloalkyl, acyl, acylamino, acyloxy, alkoxycarbonylamino, azido, cyano, halogen, hydroxy, oxo, thiocarbonyl, carboxy,

arylthio, thiol, alkylthio, aryl, aralkyl, aryloxy, aminosulfonyl, nitro, heterocyclyl, heteroaryl, heterocyclyl alkyl, heteroarylalkyl, -NHC(=O)R_x , $\text{-NR}_x\text{R}_y$, $\text{-NHC(=O)NR}_x\text{R}_y$, $\text{-C(=O)NR}_x\text{R}_y$, $\text{-O-C(=O)NR}_x\text{R}_y$ (wherein R_x and R_y are as defined earlier), $\text{-S(O)}_m\text{R}_6$ (wherein R_6 and m are as defined earlier). Unless otherwise constrained by the definition,

5 all substituents may optionally be further substituted by 1-3 substituents chosen from alkyl, carboxy, -COOR_5 (wherein R_5 is as defined earlier), hydroxy, alkoxy, halogen, CF_3 , $\text{-NR}_x\text{R}_y$, $\text{-C(=O)NR}_x\text{R}_y$, $\text{-NHC(=O)NR}_x\text{R}_y$, $\text{-C(=O)NR}_x\text{R}_y$ (wherein R_x and R_y are as defined earlier), cyano, and $\text{-S(O)}_m\text{R}_6$ (where R_6 and m are as defined earlier).

The term "cycloalkyl" refers to cyclic alkyl groups of from 3 to 20 carbon atoms

10 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 include, by way of example, single ring structures such as cyclopropyl, cyclobutyl, cyclooctyl, cyclopentenyl, and the like, or multiple ring structures such as adamantanyl, and bicyclo [2.2.1]heptane, or cyclic alkyl groups to which is fused an aryl group, for

15 example indane, and the like. Fused and spiro rings are also envisioned. Cycloalkyl groups may further be substituted with one or more substituents selected from alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, acyl, acylamino, acyloxy, alkoxycarbonylamino, azido, cyano, halogen, hydroxy, oxo, thiocarbonyl, carboxy, -COOR_5 (wherein R_5 is as defined earlier), arylthio, thiol, alkylthio, aryl, aralkyl, aryloxy, aminosulfonyl,

20 cycloheteroalkyl, cycloheteroalkylalkyl, cycloalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, $\text{-NR}_x\text{R}_y$, $\text{-NHC(=O)NR}_x\text{R}_y$, -NHC(=O)R_x , $\text{-C(=O)NR}_x\text{R}_y$, $\text{-OC(=O)NR}_x\text{R}_y$ (wherein R_x and R_y are as defined earlier), nitro, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl, $\text{S(O)}_m\text{R}_6$ (wherein R_6 and m are as defined earlier). Unless otherwise constrained by the definition, all substituents may optionally be further

25 substituted by 1-3 substituents chosen from alkyl, carboxy, hydroxy, alkoxy, halogen, CF_3 , $\text{-NR}_x\text{R}_y$, $\text{-C(=O)NR}_x\text{R}_y$, $\text{-NHC(=O)NR}_x\text{R}_y$, $\text{-OC(=O)NR}_x\text{R}_y$ (wherein R_x and R_y are as defined earlier), cyano, and $\text{-S(O)}_m\text{R}_6$ (where R_6 and m are as defined earlier).

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

The term "aralkyl" refers to alkyl-aryl linked through alkyl (wherein alkyl is as

30 defined above) portion and the alkyl portion contains carbon atoms from 1-6 and aryl is as defined below. The examples of aralkyl groups are benzyl and the like.

The term "aryl" herein refers to a carbocyclic aromatic group, for example phenyl, biphenyl or naphthyl ring and the like optionally substituted with 1 to 3 substituents selected from the group consisting of halogen (F, Cl, Br, I), hydroxy, carboxy, $-\text{COOR}_5$ (wherein R_5 is as defined earlier), alkyl, alkenyl, alkynyl, cycloalkyl, alkoxy, acyl, aryloxy, cyano, nitro, $-\text{NHC}(=\text{O})\text{R}_x$, $-\text{NR}_x\text{R}_y$, $-\text{C}(=\text{O})\text{NR}_x\text{R}_y$, $-\text{NHC}(=\text{O})\text{NR}_x\text{R}_y$, $-(\text{SO}_2)_m\text{R}_6$ (wherein R_6 , R_x , R_y and m are as defined earlier), carboxy, cycloheteroalkyl, cycloheteroalkylalkyl, heterocyclyl, heteroaryl, heterocyclalkyl or heteroarylalkyl. The aryl group may optionally be fused with cycloalkyl group, wherein the cycloalkyl group may optionally contain heteroatoms selected from O, N and S.

10 The term "aryloxy" denotes the group O-aryl wherein aryl is the same as defined above. The term "carboxy" as defined herein refers to $-\text{C}(=\text{O})\text{OH}$.

The term "heteroaryl," unless and otherwise specified, refers to an aromatic ring structure containing 5 or 6 ring atoms, or a bicyclic aromatic group having 8 to 10 ring atoms, including one or more heteroatom(s) independently selected from N, O and S, optionally substituted with 1 to 3 substituent(s) selected from halogen (F, Cl, Br, I), hydroxy, alkyl, alkenyl, alkynyl, cycloalkyl, acyl, carboxy, $-\text{COOR}_5$ (wherein R_5 as defined earlier), aryl, alkoxy, aralkyl, cyano, nitro, $-\text{NR}_x\text{R}_y$, $-\text{C}(=\text{O})\text{NR}_x\text{R}_y$ and $-\text{NHC}(=\text{O})\text{NR}_x\text{R}_y$, $-\text{SO}_2\text{R}_6$, $-\text{OC}(=\text{O})\text{NR}_x\text{R}_y$ (wherein R_6 , R_x and R_y are as defined earlier). Unless otherwise constrained by the definition, the substituents are attached to the ring atom, be it carbon or heteroatom. Examples of heteroaryl groups are pyridinyl, pyridazinyl, pyrimidinyl, pyrrolyl, oxazolyl, thiazolyl, thienyl, isoxazolyl, triazinyl, furanyl, benzofuranyl, indolyl, benzothiazolyl, benzoxazolyl, and the like.

The term "heterocyclyl," unless otherwise specified, refers to a un(saturated) monocyclic or bicyclic cycloalkyl group having 5 to 10 atoms in which 1 to 3 carbon atoms in a ring are replaced by heteroatoms selected from O, S and N, and includes optionally benzofused or fused heteroaryl of 5-6 ring members and/or are optionally substituted, wherein the substituents are selected from halogen (F, Cl, Br, I), hydroxy, alkyl, alkenyl, alkynyl, cycloalkyl, acyl, aryl, alkoxy, alkaryl, cyano, nitro, oxo, carboxy, $-\text{COOR}_5$ (wherein R_5 is as defined earlier), $-\text{C}(=\text{O})\text{NR}_x\text{R}_y$, $-\text{SO}_2\text{R}_6$, $-\text{O}-\text{C}(=\text{O})\text{NR}_x\text{R}_y$, $-\text{NHC}(=\text{O})\text{NR}_x\text{R}_y$, $-\text{NR}_x\text{R}_y$ (wherein R_x and R_y are as defined earlier). Unless otherwise constrained by the definition, the substituents are attached to a ring atom, be it carbon or heteroatom. Also, unless otherwise constrained by the definition, the heterocyclyl ring

may optionally contain one or more olefinic bond(s). Examples of heterocyclyl groups are tetrahydrofuranyl, dihydrofuranyl, dihydropyridinyl, dihydrobenzofuranyl, azabicyclohexyl, dihydroindolyl, piperidinyl or piperazinyl.

The term "cycloheteroalkyl" unless and otherwise specified, refers to nonaromatic
 5 ring structure containing 5 or 6 ring atoms, or a bicyclic aromatic group having 8 to 10 ring atoms, including one or more heteroatom(s) independently selected from N, O and S optionally substituted with 1 to 3 substituent(s) selected from halogen (F, Cl, Br, I), hydroxy, alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, heterocyclyl, heteroarylalkyl, heterocyclylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, acyl, carboxy, -COOR₅
 10 (wherein R₅ is as defined earlier), aryl, alkoxy, aralkyl, cyano, nitro, -NR_xR_y, -C(=O)NR_xR_y and -NHC(=O)NR_xR_y, -SO₂R₆, -OC(=O)NR_xR_y (wherein R₆, R_x and R_y are as defined earlier). Also the cycloheteroalkyl group contains at least one sp³-hybridized carbon. Unless otherwise constrained by the definition, the substituents are attached to a ring atom, be it carbon or heteroatom. Examples of cycloheteroalkyl groups are
 15 isoxazoline, thiazoline, oxazoline and the like.

The term "heteroarylalkyl" refers to heteroaryl group which is linked through alkyl portion, wherein the alkyl and heteroaryl are as defined earlier.

The term "heterocyclylalkyl" refers to heterocyclyl group which is linked through alkyl portion, wherein the alkyl and heterocyclyl are as defined earlier.

20 The term "cycloheteroalkylalkyl" refers to cycloheteroalkyl group which is linked through alkyl portion, wherein the alkyl and cycloheteroalkyl are as defined earlier

The term "acyl" refers to -C(=O)R'' wherein R'' is selected from the group alkyl, cycloalkyl, aryl, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl or heterocyclylalkyl.

"Substituted amino" unless otherwise specified refers to a group -N(R_k)₂ wherein
 25 each R_k is independently selected from hydrogen [provided that both R_k groups are not hydrogen (defined as "amino")], alkyl, alkenyl, alkynyl, aralkyl, carboxy, -COOR₅ (wherein R₅ is as defined earlier), cycloalkyl, aryl, cycloheteroalkyl, cycloheteroalkylalkyl, heteroaryl, heterocyclyl, heterocyclylalkyl, heteroarylalkyl, acyl, S(O)_mR₆ (wherein m and R₆ is as defined above), -C(=R_v)NR_xR_y (wherein R_v is O or S) or
 30 -NHC(=R_v)NR_xR_y (wherein R_v, R_x and R_y are as defined earlier).

Unless otherwise constrained by the definition, all substituents may optionally be further substituted by 1-3 substituents chosen from alkyl, aralkyl, cycloalkyl, aryl, carboxy, $-\text{COOR}_5$ (wherein R_5 is as defined earlier), heteroaryl, heterocyclyl, carboxy, hydroxy, alkoxy, halogen, CF_3 , cyano, $-\text{C}(=\text{R}_v)\text{NR}_x\text{R}_y$, $-\text{O}(\text{C}=\text{O})\text{NR}_x\text{R}_y$ (wherein R_x , R_y and R_v are as defined earlier) and $-\text{OC}(=\text{R}_v)\text{NR}_x\text{R}_y$, $-\text{S}(\text{O})_m\text{R}_6$ (where R_6 is as defined above and m is 0, 1 or 2).

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

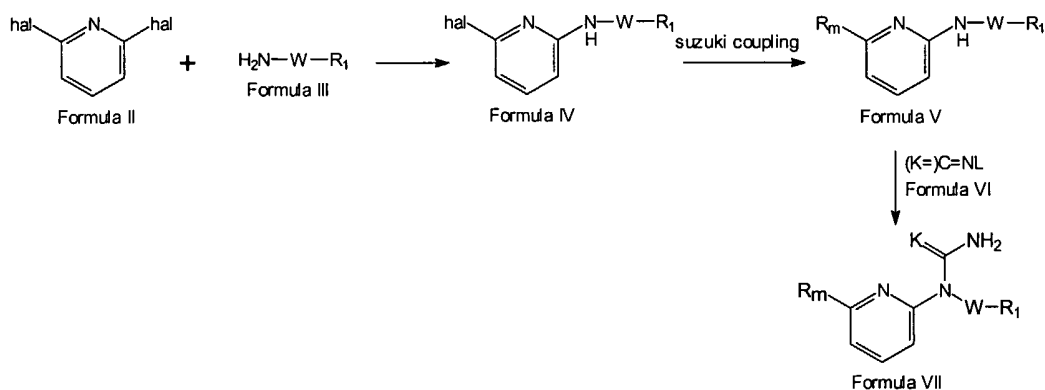
The compounds disclosed herein generally contain one or more asymmetric carbon atoms and thus can occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. All such isomeric forms of these compounds are expressly included herein. Each stereogenic carbon may be of the R or S configuration. Although the specific compounds exemplified in this application may be depicted in a particular stereochemical configuration, compounds having either the opposite stereochemistry at any given chiral center or mixtures thereof are envisioned. Although amino acids and amino acid side chains may be depicted in a particular configuration, both natural and unnatural forms are envisioned.

The term "pharmaceutically acceptable salts" refers to salts of the free acids, which substantially possess the desired pharmacological activity of the free acid and which are neither biologically nor otherwise undesirable. Suitable inorganic base addition salts include, but are not limited to aluminium, calcium, lithium, magnesium, potassium, sodium and zinc salts. Suitable organic base addition salts include, but are not limited to primary, secondary and tertiary amines, cyclic amines, *N,N'*-dibenzylethylenediamine, chlorprocaine, choline, diethanolamine, ethylenediamine and procaine salts. The pharmaceutically acceptable salts may be prepared by the conventional methods known in the prior art.

The salt forms may differ from the compound described herein in certain physical properties such as solubility.

Detailed Description of the Invention

Scheme I



The compounds disclosed herein may be prepared by techniques well known in the art and familiar to a practitioner skilled in art of this invention. In addition, the compounds of the present invention may be prepared by the processes described herein, these 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.

The compound of Formula VII can be prepared by Scheme I, thus a compound of Formula II [wherein hal is halogen (Cl, Br, I)] is reacted with a compound of Formula III (wherein W and R₁ are as defined earlier) to furnish a compound of Formula IV, which undergoes Suzuki coupling to yield a compound of Formula V (wherein R_m represents an aryl or heteroaryl group), which is reacted with a compound of Formula VI (wherein K is oxygen or sulphur and L is a leaving group, for example, chlorosulphonyl group) to furnish a compound of Formula VII.

The reaction of a compound of Formula II with a compound of Formula III to form a compound of Formula IV can be carried out with catalyst such as *tetrakis*(triphenyl phosphine)palladium (0), *tetrakis*(tricyclohexylphosphine)palladium (0) or *tetrakis*(*tert*-butylphosphine)palladium (0) in an organic solvent such as dimethylformamide, tetrahydrofuran, diethyl ether or dioxane.

The compound of Formula IV undergoes a Suzuki coupling to form a compound of Formula V with organoboron reagents such as aryl or heteroaryl boronic acid or other accepted Suzuki reagents and catalyst such as *tetrakis*(triphenylphosphine)palladium (0),

tetrakis(tricyclohexylphosphine)palladium (0) or *tetrakis*(tri-*tert*-butylphosphine)palladium (0) in an organic solvent such as dimethylformamide, tetrahydrofuran, dioxane, toluene, ethanol, or diethyl ether in the presence of a base for example, potassium carbonate, sodium carbonate, lithium carbonate or tripotassium phosphate.

Alternatively, a compound of Formula IV can undergo various C-C coupling reactions to form a compound of Formula V, as described in Li and Gribble, Palladium in Heterocyclic Chemistry: A Guide for Synthetic Chemist, Vol. 20, Pergamon, Pg 1-18 (2000).

The reaction of a compound of Formula V with a compound of Formula VI to form a compound of Formula VII can be carried out in an organic solvent such as dichloroethane, dichloromethane, carbon tetrachloride or chloroform.

Alternatively, a compound of Formula VII can also be prepared by reacting a compound of Formula V with an appropriate amine in the presence of reagents such as carbonyldiimidazole (CDI), triphosgene and ammonium hydroxide, phosgene and ammonium hydroxide or carbamates such as phenyl carbamate or *p*-nitrophenyl carbamate. Also, optionally thiocarbonyldiimidazole (TCDI), isothiocyanates or thiophosgene in ammonium hydroxide can be used.

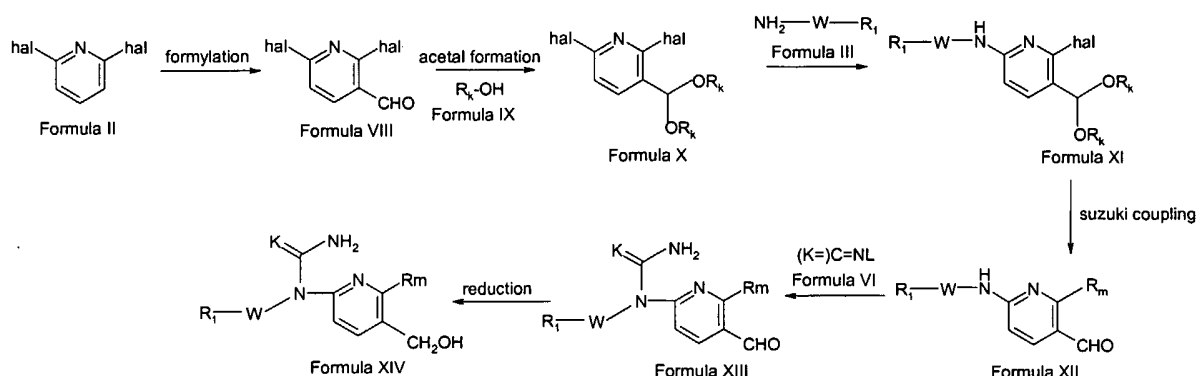
The compounds prepared following Scheme I are:

- N*-(2-Fluorobenzyl)-*N*-[6-(4-fluorophenyl)-pyridin-2-yl]-urea (Compound No. 1),
N-(2-Fluorobenzyl)-*N*-[6-(4-chlorophenyl)-pyridin-2-yl]-urea (Compound No. 2),
N-(2-Fluorobenzyl)-*N*-[6-(2-methoxyphenyl)-pyridin-2-yl]-urea (Compound No. 3),
N-(2-Fluorobenzyl)-*N*-[6-(4-methoxyphenyl)-pyridin-2-yl]-urea (Compound No. 4),
N-Benzyl-*N*-[6-(2-chlorophenyl)-pyridin-2-yl]-urea (Compound No. 5),
N-(2-Fluorobenzyl)-*N*-[6-(2-chlorophenyl)-pyridin-2-yl]-urea (Compound No. 6),
N-(4-Fluorobenzyl)-*N*-[6-(2-chlorophenyl)-pyridin-2-yl]-urea (Compound No. 7),
N-(2-Chlorobenzyl)-*N*-[6-(2-chlorophenyl)-pyridin-2-yl]-urea (Compound No. 8),
N-(2-Chlorobenzyl)-*N*-[6-(2-methoxyphenyl)-pyridin-2-yl]-urea (Compound No. 9),
N-(2-Chlorobenzyl)-*N*-[6-(4-chlorophenyl)-pyridin-2-yl]-urea (Compound No. 10),
N-(2-Chlorobenzyl)-*N*-[6-(2-fluorophenyl)-pyridin-2-yl]-urea (Compound No. 11),
N-(2-Chlorobenzyl)-*N*-[6-(4-fluorophenyl)-pyridin-2-yl]-urea (Compound No. 12),
N-(2-Chlorobenzyl)-*N*-[6-(3,5-difluorophenyl)-pyridin-2-yl]-urea (Compound No. 13),

- N*-(2-Chlorobenzyl)-*N*-[6-(3-fluorophenyl)-pyridin-2-yl]-urea (Compound No. 14),
N-(2-Chlorobenzyl)-*N*-[6-(2,5-difluorophenyl)-pyridin-2-yl]-urea (Compound No. 15),
N-(2-Chlorobenzyl)-*N*-[6-(3-chloro-4-fluorophenyl)-pyridin-2-yl]-urea (Compound No. 16),
- 5 *N*-(2-Chlorobenzyl)-*N*-[6-(3,5-dimethylphenyl)-pyridin-2-yl]-urea (Compound No. 17),
N-(2,4-Dichlorobenzyl)-*N*-[6-(2-chlorophenyl)-pyridin-2-yl]-urea (Compound No. 18),
N-(2,4-Dichlorobenzyl)-*N*-[6-(4-chlorophenyl)-pyridin-2-yl]-urea (Compound No. 19),
N-(2-Chlorobenzyl)-*N*-[6-(2-methylphenyl)-pyridin-2-yl]-urea (Compound No. 20),
N-(2-Chlorobenzyl)-*N*-[6-(2,4-difluorophenyl)-pyridin-2-yl]-urea (Compound No. 21),
- 10 *N*-(2,6-Dichlorobenzyl)-*N*-[6-(2-methylphenyl)-pyridin-2-yl]-urea (Compound No. 22),
N-(2,6-Dichlorobenzyl)-*N*-[6-(4-fluoro-2-methylphenyl)-pyridin-2-yl]-urea (Compound No. 23),
N-[6-(2-Chlorophenyl)-pyridin-2-yl]-*N*-(2,6-dichlorobenzyl)-urea (Compound No. 24),
N-(2,6-Dichlorobenzyl)-*N*-[6-(2,6-difluorophenyl)-pyridin-2-yl]-urea (Compound No. 25),
- 15 *N*-(2-Fluorobenzyl)-*N*-[6-(2-methylphenyl)-pyridin-2-yl]-urea (Compound No. 26),
N-[6-(2-Methylphenyl)-pyridin-2-yl]-*N*-(2-phenylethyl)-urea (Compound No. 27),
N-[6-(2-Chlorophenyl)-pyridin-2-yl]-*N*-(2-phenylethyl)-urea (Compound No. 28),
N-(3-Fluorobenzyl)-*N*-[6-(2-methylphenyl)-pyridin-2-yl]-urea (Compound No. 29),
N-[6-(2-Chlorophenyl)-pyridin-2-yl]-*N*-(3-fluorobenzyl)-urea (Compound No. 30),
- 20 *N*-(3-Fluorobenzyl)-*N*-[6-(4-fluoro-2-methylphenyl)-pyridin-2-yl]-urea (compound No. 31),
N-(2-Chlorobenzyl)-*N*-[6-(4-fluoro-2-methylphenyl)-pyridin-2-yl]-urea (Compound No. 39),
N-(2,6-Difluorobenzyl)-*N*-[6-(2-methylphenyl)-pyridin-2-yl]-urea (Compound No. 40),
- 25 *N*-(2,6-Difluorobenzyl)-*N*-[6-(4-fluoro-2-methylphenyl)-pyridin-2-yl]-urea (Compound No. 41),

- 16 -

Scheme II



The compounds of Formula XIII can be prepared by following the procedure as described in scheme II. Thus a compound of Formula II (wherein hal is the same as defined earlier) undergoes formylation to give a compound of Formula VIII, which is reacted with a compound of Formula IX (wherein R_k is alkyl, aryl, cycloalkyl, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl or heterocyclalkyl) to give a compound of Formula X, which is reacted with a compound of Formula III (wherein W and R_1 are the same as defined earlier) to give a compound of Formula XI, which undergoes suzuki coupling to give a compound of Formula XII (wherein R_m is the same as defined earlier), which is reacted with a compound of Formula VI (wherein K and L are the same as defined earlier) to give a compound of Formula XIII which undergoes reduction to give a compound of Formula XIV.

The formylation of a compound of Formula II to give a compound of Formula VIII can be carried out with methyl or ethyl formate in an organic solvent for example, tetrahydrofuran, dimethylformamide, diethylether or dioxane in the presence of a base for example, lithium diisopropylamide, butyllithium, triethylamine or *N*-methymorpholine. Alternatively, formylation of a compound of Formula II can also be carried with formylating agent for example, dimethyl formamide, triformamide, *tris*(diformylamino)methane, *tris*(dichloromethyl)amine or *N,N,N,N*-tetraformylhydrazine in the presence of a lewis acid for example, phosphorous oxychloride, aluminum trichloride or boron trichloride followed by deprotection with a strong mineral acid for example, hydrochloric acid, nitric acid or sulphuric acid.

The reaction of a compound of Formula VIII with a compound of Formula IX to give a compound of Formula X can be carried out in an organic solvent for example, methanol or ethanol in the presence of acid catalyst for example, sulphuric acid or dry hydrochloric acid.

- 5 The reaction of a compound of Formula X with a compound of Formula III to give a compound of Formula XI can be carried out in an organic solvent for example, dimethylformamide, tetrahydrofuran, diethylether or dioxane in the presence of a base for example, potassium carbonate, sodium carbonate, lithium carbonate or tripotassium phosphate in the presence of a catalyst selected from *bis*(triphenylphosphine)palladium (II) chloride, dichloro *bis*(tricyclohexylphosphine)palladium(II),
10 *bis*(triphenylphosphine)palladium(II) dichloride or *bis*(triphenylphosphine)palladium(II) diacetate with phosphine reagent selected from triphenylphosphine or tricyclohexylphosphine.

- The compound of Formula XI undergoes Suzuki coupling to give a compound of
15 Formula XII with organoboron reagents such as aryl or heteroaryl boronic acid or other accepted Suzuki reagents and catalyst such as *tetrakis*(triphenylphosphine)palladium (0), *tetrakis*(tricyclohexylphosphine)palladium (0) or *tetrakis*(tri-*tert*-butylphosphine)palladium (0) in an organic solvent such as dimethylformamide, tetrahydrofuran, dioxane, diethyl ether, toluene or ethanol in the presence of a base for
20 example, potassium carbonate, sodium carbonate, lithium carbonate or tripotassium phosphate.

 The reaction of a compound of Formula XII with a compound of Formula VI to give a compound of Formula XIII can be carried out in an organic solvent such as dichloroethane, dichloromethane, carbon tetrachloride or chloroform.

- 25 Alternatively, a compound of Formula XIII can also be prepared by reacting a compound of Formula XII with an appropriate amine in the presence of reagents such as carbonyldiimidazole (CDI), triphosgene and ammonium hydroxide, phosgene and ammonium hydroxide or carbamates such as phenyl carbamate or p-nitrophenyl carbamate. Also, optionally thiocarbonyldiimidazole (TCDI), isothiocyanates or
30 thiophosgene in ammonium hydroxide can be used.

The reduction of a compound of Formula XIII to give a compound of Formula XIV can be carried out with sodium borohydride, sodium cyanoborohydride or lithium borohydride.

Also, a compound of Formula XI can undergo various C-C coupling reactions following the procedure as described in Li and Gribble, Palladium in Heterocyclic Chemistry: A Guide for Synthetic Chemist, Vol. 20, Pergamon, Pg 1-18 (2000).

Compounds prepared following scheme II are:

N-[6-(2-Chlorophenyl)-5-(hydroxymethyl)-pyridin-2-yl]-*N*-(2-fluorobenzyl)-urea (Compound No. 32),

N-[6-(2-Chlorophenyl)-5-(hydroxymethyl)-pyridin-2-yl]-*N*-(2,6-dichlorobenzyl)-urea (Compound No. 33),

N-(2,6-Dichlorobenzyl)-*N*-[6-(4-fluoro-2-methylphenyl)-5-(hydroxymethyl)-pyridin-2-yl]-urea (Compound No. 34),

N-(2,6-Difluorobenzyl)-*N*-[6-(2,4-difluorophenyl)-5-(hydroxymethyl)-pyridin-2-yl]-urea (Compound No. 35),

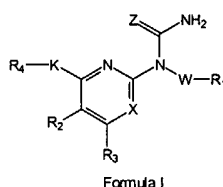
N-(2,6-Difluorobenzyl)-*N*-[6-(4-fluoro-2-methylphenyl)-5-(hydroxymethyl)-pyridin-2-yl]-urea (Compound No. 36),

N-(2,6-Dichlorobenzyl)-*N*-[5-(hydroxymethyl)-6-(2-methylphenyl)-pyridin-2-yl]-urea (Compound No. 37),

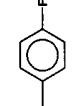
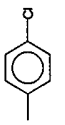
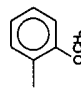
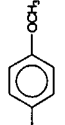
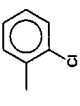
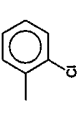
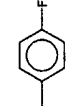
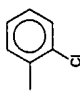
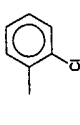
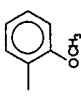
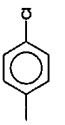
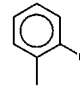
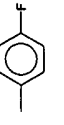
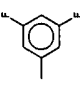
N-[6-(2-Chlorophenyl)-5-(hydroxymethyl)-pyridin-2-yl]-*N*-(2,6-difluorobenzyl)-urea (compound No. 38),

Above-mentioned compounds produced by scheme I and II are listed below in Table I

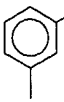
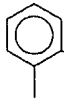
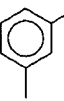
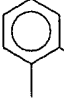
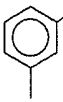
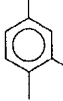
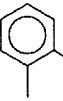
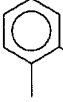
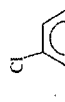
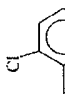
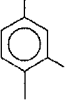
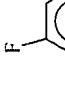
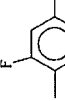
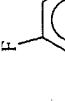
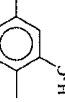
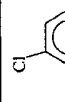
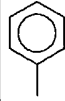
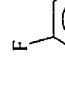
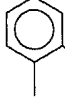
TABLE I

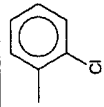
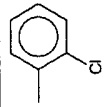
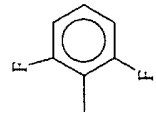
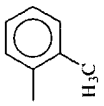
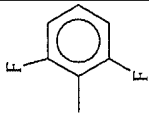
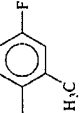


(wherein X is carbon, K is a direct bond, Z is oxygen, and R₃=H)

Compound No.	W	R ₁	R ₂	R ₄	Compound No.	W	R ₁	R ₂	R ₄
1	-CH ₂		-H		2	-CH ₂		-H	
3	-CH ₂		-H		4	-CH ₂		-H	
5	-CH ₂		-H		6	-CH ₂		-H	
7	-CH ₂		-H		8	-CH ₂		-H	
9	-CH ₂		-H		10	-CH ₂		-H	
11	-CH ₂		-H		12	-CH ₂		-H	
13 *	-CH ₂		-H		14	-CH ₂		-H	

Compound No.	W	R ₁	R ₂	R ₄	Compound No.	W	R ₁	R ₂	R ₄
15.	-CH ₂		-H		16	-CH ₂		-H	
17	-CH ₂		-H		18	-CH ₂		-H	
19	-CH ₂		-H		20	-CH ₂		-H	
21 *	-CH ₂		-H		22.	-CH ₂		-H	
23.	-CH ₂		-H		24.	-CH ₂		-H	
25.	-CH ₂		-H		26.	-CH ₂		-H	

Compound No.	W	R ₁	R ₂	R ₄	Compound No.	W	R ₁	R ₂	R ₄
27.	- C ₂ H ₅		-H		28.	- CH ₂ C H ₂		-H	
29.	-CH ₂		-H		30.	-CH ₂		-H	
31.	-CH ₂		-H		32.	-CH ₂		-CH ₂ OH	
33.	-CH ₂		-CH ₂ OH		34.	-CH ₂		-CH ₂ OH	
35.	-CH ₂		-CH ₂ OH		36.	-CH ₂		-CH ₂ OH	
37.	-CH ₂		-CH ₂ OH		38.	-CH ₂		-CH ₂ OH	

Compound No.	W	R ₁	R ₂	R ₄	Compound No.	W	R ₁	R ₂	R ₄
39.	-CH ₂		-H		40.	-CH ₂		-H	
41.	-CH ₂		-H						

* represents hypothetical compounds.

EXAMPLES

Example 1: Synthesis of *N*-(2-chlorobenzyl)-*N*-[6-(2-chlorophenyl)-pyridin-2-yl]-urea (Compound No. 8)

5 **Step a: Synthesis of (6-bromopyridin-2-yl)-(2-chlorobenzyl)-amine**

To a mixture of 2,6-dibromopyridine (2.50 g, 10.55 mmol), triphenylphosphine (0.276 g, 1.055 mmol) and dry potassium carbonate (3.208 g, 23.22 mmol) in dry dimethylformamide (15 ml), was added *bis*(triphenylphosphine)palladium (II) chloride (0.074 g, 0.105 mmol) under an argon atmosphere. The resulting mixture was stirred at room temperature for 10 minutes followed by addition of 2-chlorobenzylamine (1.279 ml, 10.55 mmol) under an argon atmosphere. The contents of the reaction mixture were heated at 110 °C for 15 hours. The reaction mixture was cooled to room temperature, filtered and evaporated under reduced pressure. The residue thus obtained was purified by column chromatography using 10% ethyl acetate in hexane as eluent to furnish the title compound (1.25 g).

Step b: Synthesis of (2-chlorobenzyl)-[6-(2-chlorophenyl)-pyridin-2-yl]-amine

To the mixture of compound obtained from step *a* above (0.335 g, 1.128 mmol) and 2-chlorobenzenboronic acid (0.352 g, 2.251 mmol) which was evacuated for 30 minutes and flushed with argon, was added dry potassium carbonate (0.32 g, 2.251 mmol), *tetrakis* (triphenylphosphine)palladium (0) (0.0652 g, 0.0564 mmol) and dry dimethylformamide (5 ml) under an argon atmosphere. The reaction mixture was heated at 90-100 °C for 12 hours. The reaction mixture was cooled to room temperature and poured into cold water. The organic compound was 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 10% ethylacetate in hexane as eluent to furnish the title compound (0.326 g).

Step c: Synthesis of *N*-(2-chlorobenzyl)-*N*-[6-(2-chlorophenyl)-pyridin-2-yl]-urea

To the solution of compound obtained from step *b* above (0.315 g, 0.960 mmol) in 1,2-dichloroethane (5 ml), was added chlorosulphonyl isocyanate (0.503 ml, 5.762 mmol). The reaction mixture was stirred at room temperature for overnight. The reaction mixture

was poured into a saturated solution of sodium bicarbonate and extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous sodium sulphate, filtered and evaporated under reduced pressure. The residue thus obtained was purified by column chromatography using 40% ethyl acetate in hexane as eluent to furnish the title compound (0.17 g).

^1H NMR (CDCl_3 , 300MHz): δ 7.66-7.63 (1H, d, $J=9.00\text{Hz}$, Ar-H), 7.54-7.50 (2H, m, Ar-H), 7.42-7.36 (3H, m, Ar-H), 7.23-7.20 (4H, m, Ar-H), 6.73-6.70 (1H, d, $J=9.00\text{Hz}$, Ar-H), and 5.31 (2H, s, $-\text{CH}_2\text{Ph}$).

Mass (positive ion mode) m/z : 374 [M^++1+2] and 372 [M^++1].

10 The analogues of *N*-(2-chlorobenzyl)-*N*-[6-(2-chlorophenyl)-pyridin-2-yl]-urea (Compound No.8) described below, were obtained by replacing appropriate amine in place of 2-chlorobenzylamine, respectively, as applicable in each case.

N-(2-Fluorobenzyl)-*N*-[6-(4-fluorophenyl)-pyridin-2-yl]-urea (Compound No. 1)

15 ^1H NMR (CDCl_3 , 300MHz): δ 7.85-7.82 (2H, m, Ar-H), 7.80-7.65 (2H, m, Ar-H), 7.32-6.84 (7H, m, Ar-H), 6.84-6.81 (1H, d, $J=9.00\text{Hz}$, Ar-H) and 5.30 (2H, s, $-\text{CH}_2\text{Ph}$).

IR (KBr): 3326 ($-\text{NH}_2$), 1683 ($-\text{C}(=\text{O})$), 1580, 1510, 1457, 1372, 1286 and 794cm^{-1}

Mass (positive in mode) m/z : 340 [M^++1].

N-(2-Fluorobenzyl)-*N*-[6-(4-chlorophenyl)-pyridin-2-yl]-urea (Compound No. 2)

20 ^1H NMR (CDCl_3 , 300MHz): δ 7.80-7.77 (2H, m, Ar-H), 7.69-7.64 (1H, m, Ar-H), 7.48-7.45 (2H, m, Ar-H), 7.34-7.32 (1H, m, Ar-H), 7.26-7.21 (2H, m, Ar-H), 7.09-7.04 (2H, m, Ar-H), 6.87-6.84 (1H, d, $J=9.00\text{Hz}$, Ar-H) and 5.30 (2H, s, $-\text{CH}_2\text{Ph}$).

IR (KBr): 3330 ($-\text{NH}_2$), 1684 ($-\text{C}(=\text{O})$), 1581, 1455, 1371, 1090 and 794cm^{-1}

Mass (positive ion mode) m/z : 358 [M^++1+2] and 356 [M^++1].

N-(2-Fluorobenzyl)-*N*-[6-(2-methoxyphenyl)-pyridin-2-yl]-urea (Compound No. 3)

25 ^1H NMR (CDCl_3 , 300MHz): δ 7.63-7.61 (2H, m, Ar-H), 7.58-7.56 (2H, m, Ar-H), 7.38-7.33 (1H, m, Ar-H), 7.09-7.02 (4H, m, Ar-H), 6.80-6.79 (2H, m, Ar-H), 5.30 (2H, s, $-\text{CH}_2\text{Ph}$) and 3.86 (3H, s, $-\text{OCH}_3$).

IR (KBr): 3393 ($-\text{NH}_2$), 1680 ($-\text{C}(=\text{O})$), 1583, 1453, 1363, 1234 and 757cm^{-1}

Mass (positive ion mode) m/z: 352 [$M^+ + 1$].

N-(2-Fluorobenzyl)-*N*-[6-(4-methoxyphenyl)-pyridin-2-yl]-urea (Compound No. 4)

^1H NMR (CDCl_3 , 300MHz): δ 7.82-7.79 (2H, d, $J=9.00\text{Hz}$, Ar-H), 7.64-7.59 (1H, m, Ar-H), 7.32-7.21 (4H, m, Ar-H), 7.10-6.99 (4H, m, Ar-H), 6.77-6.75 (2H, d, $J=9.00\text{Hz}$), 5.30
5 (2H, s, $-\text{CH}_2\text{Ph}$) and 3.87 (3H, s, $-\text{OCH}_3$).

IR (KBr): 3278 ($-\text{NH}_2$), 1685 ($-\text{C}(=\text{O})$), 1581, 1455, 1369, 1176 and 789cm^{-1} .

Mass (positive ion mode) m/z: 352 [$M^+ + 1$].

N-Benzyl-*N*-[6-(2-chlorophenyl)-pyridin-2-yl]-urea (Compound No. 5)

^1H NMR (CDCl_3 , 300MHz): δ 7.64-7.49 (3H, m, Ar-H), 7.42-7.31 (8H, m, Ar-H), 6.90-
10 6.87 (1H, d, $J=9.00\text{Hz}$, Ar-H) and 5.27 (2H, s, $-\text{CH}_2\text{Ph}$).

Mass (positive ion mode) m/z: 340 [$M^+ + 1 + 2$] and 338 [$M^+ + 1$].

N-(2-Fluorobenzyl)-*N*-[6-(2-chlorophenyl)-pyridin-2-yl]-urea (Compound No. 6)

^1H NMR (CDCl_3 , 300MHz): δ 7.86-7.84 (1H, m, Ar-H), 7.66-7.50 (1H, m, Ar-H), 7.47-
7.35 (5H, m, Ar-H), 7.24-7.04 (3H, m, Ar-H), 6.83-6.80 (1H, d, $J=9.00\text{Hz}$, Ar-H), and
15 5.32 (2H, s, $-\text{CH}_2\text{Ph}$).

IR (KBr): 3283 ($-\text{NH}_2$), 1684 ($-\text{C}(=\text{O})$), 1582, 1447, 1366, 1228 and 759cm^{-1} .

Mass (positive ion mode) m/z: 356 [$M^+ + 1$].

N-(4-Fluorobenzyl)-*N*-[6-(2-chlorophenyl)-pyridin-2-yl]-urea (Compound No. 7)

^1H NMR (CDCl_3 , 300MHz): δ 7.65 (1H, m, Ar-H), 7.52-7.30 (7H, m, Ar-H), 7.22-6.99
20 (2H, m, Ar-H), 6.87-6.84 (1H, d, $J=9.00\text{Hz}$, Ar-H) and 5.22 (2H, s, $-\text{CH}_2\text{Ph}$).

IR (KBr): 3349 ($-\text{NH}_2$), 1684 ($-\text{C}(=\text{O})$), 1582, 1509, 1364, 1224 and 759cm^{-1} .

Mass (positive ion mode) m/z: 358 [$M^+ + 1 + 2$] and 356 [$M^+ + 1$].

N-(2-Chlorobenzyl)-*N*-[6-(2-methoxyphenyl)-pyridin-2-yl]-urea (Compound No. 9)

^1H NMR (CDCl_3 , 300MHz): δ 7.63-7.59 (2H, m, Ar-H), 7.44-7.33 (3H, m, Ar-H), 7.19-
25 7.18 (3H, m, Ar-H), 7.11-6.95 (2H, m, Ar-H), 6.65-6.62 (1H, d, $J=9.00\text{Hz}$, Ar-H), 5.29
(2H, s,

$-\text{CH}_2\text{Ph}$) and 3.86 (3H, s, $-\text{OCH}_3$).

IR (KBr): 3280 (-NH₂), 1678 (-C(=O)), 1585, 1437, 1358, 1236, 1178 and 746cm⁻¹.

Mass (positive ion mode) m/z: 370 [M⁺+1+2] and 368 [M⁺+1].

N-(2-Chlorobenzyl)-N-[6-(4-chlorophenyl)-pyridin-2-yl]-urea (Compound No. 10)

¹H NMR (CDCl₃, 300MHz): δ 7.81-7.78 (1H, d, J=9.00Hz, Ar-H), 7.45-7.32 (4H, m, Ar-H), 7.20-7.09 (5H, m, Ar-H), 6.65-6.62 (1H, d, J=9.00Hz) and 5.25 (2H, s, -CH₂Ph).

Mass (positive ion mode) m/z: 374 [M⁺+1+2] and 372 [M⁺+1].

N-(2-Chlorobenzyl)-N-[6-(2-fluorophenyl)-pyridin-2-yl]-urea (Compound No. 11)

¹H NMR (CDCl₃, 300MHz): δ 7.85-7.46 (4H, brm, Ar-H), 7.44-7.27 (7H, brm, Ar-H), 7.12-7.09 (2H, m, -NH₂) and 5.20 (2H, s, -CH₂Ph).

Mass (positive ion mode) m/z: 358 [M⁺+1+2] and 356 [M⁺+1].

N-(2-Chlorobenzyl)-N-[6-(4-fluorophenyl)-pyridin-2-yl]-urea (Compound No. 12)

¹H NMR (CDCl₃, 300MHz): δ 7.86-7.82 (2H, m, Ar-H), 7.67-7.62 (1H, m, Ar-H), 7.41-7.40 (1H, m, Ar-H), 7.33-7.16 (6H, m, Ar-H), 6.70-6.67 (1H, d, J=9.00Hz, Ar-H) and 5.31 (2H, s,

-CH₂Ph).

Mass (positive ion mode) m/z: 358 [M⁺+1+2] and 356 [M⁺+1].

~~N-(2-Chlorobenzyl)-N-[6-(3,5-difluorophenyl)-pyridin-2-yl]-urea (Compound No. 13)~~

N-(2-Chlorobenzyl)-N-[6-(3-fluorophenyl)-pyridin-2-yl]-urea (Compound No. 14)

¹H NMR (CDCl₃, 300MHz): δ 7.58-7.56 (2H, m, Ar-H), 7.39-7.28 (4H, m, Ar-H), 7.18-7.06 (4H, m, Ar-H), 6.65-6.63 (1H, d, J=9.00Hz, Ar-H) and 5.23 (2H, s, -CH₂Ph).

Mass (positive ion mode) m/z: 358 [M⁺+1+2] and 356 [M⁺+1].

N-(2-Chlorobenzyl)-N-[6-(2,5-difluorophenyl)-pyridin-2-yl]-urea (Compound No. 15)

¹H NMR (CDCl₃, 300MHz): δ 7.60-7.38 (1H, m, Ar-H), 7.35-7.30 (3H, m, Ar-H), 7.19-7.04 (5H, m, Ar-H), 6.68-6.66 (1H, d, J=6.00Hz, Ar-H) and 5.24 (2H, s, -CH₂Ph).

Mass (positive ion mode) m/z: 376 [M⁺+1+2] and 374 [M⁺+1].

m.pt.: 159.6-160.5 °C.

N-(2-Chlorobenzyl)-*N*-[6-(3-chloro-4-fluorophenyl)-pyridin-2-yl]-urea (Compound No. 16)

¹H NMR (CDCl₃, 300MHz): δ 7.83-7.80 (1H, m, Ar-H), 7.66-7.56 (2H, m, Ar-H), 7.35-7.32 (1H, m, Ar-H), 7.24-7.12 (5H, m, Ar-H), 6.68-6.65 (1H, d, *J*=9.00Hz, Ar-H) and 5.24 (2H, s, -CH₂Ph).

Mass (positive ion mode) *m/z*: 392 [*M*⁺+1+2] and 390 [*M*⁺+1].

N-(2-Chlorobenzyl)-*N*-[6-(3,5-dimethylphenyl)-pyridin-2-yl]-urea (Compound No. 17)

¹H NMR (CDCl₃, 300MHz): δ 7.65-7.59 (1H, m, Ar-H), 7.52-7.10 (8H, brm, Ar-H), 6.67-6.69 (1H, d, *J*=9.00Hz, Ar-H), 5.30 (2H, s, -CH₂Ph) and 2.41 (6H, s, 2x-CH₃).

10 Mass (positive ion mode) *m/z*: 368 [*M*⁺+1+2] and 366 [*M*⁺+1].

N-(2,4-Dichlorobenzyl)-*N*-[6-(2-chlorophenyl)-pyridin-2-yl]-urea (Compound No. 18)

¹H NMR (CDCl₃, 300MHz): δ 7.68-7.51 (1H, m, Ar-H), 7.50-7.37 (4H, m, Ar-H), 7.18-7.15 (4H, m, Ar-H), 6.69-6.68 (1H, d, *J*=9.00Hz, Ar-H) and 5.25 (2H, s, -CH₂Ph).

Mass (positive ion mode) *m/z*: 408 [*M*⁺+1+2] and 406 [*M*⁺+1].

15 *N*-(2,4-Dichlorobenzyl)-*N*-[6-(4-chlorophenyl)-pyridin-2-yl]-urea (Compound No. 19)

¹H NMR (CDCl₃, 300MHz): δ 7.80-7.77 (1H, d, *J*=9.00Hz, Ar-H), 7.69-7.64 (2H, m, Ar-H), 7.48-7.34 (4H, brm, Ar-H), 7.18-7.10 (2H, m, Ar-H), 6.67-6.65 (1H, d, *J*=6.00Hz, Ar-H) and 5.25 (2H, s, -CH₂Ph).

Mass (positive ion mode) *m/z*: 408 [*M*⁺+1+2] and 406 [*M*⁺+1].

20 *N*-(2-Chlorobenzyl)-*N*-[6-(2-methylphenyl)-pyridin-2-yl]-urea (Compound No. 20)

¹H NMR (CDCl₃, 300MHz): δ 7.63-7.60 (1H, d, *J*=9.00Hz, Ar-H), 7.41-7.19 (8H, brm, Ar-H), 7.06-7.04 (1H, d, *J*=6.00Hz, Ar-H), 6.68-6.65 (1H, d, *J*=9.00Hz, Ar-H), 5.31 (2H, s, -CH₂Ph) and 2.38 (3H, s, -CH₃).

Mass (positive ion mode) *m/z*: 354 [*M*⁺+1+2] and 352 [*M*⁺+1].

25 *N*-(2,6-Dichlorobenzyl)-*N*-[6-(2-methylphenyl)-pyridin-2-yl]-urea (Compound No. 22)

¹H NMR (DMSO-*d*₆, 300 MHz): δ 7.81-7.75 (1H, t, *J*=18.00Hz, Ar-H), 7.36-7.19 (6H, m, Ar-H), 7.09-7.06 (1H, d, *J*=9.00Hz, Ar-H), 6.91 (2H, brs, Ar-H), 5.30 (2H, s, -CH₂Ph) and 2.23 (3H, s, -CH₃).

Mass (positive ion mode) m/z: 388 [$M^+ + 1 + 2$] and 386 [$M^+ + 1$].

m.pt.: 163.7-164.6 °C.

N-(2,6-Dichlorobenzyl)-*N*-[6-(4-fluoro-2-methylphenyl)-pyridin-2-yl]-urea (Compound No. 23)

- 5 ^1H NMR (DMSO- d_6 , 300 MHz): δ 7.35-7.30 (1H, m, Ar-H), 7.25-7.08 (8H, m, Ar-H), 6.80 (2H, s, -NH₂), 5.28 (2H, s, -CH₂Ph) and 2.23 (3H, s, -CH₃).

Mass (positive ion mode) m/z: 406 [$M^+ + 1 + 2$] and 404 [$M^+ + 1$].

m.pt.: 148.1-149.4 °C.

N-[6-(2-Chlorophenyl)-pyridin-2-yl]-*N*-(2,6-dichlorobenzyl)-urea (Compound No. 24)

- 10 ^1H NMR (DMSO- d_6 , 300 MHz): δ 7.84-7.79 (1H, m, Ar-H), 7.57-7.55 (1H, m, Ar-H), 7.44 (3H, brs, Ar-H), 7.36-7.31 (3H, m, Ar-H), 7.26-7.16 (2H, m, Ar-H), 6.98 (2H, s, -NH₂) and 5.31 (2H, s, -CH₂Ph).

Mass (positive ion mode) m/z: 408 [$M^+ + 1 + 2$] and 406 [$M^+ + 1$].

m.pt.: 154.1-154.9 °C.

- 15 *N*-(2,6-Dichlorobenzyl)-*N*-[6-(2,6-difluorophenyl)-pyridin-2-yl]-urea (Compound No. 25)

^1H NMR (DMSO- d_6 , 300 MHz): δ 7.86-7.81 (1H, m, Ar-H), 7.57-7.52 (1H, m, Ar-H), 7.33-7.18 (7H, m, Ar-H), 7.12 (2H, s, -NH₂) and 5.31 (2H, s, -CH₂Ph).

Mass (positive ion mode) m/z: 410 [$M^+ + 1 + 2$] and 408 [$M^+ + 1$].

m.pt.: 143.6-145.1 °C.

- 20 *N*-(2-Fluorobenzyl)-*N*-[6-(2-methylphenyl)-pyridin-2-yl]-urea (Compound No. 26)

^1H NMR (CDCl₃, 300 MHz): δ 7.67-7.62 (1H, t, $J=15.00\text{Hz}$, Ar-H), 7.39-7.21 (6H, m, Ar-H), 7.11-7.04 (3H, m, Ar-H), 6.82-6.80 (1H, m, Ar-H), 5.31 (2H, brs, -CH₂Ph) and 2.37 (3H, s, -CH₃).

Mass (positive ion mode) m/z: 336 [$M^+ + 1$].

- 25 *N*-[6-(2-Methylphenyl)-pyridin-2-yl]-*N*-(2-phenylethyl)-urea (Compound No. 27)

^1H NMR (CDCl₃, 300 MHz): δ 7.79-7.74 (1H, t, $J=15.00\text{Hz}$, Ar-H), 7.38-7.18 (9H, m, Ar-H), 7.09-7.02 (2H, m, Ar-H), 4.23-4.11 (2H, m, -NCH₂CH₂Ph), 3.07-3.02 (2H, m, -NCH₂CH₂Ph) and 2.37 (3H, brs, -CH₃).

Mass (positive ion mode) m/z: 332 [$M^+ + 1$].

- 30 *N*-[6-(2-Chlorophenyl)-pyridin-2-yl]-*N*-(2-phenylethyl)-urea (Compound No. 28)

¹H NMR (CDCl₃, 300 MHz): δ 7.87-7.78 (2H, m, Ar-H), 7.52-7.39 (4H, m, Ar-H), 7.32-7.23 (5H, m, Ar-H), 7.05-7.02 (1H, d, *J*=9.00Hz, Ar-H), 4.23-4.17 (2H, t, *J*=18.00Hz, -NCH₂CH₂Ph) and 3.07-3.02 (2H, t, *J*=15.00Hz, -NCH₂CH₂Ph).

N-(3-Fluorobenzyl)-*N*-[6-(2-methylphenyl)-pyridin-2-yl]-urea (Compound No. 29)

- 5 ¹H NMR (CDCl₃, 300 MHz): δ 7.66-7.61 (1H, m, Ar-H), 7.37-7.26 (5H, m, Ar-H), 7.10-7.04 (4H, m, Ar-H), 6.81-6.78 (1H, m, Ar-H), 5.25 (2H, s, -CH₂Ph) and 2.37 (3H, s, -CH₃).

Mass (positive ion mode) *m/z*: 336 [*M*⁺+1].

m.pt.: 83-85 °C.

- 10 *N*-[6-(2-Chlorophenyl)-pyridin-2-yl]-*N*-(3-fluorobenzyl)-urea (Compound No. 30)

¹H NMR (CDCl₃, 300 MHz): δ 7.66-7.63 (1H, m, Ar-H), 7.52-7.49 (2H, m, Ar-H), 7.39-7.36 (4H, m, Ar-H), 7.26-7.10 (3H, m, Ar-H), 6.85-6.82 (1H, m, Ar-H) and 5.24 (2H, brs, -CH₂Ph).

Mass (positive ion mode) *m/z*: 358 [*M*⁺+1+2] and 356 [*M*⁺+1].

- 15 *m.pt.*: 87-91 °C.

N-(3-Fluorobenzyl)-*N*-[6-(4-fluoro-2-methylphenyl)-pyridin-2-yl]-urea (compound No. 31)

- 20 ¹H NMR (CDCl₃, 300 MHz): δ 7.66-7.60 (1H, m, Ar-H), 7.37-7.26 (2H, m, Ar-H), 7.09-6.91 (6H, m, Ar-H), 6.81-6.78 (1H, m, Ar-H), 5.24 (2H, s, -CH₂Ph) and 2.36 (3H, s, -CH₃).

Mass (positive ion mode): 354 [*M*⁺+1].

m.pt.: 95.2-96.1 °C.

N-(2-Chlorobenzyl)-*N*-[6-(4-fluoro-2-methylphenyl)-pyridin-2-yl]-urea (Compound No. 39)

- 25 ¹H NMR (CDCl₃, 300 MHz): δ 7.66-7.61 (1H, t, *J*=8.10Hz, Ar-H), 7.42-7.34 (2H, m, Ar-H), 7.22-7.19 (3H, m, Ar-H), 7.03-6.96 (3H, m, Ar-H), 6.70-6.67 (1H, d, *J*=9.00Hz, Ar-H), 5.32 (2H, s, -CH₂Ph) and 2.38 (2H, s, -CH₃).

Mass (positive ion mode) *m/z*: 372 [*M*⁺+1+2] and 370 [*M*⁺+1].

m.pt.: 172.2-176.7 °C.

- 30 *N*-(2,6-Difluorobenzyl)-*N*-[6-(2-methylphenyl)-pyridin-2-yl]-urea (Compound No. 40)

¹H NMR (CDCl₃, 300 MHz): δ 7.71-7.66 (1H, m, Ar-H), 7.36-7.16 (5H, m, Ar-H), 7.04-7.00 (2H, m, Ar-H), 6.86-6.81 (2H, m, Ar-H), 5.30 (2H, s, -CH₂Ph) and 2.32 (3H, s, -CH₃).

Mass (positive ion mode) m/z: 354 [M⁺+1].

5 *N*-(2,6-Difluorobenzyl)-*N*-[6-(4-fluoro-2-methylphenyl)-pyridin-2-yl]-urea (Compound No. 41)

¹H NMR (CDCl₃, 300 MHz): δ 7.71-7.65 (1H, m, Ar-H), 7.34-7.29 (1H, m, Ar-H), 7.20-6.95 (4H, m, Ar-H), 6.86-6.80 (2H, m, Ar-H), 5.43 (2H, brs, -CH₂Ph) and 2.31 (3H, brs, -CH₃).

10 Mass (positive ion mode) m/z: 372 [M⁺+1].

m.pt.: 165-167 °C.

Example 2: Synthesis of *N*-[6-(2-chlorophenyl)-5-(hydroxymethyl)-pyridin-2-yl]-*N*-(2-fluorobenzyl)-urea (Compound No. 32)

Step a: Synthesis of 2,6-dibromonicotinaldehyde

15 To a solution of lithium diisopropylamide (2M in tetrahydrofuran, 31.65 ml, 63.33 mmol) at -78 °C, was added dropwise a solution of 2,6-dibromopyridine (10 g, 42.21 mmol) in dry tetrahydrofuran. The mixture was stirred at -78 °C for 30 minutes. Methyl formate (422.1 mmol, 26 ml) was added and the stirring was continued at the same temperature for 2 hours. Saturated ammonium chloride was added and the mixture was
20 warmed to room temperature. The reaction mixture was extracted with ethyl acetate, dried over anhydrous sodium sulphate and evaporated under *vacuum*. The resulting mixture was purified by column chromatography over silica gel in ethyl acetate: hexane (1:19) to afford the title compound (7 g).

Step b: Synthesis of 2,6-dibromo-3-(dimethoxymethyl)-pyridine

25 To a solution of the compound obtained from step *a* above (2.5 g, 18.87 mmol) in methanol (50 ml) was added concentrated sulphuric acid (7.5 ml) and refluxed for 2-3 hours. The reaction mixture was cooled to room temperature, neutralized with saturated sodium bicarbonate and extracted with ethyl acetate. The organic layer was then washed with water, dried over anhydrous sodium sulphate, filtered and evaporated under *vacuum*
30 to afford the title compound (5.8 g).

Step c: Synthesis of 6-bromo-5-(dimethoxymethyl)-*N*-(2-fluorobenzyl)-pyridin-2-amine

To a mixture of the compound obtained from step *b* above (2.50 g, 8.04 mmol), triphenylphosphine (0.211 g, 0.804 mmol) and dry potassium carbonate (2.44 g, 17.68 mmol) in dry dimethylformamide (15 ml), was added *bis*(triphenylphosphine)palladium (II) chloride (0.056 g, 0.08 mmol) under an argon atmosphere. The resulting reaction mixture was stirred at room temperature for 10 minutes followed by addition of 2-fluorobenzylamine (0.915 ml, 8.04 mmol) under an argon atmosphere. The contents of the reaction mixture were heated at 110 °C for 15 hours. The reaction mixture was cooled to room temperature, filtered and evaporated under *vacuum*. The residue thus obtained was purified by column chromatography using 10% ethyl acetate in hexane as eluent to furnish the title compound (1.5 g).

Step d: Synthesis of 2-(2-chlorophenyl)-6-[(2-fluorobenzyl)amino]-nicotinaldehyde

To the mixture of compound obtained from step *c* above (0.300 g, 0.920 mmol) and 2-chlorobenzeneboronic acid (0.288 g, 1.840 mmol), which was evacuated for 30 minutes and flushed with argon, was added dry potassium carbonate (0.254 g, 1.840 mmol), *tetrakis*(triphenylphosphine)palladium (0) (0.0532 g, 0.0460 mmol) and dry dimethylformamide (5 ml) under an argon atmosphere. The reaction mixture was heated at 90-100 °C for 12 hours. The reaction mixture was cooled to room temperature and poured into cold water. The organic compound was extracted with ethyl acetate, washed with water, dried over anhydrous sodium sulphate, filtered and evaporated the solvent under *vacuum*. The residue thus obtained was purified by column chromatography using 10% ethyl acetate in hexane as eluent to furnish the title compound (0.25 g).

Step e: Synthesis of *N*-[6-(2-chlorophenyl)-5-formylpyridin-2-yl]-*N*-(2-fluorobenzyl)-urea

To a solution of compound obtained from step *d* above (0.225 g, 0.662 mmol) in 1,2-dichloroethane (5 ml), was added chlorosulphonyl isocyanate (0.345 ml, 3.97 mmol). The reaction mixture was stirred at room temperature for overnight. The reaction mixture was poured into a saturated solution of sodium bicarbonate and extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous sodium sulphate, filtered and evaporated under *vacuum*. The residue thus obtained was purified by column chromatography using 40% ethyl acetate in hexane as eluent to furnish the compound (0.12 g).

Step f: Synthesis of *N*-[6-(2-chlorophenyl)-5-(hydroxymethyl)-pyridin-2-yl]-*N*-(2-fluorobenzyl)-urea

To a solution of compound obtained from step *e* (0.1 g, 0.262 mmol) in methanol (5 ml) was added sodium borohydride (0.0988 g, 2.62 mmol) at 0 °C and the solution was stirred for 30 minutes. The reaction was quenched with saturated ammonium chloride solution. The reaction mixture was then diluted with ethyl acetate and the organic layer was washed with water, dried over anhydrous sodium sulphate and evaporated under vacuum. The resulting mixture was purified by column chromatography to afford the title compound (0.07 g).

¹H NMR (CDCl₃, 300MHz): δ 7.85-7.83 (1H, m, Ar-H), 7.50-7.35 (4H, m, Ar-H), 7.26-7.19 (2H, m, Ar-H), 7.10-7.04 (2H, m, Ar-H), 6.97-6.91 (1H, m, Ar-H), 5.29 (2H, brs, -CH₂Ph) and 4.51-4.36 (2H, m, -CH₂OH).

Mass (positive ion mode) m/z: 386[M⁺+1].

m.pt.: 160-161 °C.

Analogues of *N*-[6-(2-chlorophenyl)-5-(hydroxymethyl)-pyridin-2-yl]-*N*-(2-fluorobenzyl)-urea (Compound No. 32) described below were prepared similarly,

N-[6-(2-Chlorophenyl)-5-(hydroxymethyl)-pyridin-2-yl]-*N*-(2,6-dichlorobenzyl)-urea

(Compound No. 33)

¹H NMR (CDCl₃, 300 MHz): δ 7.86-7.67 (2H, m, Ar-H), 7.46-6.98 (5H, m, Ar-H), 6.72-6.70 (2H, m, Ar-H), 5.57-5.50 (2H, m, -CH₂Ph) and 4.44-4.39 (2H, m, -CH₂OH)

Mass (positive ion mode) m/z: 440 [M⁺+1+4], 438 [M⁺+1+2] and 436 [M⁺+1].

m.pt.: 179.5-186.4 °C.

N-(2,6-Dichlorobenzyl)-*N*-[6-(4-fluoro-2-methylphenyl)-5-(hydroxymethyl)-pyridin-2-yl]-urea (Compound No. 34)

¹H NMR (CDCl₃, 300 MHz): δ 7.82-7.79 (1H, d, *J*=9.00Hz, Ar-H), 7.24-6.90 (7H, m, Ar-H), 5.59 (2H, brs, -CH₂Ph), 4.36 (2H, s, -CH₂OH) and 2.10 (3H, s, -CH₃).

Mass (positive ion mode) m/z: 438 [M⁺+1+4], 436 [M⁺+1+2] and 434 [M⁺+1].

N-(2,6-Difluorobenzyl)-*N*-[6-(2,4-difluorophenyl)-5-(hydroxymethyl)-pyridin-2-yl]-urea (Compound No. 35)

¹H NMR (CDCl₃, 300 MHz): δ 7.92-7.89 (1H, d, *J*=9.00Hz, Ar-H), 7.42-7.37 (1H, m, Ar-H), 7.20-7.11 (3H, m, Ar-H), 7.01-6.80 (4H, m, Ar-H), 5.41 (2H, s, -CH₂Ph) and 4.56-4.51 (2H, m, -CH₂OH).

Mass (positive ion mode) *m/z*: 406 [*M*⁺+1].

m.pt.: 159.9-168.2 °C.

N-(2,6-Difluorobenzyl)-*N*-[6-(4-fluoro-2-methylphenyl)-5-(hydroxymethyl)-pyridin-2-yl]-urea (Compound No. 36)

¹H NMR (CDCl₃, 300 MHz): δ 7.87-7.84 (1H, d, *J*=9.00Hz, Ar-H), 7.20-6.80 (7H, m, Ar-H), 5.41 (2H, s, -CH₂Ph), 4.37 (2H, brs, -CH₂OH) and 2.06-1.99 (3H, m, -CH₃).

Mass (positive ion mode) *m/z*: 402 [*M*⁺+1].

N-(2,6-Dichlorobenzyl)-*N*-[5-(hydroxymethyl)-6-(2-methylphenyl)-pyridin-2-yl]-urea (Compound No. 37)

¹H NMR (CDCl₃, 300 MHz): δ 7.82-7.79 (1H, d, *J*=9.00Hz, Ar-H), 7.34-7.21 (5H, m, Ar-H), 7.15-7.05 (3H, m, Ar-H), 5.56 (2H, brs, -CH₂Ph), 4.37 (2H, brs, -CH₂OH) and 2.03-2.00 (3H, brs, -CH₃).

Mass (positive ion mode) *m/z*: 418 [*M*⁺+1+2] and 416 [*M*⁺+1].

m.pt.: 70.8-74.3 °C.

N-[6-(2-Chlorophenyl)-5-(hydroxymethyl)-pyridin-2-yl]-*N*-(2,6-difluorobenzyl)-urea (compound No. 38)

¹H NMR (CDCl₃, 300 MHz): δ 7.95-7.63 (3H, m, Ar-H & -NH), 7.43-7.32 (3H, m, Ar-H), 7.18-7.16 (1H, m, Ar-H), 7.01-6.99 (1H, m, Ar-H), 6.82-6.77 (2H, m, Ar-H), 5.51 (1H, brm, -CHOH), 5.37 (2H, s, -CH₂Ph) and 4.40 (1H, brm, -CHOH).

Mass (positive ion mode) *m/z*: 406 [*M*⁺+1+2] and 404 [*M*⁺+1].

Example 3: p38 Inhibition Assays - Inhibition of phosphorylation of EGF receptor Peptide

This assay was carried out in the presence of 10 mM MgCl₂, 25 mM β-glycerophosphate, 10% glycerol and 100 mM HEPES buffer at pH 7.6. For a typical IC₅₀ determination, a stock solution is prepared containing all of the above components and activated p38 (5 nM). The stock solution was aliquoted into vials. A fixed volume of

DMSO or inhibitor in DMSO (final concentration of DMSO in reaction was 5%) was introduced to each vial, mixed and incubated for 15 minutes at room temperature.

EGF receptor peptide, KRELVEPLTPSGEAPNQALLR, a phosphoryl acceptor in p38-catalysed kinase reaction (1), was added to each vial to a final concentration of 200 μ M. The kinase reaction was initiated with ATP (100 μ M) and the vials were incubated at 30-degree celcius. After 30 minutes, the reactions were quenched with equal volume of 10% trifluoroacetic acid (TFA).

The phosphorylated peptide was quantified by HPLC analysis. Separation of the phosphorylated peptide from the unphosphorylated peptide was achieved on a reverse phase column (Deltapak, 5 μ M, C18 100D, part no. 011795) with a binary gradient of water and acetonitrile, each containing 0.1% TFA. IC₅₀ (concentration of inhibitor yielding 50% inhibition) was determined by plotting the % activity remaining against inhibitor concentration.

Cell based Assay for TNF- α release

Method of isolation of Human Peripheral Blood Mononuclear Cells:

Human whole blood was collected in vacutainer tubes containing EDTA as an anti coagulant. A blood sample (7 ml) was carefully layered over 5 ml PMN Cell Isolation Medium (Robbins Scientific) in a 15 ml round bottom centrifuge tubes. The sample was centrifuged at 450-500 x g for 30 - 35 minutes in a swing-out rotor at room temperature. After centrifugation the top band of cells were removed and washed 3 times with PBS w/o calcium or magnesium. The cells were centrifuged at 400 x g for 10 minutes at room temperature. The cells were resuspended in Macrophage Serum Free Medium (Gibco BRL) at concentration of 2 million cells/ml.

LPS stimulation of Human PBMNC's:

PBM cells (0.1 ml; 2 million/ml) were co-incubated with 0.1 ml of compound (10 - 0.41 μ M, final concentration) for 1 hour in flat bottom 96 well microtiter plate. Compounds were dissolved in DMSO initially and diluted in TCM for a final concentration of 0.1 % DMSO. LPS (Cal biochem, 20 mg/ml, final concentration) was then added at volume of 0.010 ml. Cultures were incubated overnight at 37 °C). Supernatant were then removed and tested by ELISA for TNF- α release. Viability was analyzed using MTT. After 0.1 ml supernatant was collected, 0.1 ml of 0.25 mg/ml of

MTT was added to remaining 0.1 ml of cells. The cells were incubated at 37 °C for 2-4 hours, then the optical density was measured at 490-650 nm.

The results of in-vitro tests are listed in Table-II

Compound No.	IC50	TNF- α	Compound No.	IC50	TNF- α
1	>100 μ M	ND	2	>100 μ M	ND
3	>100 μ M	ND	4	>100 μ M	ND
5	2.8 μ M	5.0 μ M	6	0.961 μ M	1.77 μ M
7	1.129 μ M	1.9 μ M	8	0.9+ 0.4 μ M	5.65 μ M
9	>100 μ M	ND	10	>100 μ M	ND
11	>100 μ M	ND	12	>100 μ M	ND
13 *	-	-	14	79.4 μ M	ND
15.	35.48 μ M	ND	16	Could not be tested as it led to precipitation	

- 36 -

Compound No.	IC50	TNF- α	Compound No.	IC50	TNF- α
17	> 100 μ M	ND	18	25.12 μ M	ND
19	~100 μ M	ND	20	0.873	>10 μ M
21 *	-	-	22.	8.91 μ M	ND
23.	2.15 μ M	~10 μ M	24.	>100 μ M	ND
25.	12.58 μ M	ND	26.	0.888 μ M	6.3 μ M
27.	0.978 μ M	>10 μ M	28.	Could not be tested as it led to precipitation	
29.	0.751 μ M	>10 μ M	30.	1.12 μ M	>10 μ M
31.	1.25 μ M	ND	32.	1.0 μ M	3.0 μ M
33.	>100 μ M	ND	34.	~100 μ M	ND

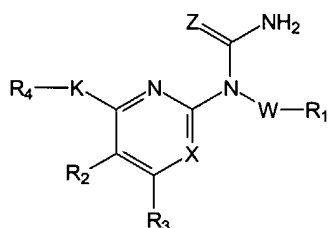
- 37 -

Compound No.	IC50	TNF- α	Compound No.	IC50	TNF- α
35.	1.58 μ M	4.7 μ M	36.	2.2 μ M	1.78 μ M
37.	>100 μ M	ND	38.	>100 μ M	ND
39.	>100 μ M	ND	40.	3.16 μ M	>10 μ M
41.	2.81 μ M	2.57 μ M			

* represents hypothetical compounds.

We Claim:

1. A compound having the structure of Formula I



Formula I

its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers, polymorphs or N-oxides wherein

Z can be oxygen, sulphur, -N(CN), -N(NO₂), or -CH(NO₂).

X can be nitrogen, or carbon.

W can be alkylene, (C₃₋₆)alkenylene, or (C₃₋₆)alkynylene (wherein double bond of said alkenylene and alkynylene cannot be attached alpha to the N atom).

K can be W or a direct bond.

R₁ can be aryl, cycloalkyl, cycloheteroalkyl, heteroaryl, or heterocyclyl.

R₂ and **R₃** can be selected from hydrogen; alkyl; alkenyl; alkynyl; cycloalkyl; cycloheteroalkyl; cycloheteroalkylalkyl; aryl; aralkyl; carboxy; -COOR₅ (wherein R₅ is selected from alkyl, aryl, aralkyl, cycloalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, heterocyclyl, heteroaryl, heteroarylalkyl, heterocyclylalkyl); -NR_pR_q (wherein R_p and R_q are independently selected from hydrogen, alkyl, cycloalkyl, cycloheteroalkyl, aryl, aralkyl, heteroaryl, heterocyclyl, cycloheteroalkylalkyl, heterocyclylalkyl, heteroarylalkyl -OC(=O)NR_xR_y [wherein R_x and R_y are selected from hydrogen, hydroxy (as restricted by the definition that both R_x and R_y cannot be -OH at the same time), alkyl, aryl, or -SO₂R₆ (wherein R₆ is selected from alkyl, cycloalkyl, cycloheteroalkyl, -NR_pR_q (wherein R_p and R_q are the same as defined above), aryl, aralkyl, heteroaryl, heterocyclyl, heterocyclylalkyl, or heteroarylalkyl), R_x and R_y may also together join to form, a heterocyclyl]; -NR_jC(=O)OR_s [wherein R_s is selected from alkyl, cycloalkyl, cycloheteroalkyl, aryl, aralkyl, heteroaryl, heterocyclyl, cycloheteroalkylalkyl, heterocyclylalkyl, or heteroarylalkyl and R_j is selected from the group consisting of hydrogen, lower (C₁-C₆) alkyl, lower (C₂-C₆) cycloalkyl, lower (C₁-C₃) aralkyl, aryl,

heteroaryl, heteroarylalkyl, or heterocyclalkyl]; $-NR_jYR_u$ [wherein Y is $-C(=O)$, $-C(=S)$ or SO_2 , R_j is the same as defined above and R_u is selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloheteroalkyl, aryl, aralkyl, heteroaryl, heterocyclalkyl, cycloheteroalkylalkyl, heterocyclalkyl, or heteroarylalkyl]; $-NR_jC(=Z)NR_xR_y$ (wherein R_j , Z, R_x and R_y are the same as defined earlier); $-CH_2OR_5$ (wherein R_5 is the same as defined above); heteroaryl; heterocyclalkyl; heteroarylalkyl or heterocyclalkyl; with the proviso that when K is a direct bond and Z is oxygen then R_3 is hydrogen or cycloheteroalkyl group.

R_4 can be aryl, cycloalkyl, cycloheteroalkyl, heteroaryl or heterocyclalkyl.

2. The compound of claim 1, wherein X is carbon, K is a direct bond, Z is oxygen, W is $-CH_2$ or $-CH_2CH_2-$, and R_2 is H or $-CH_2OH$ and R_3 are H.

3. The compound of claim 1 wherein R_1 and R_4 are optionally substituted aryl.

4. The compound of claim 3 wherein the optional substituents are halogen, alkyl or alkoxy.

5. The compound of claim 4 wherein the optional substituents are selected from chlorine, fluorine, methyl or methoxy.

6. A compound selected from the group consisting of

- N*-(2-Fluorobenzyl)-*N*-[6-(4-fluorophenyl)-pyridin-2-yl]-urea (Compound No. 1),
- N*-(2-Fluorobenzyl)-*N*-[6-(4-chlorophenyl)-pyridin-2-yl]-urea (Compound No. 2),
- N*-(2-Fluorobenzyl)-*N*-[6-(2-methoxyphenyl)-pyridin-2-yl]-urea (Compound No. 3),
- N*-(2-Fluorobenzyl)-*N*-[6-(4-methoxyphenyl)-pyridin-2-yl]-urea (Compound No. 4),
- N*-Benzyl-*N*-[6-(2-chlorophenyl)-pyridin-2-yl]-urea (Compound No. 5),
- N*-(2-Fluorobenzyl)-*N*-[6-(2-chlorophenyl)-pyridin-2-yl]-urea (Compound No. 6),
- N*-(4-Fluorobenzyl)-*N*-[6-(2-chlorophenyl)-pyridin-2-yl]-urea (Compound No. 7),
- N*-(2-Chlorobenzyl)-*N*-[6-(2-chlorophenyl)-pyridin-2-yl]-urea (Compound No. 8),
- N*-(2-Chlorobenzyl)-*N*-[6-(2-methoxyphenyl)-pyridin-2-yl]-urea (Compound No. 9),
- N*-(2-Chlorobenzyl)-*N*-[6-(4-chlorophenyl)-pyridin-2-yl]-urea (Compound No. 10),
- N*-(2-Chlorobenzyl)-*N*-[6-(2-fluorophenyl)-pyridin-2-yl]-urea (Compound No. 11),
- N*-(2-Chlorobenzyl)-*N*-[6-(4-fluorophenyl)-pyridin-2-yl]-urea (Compound No. 12),
- N*-(2-Chlorobenzyl)-*N*-[6-(3,5-difluorophenyl)-pyridin-2-yl]-urea (Compound No. 13),
- N*-(2-Chlorobenzyl)-*N*-[6-(3-fluorophenyl)-pyridin-2-yl]-urea (Compound No. 14),
- N*-(2-Chlorobenzyl)-*N*-[6-(2,5-difluorophenyl)-pyridin-2-yl]-urea (Compound No. 15),

- 17 *N*-(2-Chlorobenzyl)-*N*-[6-(3-chloro-4-fluorophenyl)-pyridin-2-yl]-urea (Compound No.
18 16),
- 19 *N*-(2-Chlorobenzyl)-*N*-[6-(3,5-dimethylphenyl)-pyridin-2-yl]-urea (Compound No. 17),
20 *N*-(2,4-Dichlorobenzyl)-*N*-[6-(2-chlorophenyl)-pyridin-2-yl]-urea (Compound No. 18),
21 *N*-(2,4-Dichlorobenzyl)-*N*-[6-(4-chlorophenyl)-pyridin-2-yl]-urea (Compound No. 19),
22 *N*-(2-Chlorobenzyl)-*N*-[6-(2-methylphenyl)-pyridin-2-yl]-urea (Compound No. 20),
23 *N*-(2-Chlorobenzyl)-*N*-[6-(2,4-difluorophenyl)-pyridin-2-yl]-urea (Compound No. 21),
24 *N*-(2,6-Dichlorobenzyl)-*N*-[6-(2-methylphenyl)-pyridin-2-yl]-urea (Compound No. 22),
25 *N*-(2,6-Dichlorobenzyl)-*N*-[6-(4-fluoro-2-methylphenyl)-pyridin-2-yl]-urea (Compound
26 No. 23),
- 27 *N*-[6-(2-Chlorophenyl)-pyridin-2-yl]-*N*-(2,6-dichlorobenzyl)-urea (Compound No. 24),
28 *N*-(2,6-Dichlorobenzyl)-*N*-[6-(2,6-difluorophenyl)-pyridin-2-yl]-urea (Compound No. 25),
29 *N*-(2-Fluorobenzyl)-*N*-[6-(2-methylphenyl)-pyridin-2-yl]-urea (Compound No. 26),
30 *N*-[6-(2-Methylphenyl)-pyridin-2-yl]-*N*-(2-phenylethyl)-urea (Compound No. 27),
31 *N*-[6-(2-Chlorophenyl)-pyridin-2-yl]-*N*-(2-phenylethyl)-urea (Compound No. 28),
32 *N*-(3-Fluorobenzyl)-*N*-[6-(2-methylphenyl)-pyridin-2-yl]-urea (Compound No. 29),
33 *N*-[6-(2-Chlorophenyl)-pyridin-2-yl]-*N*-(3-fluorobenzyl)-urea (Compound No. 30),
34 *N*-(3-Fluorobenzyl)-*N*-[6-(4-fluoro-2-methylphenyl)-pyridin-2-yl]-urea (compound
35 No. 31),
- 36 *N*-[6-(2-Chlorophenyl)-5-(hydroxymethyl)-pyridin-2-yl]-*N*-(2-fluorobenzyl)-urea
37 (Compound No. 32),
- 38 *N*-[6-(2-Chlorophenyl)-5-(hydroxymethyl)-pyridin-2-yl]-*N*-(2,6-dichlorobenzyl)-urea
39 (Compound No. 33),
- 40 *N*-(2,6-Dichlorobenzyl)-*N*-[6-(4-fluoro-2-methylphenyl)-5-(hydroxymethyl)-pyridin-2-yl]-
41 urea (Compound No. 34),
- 42 *N*-(2,6-Difluorobenzyl)-*N*-[6-(2,4-difluorophenyl)-5-(hydroxymethyl)-pyridin-2-yl]-urea
43 (Compound No. 35),
- 44 *N*-(2,6-Difluorobenzyl)-*N*-[6-(4-fluoro-2-methylphenyl)-5-(hydroxymethyl)-pyridin-2-yl]-
45 urea (Compound No. 36),
- 46 *N*-(2,6-Dichlorobenzyl)-*N*-[5-(hydroxymethyl)-6-(2-methylphenyl)-pyridin-2-yl]-urea
47 (Compound No. 37),
- 48 *N*-[6-(2-Chlorophenyl)-5-(hydroxymethyl)-pyridin-2-yl]-*N*-(2,6-difluorobenzyl)-urea
49 (compound No. 38),

50 *N*-(2-Chlorobenzyl)-*N*-[6-(4-fluoro-2-methylphenyl)-pyridin-2-yl]-urea (Compound
51 No. 39),

52 *N*-(2,6-Difluorobenzyl)-*N*-[6-(2-methylphenyl)-pyridin-2-yl]-urea (Compound No. 40),

53 *N*-(2,6-Difluorobenzyl)-*N*-[6-(4-fluoro-2-methylphenyl)-pyridin-2-yl]-urea (Compound
54 No. 41),

1 7. A method for treating mammals suffering from inflammation and associated
2 pathologies, the method comprising administration of a therapeutically effective
3 amount of compound of claim 1.

1 8. A method for treating mammals suffering from sepsis, rheumatoid arthritis,
2 inflammatory bowel disease, type-1 diabetes, asthma, chronic obstructive
3 pulmonary disorder, organ transplant rejection, acute coronary syndrome and
4 psoriasis.

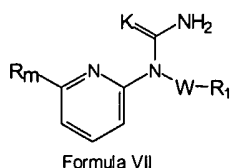
1 9. A pharmaceutical composition for the treatment of inflammation and associated
2 pathologies, the composition comprising a compound of claim 1-6, and a
3 pharmaceutically acceptable carrier.

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

1 11. A method for treating mammals suffering from inflammation and associated
2 pathologies, the method comprising administration of a composition of claim 9 and
3 10.

1 12. A method according to claim 7,8, 9, 10 and 11 wherein, the disease or disorder is
2 mediated through p38 MAP Kinase.

1 13. A method of making a compound of Formula VII, or pharmaceutically acceptable
2 salts or esters thereof

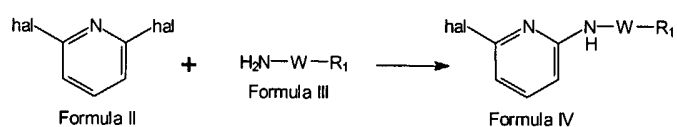


wherein

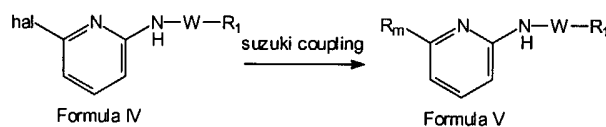
R_m is aryl or heteroaryl,

the method comprising

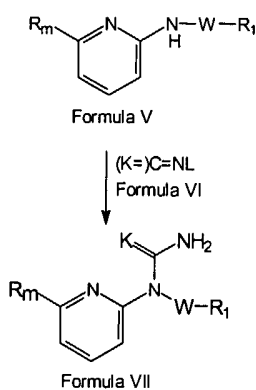
reacting a compound of Formula II (wherein hal is halogen) with a compound of Formula III (wherein W and R_1 are as defined) to form a compound of Formula IV;



carrying out Suzuki coupling of the compound of Formula IV with a Suzuki reagent to form a compound of Formula V; and

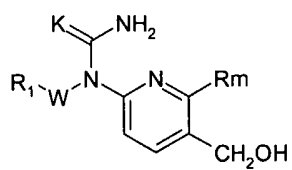


reacting the compound of Formula V with a reagent of Formula VI (wherein K is oxygen or sulfur, and L is a leaving group) to furnish a compound of Formula VII.



14. A method of making a compound of Formula XIV, or pharmaceutically acceptable salts or esters thereof

- 43 -



Formula XIV

29

30

wherein

31

hal is the same as defined earlier;

32

 R_k is alkyl, aryl, cycloalkyl, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl or

33

heterocyclalkyl;

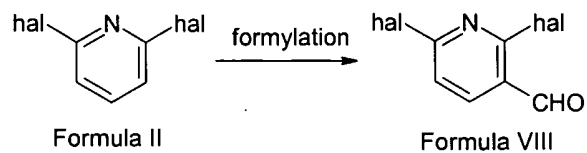
34

 W , K , L , R_m and R_1 are the same as defined earlier;

35

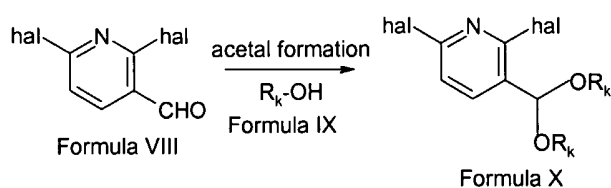
the method comprises

1 formylating a compound of Formula II to give a compound of Formula VIII,



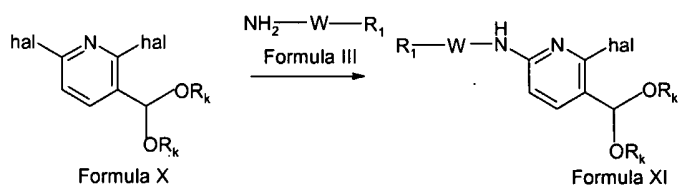
7 which is reacted with a compound of Formula IX to give a compound of

8 Formula X,

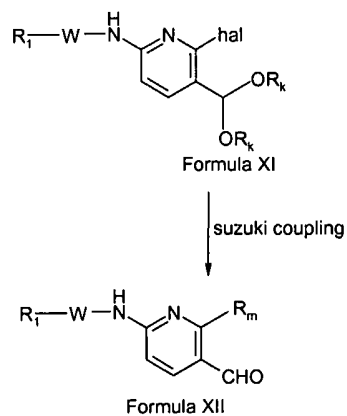


10 which is reacted with a compound of Formula III to give a compound of

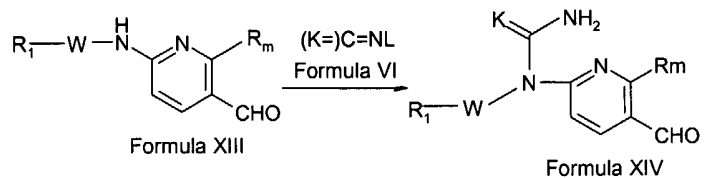
11 Formula XI,



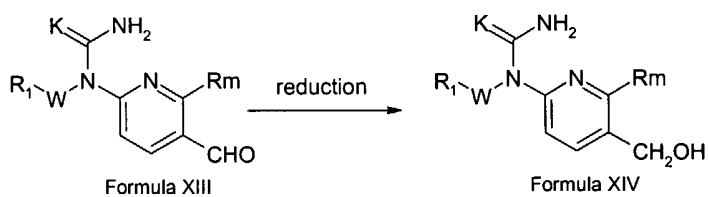
which undergoes Suzuki coupling to give a compound of Formula XII,



which is reacted with a compound of Formula VI to give a compound of Formula XIII,



which undergoes reduction to give a compound of Formula XIV



INTERNATIONAL SEARCH REPORT

International Application No

/IB2005/002287

A. CLASSIFICATION OF SUBJECT MATTER
C07D213/00 A61K31/17

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

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, WPI Data, BEILSTEIN Data, CHEM ABS 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 99/58502 A (VERTEX PHARMACEUTICALS INCORPORATED; SALITURO, FRANCESCO; GALULLO, VIN) 18 November 1999 (1999-11-18) cited in the application Schemes 3 (page 37) and 6 (page 40), example 1 (page 53), tables 5-6 (pages 28-29), claims 25-28	1-14
A	WO 98/27098 A (VERTEX PHARMACEUTICALS INCORPORATED; BEMIS, GUY, W; SALITURO, FRANCESCO) 25 June 1998 (1998-06-25) example 10 (pages 81-84), table 5 (pages 50-51), claims 25-28	1, 6, 7, 9, 13, 14
	----- -/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in 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.
- *G* document member of the same patent family

Date of the actual completion of the international search

14 December 2005

Date of mailing of the international search report

30/12/2005

Name and mailing address of the ISA

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

Authorized officer

Menchaca, R

INTERNATIONAL SEARCH REPORT

International Application No
/IB2005/002287

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 02/14281 A (COCHRAN, JOHN; GALULLO, VINCENT; BEMIS, GUY) 21 February 2002 (2002-02-21) cited in the application claims 1,20,21 -----	1,6,7,9, 13,14
A	G. BENNET, R. MASON, L. ALDEN AND J. ROACH: "Synthesis and Antiinflammatory activity of trisubstituted pyrimidines and triazines" JOURNAL OF MEDICINAL CHEMISTRY, vol. 21, no. 7, 1978, pages 623-628, XP002354281 abstract; table III; compound 4K -----	1,6,7,9, 13,14

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2005/002287

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. ☒ Claims Nos.: 7-8, 11-12 (as far as industrial applicability is concerned) because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 7-8 and 11-12 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

/IB2005/002287

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9958502	A	18-11-1999	AU 764047 B2	07-08-2003
			AU 3792399 A	29-11-1999
			BG 105031 A	31-10-2001
			BR 9911786 A	03-04-2001
			CA 2331460 A1	18-11-1999
			CN 1306512 A	01-08-2001
			EE 200000610 A	15-04-2002
			EP 1077943 A1	28-02-2001
			HU 0105174 A2	29-04-2002
			JP 2002514625 T	21-05-2002
			NO 20005673 A	10-01-2001
			NZ 508653 A	25-07-2003
			PL 344046 A1	24-09-2001
			SK 16882000 A3	10-05-2001
WO 9827098	A	25-06-1998	AP 1136 A	31-01-2003
			AT 236165 T	15-04-2003
			AU 738000 B2	06-09-2001
			AU 5610598 A	15-07-1998
			BG 64533 B1	30-06-2005
			BG 103575 A	30-06-2000
			BR 9714415 A	18-04-2000
			CA 2274825 A1	25-06-1998
			CN 1519240 A	11-08-2004
			CN 1244867 A	16-02-2000
			CZ 9902163 A3	15-09-1999
			DE 69720522 D1	08-05-2003
			DE 69720522 T2	27-11-2003
			DK 951467 T3	21-07-2003
			EA 2855 B1	31-10-2002
			EE 9900252 A	15-12-1999
			EP 0951467 A1	27-10-1999
			ES 2202658 T3	01-04-2004
			HK 1023340 A1	24-12-2003
			HU 0001125 A2	28-10-2000
			ID 21919 A	12-08-1999
			JP 2001506266 T	15-05-2001
			NO 992960 A	17-08-1999
			NZ 336146 A	29-09-2000
			PL 334133 A1	14-02-2000
			PT 951467 T	29-08-2003
			SK 80599 A3	18-01-2000
			TR 9902194 T2	21-06-2000
			TW 521071 B	21-02-2003
WO 0214281	A	21-02-2002	AU 8323701 A	25-02-2002
			CA 2418389 A1	21-02-2002
			EP 1309560 A1	14-05-2003
			JP 2004506042 T	26-02-2004