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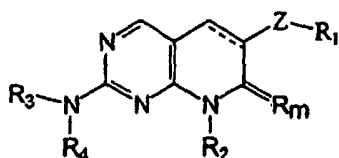
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(54) Title: AZABICYCLO DERIVATIVES AS ANTI-INFLAMMATORY AGENTS



(I)

(57) Abstract: The present invention relates to novel azabicyclo derivatives of Formula (I) as anti-inflammatory agents which are useful for inhibition and prevention of inflammation and associated pathologies including inflammatory and autoimmune diseases such as sepsis, rheumatoid arthritis, inflammatory bowel disease, type-1 diabetes, asthma, chronic obstructive pulmonary disorder, organ transplant rejection and psoriasis.

AZABICYCLO DERIVATIVES AS ANTI-INFLAMMATORY AGENTS

Field of the Invention

5 The present invention relates to novel azabicyclo derivatives as anti-inflammatory agents.

 The compounds of this invention were useful for inhibition and prevention of inflammation and associated pathologies including inflammatory and autoimmune diseases such as sepsis, rheumatoid arthritis, inflammatory bowel disease, type-1 diabetes, asthma, chronic obstructive pulmonary disorder, organ transplant rejection and psoriasis.

10 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 and psoriasis, and other inflammatory and/or autoimmune disorders, using the compounds.

15

Background of the Invention

 During the last decade, numerous 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
20 immunological and inflammatory processes. Advances in our understanding of their role in immune and inflammatory disorders have led to the development of cytokine-based therapies-that is, therapies that aim to inhibit or restore the activity of specific cytokines. Today, drugs that block inflammatory cytokines, such as tumor necrosis factor-alpha (TNF- α), are among the most successful agents being introduced to the market.

25 Elevated levels of proinflammatory cytokines viz TNF- α and IL- β 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 and psoriasis. Inflammation is regulated by a large number of pro- and anti-inflammatory mediators, which include

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cytokines, eicosanoids, nitric oxide, and reactive oxygen species. The central role of these inflammatory mediators in the pathogenesis of both chronic and acute inflammatory diseases is well documented. Until a few years ago, inflammatory disorders were treated primarily with relatively non-selective anti-inflammatory agents, such as corticosteroids and various non-steroidal anti-inflammatory drugs. In recent years, novel therapies have been developed that specifically interfere with the action of selected pro-inflammatory mediators, such as TNF- α and PGE-2. These specific anti-inflammatory therapies have already proven to be very successful in the treatment of rheumatoid arthritis, inflammatory bowel disease, and several other inflammatory diseases.

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

 Numerous studies have now clearly established that the pathogenesis of inflammatory diseases requires cytokine-mediated communication between endothelial
25 cells, infiltrating leukocytes, resident macrophages, mast cells, epithelial cells and osteoclasts. The p38 mitogen activated protein kinase (p38MAPK) regulates cytokine levels and therefore plays a central role in both the cellular infiltration and activation responses associated with inflammatory diseases.

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

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

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

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

PCT Application WO 01/44258 discloses bone-targeting groups useful for treating a variety of disorders and conditions. PCT Application WO 02/18380 and U.S. Patent Nos.

6,518,276 and 6,506,749 discloses 7-oxopyridopyrimidines as inhibitors of cell proliferation. PCT Application WO 03/057165 describes the compositions and methods for prevention and treatment of amyloid- β -peptide related disorders. U.S. Patent No. 6,316,464 discloses compounds as p-38 kinase inhibitors. U.S. Patent No. 6,451,804
5 discloses heteroalkylamino substituted bicyclic nitrogen heterocycles. U.S. Patent No. 6,696,566 discloses 6-substituted pyrido-pyrimidines useful for the treatment of p-38 mediated disorders. U.S. Patent No. 6,479,507 discloses p-38 kinase inhibitors. U.S. Publication No. 2003/0153586 discloses 7-oxo-pyridopyridopyrimidines for the treatment of p-38 mediated disorders. WO 2003/00270 discloses pyridopyrimidones and uses
10 thereof. U.S. Patent No. 6,630,485 discloses p-38 kinase inhibitors, pharmaceutical compositions containing them, method for their use, and methods for preparing these compounds. WO 04/019210 discloses pyridopyrimidine, naphthyridines and pyridopyrazine derivatives as cyclin dependent kinase and tyrosine kinase inhibitors.

15

Summary of the Invention

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

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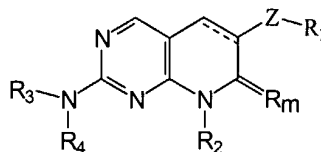
Pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers or N-oxides of these compounds having the same type of activity are also provided.

25

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

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

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



Formula I

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

10 wherein

R₁ is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl, or heterocyclalkyl;

when R_m is oxygen or sulphur

15 R₂ is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, heterocyclyl, heterocyclalkyl or heteroarylalkyl;

when R_m is -NH, -N-acyl, -N(CN), -N(NO₂), -C(R₃)₂ or -CH(NO₂)

20 R₂ is hydroxy, alkoxy, aryloxy, -CHO, -CN, alkyl, alkenyl, alkynyl, cycloalkyl, carboxy, halogen, aryl, aralkyl, acyl, heteroaryl, heterocyclyl, -SO₂R₅, -COOR₆, -C(=O)NR_xR_y, -NR_xR_y or -OC(=O)NR_xR_y or -NHC(=O)R_x;

---- represents a single bond or a double bond;

25 R₃ is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, aralkyl, heteroarylalkyl or heterocyclalkyl;

- R_4 is  (wherein  represents a cyclic ring containing 4-8 carbon atoms wherein 1-3 carbon atoms may optionally be replaced by heteroatoms selected from oxygen, -NH or sulphur; T is $-(CH_2)_n-$, $-CH(Q)CH_2-$, $-CH_2CH(Q)CH_2-$, $-CH(Q)-$, $-CH_2-O-CH_2-$, $-CH_2-NH-CH_2-$, $-CH_2-N(CH_3)-CH_2-$;
- 5 n is an integer selected from 0-3 (wherein when n is zero then T represents a direct bond);
- R_5 is alkyl, alkenyl, alkynyl, cycloalkyl, $-NR_pR_q$ (wherein R_p and R_q are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, heterocyclalkyl or
- 10 heteroarylalkyl; R_p and R_q may also together join to form a heterocycl ring), aryl, aralkyl, heteroaryl, heterocyclyl, heterocyclalkyl or heteroarylalkyl;
- R_6 is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroarylalkyl or heterocyclalkyl;
- Z is a direct bond, oxygen, sulphur, -NH or $-(CH_2)_n$;
- 15 R_x and R_y are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, alkoxy, aryl, aralkyl, $-SO_2R_5$ (wherein R_5 is the same as defined above), heteroaryl, heterocyclyl, heteroarylalkyl or heterocyclalkyl;
- Q is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroarylalkyl or heterocyclalkyl.

20

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

In accordance with third aspect, there is provided a method for the treatment of mammal suffering from inflammatory diseases and associated pathologies including

25 sepsis, rheumatoid arthritis, inflammatory bowel disease, type-1 diabetes, asthma, chronic obstructive pulmonary disorder, organ transplant rejection and psoriasis.

In accordance with fourth aspect, there are provided a pharmaceutical compositions containing the compounds, and which may also contain pharmaceutically

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

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

In accordance with sixth aspect, the compounds of the present invention are screened as p38 kinase inhibitors.

The following definitions apply to terms as used herein:

- 10 The term "alkyl," unless otherwise specified, refers to a monoradical branched or unbranched saturated hydrocarbon chain having from 1 to 20 carbon atoms. Alkyl groups can be optionally interrupted by atom(s) or group(s) independently selected from oxygen, sulfur, a phenylene, sulphinyl, sulphonyl group or $-NR_a-$, wherein R_a can be hydrogen, alkyl, alkenyl, alkynyl cycloalkyl or aryl. This term can be exemplified by groups such as
- 15 methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, t-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, n-decyl, tetradecyl, and the like. Alkyl groups may be substituted further (referred herein as "substituted alkyl") with one or more substituents selected from alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkenyl, acyl, acylamino, acyloxy, alkoxycarbonylamino, azido, cyano, halogen, hydroxy, keto, oxo, thiocarbonyl, carboxy,
- 20 carboxyalkyl, aryl, heterocyclyl, heteroaryl, (heterocyclyl)alkyl, cycloalkoxy, $-CH=N-O(C_{1-6}alkyl)$, $-CH=N-NH(C_{1-6}alkyl)$, $-CH=N-NH(C_{1-6}alkyl)-C_{1-6}alkyl$, arylthio, thiol, alkylthio, aryloxy, nitro, aminosulfonyl, aminocarbonylamino, $-NHC(=O)R_p$, $-NR_pR_q$, $-C(=O)NR_pR_q$, $-NHC(=O)NR_pR_q$, $-C(=O)heteroaryl$, $C(=O)heterocyclyl$, $-O-C(=O)NR_pR_q$ {wherein R_p and R_q are independently selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, alkoxy, cycloalkenyl, aryl, aralkyl, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl}, nitro, hydroxyamino, alkoxyamino or $S(O)_mR_{66}$ (wherein m is an integer from 0-2 and R_{66} is alkyl, alkenyl, alkynyl, cycloalkyl, aralkyl, aryl, heterocyclyl, heteroaryl, heteroarylalkyl or heterocyclylalkyl). Unless otherwise constrained by the definition, alkyl substituents may be further substituted by 1-3 substituents selected from
- 30 alkyl, alkenyl, alkynyl, carboxy, $-NR_pR_q$, $-C(=O)NR_pR_q$, $-OC(=O)NR_pR_q$, $-NHC(=O)NR_pR_q$ (wherein R_p and R_q are the same as defined earlier), hydroxy, alkoxy,

halogen, CF_3 , cyano, and $\text{S}(\text{O})_m\text{R}_{66}$ (wherein m is an integer from 0-2 and R_{66} are the same as defined earlier); or an alkyl group also may be interrupted by 1-5 atoms of groups independently selected from oxygen, sulfur or $-\text{NR}_a-$ {wherein R_a is selected from hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, acyl, aralkyl, $-\text{C}(=\text{O})\text{OR}_p$ (wherein R_p is the same as defined earlier), $\text{S}(\text{O})_m\text{R}_{66}$ (wherein m is an integer from 0-2 and R_{66} is as defined earlier), or $-\text{C}(=\text{O})\text{NR}_p\text{R}_q$ (wherein R_p and R_q are as defined earlier)}. Unless otherwise constrained by the definition, all substituents may be substituted further by 1-3 substituents selected from alkyl, carboxy, carboxyalkyl, $-\text{NR}_p\text{R}_q$, $-\text{C}(=\text{O})\text{NR}_p\text{R}_q$, $-\text{O}-\text{C}(=\text{O})\text{NR}_p\text{R}_q$ (wherein R_p and R_q are the same as defined earlier) hydroxy, alkoxy, halogen, CF_3 , cyano, and $\text{S}(\text{O})_m\text{R}_{66}$ (wherein m is an integer from 0-2 and R_{66} is same as defined earlier); or an alkyl group as defined above that has both substituents as defined above and is also interrupted by 1-5 atoms or groups as defined above.

The term "alkenyl," unless otherwise specified, refers to a monoradical of a branched or unbranched unsaturated hydrocarbon group having from 2 to 20 carbon atoms with cis, trans, or geminal geometry. It can be optionally interrupted by atom(s) or group(s) independently chosen from oxygen, sulfur, phenylene, sulphinyl, sulphonyl and $-\text{NR}_a-$, wherein R_a can be hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl or aryl. In the event that alkenyl is attached to a heteroatom, the double bond cannot be alpha to the heteroatom. Alkenyl groups may be substituted further (referred to herein as "substituted alkenyl") with one or more substituents selected from alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkenyl, acyl, acylamino, acyloxy, $-\text{NHC}(=\text{O})\text{R}_p$, $-\text{NR}_p\text{R}_q$, $-\text{C}(=\text{O})\text{NR}_p\text{R}_q$, $-\text{NHC}(=\text{O})\text{NR}_p\text{R}_q$, $-\text{O}-\text{C}(=\text{O})\text{NR}_p\text{R}_q$ (wherein R_p and R_q are the same as defined earlier), alkoxycarbonylamino, azido, cyano, halogen, hydroxy, oxo, keto, carboxyalkyl, thiocarbonyl, carboxy, arylthio, thiol, alkylthio, aryl, aralkyl, aryloxy, heterocyclyl, heteroaryl, heterocyclyl alkyl, heteroaryl alkyl, aminosulfonyl, aminocarbonylamino, alkoxyamino, hydroxyamino, alkoxyamino, nitro, or SO_2R_{66} (wherein R_{66} are is same as defined earlier). Unless otherwise constrained by the definition, alkenyl substituents optionally may be substituted further by 1-3 substituents selected from alkyl, carboxy, hydroxy, alkoxy, halogen, $-\text{CF}_3$, cyano, $-\text{NR}_p\text{R}_q$, $-\text{C}(=\text{O})\text{NR}_p\text{R}_q$, $-\text{O}-\text{C}(=\text{O})\text{NR}_p\text{R}_q$ (wherein R_p and R_q are the same as defined earlier) and $-\text{SO}_2\text{R}_{66}$ (wherein R_{66} is same as defined earlier). Groups, such as ethenyl or vinyl ($\text{CH}=\text{CH}_2$), 1-propylene or allyl

($-\text{CH}_2\text{CH}=\text{CH}_2$), iso-propylene ($-\text{C}(\text{CH}_3)=\text{CH}_2$), bicyclo[2.2.1]heptene, and the like, exemplify this term.

The term “alkynyl,” unless otherwise specified, refers to a monoradical of an unsaturated hydrocarbon, having from 2 to 20 carbon atoms. It can be optionally interrupted by atom(s) or group(s) independently chosen from oxygen, sulfur, phenylene, sulphinyl, sulphonyl and $-\text{NR}_a-$, wherein R_a can be hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl or aryl. In the event that alkynyl is attached to a heteroatom, the triple bond cannot be alpha to the heteroatom. Alkynyl groups may be substituted further (referred to herein as “substituted alkynyl”) with one or more substituents selected from alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkenyl, acyl, acylamino, acyloxy, alkoxy-carbonylamino, azido, cyano, halogen, hydroxy, keto, oxo, thiocarbonyl, carboxy, carboxyalkyl, arylthio, thiol, alkylthio, aryl, aralkyl, aryloxy, aminosulfonyl, aminocarbonylamino, hydroxyamino, alkoxyamino, nitro, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl, $-\text{NHC}(=\text{O})\text{R}_p$, $-\text{NR}_p\text{R}_q$, $-\text{NHC}(=\text{O})\text{NR}_p\text{R}_q$, $-\text{C}(=\text{O})\text{NR}_p\text{R}_q$, $-\text{O}-\text{C}(=\text{O})\text{NR}_p\text{R}_q$ (wherein R_p and R_q are the same as defined earlier), $\text{S}(\text{O})_m\text{R}_{66}$ (wherein m is an integer from 0-2 and R_{66} is as defined earlier). Unless otherwise constrained by the definition, alkynyl substituents optionally may be substituted further by 1-3 substituents selected from alkyl, carboxy, carboxyalkyl, hydroxy, alkoxy, halogen, CF_3 , $-\text{NR}_p\text{R}_q$, $-\text{C}(=\text{O})\text{NR}_p\text{R}_q$, $-\text{NHC}(=\text{O})\text{NR}_p\text{R}_q$, $-\text{C}(=\text{O})\text{NR}_p\text{R}_q$ (wherein R_p and R_q are the same as defined earlier), cyano, or $\text{S}(\text{O})_m\text{R}_{66}$ (wherein m is an integer from 0-2 and R_{66} is same as defined earlier). Groups such as ethynyl, ($-\text{C}\equiv\text{CH}$), propargyl (or propynyl, $-\text{CH}_2\text{C}\equiv\text{CH}$), and the like exemplify this term.

The term “cycloalkyl,” unless otherwise specified, refers to cyclic alkyl groups of from 3 to 20 carbon atoms having a single cyclic ring or multiple condensed rings, which may optionally contain one or more olefinic bonds, unless otherwise constrained by the definition. Such cycloalkyl groups can include, for example, single ring structures, including cyclopropyl, cyclobutyl, cyclooctyl, cyclopentenyl, and the like, or multiple ring structures, including adamantanyl, and bicyclo [2.2.1] heptane, or cyclic alkyl groups to which is fused an aryl group, for example, indane, and the like. Spiro and fused ring structures can also be included. Cycloalkyl groups may be substituted further with one or more substituents selected from alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkenyl,

acyl, acylamino, acyloxy, alkoxycarbonylamino, azido, cyano, halogen, hydroxy, oxo, thiocarbonyl, carboxy, carboxyalkyl, arylthio, thiol, alkylthio, aryl, aralkyl, aryloxy, aminosulfonyl, aminocarbonylamino, $-NR_pR_q$, $-NHC(=O)NR_pR_q$, $-NHC(=O)R_p$, $-C(=O)NR_pR_q$, $-O-C(=O)NR_pR_q$ (wherein R_p and R_q are the same as defined earlier), nitro, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl, or $S(O)_mR_{66}$ (wherein m is an integer from 0-2 and R_{66} is same as defined earlier). Unless otherwise constrained by the definition, cycloalkyl substituents optionally may be substituted further by 1-3 substituents selected from alkyl, carboxy, hydroxy, alkoxy, halogen, CF_3 , $-NR_pR_q$, $-C(=O)NR_pR_q$, $-NHC(=O)NR_pR_q$, $-O-C(=O)NR_pR_q$ (wherein R_p and R_q are the same as defined earlier), cyano or $S(O)_mR_{66}$ (wherein m is an integer from 0-2 and R_{66} is same as defined earlier).

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

The term "aryl" herein refers to aromatic system having 6 to 14 carbon atoms, wherein the ring system can be mono-, bi- or tricyclic and are carbocyclic aromatic groups. For example, aryl groups include, but are not limited to, phenyl, biphenyl, anthryl or naphthyl ring and the like, optionally substituted with 1 to 3 substituents selected from halogen (e.g., F, Cl, Br, I), hydroxy, alkyl, alkenyl, alkynyl, cycloalkyl, alkoxy, acyl, aryloxy, CF₃, cyano, nitro, COOR_s (wherein R_s is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aralkyl, heterocyclylalkyl, heteroarylalkyl), NHC(=O)R_p, -NR_pR_q, -C(=O)NR_pR_q, -NHC(=O)NR_pR_q, -O-C(=O)NR_pR_q, S(O)_mR₆₆ (wherein m is an integer from 0-2 and R₆₆ is same as defined earlier), carboxy, optionally substituted heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl, amino carbonyl amino, mercapto, haloalkyl, optionally substituted aryl, optionally substituted heterocyclylalkyl, thioalkyl, -CONHR_p, -OCOR_p, -COR_p, -NHSO₂R_p, or -SO₂NHR_p (wherein R_p and R_q are the same as defined earlier). The aryl group optionally may be fused with a cycloalkyl group, wherein the cycloalkyl group may optionally contain heteroatoms selected from O, N or S. Groups such as phenyl, naphthyl, anthryl, biphenyl, and the like exemplify this term.

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

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

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

The term "heteroaryl," unless otherwise specified, refers to an aromatic ring structure containing 5 or 6 ring atoms, or a bicyclic or tricyclic aromatic group having from 8 to 14 ring atoms, with one or more heteroatom(s) independently selected from N, O or S. Heteroaryl groups can be optionally substituted with 1 to 4 substituent(s) (referred herein as "substituted heteroaryl") selected from halogen (*e.g.*, F, Cl, Br, I), hydroxy, alkyl, alkenyl, alkynyl, cycloalkyl, acyl, carboxy, aryl, alkoxy, aralkyl, cyano, nitro, heterocyclyl, heteroaryl, $-NR_pR_q$, $CH=NOH$, $-(CH_2)_wC(=O)R_t$ {wherein *w* is an integer from 0-4 and R_t is hydrogen, hydroxy, OR_p , NR_pR_q , $-NHOR_z$ or $-NHOH$ }, $-C(=O)NR_pR_q$ and $-NHC(=O)NR_pR_q$, $S(O)_mR_{66}$, $-O-C(=O)NR_pR_q$, $-O-C(=O)R_p$, $-O-C(=O)OR_p$ (wherein *m*, R_{66} , R_p and R_q are as defined earlier, and R_z is alkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, heteroarylalkyl or heterocyclylalkyl). Unless otherwise constrained by the definition, the substituents are attached to a ring atom, *i.e.*, carbon or heteroatom in the ring. Examples of heteroaryl groups include oxazolyl, imidazolyl, pyrrolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, thiazolyl, oxadiazolyl, benzoimidazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, thienyl, isoxazolyl, triazinyl, furanyl, benzofuranyl, indolyl, benzothiazolyl, or benzoxazolyl, benzthiazinyl, benzthiazinonyl, benzoxazinyl, benzoxazinonyl, quinazonyl, carbazolyl phenothiazinyl, phenoxazinyl and the like.

The term "heterocyclyl," unless otherwise specified, refers to a non-aromatic monocyclic or bicyclic cycloalkyl group having 5 to 10 atoms wherein 1 to 4 carbon atoms in a ring are replaced by heteroatoms selected from O, S or N, and optionally are benzofused or fused heteroaryl having 5-6 ring members and/or optionally are substituted, wherein the substituents are selected from halogen (*e.g.*, F, Cl, Br, I), hydroxy, alkyl, alkenyl, alkynyl, cycloalkyl, acyl, optionally substituted aryl, alkoxy, alkaryl, cyano, nitro, oxo, carboxy, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, $-O-C(=O)R_p$, $-O-C(=O)OR_p$, $-C(=O)NR_pR_q$, $S(O)_mR_{66}$, $-O-C(=O)NR_pR_q$, $-NHC(=O)NR_pR_q$, $-NR_pR_q$, NR_pR_q , mercapto, haloalkyl, thioalkyl, $-COOR_p$, $-COONH R_p$, $-CO R_p$, $-NH SO_2 R_p$, $SO_2NH R_p$ (wherein *m*, R_{66} , R_p and R_q are as defined earlier) or guanidine. Such ring systems can be mono-, bi- or tricyclic. Carbonyl

or sulfonyl group can replace carbon atom(s) of heterocyclyl. Unless otherwise constrained by the definition, the substituents are attached to the ring atom, *i.e.*, carbon or heteroatom in the ring. Also, unless otherwise constrained by the definition, the heterocyclyl ring optionally may contain one or more olefinic bond(s). Examples of heterocyclyl groups include oxazolidinyl, tetrahydrofuranyl, dihydrofuranyl, benzoxazinyl, benzthiazinyl, imidazolyl, benzimidazolyl, tetrazolyl, carbaxolyl, indolyl, phenoxazinyl, phenothiazinyl, dihydropyridinyl, dihydroisoxazolyl, dihydrobenzofuryl, azabicyclohexyl, thiazolidinyl, dihydroindolyl, pyridinyl, isoindole 1,3-dione, piperidinyl, tetrahydropyranyl, piperazinyl, 3H-imidazo[4,5-b]pyridine, isoquinolinyl, 1H-pyrrolo[2,3-b]pyridine, and the like.

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

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

“Acyl” refers to $-C(=O)R''$ wherein R'' is selected from hydrogen, alkyl, cycloalkyl, aryl, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl or heterocyclylalkyl.

“Thiocarbonyl” refers to $-C(=S)H$.

“Substituted thiocarbonyl” refers to $-C(=S)R''$, wherein R'' is selected from alkyl, cycloalkyl, aryl, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl or heterocyclylalkyl, amine or substituted amine.

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

The term “protecting groups” refers to moieties that prevent chemical reaction at a location of a molecule intended to be left unaffected during chemical modification of such molecule. Unless otherwise specified, protecting groups may be used on groups, such as hydroxy, amino, or carboxy. Examples of protecting groups are found in T.W. Greene and P.G.M. Wuts, “Protective Groups in Organic Synthesis”, 2nd Ed., John Wiley and Sons, New York, N.Y., which is incorporated herein by reference. The species of the carboxylic

protecting groups, amino protecting groups or hydroxy protecting groups employed are not critical, as long as the derivatised moieties/moiety is/are stable to conditions of subsequent reactions and can be removed without disrupting the remainder of the molecule.

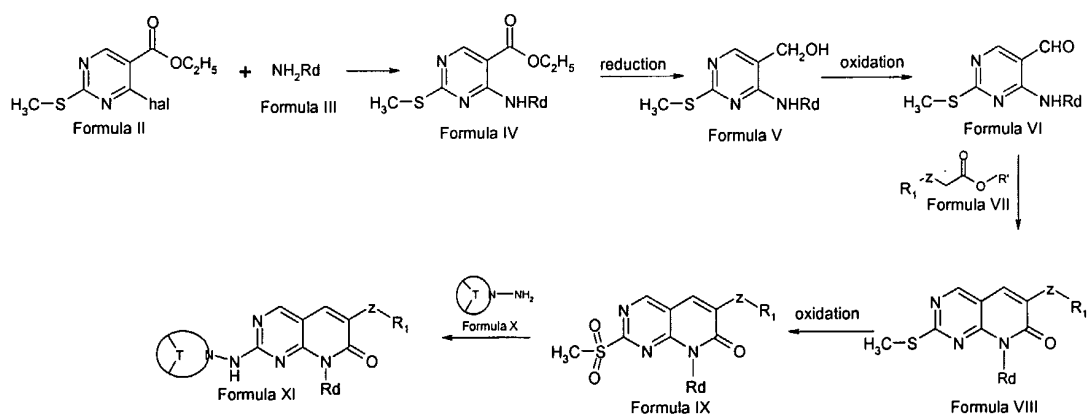
- 5 The term “pharmaceutically acceptable salts” refers to derivatives of compounds that were modified by forming their corresponding acid or base salts. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acids salts of basic residues (such as amines), or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

10

Detailed Description of the Invention

- The compounds of the present invention 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, or example, processes described herein, although such processes are not the only means by which the compounds described may be synthesised. Further, the various synthetic steps described herein may be performed in an alternate sequence in order to give the desired compounds.

Scheme I



- 20 The compounds of Formulae XI and XII can be and were prepared by following the reaction sequence of Scheme I. Thus, a compound of Formula II [wherein hal is halogen (Cl, Br or I)] can be reacted with a compound of Formula III (wherein R_d is

hydrogen, optionally substituted alkyl, cycloalkyl, aralkyl or aryl) to give a compound of Formula IV, which can undergo reduction to give a compound of Formula V, which can be further oxidized to give a compound of Formula VI, which can be reacted with an ester of Formula VII (wherein R' is alkyl; R₁ and Z are the same as defined earlier) to give a
5 compound of Formula VIII, which can be oxidized to give a compound of Formula IX, which can be reacted with a compound of Formula X [wherein T is the same as defined earlier], to give a compound of Formula XI.

The reaction of a compound of Formula II with a compound of Formula III to give a compound of Formula IV can be carried out in an organic solvent, for example
10 tetrahydrofuran, dimethylformamide, dioxane or diethyl ether, in the presence of a base, for example, triethylamine, N-ethyldiisopropylamine, N-methylmorpholine or pyridine.

The compound of Formula IV can be reduced to give a compound of Formula V in an organic solvent, for example, tetrahydrofuran, dimethylformamide, dioxane or diethylether, with reducing agents, for example, lithium aluminium hydride, lithium
15 borohydride, sodium cyanoborohydride or sodium borohydride.

The oxidation of a compound of Formula V to give a compound of Formula VI can be carried out in an organic solvent, for example, dichloromethane, dichloroethane, carbon tetrachloride or chloroform with an oxidizing agent for example, manganese dioxide, potassium permanganate, Dess-Martin periodinane (DMP), pyridinium dichromate (PDC),
20 pyridinium chlorochromate (PCC) or chromic anhydride, although numerous other methods were employed (see, for example, Advanced Organic Chemistry, 4th Edn., Merck, John Wiley & Sons, 1992).

The reaction of a compound of Formula VI with a compound of Formula VII to give a compound of Formula VIII can be carried out in an organic solvent, for example,
25 N-methylpyrrolidinone, dimethylformamide, tetrahydrofuran, diethylether or dioxane in the presence of a base, for example, potassium carbonate, sodium carbonate or lithium carbonate, potassium bicarbonate, lithium bicarbonate or sodium bicarbonate.

The oxidation of a compound of Formula VIII to give a compound of Formula IX can be carried out with an oxidizing agent, for example, *m*-chloroperbenzoic acid or oxone

(KHSO₅) in an organic solvent, for example, chloroform, carbon tetrachloride, dichloromethane, ethanol or tetrahydrofuran.

The reaction of a compound of Formula IX with a compound of Formula X to give a compound of Formula XI can be carried in the presence of a base, for example, pyridine,
5 N-methylmorpholine, N-ethyldiisopropylamine, sodium hydride or triethylamine.

Alternatively, in some cases rather than using a compound of Formula IX, a compound of Formula VIII can be reacted directly with a compound of Formula X to give a compound of Formula XI.

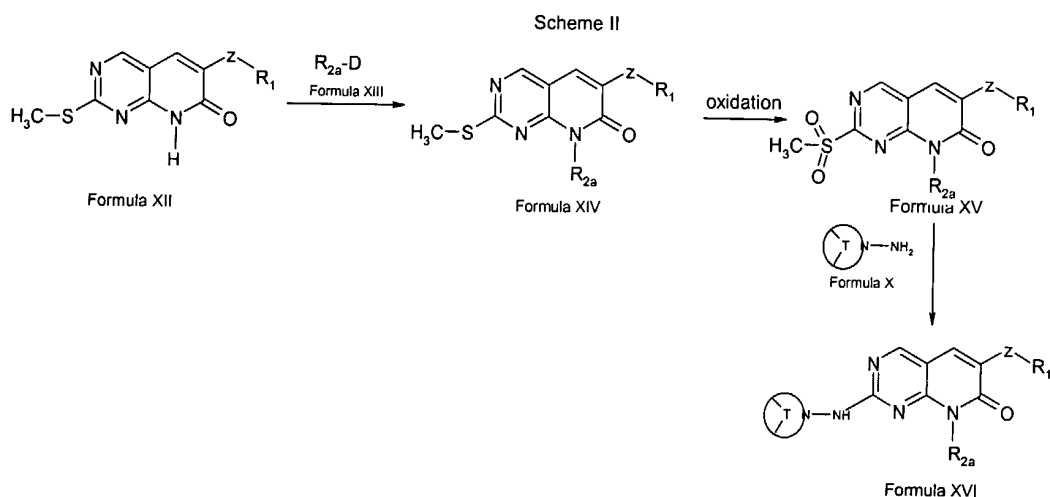
Particular compounds are mentioned below:

- 10 6-(2-Chlorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-
d]pyrimidin-7(8*H*)-one (Compound No. 1),
6-(2-Methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-
d]pyrimidin-7(8*H*)-one (Compound No. 2),
6-(2-Fluorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-
15 *d*]pyrimidin-7(8*H*)-one (Compound No. 3),
6-(2,4-Difluorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-
d]pyrimidin-7(8*H*)-one (Compound No. 4),
6-(3-Chlorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-
d]pyrimidin-7(8*H*)-one (Compound No. 5),
20 6-(4-Chlorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-
d]pyrimidin-7(8*H*)-one (Compound No. 6),
6-(4-Methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-
d]pyrimidin-7(8*H*)-one (Compound No. 7),
6-(4-Fluorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-
25 *d*]pyrimidin-7(8*H*)-one (Compound No. 8),
6-(2-Methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-benzylpyrido[2,3-
d]pyrimidin-7(8*H*)-one (Compound No. 9),
6-(2-Methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(4-fluorobenzyl)-pyrido[2,3-
d]pyrimidin-7(8*H*)-one (Compound No. 10),
30 6-(2-Methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(4-*tert*-butylbenzyl)-
pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 11),

- 6-(2-Methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(3-trifluoromethoxybenzyl)-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 12),
- 6-(2-Fluorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(4-fluorobenzyl)-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 13),
- 5 6-(2-Fluorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(3-chloro-2-fluorobenzyl)-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 14),
- 6-(2-Chlorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-benzylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 15),
- 10 6-(2-Chlorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(4-fluorobenzyl)-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 16),
- 6-(2-Chlorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(4-*tert*-butylbenzyl)-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 17),
- 6-(2-Chlorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(3-trifluoromethoxybenzyl)-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 18),
- 15 6-(2-Methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 30),
- 6-(2-Fluorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 31),
- 20 6-(2-Methylphenyl)-2-(7-azabicyclo[4.3.0]non-7-yl-amino)-8-(cyclopropyl)-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 41),
- 6-(2-Methylphenyl)-2-(7-azabicyclo[4.3.0]non-7-yl-amino)-8-methyl-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 42),
- 6-(2-Chlorophenyl)-2-(7-azabicyclo[4.3.0]non-7-yl-amino)-8-methyl-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 43),
- 25 6-(2-Chlorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-cyclopropyl-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 52),
- 6-(2-Chlorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-7-oxopyrido[2,3-*d*]pyrimidin-8(7*H*)-yl acetonitrile (Compound No. 53),
- 30 6-(1-Naphthyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-cyclopropyl-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 54),
- 6-(2-Chlorophenoxy)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-cyclopropyl-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 55),
- 6-(3-Methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methyl-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 56),

- 6-(2-Methylphenoxy)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-cyclopropyl-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 57),
- 6-(2-Methylphenoxy)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 58),
- 5 6-(2-Fluorophenoxy)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-cyclopropyl-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 59),
- 6-(4-Chlorophenoxy)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-cyclopropylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 60),
- 10 6-(4-Chlorophenoxy)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 61),
- 6-Methoxy-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 62),
- 6-(4-Isopropylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 63),
- 15 6-(2-Fluorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(cyclopropyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 64),
- 6-(2,4-Dichlorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 65),
- 20 6-(4-Nitrophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methyl-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 66),
- 6-(3-Methoxyphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 67),
- 6-(2,6-Dichlorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 68),
- 25 6-(2-Nitrophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methyl-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 69),
- 6-(3-Fluorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 70),
- 30 6-(2-Chloro-4-fluorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 71),
- 6-(4-Nitrophenoxy)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methyl-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 72),
- 6-(2-Chlorophenoxy)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 73),

- 6-(2-Fluorophenoxy)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 74),
- 6-(4-Chloro-2-fluorophenoxy)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 75),
- 5 6-(4-Chloro-2-fluorophenoxy)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-cyclopropylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 76),
- 6-(3-Methoxyphenoxy)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(cyclopropyl)-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 77),
- 10 6-(3-Methylphenoxy)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(cyclopropyl)-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 78).



- Compounds of Formula XVI can be and were prepared following the procedure as depicted in Scheme II. An exemplary reaction can comprise reacting a compound of
- 15 Formula XII (wherein Z and R₁ are the same as defined earlier) with a compound of Formula XIII (wherein R_{2a} is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, heterocyclyl, heterocyclylalkyl or heteroarylalkyl and D is hal (Br, Cl or I) or -OH) are the same as defined earlier) to give a compound of Formula XIV, which can undergo
- oxidation to give a compound of Formula XV, which can be reacted with a compound of
- 20 Formula X (wherein T is the same as defined earlier) to give a compound of Formula XVI.

The reaction of a compound of Formula XII with a compound of Formula XIII (when D is hal) to give a compound of Formula XIV can be carried out in the presence of

a base, for example, sodium hydride, potassium hydride or lithium hydride, in an organic solvent, for example, N-methylpyrrolidone, dimethylformamide, tetrahydrofuran or dimethylsulphoxide.

Alternatively, the reaction of a compound of Formula XII with a compound of
5 Formula XIII (when D is hal) can be also carried out in the presence of a base, for example, potassium carbonate, sodium carbonate, lithium carbonate or sodium bicarbonate, and a catalyst, for example, tetrabutylammonium bromide, tetrabutylammonium iodide or tetrabutylammonium chloride.

The reaction of a compound of Formula XII with a compound of Formula XIII
10 (when D is -OH) to give a compound of Formula XIV can be carried out in an organic solvent, for example, tetrahydrofuran, diethylether, dioxane, toluene, benzene or dimethylformamide, in the presence of a redox couple. The redox couple agents may be any one of those known to a person skilled in the art of organic synthesis. The oxidizing part of the redox couple can be, for example, diisopropylazodicarboxylate (DIAD),
15 diethylazodicarboxylate (DEAD), N,N,N',N'-tetramethylazodicarboxamide (TMAD), 1,1'-(azodicarbonyl)dipiperidine (ADDP), cyanomethylenetriethylphosphorane (CMBP), 4,7-dimethyl-3,5,7-hexahydro-1,2,4,7-tetrazocin-3,8-dione (DHTD) or N,N,N'-tetraisopropylazodicarboxamide (TIPA). The reduction part of the redox couple can be, for example, a phosphine, for example, trialkylphosphine (such as tributylphosphine),
20 triarylphosphine (such as triphenylphosphine), tricycloalkylphosphine (such as tricyclohexylphosphine) or triheteroarylphosphine. Phosphine reagents, together with a combination of aryl, alkyl or heteroaryl substituents, may also be used (such as diphenylpyridylphosphine).

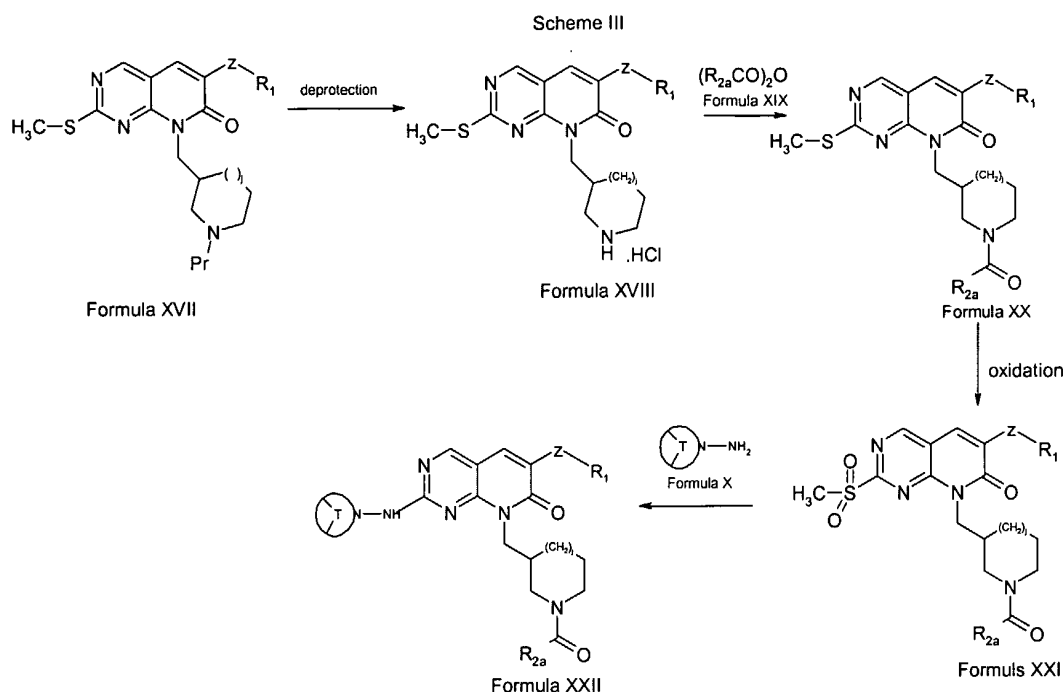
The oxidation of a compound of Formula XIV to give a compound of Formula XV
25 can be carried out with an oxidizing agent, for example, m-chloroperbenzoic acid or oxone (KHSO₅), in an organic solvent, for example, chloroform, dichloroethane, carbon tetrachloride, dichloromethane, ethanol or tetrahydrofuran.

The reaction of a compound of Formula XV with a compound of Formula X to
30 give a compound of Formula XVI can be carried in the presence of a base, for example, pyridine, N-methylmorpholine, diisopropylethylamine, sodium hydride or triethylamine.

Alternatively, in some cases, rather than using a compound of Formula XV, a compound of Formula XIV can be reacted directly with a compound of Formula X to give a compound of Formula XVI.

Particular compounds are mentioned below:

- 5 6-(2-Methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(cyclopropyl methyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 19),
Ethyl 2-[6-(2-fluorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-7-oxopyrido[2,3-*d*]pyrimidin-8(7*H*)-yl]propanoate (Compound No. 20),
Ethyl 2-[6-(2-methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-7-oxopyrido[2,3-*d*]pyrimidin-8(7*H*)-yl]propanoate (Compound No. 21),
10 6-(2-Fluorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(cyclopentyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 22),
6-(2-Fluorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(cyclopropyl methyl)-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 23),
15 6-(2-Methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(2-chloroethyl)-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 24),
6-(2-Chlorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(2-ethoxyethyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 25),
20 2-[6-(2-Chlorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-7-oxopyrido[2,3-*d*]pyrimidin-8(7*H*)-yl]ethyl acetate (Compound No. 26),
6-(2-Chlorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(2-methoxyethyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 27),
6-(2-Methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-[2-(2-methoxyethoxy)ethyl]-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 28),
25 6-(2-Chlorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-[2-(2-methoxyethoxy)ethyl]pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 29),
Tert-butyl 4- {[2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-6-(2-methylphenyl)-7-oxopyrido[2,3-*d*]pyrimidin-8(7*H*)-yl]methyl} piperidine-1-carboxylate (Compound No. 32),
30 2-{2-[2-(3-Azabicyclo[3.3.0]oct-3-yl-amino)-6-(2-methylphenyl)-7-oxopyrido[2,3-*d*]pyrimidin-8(7*H*)-yl]ethyl}-1*H*-isoindole-1,3(2*H*)-dione (Compound No. 34),
Ethyl[2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-6-(2-methylphenyl)-7-oxopyrido[2,3-*d*]pyrimidin-8(7*H*)-yl]acetate (Compound No. 44).



Compounds of Formula XXII can be and were prepared following the procedure as depicted in Scheme III. An exemplary reaction can comprise deprotecting a compound of

5 Formula XVII (wherein j is an integer from 0-2 and Pr is protecting group for example, $-\text{C}(=\text{O})\text{OC}(\text{CH}_3)_3$, $-\text{C}(=\text{O})\text{OC}(\text{CH}_3)_2\text{CHBr}_2$ or $-\text{C}(=\text{O})\text{OC}(\text{CH}_3)_2\text{CCl}_3$) to give a compound of Formula XVIII, which can be reacted with a compound of Formula XIX (wherein R_{2a} and hal are the same as defined earlier) to give a compound of Formula XX, which can be oxidized to give a compound of Formula XXI, which can be reacted with a compound of

10 Formula X to give a compound of Formula XXII.

The deprotection of a compound of Formula XVII (wherein Pr can be $-\text{C}(=\text{O})\text{OC}(\text{CH}_3)_3$ or $-\text{C}(=\text{O})\text{OC}(\text{CH}_3)_2\text{CHBr}_2$) to give a compound of Formula XVIII can be carried out in an acidic solution of an alcohol (for example, hydrochloric acid solution of methanol, ethanol, propanol, isopropylalcohol, ethylacetate or ether) or trifluoroacetic

15 acid in dichloromethane.

The deprotection of a compound of Formula XVII (wherein Pr can be $-\text{C}(=\text{O})\text{OC}(\text{CH}_3)_2\text{CCl}_3$) to give a compound of Formula XVIII can be carried out by a

supernucleophile (for example, lithium cobalt (I) phthalocyanine, zinc and acetic acid or cobalt phthalocyanine).

The reaction of a compound of Formula XVIII with a compound of Formula XIX to give a compound of Formula XX can be carried out in the presence of a base, for example, pyridine, N-methylmorpholine or diisopropylethylamine.

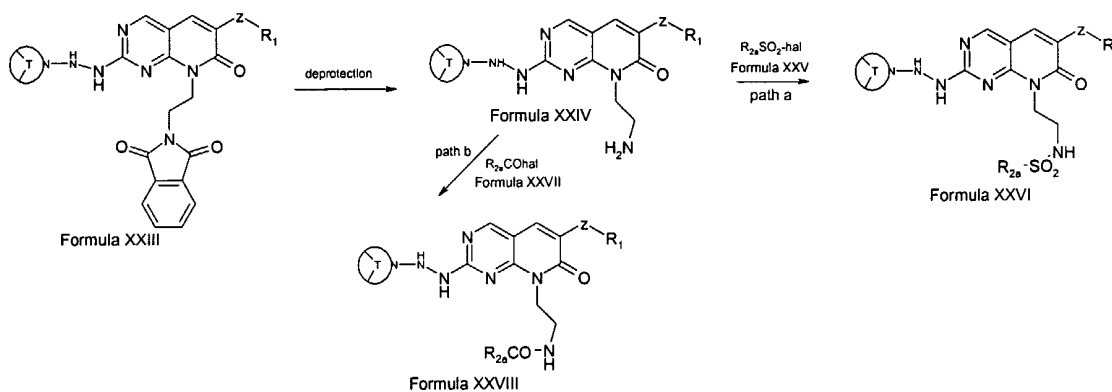
The oxidation of a compound of Formula XX to give a compound of Formula XXI can be carried out with an oxidizing agent, for example, m-chloroperbenzoic acid or oxone (KHSO₅), in an organic solvent, for example, chloroform, carbon tetrachloride, dichloromethane, ethanol or tetrahydrofuran.

The reaction of a compound of Formula XXI with a compound of Formula X to give a compound of Formula XXII can be carried out in the presence of a base, for example, pyridine, N-methylmorpholine, N-ethyldiisopropylamine, sodium hydride or triethylamine.

Illustrative compounds include that mentioned below:

6-(2-Methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-[(1-acetylpiiperidin-4-yl)methyl]-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 33).

Scheme IV



Compounds of Formulae XXVI and XXVIII can be and were prepared following a procedure, such as that depicted in Scheme IV. An exemplary reaction can comprise deprotecting a compound of Formula XXIII (wherein Z and R₁ are the same as defined earlier) to give a compound of Formula XXIV,

Path a: reacting a compound of Formula XXIV with a compound of Formula XXV (wherein R_{2a} and hal are the same as defined earlier) to give a compound of Formula XXVI.

- 5 Path b: reacting a compound of Formula XXIV with a compound of Formula XXVII (wherein R_{2a} and hal are the same as defined earlier) to give a compound of Formula XXVIII.

The deprotection of a compound of Formula XXIII to give a compound of Formula XXIV can be carried out with, for example, aqueous hydrazine, in an organic solvent, for example, ethanol, methanol, propanol or isopropanol.

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

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

- 20 Illustrative compounds include those mentioned below:

6-(2-Methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(2-aminoethyl)-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 35),

N-{2-[2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-6-(2-methylphenyl)-7-oxopyrido[2,3-*d*]pyrimidin-8(7*H*)-yl]ethyl}acetamide (Compound No. 36),

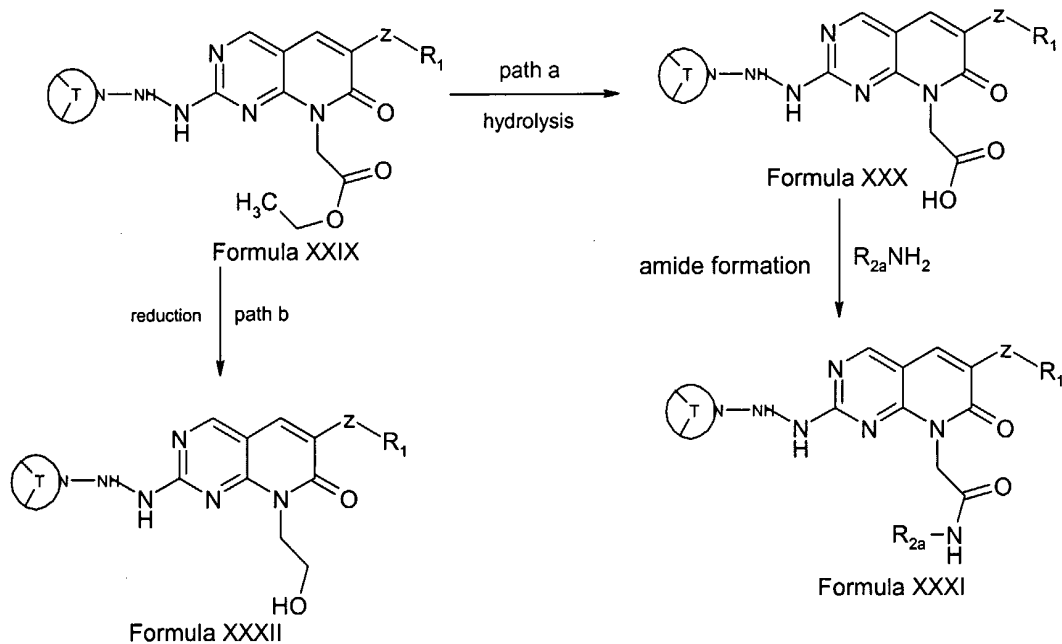
- 25 *N*-{2-[2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-6-(2-methylphenyl)-7-oxopyrido[2,3-*d*]pyrimidin-8(7*H*)-yl]ethyl}propanamide (Compound No. 37),

N-{2-[2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-6-(2-methylphenyl)-7-oxopyrido[2,3-*d*]pyrimidin-8(7*H*)-yl]ethyl}methanesulfonamide (Compound No. 38),

N-{2-[2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-6-(2-methylphenyl)-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl]ethyl}propane-1-sulfonamide (Compound No. 39),

N-{2-[2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-6-(2-methylphenyl)-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl]ethyl}butane-1-sulfonamide (Compound No. 40).

Scheme V



5

Compounds of Formulae XXX, XXXI and XXXII can be and were prepared following procedures, for example, as depicted in Scheme V. Exemplary reactions can comprise hydrolyzing a compound of Formula XXIX (Path a) (wherein Z, R₁, T are the same as defined earlier) to give a compound of Formula XXX, which can be reacted with a compound of Formula R_{2a}NH₂ (wherein R_{2a} is the same as defined earlier) to compound of Formula XXXI. The compound of Formula XXIX can be reduced to give a compound of Formula XXXII.

The hydrolysis of the compound of Formula XXIX (path a) to give a compound of Formula XXX can be carried out in the presence of a base, for example, lithium hydroxide, potassium hydroxide or sodium hydroxide, in an organic solvent, for example, methanol, ethanol, propanol, tetrahydrofuran or mixtures thereof.

The compound of Formula XXX can be converted to a compound of Formula XXXI in the presence of a base, for example, N-methylmorpholine, triethylamine,

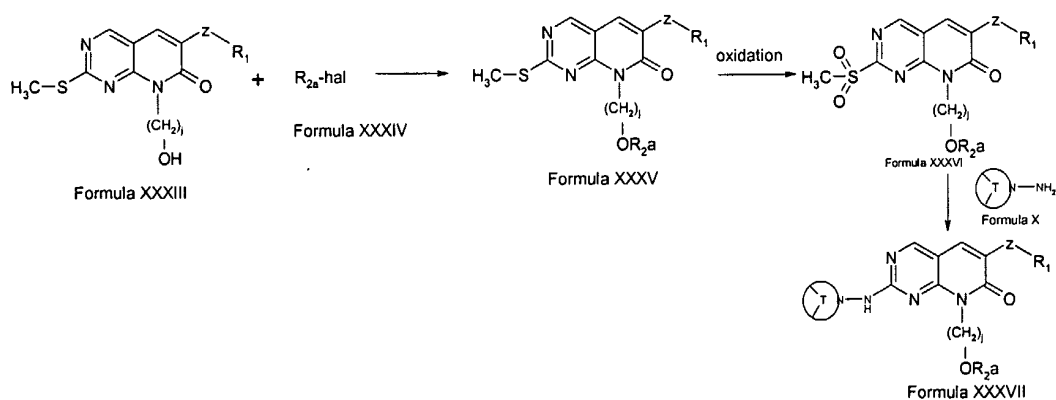
diisopropylethylamine or pyridine, in an organic solvent, for example, tetrahydrofuran, dimethylformamide, diethyl ether or dioxane, with a condensing agent, for example, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC.HCl) or dicyclohexylcarbodiimide (DCC).

- 5 The reduction of the compound of Formula XXIX (path b) to give a compound of Formula XXXII can be carried out in the presence of reducing agent, for example, sodium borohydride, lithium borohydride or sodium cyanoborohydride.

Particular illustrative compounds include those mentioned below:

- 10 6-(2-Methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(2-hydroxyethyl) pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 45),
- 6-(2-Methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-7-oxopyrido[2,3-*d*]pyrimidin-8(7*H*)-yl-*N*-methoxyacetamide (Compound No. 46),
- N*-Cyclobutyl-2-[2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-6-(2-methylphenyl)-7-oxopyrido[2,3-*d*]pyrimidin-8(7*H*)-yl]acetamide (Compound No. 47),
- 15 6-(2-Methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(2-oxo-2-pyrrolidin-1-ylethyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 48),
- 6-(2-Methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-7-oxopyrido[2,3-*d*]pyrimidin-8(7*H*)-yl-*N*-isopropylacetamide (Compound No. 49),
- 20 6-(2-Methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-7-oxopyrido[2,3-*d*]pyrimidin-8(7*H*)-yl]acetic acid (Compound No. 79),
- N*-Cyclopropyl-2-[2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-6-(2-methylphenyl)-7-oxopyrido[2,3-*d*]pyrimidin-8(7*H*)-yl]acetamide (Compound No. 80).

Scheme VI



Compounds of Formulae XXXVII can be prepared following, for example, a procedure as depicted in Scheme VI. Thus, an exemplary reaction can comprise reacting a compound of Formula XXXIII (wherein j is an integer from 0-2, and Z , R_1 and T are the same as defined earlier) with a compound of Formula XXXIV (wherein R_{2a} and hal are the same as defined earlier) to give a compound of Formula XXXV, which can be oxidized to give a compound of Formula XXXVI, which can be reacted with a compound of Formula X to give a compound of Formula XXXVII.

The reaction of a compound of Formula XXXIII with a compound of Formula XXXIV to give a compound of Formula XXXV can be carried out in the presence of a base, for example, sodium hydride, potassium hydride or lithium hydride, in an organic solvent, for example, N-methylpyrrolidone, dimethylformamide, tetrahydrofuran or dimethylsulphoxide.

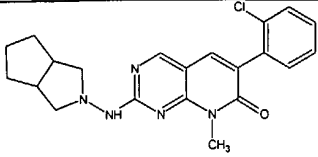
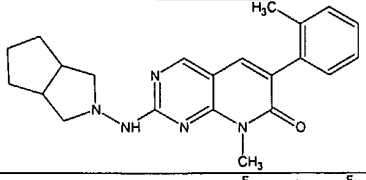
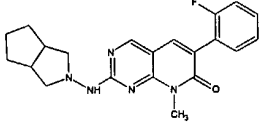
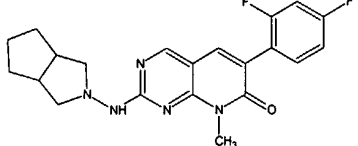
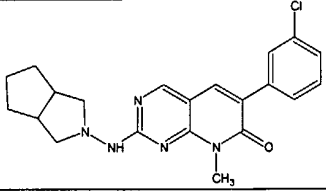
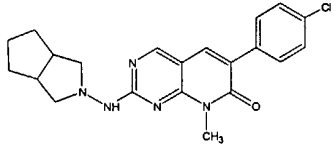
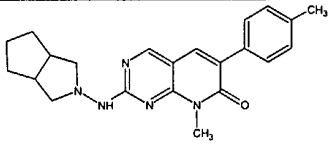
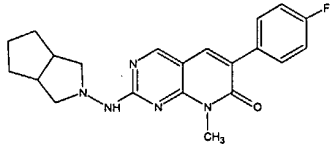
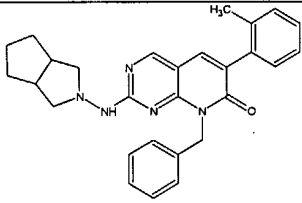
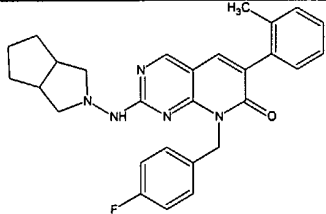
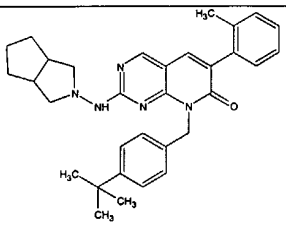
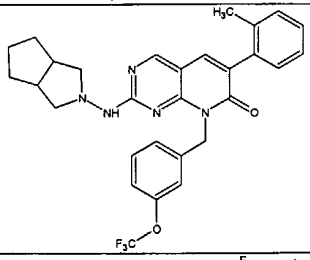
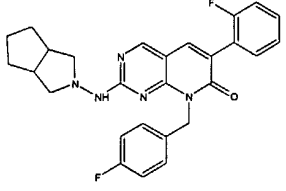
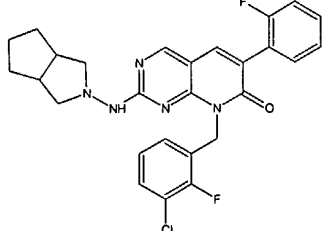
The oxidation of a compound of Formula XXXV to give a compound of Formula XXXVI can be carried out with an oxidizing agent, for example, m-chloroperbenzoic acid or oxone ($KHSO_5$), in an organic solvent, for example, chloroform, dichloroethane, carbon tetrachloride, dichloromethane, ethanol or tetrahydrofuran.

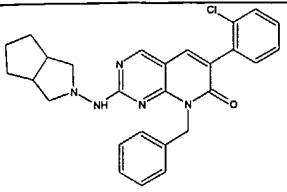
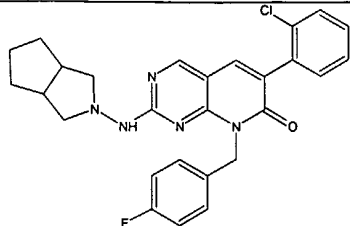
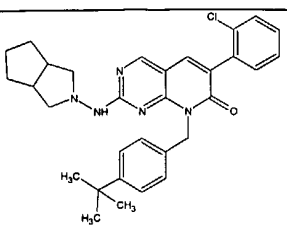
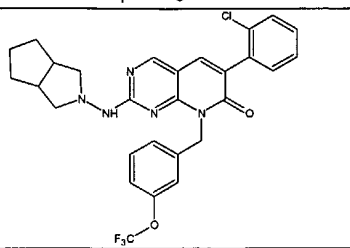
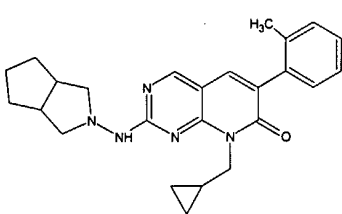
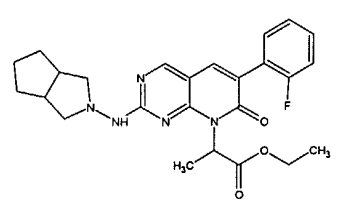
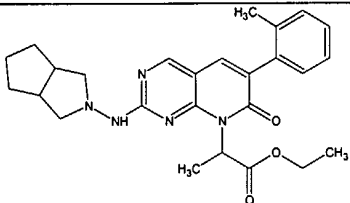
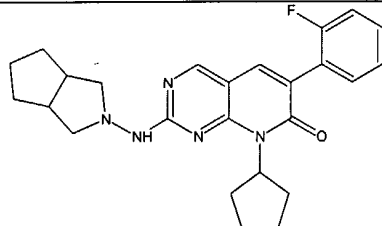
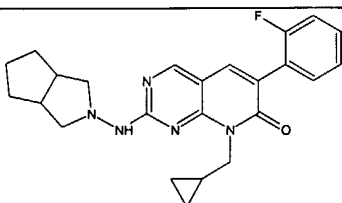
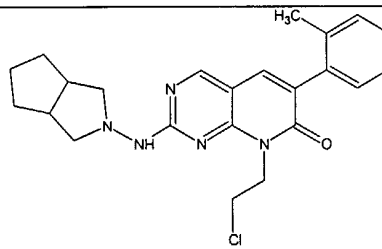
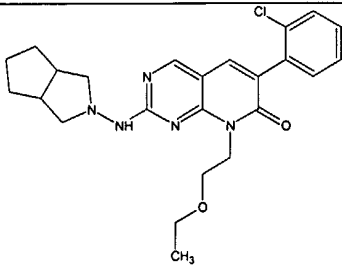
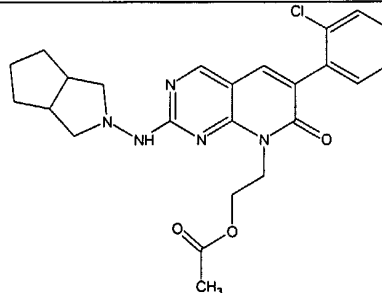
The reaction of a compound of Formula XXXVI with a compound of Formula X to give a compound of Formula XXXVII can be carried in the presence of a base, for example, pyridine, N-methylmorpholine, N-ethyl-diisopropylamine, sodium hydride or triethylamine.

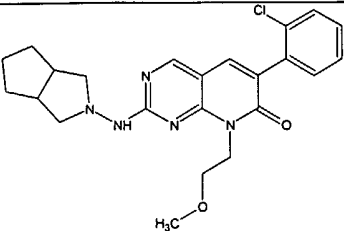
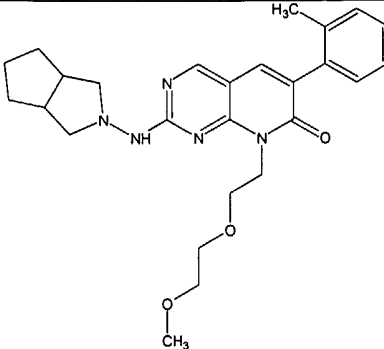
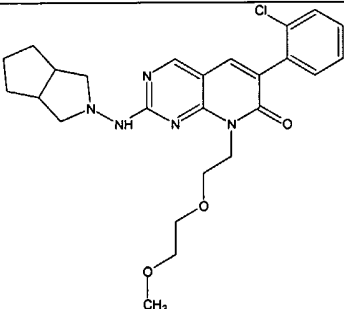
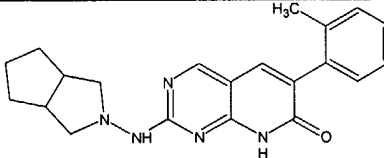
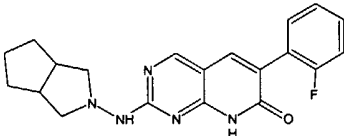
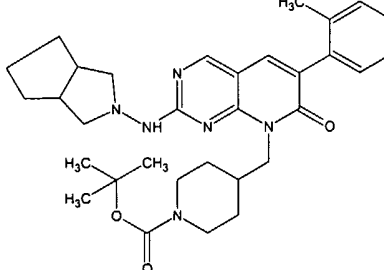
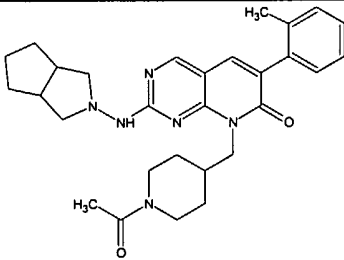
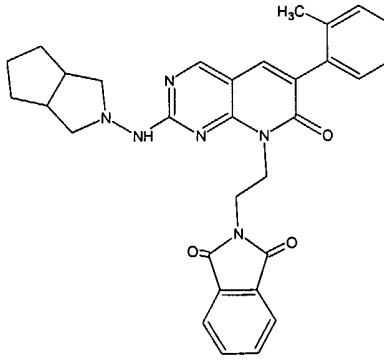
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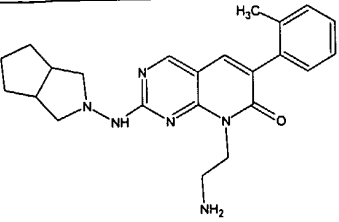
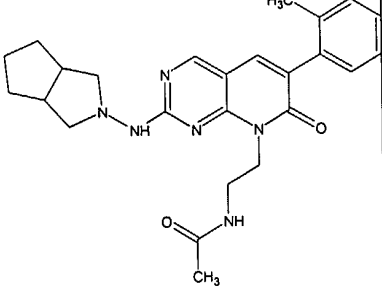
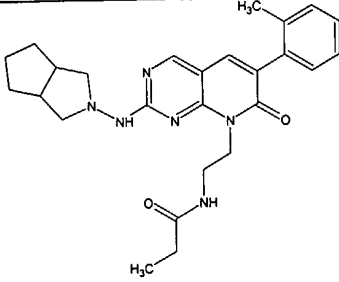
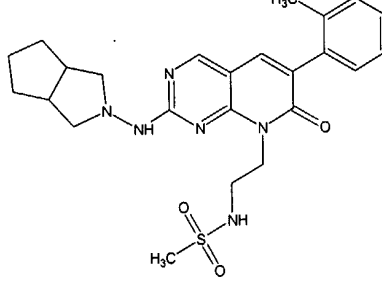
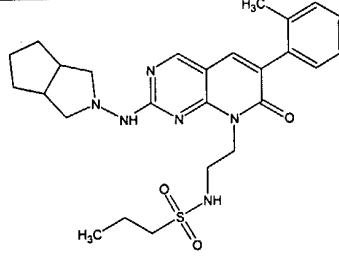
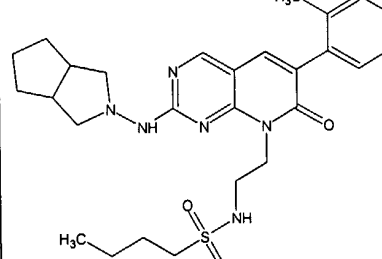
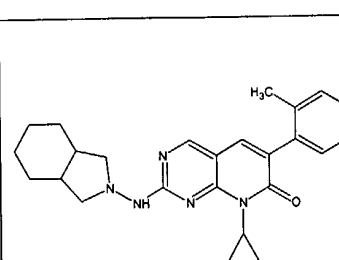
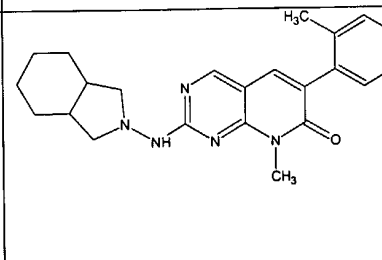
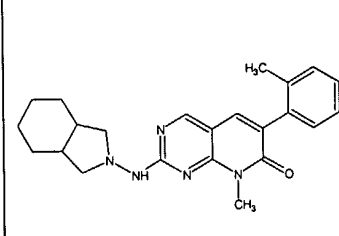
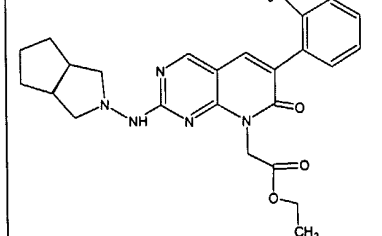
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- 6-(2-Methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(2-ethoxyethyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 51).

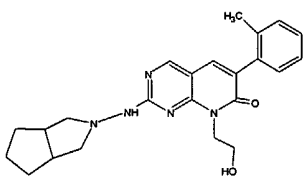
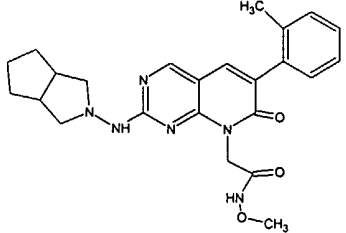
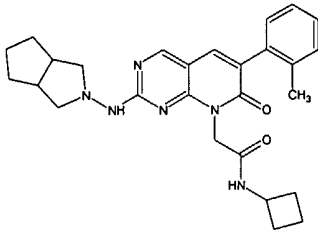
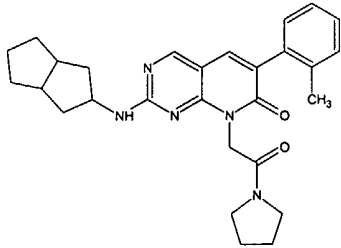
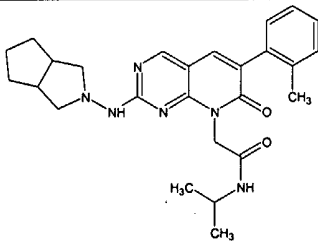
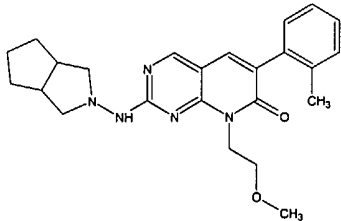
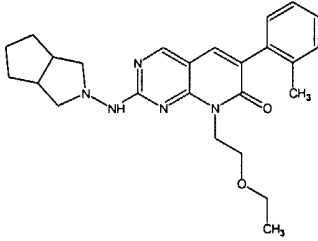
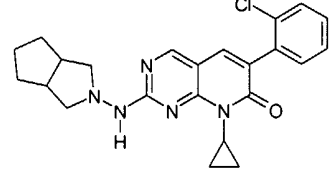
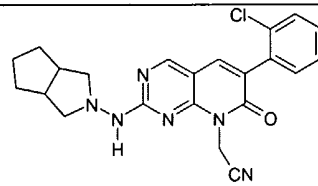
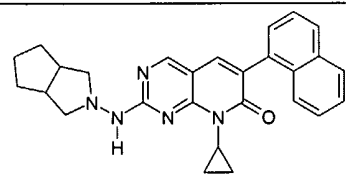
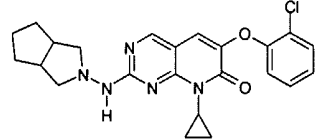
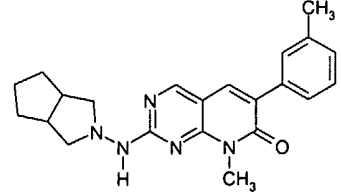
Particular illustrative compounds which can be produced by Scheme I, are listed in table below:

Compound No	Structure	Compound No.	Structure
1.		2.	
3.		4.	
5.		6.	
7.		8.	
9.		10.	
11.		12.	
13.		14.	

15.		16.	
17.		18.	
19		20	
21		22	
23		24	
25		26	

27.		28.	
29.		30.	
31.		32.	
33.		34.	

35.		36.	
37.		38.	
39.		40.	
41.		42.	
43.		44.	

45.		46.	
47.		48.	
49.		50.	
51.		52.	
53.		54.	
55.		56.	

57.		58.	
59.		60.	
61.		62.	
63.		64.	
65.		66.	
67.		68.	
69.		70.	
71.		72.	

73.		74.	
75.		76.	
77		78.	
79		80	

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

5

EXAMPLES

Example 1: Synthesis of 6-(2-chlorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 1)

Step a: 4-Methylamino-2-methylthio-pyrimidine-5-carboxylic acid ethyl ester

10 To a suspension of ethyl-4-chloro-2-methylthio-5-pyrimidine-carboxylate (commercially available) (8.0 g, 34 mmol) in dry tetrahydrofuran (60 ml), was added triethylamine (4.3 g, 42 mmol) and aqueous methylamine (40%, 3.2 g, 36.2 mmol) at room temperature and stirred for 2 hours. The organic solvent was evaporated under

reduced pressure followed by addition of cold water. A white solid thus obtained was filtered, washed with water and dried under vacuum. Yield = 6.2 g.

Step b: [4-(Methylamino)-2-(methylthio)-pyrimidin-5-yl]-methanol

To a suspension of lithium aluminium hydride (1.21 g, 32 mmol) in dry
5 tetrahydrofuran (60 ml) at -70°C, was added a solution of the compound obtained from step *a* above (6.0 g, 26 mmol) in tetrahydrofuran (20 ml) dropwise. The reaction mixture was stirred between -70°C -60°C for 1 hour and then at room temperature till completion. The reaction mixture was cooled to 0°C and diluted with ethylacetate, followed by
addition of 30% aqueous solution of sodium hydroxide dropwise. The reaction mixture
10 was then filtered through a celite pad and washed with ethylacetate and dichloromethane. The filtrate was evaporated under reduced pressure followed by addition of water. A white solid thus obtained was filtered and dried under vacuum. Yield = 4.0 g.

Step c: 4-Methylamino-2-methylthio-pyrimidin-5-carboxaldehyde

To a suspension of compound obtained from step *b* above (3.8 g, 20.7 mmol) in
15 dichloromethane (100 ml), was added manganese dioxide (12.7 g, 145 mmol) at room temperature and stirred for 24-36 hours. The reaction mixture was filtered over a celite pad and evaporated under reduced pressure. The residue thus obtained was purified by column chromatography using ethylacetate in hexane (1:4) solvent mixture as eluent to furnish the title compound. Yield = 3.2 g.

20 A particular exemplary compound was prepared analogously, namely, 4-Cyclopropylamino-2-methylthio-pyrimidin-5-carboxaldehyde.

Step d: 6-(2-Chlorophenyl)-8-methyl-2-methylthio-8H-pyrido[2,3-d]pyrimidin-7-one

To a solution of the compound obtained from step *c* above (3.2 g, 17.7 mmol) in
N-methylpyrrolidinone (20 ml), was added 2-chlorophenyl acetic acid methyl ester (4.9 g,
25 26.6 mmol) and potassium carbonate (7.4 g, 53.04 mmol) and heated at 110°C for 2 hours. The reaction mixture was diluted with ethylacetate and poured into water. It was then 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 ethylacetate in hexane (1:3) as eluent. Yield = 3.2 g.

Step e: 6-(2-Chlorophenyl)-2-methanesulphonyl-8-methyl-8H-pyrido[2,3-d]pyrimidin-7-one

To a solution of the compound obtained from step *d* above (1.5 g, 4.7 mmol) in chloroform (20 ml) was added *m*-chloroperbenzoic acid (70%) (3.5 g, 14.2 mmol) at 0°C and stirred at room temperature for 30 minutes. To it was added a saturated solution of aqueous sodium bisulphate followed by aqueous sodium bicarbonate solution at 0°C. The reaction mixture was then extracted with dichloromethane and the organic layer was washed with water, dried over anhydrous sodium sulphate, filtered and evaporated under reduced pressure. The residue thus obtained was washed thoroughly with hexane to furnish the title compound. Yield = 1.1 g

Step f: 6-(2-Chlorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-d]pyrimidine-7(8H)-one

To the compound obtained from step *e* above (0.1 g, 0.286 mmol), was added 3-amino-3-azabicyclo[3.3.0]octane (commercially available) (0.116 g, 0.715 mmol) and heated to 80°C for 2 hours. The reaction mixture was diluted with dichloromethane and the compound was purified by column chromatography using (1:1) ethyl acetate: hexane as eluent to afford a yellow residue which was then further purified by preparative TLC using ethyl acetate in dichloromethane as solvent of elution. Yield = 35 mg.

m.p.: 85-87°C.

¹H NMR (CDCl₃): δ 8.55 (1H, s, Ar-H), 7.54 (1H, s, Ar-H), 7.48-7.44 (1H, t, J=3.0 Hz, Ar-H), 7.35-7.30 (3H, m, Ar-H), 3.72 (3H, s, -NCH₃), 3.32 (2H, brs, -NCH₂), 2.74 (2H, brs, -NCH₂), 2.49 (2H, brs, -2x-CH) and 1.73-1.53 (6H, m, 3x-CH₂).

Mass spectrum (m/z, +ve ion mode): 398 [M⁺+1+2] and 396 [M⁺+1].

Analogues of 6-(2-chlorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 1) described below were prepared by using appropriate amine in place of 3-amino-3-azabicyclo[3.3.0]octane, respectively, as applicable in each case.

6-(2-Methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-
d]pyrimidin-7(8H)-one (Compound No. 2)

- m.p: 69.8-79.8°C; ¹H NMR (CDCl₃ + CD₃OD): δ 9.09 (s, 1H, Ar-H), 7.52 (s, 1H, Ar-H),
7.33-7.17 (m, 4H, Ar-H), 3.74 (s, 3H, -NCH₃), 2.63-2.56 (m, 6H, 2x-NCH₂ & 2x-CH),
5 2.21 (s, 3H, -ArCH₃) and 1.73-1.70 (m, 6H, 3x-CH₂); Mass spectrum (m/z, +ve ion mode):
376 [M⁺+1].

6-(2-Fluorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-
d]pyrimidin-7(8H)-one (Compound No. 3),

- 10 6-(2,4-Difluorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-
d]pyrimidin-7(8H)-one (Compound No. 4),

6-(3-Chlorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-
d]pyrimidin-7(8H)-one (Compound No. 5),

6-(4-Chlorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-
d]pyrimidin-7(8H)-one (Compound No. 6),

- 15 6-(4-Methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-
d]pyrimidin-7(8H)-one (Compound No. 7),

6-(4-Fluorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-
d]pyrimidin-7(8H)-one (Compound No. 8),

- 20 6-(2-Methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(benzyl)-pyrido[2,3-
d]pyrimidin-7(8H)-one (Compound No. 9),

6-(2-Methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(4-fluorobenzyl)-pyrido[2,3-
d]pyrimidin-7(8H)-one (Compound No. 10),

6-(2-Methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(tert-butylbenzyl)-
pyrido[2,3-d]pyrimidin-7(8H)-one (Compound No. 11),

- 25 6-(2-Methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(3-trifluoromethoxybenzyl)-
pyrido[2,3-d]pyrimidin-7(8H)-one (Compound No. 12),

6-(2-Fluorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(4-fluorobenzyl)-pyrido[2,3-
d]pyrimidin-7(8H)-one (Compound No. 13),

- 30 6-(2-Fluorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(3-chloro-2-fluorobenzyl)-
pyrido[2,3-d]pyrimidin-7(8H)-one (Compound No. 14),

6-(2-Chlorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(benzyl)-pyrido[2,3-
d]pyrimidin-7(8H)-one (Compound No. 15),

- 6-(2-Chlorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(4-fluorobenzyl)-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 16),
- 6-(2-Chlorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(4-tert-butylbenzyl)-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 17),
- 5 6-(2-Chlorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(3-trifluoromethoxybenzyl)-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 18),
- 6-(2-Methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 30),
- 10 6-(2-Fluorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 31),
- 6-(2-Methylphenyl)-2-(7-azabicyclo[4.3.0]non-7-yl-amino)-8-(cyclopropyl)-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 41),
- 6-(2-Methylphenyl)-2-(7-azabicyclo[4.3.0]non-7-yl-amino)-8-methyl-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 42),
- 15 6-(2-Chlorophenyl)-2-(7-azabicyclo[4.3.0]non-7-yl-amino)-8-methyl-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 43),
- 6-(2-Chlorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-cyclopropyl-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 52),
- 20 6-(2-Chlorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-7-oxopyrido[2,3-*d*]pyrimidin-8(7*H*)-ylacetonitrile (Compound No. 53),
- 6-(1-Naphthyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-cyclopropyl-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 54),
- 6-(3-Methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methyl-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 56),
- 25 6-(4-Isopropylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 63),
- 6-(2-Fluorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(cyclopropyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 64),
- 30 6-(2,4-Dichlorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 65),
- 6-(4-Nitrophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methyl-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 66),
- 6-(3-Methoxyphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 67),

6-(2,6-Dichlorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 68),

6-(2-Nitrophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 69),

5 6-(3-Fluorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 70),

6-(2-Chloro-4-fluorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 71),

10 Example 1a: Synthesis of 6-(2-fluorophenoxy)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-cyclopropyl-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 59)

Step a: 1-(2-Fluorophenoxy)acetic acid ethyl ester

To a solution of 2-fluorophenol (5.0 g, 44.64 mmol) in N-methylpyrrolidone (20 ml) added potassium carbonate (18.51 g, 133.92 mmol) and stirred for 10 minutes.

15 To it ethylbromoacetate (8.95 g, 53.56 mmol) was added and the contents were stirred at room temperature overnight. The reaction mixture was poured into water, extracted with ethyl acetate, washed with water, dried over anhydrous sodium sulphate, filtered and the solvent evaporated under vacuum to furnish the title compound.

Step b: 8-Cyclopropyl-6-(2-fluorophenoxy)-2-(methylthio)-8H-pyrido[2,3-*d*]pyrimidin-7-one

20 To a solution of the compound 4-cyclopropylamino-2-methylthio-pyrimidin-5-carboxaldehyde (1.0 g, 4.78 mmol) in N-methylpyrrolidone (10 ml) was added potassium carbonate (1.98 g, 14.35 mmol) and stirred at room temperature for 10 min. To it was added the compound obtained from step *a* above (1.14 g, 5.74 mmol) and the contents
25 were stirred at 110 °C for 5 hrs. The reaction mixture was poured into water and stirred. The solid thus separated out was filtered and dried under vacuum to furnish the title compound.

Step c: 8-Cyclopropyl-6-(2-fluorophenoxy)-2-(methylsulphonyl)-8H-pyrido[2,3-*d*]pyrimidin-7-one

The title compound was prepared following the procedure as described in Example 1, step e.

Step d: 6-(2-Fluorophenoxy)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-cyclopropyl-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 59)

5 A solution of the compound 3-amino-3-azabicyclo[3.3.0]octane (commercially available) (0.390 g, 2.40 mmol) in Hunig's base (1.4 ml, 8.0 mmol) was stirred at room temperature for 15 min. To it was added a solution of the compound obtained from step c above (0.30 g, 8.0 mmol) and heated at 110 °C for 1 hr. The reaction mixture was poured into water, extracted with ethyl acetate, dried over anhydrous sodium sulphate, filtered and
10 evaporated under vacuum. The residue thus obtained was purified by column chromatography using 20 % ethyl acetate in hexane as eluent and finally by preparative TLC using 10 % ethyl acetate in dichloromethane as eluent to furnish the title compound. Yield: 40 mg; ¹H NMR (CDCl₃): δ 8.36 (1H, s, Ar-H), 7.21-6.78 (3H, m, Ar-H), 6.78 (1H, s, Ar-H), 5.90 (1H, brs, -NH), 3.32-3.31 (2H, brm, -NCH₂), 3.00-2.97 (1H, brm, -NCH),
15 2.74-2.72 (2H, brm, -NCH₂), 2.46 (2H, brm, 2x-CH) and 1.70-1.52 (6H, m, 3x-CH₂), 1.32-1.26 (2H, m, -CH₂) and 0.97-0.96 (2H, m, -CH₂); Mass spectrum (m/z, +ve ion mode): 422 [M⁺+1].

The following illustrative compounds were prepared analogously,

20 6-(2-Chlorophenoxy)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-cyclopropyl-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 55)

 6-(2-Methylphenoxy)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-cyclopropyl-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 57)

 6-(2-Methylphenoxy)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 58)

25 6-(4-Chlorophenoxy)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-cyclopropylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 60)

 6-(4-Chlorophenoxy)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 61)

30 6-Methoxy-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 62)

- 6-(4-Nitrophenoxy)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methyl-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 72)
- 6-(2-Chlorophenoxy)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 73)
- 5 6-(2-Fluorophenoxy)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 74)
- 6-(4-Chloro-2-fluorophenoxy)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 75)
- 10 6-(4-Chloro-2-fluorophenoxy)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-cyclopropyl-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 76)
- 6-(3-Methoxyphenoxy)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(cyclopropyl)-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 77)
- 6-(3-Methylphenoxy)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(cyclopropyl)-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 78).
- 15

Scheme II, Procedure

Example 2: Synthesis of 6-(2-methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(cyclopropyl methyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 19)

Step a: 6-(2-Methylphenyl)-2-methylthio-8H-pyrido[2,3-*d*]pyrimidin-7-one

- 20 The title compound was prepared following the procedure as described in Example 1, steps **a** to **d**, by using ammonia in place of methyl amine in step **a** and by using 2-methylphenyl acetic acid methyl ester in place of 2-chlorophenyl acetic acid methyl ester.

Step b: 8-Cyclopropylmethyl-6-(2-methylphenyl)-2-methylthio-8H-pyrido[2,3-*d*]pyrimidin-7-one

- 25 To a suspension of sodium hydride (0.040 g, 0.97 mmol) in dimethylformamide at 0°C was added the compound obtained from step *a* above (0.250 g, 0.88 mmol). The reaction mixture was stirred at room temperature for 30 minutes. To it was added cyclopropylmethyl bromide (0.13g, 0.97 mmol) at 0°C. The reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was then poured in water, extracted
- 30 with ethyl acetate, washed with water dried over anhydrous sodium sulphate, filtered and

evaporated under reduced pressure. The residue thus obtained was then purified by column chromatography using 30 % ethyl acetate in hexane to afford the title compound.

Step c: 8-Cyclopropylmethyl-6-(2-Methylphenyl)-2-methanesulphonyl-8H-pyrido[2,3-d]pyrimidin-7-one

5 The title compound was prepared following the procedure as described in Example 1, step e, by oxidizing the compound obtained from step b above.

Step d: 6-(2-Methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(cyclopropylmethyl)pyrido[2,3-d]pyrimidin-7(8H)-one (Compound No. 19)

10 The title compound was prepared following the procedure as described in Example 1, step f.

Yield: 28 mg; ¹H NMR (CDCl₃): δ 8.53 (1H, s, Ar-H), 7.46 (1H, s, Ar-H), 7.26-7.22 (4H, m, Ar-H), 4.32-4.31 (2H, d, J = 4Hz), 2.72-2.70 (2H, m), 2.24 (3H, s), 1.75-1.72 (4H, m), 1.60-1.53 (6H, m), 1.44-1.40 (3H, m), 1.26 (2H, s); Mass spectrum (m/z, +ve ion mode): 416 [M⁺+1].

15

Example 3: Synthesis of Ethyl 2-[6-(2-fluorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl]propanoate (Compound No. 20)

Step a: 6-(2-Fluorophenyl)-2-methylthio-8H-pyrido[2,3-d]pyrimidin-7-one

20 The title compound was prepared following the procedure as described in Example 1, steps a to d, by using ammonia in place of methyl amine in step a and by using 2-fluorophenyl acetic acid methyl ester in place of 2-chlorophenyl acetic acid methyl ester.

Step b: 2-[6-(2-Fluorophenyl)-2-methylthio-7-oxo-7H-pyrido[2,3-d]pyrimidin-8-yl]-propionic acid ethyl ester

25 To a solution of the compound obtained from step a above (0.500 g, 1.7 mmol) in acetone (10 ml) was added potassium carbonate (0.73 g, 5.3 mmol), *tetra-n*-butylammonium iodide (0.98 g, 2.6 mmol), ethyl-2-bromopropionate (0.39 g, 2.1 mmol) and acetone. The reaction mixture was then refluxed for 8 hours. The reaction mixture was cooled to room temperature and filtered. The filtrate was concentrated to obtain the

crude product. Crude product was then purified by column chromatography using 20 % ethyl acetate in hexane to furnish the title compound.

Step c: 2-[6-(2-Fluorophenyl)-2-methylsulphonyl-7-oxo-7H-pyrido[2,3-d]pyrimidin-8-yl]-propionic acid ethyl ester

5 The title compound was prepared following the procedure as described in Example 1, step e, by oxidizing the compound obtained from step b above.

Step d: Ethyl 2-[6-(2-fluorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl]propanoate (Compound No. 20)

10 The title compound was prepared following the procedure as described in Example 1, step f.

Yield: 300 mg; ¹H NMR (CDCl₃): δ8.59 (1H, s, Ar-H), 7.66 (1H, s, Ar-H), 7.65-7.51 (1H, m, Ar-H), 7.33 (1H, s, Ar-H), 7.20-7.11 (2H, m, Ar-H), 5.95 (1H, s, -NCH), 4.25-4.19 (1H, m, -OCH), 4.12-4.08 (1H, m, -OCH), 3.30 (2H, brs, -NCH₂), 2.72 (2H, brs), 2.4 (2H, brs, -NCH₂), 1.69-1.68 (3H, d, J = 4 Hz, -CHCH₃), 1.53 (2H, brs), 1.42-1.41 (2H, m),
15 1.18-1.16 (3H, t, -OCH₂CH₃), 0.98-0.88 (2H, m); Mass spectrum (m/z, +ve ion mode): 466 [M⁺+1].

The following illustrative compounds were prepared analogously,

Ethyl 2-[6-(2-methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl]propanoate (Compound No. 21)

20 6-(2-Fluorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(cyclopentyl) pyrido[2,3-d]pyrimidin-7(8H)-one (Compound No. 22)

6-(2-Fluorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(cyclopropylmethyl)-pyrido[2,3-d]pyrimidin-7(8H)-one (Compound No. 23)

25 6-(2-Methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(2-chloroethyl)pyrido[2,3-d]pyrimidin-7(8H)-one (Compound No. 24)

6-(2-Chlorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(2-ethoxyethyl)pyrido[2,3-d]pyrimidin-7(8H)-one (Compound No. 25)

2-[6-(2-Chlorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl]ethyl acetate (Compound No. 26)

6-(2-Chlorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(2-methoxyethyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 27)

6-(2-Methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-[2-(2-methoxyethoxy)ethyl]-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 28)

- 5 6-(2-Chlorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-[2-(2-methoxyethoxy)ethyl]pyrido [2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 29)

(2-{2-[2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-6-(2-methylphenyl)-7-oxopyrido[2,3-*d*]pyrimidin-8(7*H*)-yl]ethyl}-1*H*-isoindole-1,3(2*H*)-dione (Compound No. 34)

- 10 Ethyl [2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-6-(2-methylphenyl)-7-oxopyrido[2,3-*d*]pyrimidin-8(7*H*)-yl]acetate (Compound No. 44)

Example 4: Synthesis of tert-butyl 4-{{2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-6-(2-methylphenyl)-7-oxopyrido[2,3-*d*]pyrimidin-8(7*H*)-yl)methyl}piperidine-1-carboxylate (Compound No. 32)

- 15 **Step a: 4-(2-Methylthio-7-oxo-6-(2-methylphenyl)-7*H*-pyrido[2,3*d*]-pyrimidin-8-ylmethyl)-piperidine-1-carboxylic acid tert-butyl ester**

- To the compound 6-(2-Methylphenyl)-2-methylthio-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (0.500 g, 1.6 mmol) was added *N*-*tert*-butoxy carbonyl piperidine-4-methanol (0.750 g, 3.47 mmol), triphenylphosphine (0.91 g, 3.47 mmol) and evacuated for 30 minutes
 20 followed by the addition of dimethylformamide was added. To the reaction mixture was added diisopropylazadicarboxylate (0.71 g, 3.47 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was poured into water and extracted with ethyl acetate, washed with water, dried over anhydrous sodium sulphate, and concentrated under reduced pressure. The residue thus obtained was purified by
 25 column chromatography using 20 % ethyl acetate in hexane as eluent to furnish the title compound.

Yield = 0.500 g.

The following illustrative intermediate was prepared analogously,

- 30 3-[2-Methylthio-7-oxo-6-(2-methylphenyl)-7*H*-pyrido[2,3*d*]pyrimidin-8-ylmethyl)-piperidine-1-carboxylic acid *tert*-butyl ester.

Step b: 4-(2-Methylsulphonyl-7-oxo-6-(2-methylphenyl)-7H-pyrido[2,3d-pyrimidin-8-ylmethyl)-piperidine-1-carboxylic acid tert-butyl ester

The title compound was prepared following the procedure as described in Example 1, step e, by oxidizing the compound obtained from step a above.

Step c: *Tert*-butyl 4-{{2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-6-(2-methylphenyl)-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl}methyl}piperidine-1-carboxylate (Compound No. 32)

The title compound was prepared following the procedure as described in Example 1, step f. ¹H NMR (CDCl₃): δ 8.5 (1H, s, Ar-H), 7.48 (1H, s, Ar-H), 7.25-7.17 (4H, m, Ar-H), 4.36-4.34 (2H, m), 3.18 (2H, brs), 2.69 (6H, brs), 2.20 (3H, s, -CH₃), 1.75 (2H, s), 1.60-1.55 (6H, m), 1.4-1.26 (4H, m); Mass spectrum (m/z, +ve ion mode): 559 [M⁺+1].

Scheme III, procedure

Example 5: Synthesis of 6-(2-methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-[(1-acetylpiperidin-4-yl)methyl]-pyrido[2,3-d]pyrimidin-7(8H)-one (Compound No. 33)

Step a: Hydrochloride salt of 2-methylthio-8-piperidin-3-yl-methyl-6-(2-methylphenyl)-8H-pyrido[2,3d]pyrimidin-7-one

To a solution of the compound 3-[2-methylthio-7-oxo-6-(2-methylphenyl)-7H-pyrido[2,3d]pyrimidin-8-ylmethyl)-piperidine-1-carboxylic acid *tert*-butyl ester (0.600 g) in dichloromethane was added ethereal hydrochloric acid solution (2 ml) at 0 °C. The reaction was stirred at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure. The residue thus obtained was purified by washing with diethylether to furnish the title compound, which was finally dried under reduced pressure.

Step b: 8-(1-Scetyl-piperidine-3-ylmethyl)-2-methylthio-6-(2-methylphenyl)-8H-pyrido[2,3d]pyrimidin-7-one

To the compound (0.350 mmol) obtained from step a above was added pyridine at 0 °C followed by the addition of acetic anhydride (2.0 ml) at 0 °C. The reaction mixture

was stirred at room temperature for 3 hours and subsequently diluted with water. The white solid thus obtained was filtered and dried under high vacuum to furnish the title compound.

Step c: 8-(1-Acetyl-piperidine-3-ylmethyl)-2-methylsulphonyl-6-(2-methylphenyl)-8H-pyrido[2,3-d]pyrimidin-7-one

The title compound was prepared following the procedure as described Example 1, step e, by oxidizing the compound obtained from step b above.

Step d: 6-(2-Methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-[(1-acetylpiperidin-4-yl)methyl]-pyrido[2,3-d]pyrimidin-7(8H)-one (Compound No. 33)

The title compound was prepared following the procedure as described in Example 1, step f. Yield: 100 mg; ¹H NMR (CDCl₃): δ 8.53 (1H, s, Ar-H), 7.48 (1H, s, Ar-H), 7.22-7.17 (4H, m, Ar-H), 4.37-4.30 (3H, m), 3.2 (2H, brs), 2.91-2.89 (4H, m), 2.71-2.69 (2H, m), 2.22 (3H, s), 2.21-2.17 (2H, m), 1.97-1.74 (7H, m), 1.60-1.53 (6H, m); Mass spectrum (m/z, +ve ion mode): 501[M⁺+1].

Scheme IV, Procedure

Example 6: Synthesis of N-{2-[2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-6-(2-methylphenyl)-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl]ethyl}methanesulfonamide (Compound No. 38)

Step a: 6-(2-Methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(2-aminoethyl)-pyrido[2,3-d]pyrimidin-7(8H)-one (Compound No. 35)

To a solution of the Compound No. 34 (0.90 g, 1.68 mmol) in ethanol (10 ml) was added aqueous solution of hydrazine (0.53 g, 16.8 mmol) and stirred the reaction mixture for 4 hours at room temperature. The solvent was evaporated under reduced pressure and the residue thus obtained was dissolved in ethanol. The mixture was concentrated under reduced pressure to furnish the title compound. Yield: 790 mg.

Step b: N-{2-[2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-6-(2-methylphenyl)-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl]ethyl}methanesulfonamide (Compound No. 38)

To a solution of the compound obtained from step a above (0.80 g, 0.19 mmol) in dichloromethane (10 ml) was added methanesulphonyl chloride (0.034 g, 0.29 mmol) and

triethylamine (0.060 g, 0.59 mmol) at 0 °C. The reaction mixture was stirred for 2 hours and subsequently diluted with dichloromethane. The mixture was extracted with sodium bicarbonate solution. The organic layer was collected, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The residue thus obtained was purified
5 by preparative column chromatography using 10% methanol in dichloromethane as eluent to furnish the title compound.

Yield: 23 mg; ¹H NMR (CDCl₃): δ 8.54 (s, 1H, Ar-H), 7.52 (s, 1H, Ar-H), 7.30-7.17 (m, 4H, Ar-H), 3.66 (brs, 1H, -NCH), 3.492 (m, 2H, -NCH₂), 3.40-3.34 (m, 5H, 2x-NCH₂ & -NCH), 2.99 (s, 3H, -SO₂CH₃), 2.54-2.53 (m, 2H, 2x-CH), 2.21 (s, 3H, Ar-CH₃), 1.71-1.54
10 (m, 6H, 3x-CH₂); Mass spectrum (m/z, +ve ion mode): 483 [M⁺+1].

The following illustrative compounds were prepared analogously,

N-{2-[2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-6-(2-methylphenyl)-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl]ethyl}propane-1-sulfonamide (Compound No. 39)

N-{2-[2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-6-(2-methylphenyl)-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl]ethyl}butane-1-sulfonamide (Compound No. 40)
15

Example 7: Synthesis of N-{2-[2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-6-(2-methylphenyl)-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl]ethyl}acetamide (Compound No. 36)

To a solution of the Compound No. 34 (0.80 g, 0.19 mmol) in dichloromethane (10
20 ml) was added acetyl chloride (0.02g, 0.29 mmol) and triethylamine (0.058 g, 3.0 mmol) at 0°C under nitrogen atmosphere. The reaction mixture was stirred for 4 hours. The reaction mixture was diluted with dichloromethane (20 ml) and extracted with sodium bicarbonate solution. The organic layer was separated, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The residue thus obtained was purified
25 by preparative column chromatography by using 10% methanol in dichloromethane as eluent to furnish the title compound. Yield: 13 mg; ¹H NMR (CDCl₃): δ 8.56 (s, 1H, Ar-H), 7.52 (s, 1H, Ar-H), 7.32-7.16 (m, 4H, Ar-H), 3.66-3.58 (m, 4H, -NCH₂ + -NCH₂), 3.37-3.32 (m, 4H, 2 x -NCH₂), 2.54-2.47 (m, 2H, 2 x -CH), 2.21 (s, 3H, Ar-CH₃), 1.90 (s, 3H, -COCH₃), 1.72-1.26 (m, 6H, 3x -CH₂); Mass spectrum (m/z, +ve ion mode): 447
30 [M⁺+ 12].

The following illustrative compound was prepared analogously,

N-{2-[2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-6-(2-methylphenyl)-7-oxopyrido[2,3-*d*]pyrimidin-8(7*H*)-yl]ethyl}propanamide (Compound No. 37)

Scheme V, Procedure

5 **Example 8: Synthesis of 6-(2-methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-7-oxopyrido[2,3-*d*]pyrimidin-8(7*H*)-yl]acetic acid (Compound No. 79)**

To a solution of the Compound No. 44 (0.3 g, 0.69 mmol) in methanol: tetrahydrofuran: water (1: 3: 1, 10 ml) was added lithium hydroxide (0.0668, 2.77 mmol) at 0 °C and the reaction mixture was stirred for 20 minutes. The mixture was allowed to warm upto room temperature and stirred for 4 hours. The solvents were removed under reduced pressure. The aqueous layer was extracted with diethyl ether. The organic layer was discarded and aqueous layer was collected, which was neutralized with hydrochloric acid (1 N) to maintain the pH at 2-3. The mixture was extracted with ethyl acetate and the organic layer was collected, dried over anhydrous sodium sulphate and concentrated under reduced pressure to furnish the title compound. Yield: 0.21 g; ¹H NMR (CDCl₃): δ 8.45 (1H, s, Ar-H), 7.57 (1H, s, Ar-H), 7.31-7.17 (4H, m, Ar-H), 5.30 (2H, s, -NCH₂COOH), 3.49-3.46 (2H, t, J = 3.0 and 6 Hz, -NCH₂), 2.74 (brs, 2H, -NCH₂), 2.4-2.39 (d, 2H, J = 3 Hz, 2 x -CH), 2.23-2.18 (m, 5H, Ar-CH₃ & -CH₂), 1.44-1.19 (m, 4H, 2 x -CH₂); Mass spectrum (m/z, +ve ion mode): 420 [M⁺+1].

20

Example 9: Synthesis of *N*-cyclopropyl-2-[2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-6-(2-methylphenyl)-7-oxopyrido[2,3-*d*]pyrimidin-8(7*H*)-yl]acetamide (Compound No. 80)

To a solution of the Compound No. 79 (0.10 g, 0.24 mmol) in tetrahydrofuran (10 ml) at 0 °C was added *N*-methylmorpholine (0.074 g, 0.72 mmol), hydroxybenzotriazole (0.03 g, 0.24 mmol) and cyclopropylamine (0.014g, 0.24 mmol). The reaction mixture was stirred at the same temperature for 20 minutes followed by the addition of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.059 g, 0.3 mmol) and stirred the reaction mixture for 2 hours at room temperature. The solvent was evaporated under reduced pressure and the residue thus obtained was dissolved in ethyl acetate and extracted with water. The organic layer was separated, dried over anhydrous sodium sulphate and

30

concentrated under reduced pressure. The residue thus obtained was purified by column chromatography using 10% methanol in dichloromethane as eluent to furnish the title compound. Yield: 32 mg; ^1H NMR (CDCl_3): δ 8.53 (1H, s, Ar-H), 7.539 (1H, s, Ar-H), 7.37-7.36 (2H, d, $J = 4.5$ Hz, Ar-H), 5.03 (1H, brs, -NH), 3.65 (1H, s, -NCH), 3.37-3.34 (3H, dd, $J = 9.0$ Hz, -NCH₂ + -NCH), 2.72-2.66 (3H, m, -NCH₂, -CH), 2.407 (1H, brs, -CH), 2.21 (3H, s, Ar-H), 1.69 (6H, m, 3x-CH₂), 0.75-0.71 (2H, m, -CH₂), 0.508 (2H, brs, -CH₂); Mass spectrum (m/z , +ve ion mode): 459 [$M^+ + 1$].

The following illustrative compounds were prepared analogously,

- 10 6-(2-Methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-7-oxopyrido[2,3-*d*]pyrimidin-8(7*H*)-yl-*N*-methoxyacetamide (Compound No. 46),
- N*-Cyclobutyl-2-[2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-6-(2-methylphenyl)-7-oxopyrido[2,3-*d*]pyrimidin-8(7*H*)-yl]acetamide (Compound No. 47),
- 6-(2-Methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(2-oxo-2-pyrrolidin-1-ylethyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 48),
- 15 6-(2-Methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-7-oxopyrido[2,3-*d*]pyrimidin-8(7*H*)-yl-*N*-isopropylacetamide (Compound No. 49).

Example 10: Synthesis of 6-(2-methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(2-hydroxyethyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 45)

- 20 To a solution of the Compound No. 44 (0.35 g, 0.80 mmol) in ethanol: tetrahydrofuran mixture (1:1, 30 ml) at 0 °C was added sodium borohydride (0.076 g, 2.0 mmol) and stirred the reaction mixture at room temperature overnight. To the reaction mixture was added ice-cold saturated ammonium chloride solution. Solvents were evaporated under reduced pressure and the aqueous layer was extracted with ethyl acetate.
- 25 The organic layer was collected, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The residue thus obtained was purified by column chromatography using 70-80% ethyl acetate in hexane to furnish the title compound.

- Yield: 35 mg; ^1H NMR (CDCl_3): δ 8.51 (1H, s, Ar-H), 7.51 (1H, brs, Ar-H), 7.50-7.12 (4H, m, Ar-H), 5.329-5.327 (2H, d, $J = 6.0$ Hz, -CH₂OH), 3.93-3.91 (2H, t, $J = 7.5$ Hz, -CH₂OH), 3.38-3.30 (2H, m, -NCH₂), 2.73 (2H, brs, -NCH₂), 2.47 (brs, 2H, 2 x -CH), 2.21
- 30

(s, 3H, Ar-CH₃), 1.72-1.55 (6H, m, 2 x -CH₂); Mass spectrum (m/z, +ve ion mode): 406 [M⁺+1].

Scheme VI, procedure

- 5 **Example 11: Synthesis of 6-(2-methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(2-methoxyethyl)-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 50)**

Step a: 8-(2-Hydroxyethyl)-6-(2-methylphenyl)-2-(methylthio)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one

To a solution of the compound 6-(2-methylphenyl)-2-(methylthio)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (1.0 g, 3.53 mmol) in acetone (20 ml) was added ethyl bromide (1.32, 1.06 mmol), potassium carbonate (2.43 g, 17.6 mmol) and *tetra*-butyl ammonium iodide (0.65 g, 1.75 mmol). The reaction mixture was refluxed for overnight. Solid thus separated out was filtered off and the organic solvent was evaporated under reduced pressure. The residue thus obtained was purified by column chromatography using 50 % ethyl acetate in hexane as eluent to furnish the title compound.

Step b: 8-(2-Methoxyethyl)-6-(2-methylphenyl)-2-(methylthio)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one

A suspension of sodium hydride (0.098g, 4 mmol) in dry dimethylformamide (5.0 ml) at 0°C under nitrogen atmosphere was added the compound obtained from step *a* above (0.32 g, 1 mmol). The reaction mixture was stirred at same temperature for 1 hour. To the resulting reaction mixture was added iodomethane (0.567 g, 4.0 mmol) and stirred for 2 hours. The mixture was diluted with ice-cold water and extracted with ethyl acetate. The organic layer was collected, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The residue thus obtained was purified by column chromatography using 25 % ethyl acetate in hexane to furnish the title compound.

Step c: 8-(2-Methoxyethyl)-6-(2-methylphenyl)-2-(methylsulfonyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one

The title compound was prepared following the procedure as described in Example 1, step *e*, by oxidizing the compound obtained from step *b* above.

Step d: 6-(2-Methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(2-methoxyethyl)-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 50)

The title compound was prepared following the procedure as described in Example 1, step f. Yield 15 mg; ¹H NMR (CDCl₃): δ 8.52 (1H, s, Ar-H), 7.44 (1H, s, Ar-H), 7.24-7.18 (4H, m, Ar-H), 5.31-5.30 (1H, brs, -NH), 3.75 (2H, brs, -OCH₂), 3.64 (2H, brs, -NCH₂), 3.59 (s, 1H, -OCH₃), 3.40 (2H, brs, -NCH₂), 2.63 (2H, brs, -NCH₂), 2.50-2.34 (2H, m, 2 x -CH), 2.22 (3H, s, Ar-CH₃), 1.72-1.33 (6H, m, 3 x -CH₂); Mass spectrum (m/z, +ve ion mode): 420 [M⁺+1].

The following illustrative compound was prepared analogously,

10 6-(2-Methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(2-ethoxyethyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 51).

Methodology

p38 Inhibition Assays - Inhibition of phosphorylation of EGF receptor Peptide

15 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 was prepared containing all of the above components and activated p38 (5nM). 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
20 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 μM. The kinase reaction was initiated with ATP (100 μM) and the vials were incubated at 30°C. After 30 minutes, the reactions were quenched with equal volume of
25 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 μM, 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.

Specific exemplary compounds were investigated and exhibited IC₅₀ for the p38 enzyme assay of from about 10 μ M to about 60 nM, for example from about 800 nM to about 60 nM, or from about 300 nM to about 60 nM, or from about 150 nM to about 60 nM, or from about 100 nM to about 60 nM (Compound No. 13 formed a precipitate).

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 400x 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:

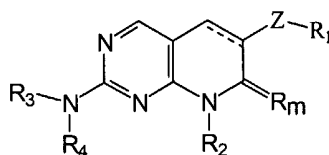
PBM cells (0.1 ml ; 2 million/ml) were co-incubated with 0.1 ml of compound (10 -0.41 μ M, final concentration) for 1 hour in flat bottom 96 well microtiter plate. Compounds were dissolved in DMSO initially and diluted in TCM for a final concentration of 0.1% DMSO. LPS (Cal biochem, 20ng/ml, final concentration) 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 0.25mg/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 O.D was measured at 490-650 nm.

The TNF- α levels released in the culture medium was quantitated by ELISA. Inhibitory potency was expressed as IC₅₀. Compounds 1, 20-23, 25, 40, 44, 47, 50-52, 59,

68, 69 and 71 were tested, and these compounds showed IC₅₀ for p38 inhibitory activity of from about 3 μ M to about 140 nM, for example from about 950 nM to about 140 nM, or from about 630 nM to about 140 nM, or from about 375 nM to about 140 nM, or from about 200 nM to about 140 nM.

We Claim:

1. A compound having the structure of Formula I



Formula I

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

wherein

R₁ is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl, or heterocyclalkyl;

when R_m is oxygen or sulphur

R₂ is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, heterocyclyl, heterocyclalkyl or heteroarylalkyl;

when R_m is -NH, -N-acyl, -N(CN), -N(NO₂), -C(R₃)₂ or -CH(NO₂)

R₂ is hydroxy, alkoxy, aryloxy, -CHO, -CN, alkyl, alkenyl, alkynyl, cycloalkyl, carboxy, halogen, aryl, aralkyl, acyl, heteroaryl, heterocyclyl, -SO₂R₅, -COOR₆, -C(=O)NR_xR_y, -NR_xR_y or -OC(=O)NR_xR_y or -NHC(=O)R_x;

---- represents a single bond or a double bond;

R₃ is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, aralkyl, heteroarylalkyl or heterocyclalkyl;

R₄ is  (wherein  represents a cyclic ring containing 4-8 carbon atoms wherein 1-3 carbon atoms may optionally be replaced by heteroatoms selected from oxygen, -NH or sulphur; T is -(CH₂)_n-, -CH(Q)CH₂-, -CH₂CH(Q)CH₂-, -CH(Q)-, -CH₂-O-CH₂-, -CH₂-NH-CH₂-, -CH₂-N(CH₃)-CH₂);

- 25 n is an integer selected from 0-3 (wherein when n is zero then T represents a direct
26 bond);
- 27 R₅ is alkyl, alkenyl, alkynyl, cycloalkyl, -NR_pR_q (wherein R_p and R_q are
28 independently selected from the group consisting of hydrogen, alkyl, alkenyl,
29 alkynyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, heterocyclylalkyl or
30 heteroarylalkyl; R_p and R_q may also together join to form a heterocyclyl ring), aryl,
31 aralkyl, heteroaryl, heterocyclyl, heterocyclylalkyl or heteroarylalkyl;
- 32 R₆ is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroarylalkyl or
33 heterocyclylalkyl;
- 34 Z is a direct bond, oxygen, sulphur, -NH or -(CH₂)_n;
- 35 R_x and R_y are independently selected from the group consisting of hydrogen, alkyl,
36 alkenyl, alkynyl, cycloalkyl, alkoxy, aryl, aralkyl, -SO₂R₅ (wherein R₅ is the same as
37 defined above), heteroaryl, heterocyclyl, heteroarylalkyl or heterocyclylalkyl;
- 38 Q is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, aralkyl,
39 heteroarylalkyl or heterocyclylalkyl.
- 1 2. A compound selected from the group consisting of :
- 2 6-(2-Chlorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-
3 d]pyrimidin-7(8H)-one (Compound No. 1),
- 4 6-(2-Methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-
5 d]pyrimidin-7(8H)-one (Compound No. 2),
- 6 6-(2-Fluorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-
7 d]pyrimidin-7(8H)-one (Compound No. 3),
- 8 6-(2,4-Difluorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-
9 d]pyrimidin-7(8H)-one (Compound No. 4),
- 10 6-(3-Chlorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-
11 d]pyrimidin-7(8H)-one (Compound No. 5),
- 12 6-(4-Chlorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-
13 d]pyrimidin-7(8H)-one (Compound No. 6),
- 14 6-(4-Methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-
15 d]pyrimidin-7(8H)-one (Compound No. 7),

- 16 6-(4-Fluorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-
17 d]pyrimidin-7(8H)-one (Compound No. 8),
- 18 6-(2-Methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-benzylpyrido[2,3-
19 d]pyrimidin-7(8H)-one (Compound No. 9),
- 20 6-(2-Methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(4-fluorobenzyl)-pyrido[2,3-
21 d]pyrimidin-7(8H)-one (Compound No. 10),
- 22 6-(2-Methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(4-tert-butylbenzyl)-
23 pyrido[2,3-d]pyrimidin-7(8H)-one (Compound No. 11),
- 24 6-(2-Methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(3-trifluoromethoxybenzyl)-
25 pyrido[2,3-d]pyrimidin-7(8H)-one (Compound No. 12),
- 26 6-(2-Fluorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(4-fluorobenzyl)-pyrido[2,3-
27 d]pyrimidin-7(8H)-one (Compound No. 13),
- 28 6-(2-Fluorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(3-chloro-2-fluorobenzyl)-
29 pyrido[2,3-d]pyrimidin-7(8H)-one (Compound No. 14),
- 30 6-(2-Chlorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-benzylpyrido[2,3-
31 d]pyrimidin-7(8H)-one (Compound No. 15),
- 32 6-(2-Chlorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(4-fluorobenzyl)-pyrido[2,3-
33 d]pyrimidin-7(8H)-one (Compound No. 16),
- 34 6-(2-Chlorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(4-tert-butylbenzyl)-
35 pyrido[2,3-d]pyrimidin-7(8H)-one (Compound No. 17),
- 36 6-(2-Chlorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(3-trifluoromethoxybenzyl)-
37 pyrido[2,3-d]pyrimidin-7(8H)-one (Compound No. 18),
- 38 6-(2-Methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(cyclopropyl
39 methyl)pyrido[2,3-d]pyrimidin-7(8H)-one (Compound No. 19),
- 40 Ethyl 2-[6-(2-fluorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-7-oxopyrido[2,3-
41 d]pyrimidin-8(7H)-yl]propanoate (Compound No. 20),
- 42 Ethyl 2-[6-(2-methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-7-oxopyrido[2,3-
43 d]pyrimidin-8(7H)-yl]propanoate (Compound No. 21),
- 44 6-(2-Fluorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(cyclopentyl) pyrido[2,3-
45 d]pyrimidin-7(8H)-one (Compound No. 22),
- 46 6-(2-Fluorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(cyclopropyl methyl)-
47 pyrido[2,3-d]pyrimidin-7(8H)-one (Compound No. 23),
- 48 6-(2-Methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(2-chloroethyl)- pyrido[2,3-
49 d]pyrimidin-7(8H)-one (Compound No. 24),

- 50 6-(2-Chlorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(2-ethoxy ethyl)pyrido[2,3-
51 *d*]pyrimidin-7(8*H*)-one (Compound No. 25),
- 52 2-[6-(2-Chlorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-7-oxopyrido[2,3-
53 *d*]pyrimidin-8(7*H*)-yl]ethyl acetate (Compound No. 26),
- 54 6-(2-Chlorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(2-methoxyethyl)pyrido[2,3-
55 *d*]pyrimidin-7(8*H*)-one (Compound No. 27),
- 56 6-(2-methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-[2-(2-methoxyethoxy)ethyl]-
57 pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 28),
- 58 6-(2-Chlorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-[2-(2-
59 methoxyethoxy)ethyl]pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 29),
- 60 6-(2-Methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-pyrido[2,3-*d*]pyrimidin-7(8*H*)-
61 one(Compound No. 30),
- 62 6-(2-Fluorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)pyrido[2,3-*d*]pyrimidin-7(8*H*)-
63 one(Compound No. 31),
- 64 tert-butyl 4- {[2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-6-(2-methylphenyl)-7-oxopyrido[2,3-
65 *d*]pyrimidin-8(7*H*)-yl]methyl}piperidine-1-carboxylate (Compound No. 32),
- 66 6-(2-Methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-[(1-acetylpiperidin-4-
67 yl)methyl]-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 33),
- 68 2-{2-[2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-6-(2-methylphenyl)-7-oxopyrido[2,3-
69 *d*]pyrimidin-8(7*H*)-yl]ethyl}-1*H*-isoindole-1,3(2*H*)-dione (Compound No. 34),
- 70 6-(2-Methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(2-aminoethyl)-pyrido[2,3-
71 *d*]pyrimidin-7(8*H*)-one (Compound No. 35),
- 72 *N*-{2-[2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-6-(2-methylphenyl)-7-oxopyrido[2,3-
73 *d*]pyrimidin-8(7*H*)-yl]ethyl}acetamide (Compound No. 36),
- 74 *N*-{2-[2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-6-(2-methylphenyl)-7-oxopyrido[2,3-
75 *d*]pyrimidin-8(7*H*)-yl]ethyl}propanamide (Compound No. 37),
- 76 *N*-{2-[2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-6-(2-methylphenyl)-7-oxopyrido[2,3-
77 *d*]pyrimidin-8(7*H*)-yl]ethyl}methanesulfonamide (Compound No. 38),
- 78 *N*-{2-[2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-6-(2-methylphenyl)-7-oxopyrido[2,3-
79 *d*]pyrimidin-8(7*H*)-yl]ethyl}propane-1-sulfonamide (Compound No. 39),
- 80 *N*-{2-[2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-6-(2-methylphenyl)-7-oxopyrido[2,3-
81 *d*]pyrimidin-8(7*H*)-yl]ethyl}butane-1-sulfonamide (Compound No. 40),
- 82 6-(2-Methylphenyl)-2-(7-azabicyclo[4.3.0]non-7-yl-amino)-8-(cyclopropyl)-pyrido[2,3-
83 *d*]pyrimidin-7(8*H*)-one (Compound No. 41),

- 84 6-(2-Methylphenyl)-2-(7-azabicyclo[4.3.0]non-7-yl-amino)-8-methyl-pyrido[2,3-
85 *d*]pyrimidin-7(8*H*)-one (Compound No. 42),
- 86 6-(2-Chlorophenyl)-2-(7-azabicyclo[4.3.0]non-7-yl-amino)-8-methyl-pyrido[2,3-
87 *d*]pyrimidin-7(8*H*)-one(Compound No. 43),
- 88 Ethyl[2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-6-(2-methylphenyl)-7-oxopyrido[2,3-
89 *d*]pyrimidin-8(7*H*)-yl]acetate (Compound No. 44)
- 90 6-(2-Methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(2-hydroxyethyl) pyrido[2,3-
91 *d*]pyrimidin-7(8*H*)-one (Compound No. 45),
- 92 6-(2-Methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-7-oxopyrido[2,3-*d*]pyrimidin-
93 8(7*H*)-yl-*N*-methoxyacetamide (Compound No. 46),
- 94 *N*-Cyclobutyl-2-[2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-6-(2-methylphenyl)-7-
95 oxopyrido[2,3-*d*]pyrimidin-8(7*H*)-yl]acetamide (Compound No. 47),
- 96 6-(2-Methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(2-oxo-2-pyrrolidin-1-
97 ylethyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 48),
- 98 6-(2-Methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-7-oxopyrido[2,3-*d*]pyrimidin-
99 8(7*H*)-yl-*N*-isopropylacetamide (Compound No. 49),
- 100 6-(2-Methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(2-methoxyethyl)-
101 pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 50),
- 102 6-(2-Methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(2-ethoxyethyl)pyrido[2,3-
103 *d*]pyrimidin-7(8*H*)-one (Compound No. 51),
- 104 6-(2-Chlorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-cyclopropyl-pyrido[2,3-
105 *d*]pyrimidin-7(8*H*)-one(Compound No. 52),
- 106 6-(2-Chlorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-7-oxopyrido[2,3-*d*]pyrimidin-
107 8(7*H*)-yl acetonitrile (Compound No. 53),
- 108 6-(1-Naphthyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-cyclopropyl-pyrido[2,3-
109 *d*]pyrimidin-7(8*H*)-one (Compound No. 54),
- 110 6-(2-Chlorophenoxy)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-cyclopropyl-pyrido[2,3-
111 *d*]pyrimidin-7(8*H*)-one (Compound No. 55),
- 112 6-(3-Methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methyl-pyrido[2,3-
113 *d*]pyrimidin-7(8*H*)-one (Compound No. 56),
- 114 6-(2-Methylphenoxy)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-cyclopropyl-pyrido[2,3-
115 *d*]pyrimidin-7(8*H*)-one (Compound No. 57),
- 116 6-(2-Methylphenoxy)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-
117 *d*]pyrimidin-7(8*H*)-one (Compound No. 58),

- 118 6-(2-Fluorophenoxy)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-cyclopropyl-pyrido[2,3-
119 *d*]pyrimidin-7(8*H*)-one (Compound No. 59),
- 120 6-(4-Chlorophenoxy)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-cyclopropylpyrido[2,3-
121 *d*]pyrimidin-7(8*H*)-one (Compound No. 60),
- 122 6-(4-Chlorophenoxy)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-
123 *d*]pyrimidin-7(8*H*)-one (Compound No. 61),
- 124 6-Methoxy-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-
125 one (Compound No. 62),
- 126 6-(4-Isopropylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-
127 *d*]pyrimidin-7(8*H*)-one (Compound No. 63),
- 128 6-(2-Fluorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(cyclopropyl)pyrido[2,3-
129 *d*]pyrimidin-7(8*H*)-one (Compound No. 64),
- 130 6-(2,4-Dichlorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-
131 *d*]pyrimidin-7(8*H*)-one (Compound No. 65),
- 132 6-(4-Nitrophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methyl-pyrido[2,3-
133 *d*]pyrimidin-7(8*H*)-one (Compound No. 66),
- 134 6-(3-Methoxyphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-
135 *d*]pyrimidin-7(8*H*)-one (Compound No. 67),
- 136 6-(2,6-Dichlorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-
137 *d*]pyrimidin-7(8*H*)-one (Compound No. 68),
- 138 6-(2-Nitrophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methyl-pyrido[2,3-
139 *d*]pyrimidin-7(8*H*)-one (Compound No. 69),
- 140 6-(3-Fluorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-
141 *d*]pyrimidin-7(8*H*)-one (Compound No. 70),
- 142 6-(2-Chloro-4-fluorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-
143 *d*]pyrimidin-7(8*H*)-one (Compound No. 71),
- 144 6-(4-Nitrophenoxy)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methyl-pyrido[2,3-
145 *d*]pyrimidin-7(8*H*)-one (Compound No. 72),
- 146 6-(2-Chlorophenoxy)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-
147 *d*]pyrimidin-7(8*H*)-one (Compound No. 73),
- 148 6-(2-Fluorophenoxy)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-
149 *d*]pyrimidin-7(8*H*)-one (Compound No. 74),
- 150 6-(4-Chloro-2-fluorophenoxy)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-
151 *d*]pyrimidin-7(8*H*)-one (Compound No. 75),

- 152 6-(4-Chloro-2-fluorophenoxy)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-cyclopropyl-
153 pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 76),
- 154 6-(3-Methoxyphenoxy)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(cyclopropyl)-
155 pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 77),
- 156 6-(3-Methylphenoxy)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(cyclopropyl)-pyrido[2,3-
157 *d*]pyrimidin-7(8*H*)-one (Compound No. 78).
- 158 6-(2-Methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-7-oxopyrido[2,3-*d*]pyrimidin-
159 8(7*H*)-yl]acetic acid (Compound No. 79),
- 160 *N*-Cyclopropyl-2-[2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-6-(2-methylphenyl)-7-
161 oxopyrido[2,3-*d*]pyrimidin-8(7*H*)-yl]acetamide (Compound No. 80).

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

1 4. A method for treating mammals suffering from sepsis, rheumatoid arthritis,
2 inflammatory bowel disease, type-1 diabetes, asthma, chronic obstructive pulmonary
3 disorder, organ transplant rejection, acute coronary syndrome and psoriasis, the method
4 comprising administration of a therapeutically effective amount of a compound of claim
5 1..

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

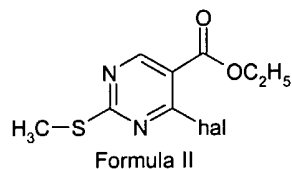
1 6. A pharmaceutical composition for treating mammals suffering from sepsis,
2 rheumatoid arthritis, inflammatory bowel disease, type-1 diabetes, asthma, chronic
3 obstructive pulmonary disorder, organ transplant rejection, acute coronary syndrome and
4 psoriasis, the composition comprising a compound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

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

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

1 9. A method of making a compound of Formula XII, or pharmaceutically acceptable
2 salts or esters thereof, wherein the reaction comprises

3 a. reacting a compound of Formula II

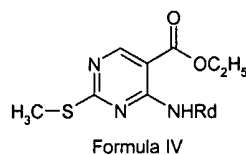


5 with a compound of Formula III

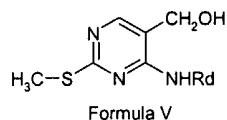


Formula III

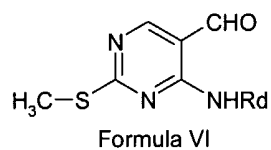
7 to give a compound of Formula IV;



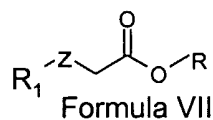
9 b. reducing a compound of Formula IV to give a compound of Formula V;



11 c. oxidizing a compound of Formula V to give a compound of Formula VI;

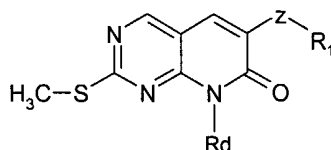


13 d. reacting a compound of Formula VI with an ester of Formula VII



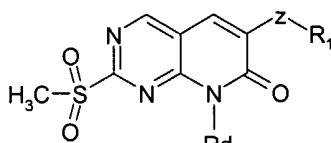
15 to give a compound of Formula VIII;

61



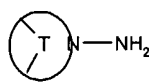
Formula VIII

- e. oxidizing a compound of Formula VIII to give a compound of Formula IX;
and



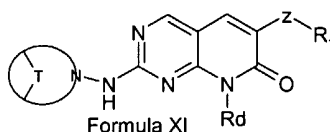
Formula IX

- f. reacting a compound of Formula IX with a compound of Formula X



Formula X

- to give a compound of Formula XI,



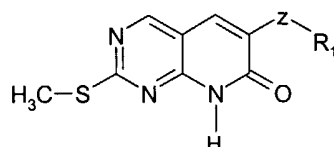
Formula XI

- wherein
hal is halogen (Cl, Br or I);
 R_d is hydrogen, optionally substituted alkyl, cycloalkyl, aralkyl or aryl;
 R' is alkyl;
 R_1 is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl, or heterocyclalkyl;
 Z is a direct bond, oxygen, sulphur, -NH or $-(CH_2)_n$;
 n is an integer selected from 0-3 (wherein when n is zero then T represents a direct bond);

33 T is $-(CH_2)_n-$, $-CH(Q)CH_2-$, $-CH_2CH(Q)CH_2-$, $-CH(Q)-$, $-CH_2-O-CH_2-$, $-CH_2-NH-$
 34 CH_2- , $-CH_2-N(CH_3)-CH_2$;

1 10. A method of making a compound of Formula XVI, or pharmaceutically acceptable
 2 salts or esters thereof, wherein the reaction comprises

3 a. reacting a compound of Formula XII



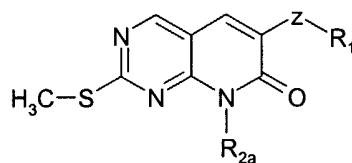
4 Formula XII

5 with a compound of Formula XIII



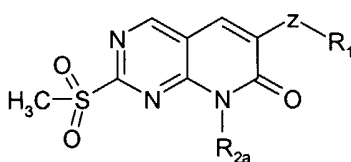
6 Formula XIII

7 to give a compound of Formula XIV;



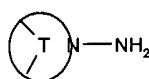
8 Formula XIV

9 b. oxidizing a compound of Formula XIV to give a compound of Formula XV;
 10 and



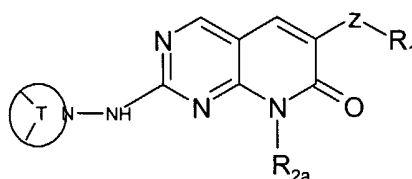
11 Formula XV

13 c. reacting a compound of Formula XV with a compound of Formula X



14 Formula X

15 to give a compound of Formula XVI,



Formula XVI

16 wherein

17 R_1 is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, heterocyclyl,
18 heteroarylalkyl, or heterocyclalkyl;

19 Z is a direct bond, oxygen, sulphur, -NH or $-(CH_2)_n$;

20 n is an integer selected from 0-3 (wherein when n is zero then T represents a direct
21 bond);

22 T is $-(CH_2)_n$ -, $-CH(Q)CH_2$ -, $-CH_2CH(Q)CH_2$ -, $-CH(Q)$ -, $-CH_2-O-CH_2$ -, $-CH_2-NH$ -
23 CH_2 -, $-CH_2-N(CH_3)-CH_2$;

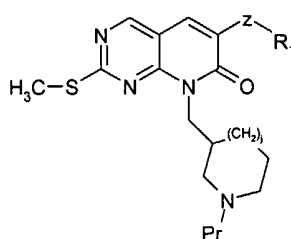
24 Q is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, aralkyl,
25 heteroarylalkyl or heterocyclalkyl.

26 R_{2a} is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, heterocyclyl,
27 heterocyclalkyl or heteroarylalkyl;

28 D is hal or $-OH$;

1 11. A method of making a compound of Formula XXII, or pharmaceutically
2 acceptable salts or esters thereof, wherein the reaction comprises

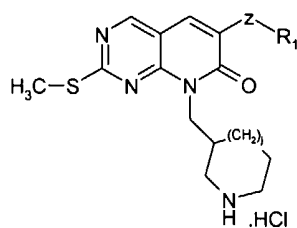
3 a. deprotecting a compound of Formula XVII



Formula XVII

64

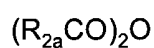
5 to give a compound of Formula XVIII;



Formula XVIII

6

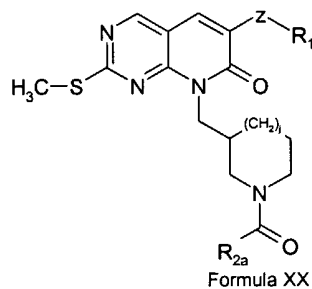
7 b. reacting a compound of Formula XVIII with a compound of Formula XIX



Formula XIX

8

9 to give a compound of Formula XX;

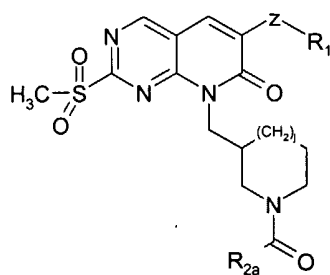


Formula XX

10

11 c. oxidizing a compound of Formula XX to give a compound of Formula XXI;

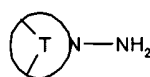
12 and



Formuls XXI

13

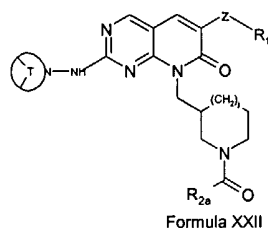
14 d. reacting a compound of Formula XXI with a compound of Formula X



Formula X

15

16 to give a compound of Formula XXII,



17

18 wherein

19 j is an integer from 0-2;

20 Pr is $-\text{C}(=\text{O})\text{OC}(\text{CH}_3)_3$, $-\text{C}(=\text{O})\text{OC}(\text{CH}_3)_2\text{CHBr}_2$ or $-\text{C}(=\text{O})\text{OC}(\text{CH}_3)_2\text{CCl}_3$;

21 R_{2a} is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, heterocyclyl,
22 heterocyclalkyl or heteroarylalkyl;

23 hal is halogen (Cl, Br or I);

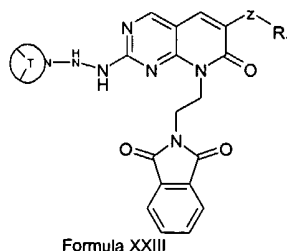
24 T is $-(\text{CH}_2)_n-$, $-\text{CH}(\text{Q})\text{CH}_2-$, $-\text{CH}_2\text{CH}(\text{Q})\text{CH}_2-$, $-\text{CH}(\text{Q})-$, $-\text{CH}_2-\text{O}-\text{CH}_2-$, $-\text{CH}_2-\text{NH}-$
25 CH_2- , $-\text{CH}_2-\text{N}(\text{CH}_3)-\text{CH}_2$;

26 Q is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, aralkyl,
27 heteroarylalkyl or heterocyclalkyl.

28 n is an integer selected from 0-3 (wherein when n is zero then T represents a direct
29 bond);

1 12. A method of making a compound of Formula XXVI, or pharmaceutically
2 acceptable salts or esters thereof, wherein the reaction comprises

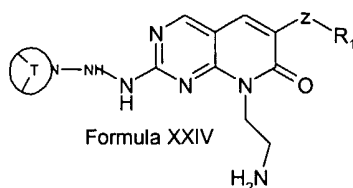
3 a. deprotecting a compound of Formula XXIII



4

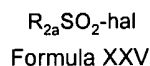
5 to give a compound of Formula XXIV; and

66



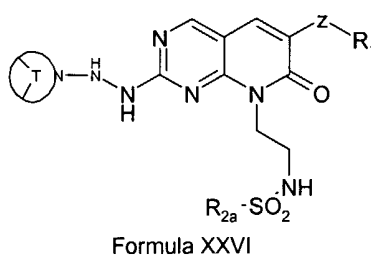
6

7 b. reacting a compound of Formula XXIV with a compound of Formula XXV



8

9 to give a compound of Formula XXVI,



10

11 wherein

12 R_{2a} is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, heterocyclyl,
13 heterocyclalkyl or heteroarylalkyl;

14 hal is halogen (Cl, Br or I);

15 R_1 is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, heterocyclyl,
16 heteroarylalkyl, or heterocyclalkyl;

17 Z is a direct bond, oxygen, sulphur, -NH or $-(CH_2)_n$;

18 T is $-(CH_2)_n$ -, $-CH(Q)CH_2$ -, $-CH_2CH(Q)CH_2$ -, $-CH(Q)$ -, $-CH_2-O-CH_2$ -, $-CH_2-NH$ -
19 CH_2 -, $-CH_2-N(CH_3)-CH_2$;

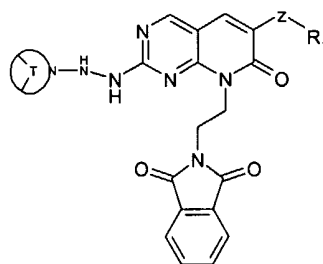
20 Q is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, aralkyl,
21 heteroarylalkyl or heterocyclalkyl;

22 n is an integer selected from 0-3 (wherein when n is zero then T represents a direct
23 bond);

1 13. A method of making a compound of Formula XXVIII, or pharmaceutically
2 acceptable salts or esters thereof, wherein the reaction comprises

67

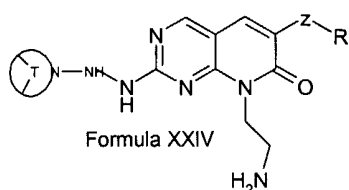
3 a. deprotecting a compound of Formula XXIII



Formula XXIII

4

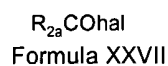
5 to give a compound of Formula XXIV; and



Formula XXIV

6

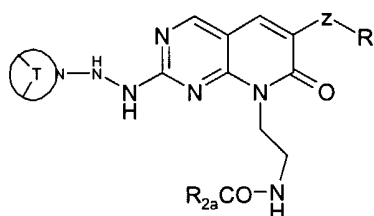
7 b. reacting a compound of Formula XXIV with a compound of Formula XXVII



Formula XXVII

8

9 to give a compound of Formula XXVIII,



Formula XXVIII

10

11 wherein

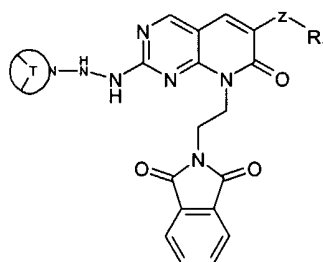
12 R_{2a} is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, heterocyclyl,
13 heterocyclylalkyl or heteroarylalkyl;

14 hal is halogen (Cl, Br or I);

15 R_1 is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, heterocyclyl,
16 heteroarylalkyl, or heterocyclylalkyl;

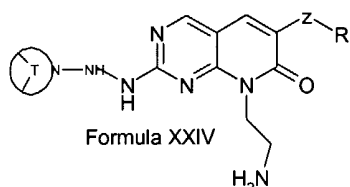
17 Z is a direct bond, oxygen, sulphur, -NH or $-(\text{CH}_2)_n$;

- 3 a. deprotecting a compound of Formula XXIII



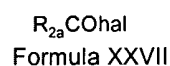
Formula XXIII

- 5 to give a compound of Formula XXIV; and

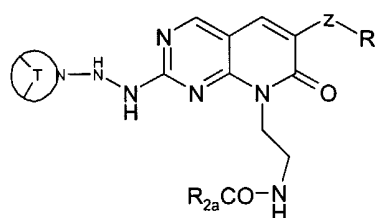


Formula XXIV

- 7 b. reacting a compound of Formula XXIV with a compound of Formula XXVII



- 9 to give a compound of Formula XXVIII,



Formula XXVIII

11 wherein

12 R_{2a} is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, heterocyclyl,
13 heterocyclalkyl or heteroarylalkyl;

14 hal is halogen (Cl, Br or I);

15 R_1 is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, heterocyclyl,
16 heteroarylalkyl, or heterocyclalkyl;

17 Z is a direct bond, oxygen, sulphur, -NH or $-(\text{CH}_2)_n$;

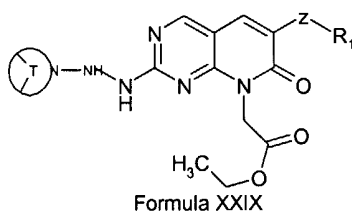
18 T is $-(CH_2)_n-$, $-CH(Q)CH_2-$, $-CH_2CH(Q)CH_2-$, $-CH(Q)-$, $-CH_2-O-CH_2-$, $-CH_2-NH-$
 19 CH_2- , $-CH_2-N(CH_3)-CH_2$;

20 n is an integer selected from 0-3 (wherein when n is zero then T represents a direct
 21 bond);

22 Q is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, aralkyl,
 23 heteroarylalkyl or heterocyclylalkyl;

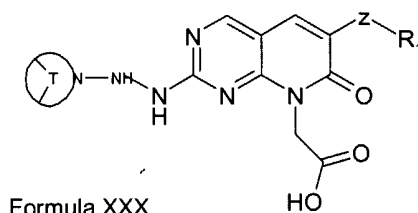
24 14. A method of making a compound of Formula XXXI, or pharmaceutically
 25 acceptable salts or esters thereof, wherein the reaction comprises

26 a. hydrolyzing a compound of Formula XXIX



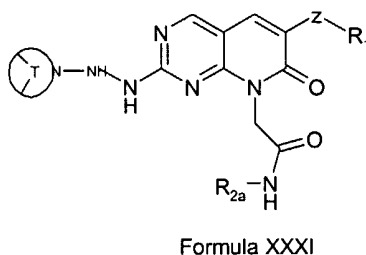
27

28 to give a compound of Formula XXX; and



29

30 b. reacting a compound of Formula XXX with a compound of Formula $R_{2a}NH_2$ to
 31 compound of Formula XXXI,

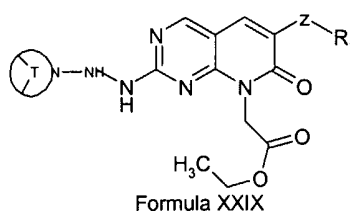


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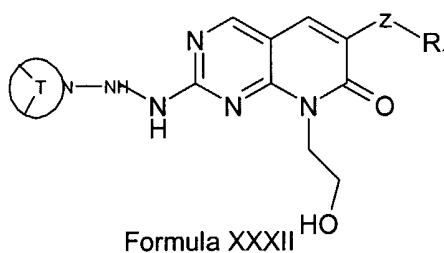
33 wherein

- 34 R_{2a} is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, heterocyclyl,
 35 heterocyclalkyl or heteroarylalkyl;
- 36 R_1 is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, heterocyclyl,
 37 heteroarylalkyl, or heterocyclalkyl;
- 38 Z is a direct bond, oxygen, sulphur, -NH or $-(CH_2)_n$;
- 39 T is $-(CH_2)_n$ -, $-CH(Q)CH_2$ -, $-CH_2CH(Q)CH_2$ -, $-CH(Q)$ -, $-CH_2-O-CH_2$ -, $-CH_2-NH$ -
 40 CH_2 -, $-CH_2-N(CH_3)-CH_2$;
- 41 n is an integer selected from 0-3 (wherein when n is zero then T represents a direct
 42 bond);
- 43 Q is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, aralkyl,
 44 heteroarylalkyl or heterocyclalkyl;

- 1 15. A method of making a compound of Formula XXXII, or pharmaceutically
 2 acceptable salts or esters thereof, wherein the reaction comprises
- 3 a. reducing a compound of Formula XXIX



- 4
- 5 to give a compound of Formula XXXII,



- 6
- 7 wherein
- 8 R_{2a} is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, heterocyclyl,
 9 heterocyclalkyl or heteroarylalkyl;

10 hal is halogen (Cl, Br or I);

11 R₁ is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, heterocyclyl,
12 heteroarylalkyl, or heterocyclalkyl;

13 Z is a direct bond, oxygen, sulphur, -NH or -(CH₂)_n;

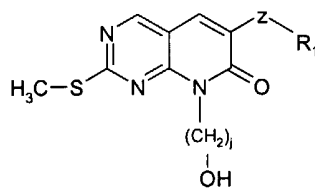
14 n is an integer selected from 0-3 (wherein when n is zero then T represents a direct
15 bond);

16 T is -(CH₂)_n-, -CH(Q)CH₂-, -CH₂CH(Q)CH₂-, -CH(Q)-, -CH₂-O-CH₂-, -CH₂-NH-
17 CH₂-, -CH₂-N(CH₃)-CH₂;

18 Q is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, aralkyl,
19 heteroarylalkyl or heterocyclalkyl;

1 16. A method of making a compound of Formula XXXVII, or pharmaceutically
2 acceptable salts or esters thereof, wherein the reaction comprises

3 a. reacting a compound of Formula XXXIII



Formula XXXIII

4

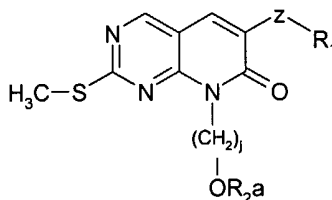
5 with a compound of Formula XXXIV



Formula XXXIV

6

7 to give a compound of Formula XXXV;

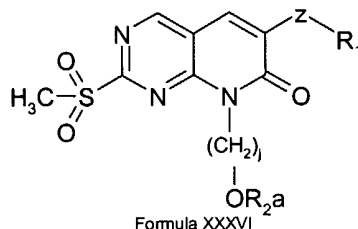


Formula XXXV

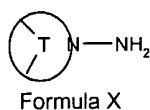
8

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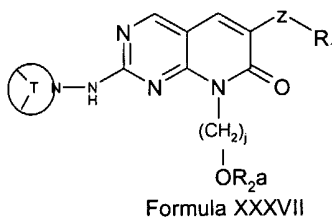
- 9 b. oxidizing a compound of Formula XXXV to give a compound of Formula
 10 XXXVI; and



- 11
 12 c. reacting a compound of Formula XXXVI with a compound of Formula X



- 13
 14 to give a compound of Formula XXXVII,



- 15
 16 wherein
 17 R_{2a} is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, heterocyclyl,
 18 heterocyclylalkyl or heteroarylalkyl;
 19 hal is halogen (Cl, Br or I);
 20 R_1 is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, heterocyclyl,
 21 heteroarylalkyl, or heterocyclylalkyl;
 22 Z is a direct bond, oxygen, sulphur, -NH or $-(CH_2)_n$;
 23 n is an integer selected from 0-3 (wherein when n is zero then T represents a direct
 24 bond);
 25 T is $-(CH_2)_n$ -, $-CH(Q)CH_2$ -, $-CH_2CH(Q)CH_2$ -, $-CH(Q)$ -, $-CH_2-O-CH_2$ -, $-CH_2-NH$ -
 26 CH_2 -, $-CH_2-N(CH_3)-CH_2$;

- 27 Q is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, aralkyl,
28 heteroarylalkyl or heterocyclylalkyl;
29 j is an integer from 0-2;

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2006/000177

A. CLASSIFICATION OF SUBJECT MATTER INV. C07D471/04 A61K31/519 A61P29/00		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) C07D A61K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, CHEM ABS Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 02/18380 A1 (F. HOFFMANN-LA ROCHE AG, SWITZ.) 7 March 2002 (2002-03-07) cited in the application compounds 83-85, 112 claims -----	1-16
☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
* Special categories of cited documents : *A* document defining the general state of the art which is not considered to be of particular relevance *E* earlier document but published on or after the international filing date *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) *O* document referring to an oral disclosure, use, exhibition or other means *P* document published prior to the international filing date but later than the priority date claimed *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. *G* document member of the same patent family		
Date of the actual completion of the international search 9 May 2006		Date of mailing of the international search report 01/06/2006
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 Bosma, P

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2006/000177

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.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 3,4,7,8 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2006/000177

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0218380	A1	07-03-2002	
		AU 9378401 A	13-03-2002
		BR 0113628 A	01-07-2003
		CA 2420286 A1	07-03-2002
		CN 1451005 A	22-10-2003
		EP 1315726 A1	04-06-2003
		JP 2004507541 T	11-03-2004
		MX PA03001821 A	04-06-2003
		ZA 200301079 A	07-05-2004
