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

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

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## HETEROCYCLIC DERIVATIVES AS ANTI-INFLAMMATORY AGENTS

### Field of the Invention

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

### Background of the Invention

During the last decade, the roles played by cytokines, a unique class of intercellular regulatory proteins, in the pathogenesis of many diseases have been investigated. Cytokines play a crucial role in initiating, maintaining, and regulating immunological and inflammatory processes. Advances in our understanding of their role in immune and inflammatory disorders have led to the development of cytokine-based therapies—that is, therapies that aim to inhibit or restore the activity of specific cytokines. Drugs that block inflammatory cytokines, such as tumor necrosis factor-alpha (TNF- $\alpha$ ), have been introduced to the market.

Elevated levels of proinflammatory cytokines viz TNF- $\alpha$  and IL-1 $\alpha$  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 cytokines, eicosanoids, nitric oxide, and reactive oxygen species. 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, specific interference with the action of selected pro-inflammatory mediators, such as TNF $\alpha$  and PGE2 has been used in therapy. These specific anti-

inflammatory therapies have been used in the treatment of rheumatoid arthritis, inflammatory bowel disease, and several other inflammatory diseases.

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 signaling pathways also include the extracellular regulated kinases (ERK) & the c-jun N terminal kinases (JNK). MAP kinases are Serine Threonine Kinases that transduce environmental stimuli to the nucleus and they themselves are activated by upstream MAPK kinases by phosphorylation on both Tyrosine and Threonine residues.

10 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 $\alpha$  MAPK was first identified as a tyrosine phosphorylated protein in LPS (Lipopolysaccharide) stimulated macrophages. The human p38 $\alpha$  MAPK was identified as the target of pyridinyl imidazole compounds (cytokine suppressive anti-

15 inflammatory drugs) that were known to block TNF- $\alpha$  and IL-1 release from LPS stimulated monocytes. After the cloning of first p38MAPK (p38 $\alpha$ ), additional members of the p38MAPK family were cloned by homology, including the p38 $\alpha$ , p38 $\beta$  and p38 $\gamma$ .

The p38 pathway controls the activity of multiple transcription factor s and the expression of many genes. There is ample evidence implicating a pivotal

20 role for p38 in inflammatory processes mediated by IL-1 and TNF- $\alpha$ . p38 inhibitors have been shown to effectively block both TNF- $\alpha$  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

25 human neutrophils with GM-CSF, TNF- $\alpha$  or TGF- $\alpha$  results in p38 activation. GM-CSF and

TNF- $\alpha$  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

30 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.

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

- PCT application WO 00/12074, WO 01/64676 and U.S. Patent No. 6,410,540 disclose compounds that are described as being useful in treating inflammation. The  
10   disclosed compounds include N-containing heterocycles. U.S. Patent No. 6,541,477 discloses methods for treating conditions mediated by p38 $\alpha$  kinase. U.S. application 2002/0115671 discloses compounds that are said to be useful in treating inflammation and cardiac conditions. The disclosed compounds include N containing heterocycles.

#### Summary of the Invention

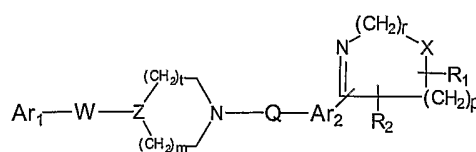
- 15           Heterocyclic derivatives, which can be used for the for inhibition and prevention of inflammation and associated pathologies such as sepsis, rheumatoid arthritis, inflammatory bowel disease, type-1 diabetes, asthma, chronic obstructive pulmonary disorder, organ transplant rejection and psoriasis, are disclosed herein. Pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers or N-  
20   oxides of these compounds having the same type of activity are also provided.

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

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

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

- 4 -



Formula Ia

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

- 5 X can be oxygen, sulphur, or -NR (wherein R can be alkyl, or aryl).

Each of r and p represents an integer from 0-4, with the proviso that both r and p cannot be zero at the same time.

- Q can be alkylene, alkenylene, alkynylene, or -C(=T) (wherein T can be oxygen, sulphur, -N(CN), -N(NO<sub>2</sub>), or -CH(NO<sub>2</sub>)) (wherein double bond of said alkenylene or triple bond of said alkynylene cannot be attached directly to N atom).
- 10

Z can be nitrogen, or -CH.

W can be alkylene, alkenylene, or alkynylene (wherein when Z is nitrogen double bond of said alkenylene or triple bond of said alkynylene cannot be attached directly to Z atom).

The subscript m is an integer from 0-3, and the subscript t is an integer from 0-4.

- 15 R<sub>1</sub> and R<sub>2</sub> can independently be hydrogen, cyano, alkyl, alkenyl, alkynyl, hydroxyalkyl, alkoxy, acyl, aryloxy, cycloalkyl, aryl, aralkyl, carboxy, -COOR<sub>3</sub> (wherein R<sub>3</sub> can be alkyl, alkenyl, alkynyl, aryl, aralkyl, cycloalkyl, heterocyclyl, heteroaryl, heterocyclylalkyl or heteroarylalkyl), -NR<sub>p</sub>R<sub>q</sub> (wherein R<sub>p</sub> and R<sub>q</sub> can independently be hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl or heterocyclylalkyl, or R<sub>p</sub> and R<sub>q</sub> may also together join to form a heterocyclic ring), -OC(=O)NR<sub>x</sub>R<sub>y</sub> [wherein R<sub>x</sub> and R<sub>y</sub> can independently be hydrogen, hydroxy (excepting that both R<sub>x</sub> and R<sub>y</sub> cannot be -OH at the same time), alkyl, cycloalkyl, alkoxy, hydroxyalkyl, aryloxy, heterocyclylalkyl, aralkyloxy, aryl, aralkyl, or -SO<sub>2</sub>R<sub>4</sub> (wherein R<sub>4</sub> can be alkyl, alkenyl, alkynyl, cycloalkyl, -NR<sub>p</sub>R<sub>q</sub> wherein R<sub>p</sub> and R<sub>q</sub> as defined above, aryl, aralkyl, heteroaryl, heterocyclyl, heterocyclylalkyl, or heteroarylalkyl), or R<sub>x</sub> and R<sub>y</sub> may also together join to form a heterocyclyl or heteroaryl ring], -NR<sub>j</sub>(C=O)OR<sub>s</sub> (wherein R<sub>s</sub> can be alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heterocyclylalkyl, or heteroarylalkyl, and wherein R<sub>j</sub> can be hydrogen, lower (C<sub>1</sub>-C<sub>6</sub>)
- 20
- 25

alkyl, lower (C<sub>3</sub>-C<sub>6</sub>) cycloalkyl, lower (C<sub>1</sub>-C<sub>3</sub>) aralkyl, aryl, heteroaryl, heteroarylalkyl, or heterocyclalkyl), NR<sub>J</sub>YR<sub>U</sub> (wherein Y can be -C(=O), -C(=S) or SO<sub>2</sub>, R<sub>J</sub> is as defined above, and R<sub>U</sub> can be alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, heterocyclalkyl, or heterocyclalkyl), -NR<sub>J</sub>(=T)NR<sub>x</sub>R<sub>y</sub> (wherein R<sub>J</sub>, T, R<sub>x</sub> and R<sub>y</sub> are as defined above), -C(=K)NR<sub>x</sub>R<sub>y</sub> (wherein K is O or S), -CH<sub>2</sub>OR<sub>s</sub> (wherein R<sub>s</sub> is the same as defined above), heteroaryl, heterocyclalkyl, heteroarylalkyl or heterocyclalkyl.

Ar<sub>1</sub> and Ar<sub>2</sub> can independently be aryl, heteroaryl, or heterocyclalkyl.

In some particular embodiments, for example, Ar<sub>1</sub> can be phenyl, W can be methylene, Z can be -CH-, t and m can be 1, Q can be carbonyl, Ar<sub>2</sub> can be 1,2-, 1,3-, or 1,4-disubstituted phenyl, r can be 0, p can be 1, and X can be oxygen. Of such compounds, R<sub>1</sub> can be alkyl (e.g., methyl), and R<sub>2</sub> can be COOR<sub>3</sub> or C(=K)NR<sub>x</sub>R<sub>y</sub>. In other particular embodiments, Ar<sub>2</sub> can be a trisubstituted phenyl.

In accordance with a second aspect, there are provided methods for the treatment of mammals suffering from inflammation and associated pathologies.

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

In accordance with a fourth aspect, there are provided processes for the preparation of compounds provided herein.

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

The following definitions apply to terms as used herein

The term "alkyl" unless otherwise specified, refers to a monoradical branched or unbranched saturated hydrocarbon chain having from 1 to 20 carbon atoms. This term is exemplified by groups such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, t-butyl, n-hexyl, n-decyl, tetradecyl, and the like. Alkyl may further be substituted with one or more substituents selected from alkenyl, alkynyl, alkoxy, cycloalkyl, acyl, acylamino, acyloxy, alkoxycarbonylamino, azido, cyano, halogen, hydroxy, oxo, thiocarbonyl, carboxy, arylthio, thiol, alkylthio, aryloxy, aralkyloxy, heteroaryloxy, aminosulfonyl, -COOR<sub>3</sub> (wherein R<sub>3</sub> is the same as defined earlier), -NHC(=O)R<sub>x</sub>, -NR<sub>x</sub>R<sub>y</sub>, -C(=O)NR<sub>x</sub>R<sub>y</sub>,

-NHC(=O)NR<sub>x</sub>R<sub>y</sub>, -C(=O)heteroaryl, C(=O)heterocyclyl, -OC(=O)NR<sub>x</sub>R<sub>y</sub> (wherein R<sub>x</sub> and R<sub>y</sub> are the same as defined earlier), nitro, -S(O)<sub>m</sub>R<sub>4</sub> (wherein m is an integer from 0-2 and R<sub>4</sub> is the same as defined earlier). Unless otherwise constrained by the definition, all substituents may be further substituted by 1-3 substituents chosen from alkyl, carboxy, -

5 COOR<sub>3</sub> (wherein R<sub>3</sub> is the same as defined earlier), -NR<sub>x</sub>R<sub>y</sub>, -C(=O)NR<sub>x</sub>R<sub>y</sub>, -O-C(=O)NR<sub>x</sub>R<sub>y</sub>, -NHC(=O)NR<sub>x</sub>R<sub>y</sub> (wherein R<sub>x</sub> and R<sub>y</sub> are the same as defined earlier), hydroxy, alkoxy, halogen, CF<sub>3</sub>, cyano, and -S(O)<sub>m</sub>R<sub>4</sub> (where R<sub>4</sub> and m are the same as defined earlier). Alkyl groups as defined above may also be interrupted by 1-5 atoms of

10 groups independently chosen from oxygen, sulfur and -NR<sub>a</sub>- [where R<sub>a</sub> is chosen from hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, acyl, aralkyl, -C(=O)OR<sub>3</sub> (wherein R<sub>3</sub> is the same as defined earlier), S(O)<sub>2</sub>R<sub>4</sub> (where R<sub>4</sub> is as defined earlier) or -C(=O)NR<sub>x</sub>R<sub>y</sub> (wherein R<sub>x</sub> and R<sub>y</sub> are as defined earlier)]. Unless otherwise constrained by the definition, all substituents may be further substituted by 1-3 substituents chosen from

15 alkyl, carboxy, -NR<sub>x</sub>R<sub>y</sub>, -C(=O)NR<sub>x</sub>R<sub>y</sub>, -OC(=O)NR<sub>x</sub>R<sub>y</sub> (wherein R<sub>x</sub> and R<sub>y</sub> are the same as defined earlier), hydroxy, alkoxy, halogen, CF<sub>3</sub>, cyano, and -S(O)<sub>m</sub>R<sub>4</sub> (where m and R<sub>4</sub> are the same as defined earlier).

The term "alkylene," unless otherwise specified, refers to a diradical branched or unbranched saturated hydrocarbon chain having from 1 to 6 carbon atoms. This term is exemplified by groups such as methylene, ethylene, propylene isomers and the like.

20 Alkylene may further be substituted with one or more substituents such as alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, acyl, acylamino, acyloxy, alkoxycarbonylamino, azido, cyano, halogen, hydroxy, oxo, thiocarbonyl, carboxy, arylthio, thiol, alkylthio, aryloxy, heteroaryloxy, aminosulfonyl, -COOR<sub>3</sub> (wherein R<sub>3</sub> is the same as defined earlier), -NHC(=O)R<sub>x</sub>, -NR<sub>x</sub>R<sub>y</sub>, -C(=O)NR<sub>x</sub>R<sub>y</sub>, -NHC(=O)NR<sub>x</sub>R<sub>y</sub>, -C(=O)heteroaryl,

25 C(=O)heterocyclyl, -OC(=O)NR<sub>x</sub>R<sub>y</sub> (wherein R<sub>x</sub> and R<sub>y</sub> are the same as defined earlier), nitro, -S(O)<sub>m</sub>R<sub>4</sub> (wherein m is an integer from 0-2 and R<sub>4</sub> is the same as defined earlier). Unless otherwise constrained by the definition, all substituents may be further substituted by 1-3 substituents chosen from alkyl, carboxy, -COOR<sub>3</sub> (wherein R<sub>3</sub> is the same as defined earlier), -NR<sub>x</sub>R<sub>y</sub>, -C(=O)NR<sub>x</sub>R<sub>y</sub>, -O-C(=O)NR<sub>x</sub>R<sub>y</sub>, -NHC(=O)NR<sub>x</sub>R<sub>y</sub> (wherein R<sub>x</sub>

30 and R<sub>y</sub> are the same as defined earlier), hydroxy, alkoxy, halogen, CF<sub>3</sub>, cyano, and -S(O)<sub>m</sub>R<sub>6</sub> (where R<sub>6</sub> and m are the same as defined earlier). Alkylene groups as defined above may also be interrupted by 1-5 atoms of groups independently chosen from oxygen,

sulfur and  $-NR_a$  [where  $R_a$  is chosen from hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, acyl, aralkyl,  $-C(=O)OR_3$  (wherein  $R_3$  is the same as defined earlier),  $-S(O)_mR_4$  (where  $R_4$  is as defined earlier) or  $-C(=O)NR_xR_y$  (wherein  $R_x$  and  $R_y$  are as defined earlier)]. Unless otherwise constrained by the definition, all substituents may  
 5 be further substituted by 1-3 substituents chosen from alkyl, carboxy,  $-NR_xR_y$ ,  $-C(=O)NR_xR_y$ ,  $-OC(=O)NR_xR_y$  (wherein  $R_x$  and  $R_y$  are the same as defined earlier), hydroxy, alkoxy, halogen,  $CF_3$ , cyano, and  $-S(O)_mR_4$  (where  $m$  and  $R_4$  are the same as defined earlier).

The term "alkenyl," unless otherwise specified, refers to a monoradical of a  
 10 branched or unbranched unsaturated hydrocarbon group preferably having from 2 to 20 carbon atoms with cis or trans geometry. In the event that alkenyl is attached to the heteroatom, the double bond cannot be alpha to the heteroatom. Conjugated or unconjugated multiply unsaturated systems are also contemplated.

Alkenyl may further be substituted with one or more substituents selected alkyl,  
 15 alkynyl, alkoxy, cycloalkyl, acyl, acylamino, acyloxy,  $-NHC(=O)R_x$ ,  $-NR_xR_y$ ,  $-C(=O)NR_xR_y$ ,  $-NHC(=O)NR_xR_y$ ,  $-OC(=O)NR_xR_y$  (wherein  $R_x$  and  $R_y$  are the same as defined earlier), alkoxycarbonylamino, azido, cyano, halogen, hydroxy, oxo, thiocarbonyl, carboxy,  $-COOR_3$  (wherein  $R_3$  is the same as defined earlier), arylthio, thiol, alkylthio, aryl, aralkyl, aryloxy, heterocyclyl, heteroaryl, heterocyclyl alkyl, heteroaryl alkyl,  
 20 aminosulfonyl, alkoxyamino, nitro,  $S(O)_mR_4$  (wherein  $R_4$  and  $m$  are the same as defined earlier). Unless otherwise constrained by the definition, all substituents may optionally be further substituted by 1-3 substituents chosen from alkyl, carboxy,  $-COOR_3$  (wherein  $R_3$  is the same as defined earlier), hydroxy, alkoxy, halogen,  $-CF_3$ , cyano,  $-NR_xR_y$ ,  $-C(=O)NR_xR_y$ ,  $-O-C(=O)NR_xR_y$  (wherein  $R_x$  and  $R_y$  are the same as defined earlier) and -  
 25  $S(O)_mR_4$  (where  $R_4$  and  $m$  are the same as defined earlier).

The term "alkenylene" unless otherwise specified, refers to a diradical of a branched or unbranched unsaturated hydrocarbon group preferably having from 2 to 6 carbon atoms with cis or trans geometry. In the event that alkenylene is attached to a heteroatom, any double bond cannot be alpha to the heteroatom. The alkenylene group  
 30 can be connected by two bonds to the rest of the structure of compound of Formula Ia.

Alkenylene may further be substituted with one or more substituents selected from the group consisting of alkyl, alkynyl, alkoxy, cycloalkyl, acyl, acylamino, acyloxy, -NHC(=O)R<sub>x</sub>, -NR<sub>x</sub>R<sub>y</sub>, -C(=O)NR<sub>x</sub>R<sub>y</sub>, -NHC(=O)NR<sub>x</sub>R<sub>y</sub>, -OC(=O)NR<sub>x</sub>R<sub>y</sub> (wherein R<sub>x</sub> and R<sub>y</sub> are the same as defined earlier), alkoxycarbonylamino, azido, cyano, halogen, hydroxy, 5 oxo, thiocarbonyl, carboxy, -COOR<sub>3</sub> (wherein R<sub>3</sub> is the same as defined earlier), arylthio, thiol, alkylthio, aryl, aralkyl, aryloxy, heterocyclyl, heteroaryl, heterocyclyl alkyl, heteroaryl alkyl, aminosulfonyl, alkoxyamino, nitro, -S(O)<sub>m</sub>R<sub>4</sub> (wherein R<sub>4</sub> and m are the same as defined earlier). Unless otherwise constrained by the definition, all substituents may optionally be further substituted by 1-3 substituents chosen from alkyl, carboxy, -10 COOR<sub>3</sub> (wherein R<sub>3</sub> is the same as defined earlier), hydroxy, alkoxy, halogen, -CF<sub>3</sub>, cyano, -NR<sub>x</sub>R<sub>y</sub>, -C(=O)NR<sub>x</sub>R<sub>y</sub>, -OC(=O)NR<sub>x</sub>R<sub>y</sub> (wherein R<sub>x</sub> and R<sub>y</sub> are the same as defined earlier) and -S(O)<sub>m</sub>R<sub>4</sub> (where R<sub>4</sub> and m are the same as defined earlier).

The term "alkynyl," unless otherwise specified, refers to a monoradical of an unsaturated hydrocarbon, preferably having from 2 to 20 carbon atoms.

15 In the event that alkynyl is attached to a heteroatom, any triple bond cannot be alpha to the heteroatom. Alkynyl may further be substituted with one or more substituents selected from alkyl, alkenyl, alkoxy, cycloalkyl, acyl, acylamino, acyloxy, alkoxycarbonylamino, azido, cyano, halogen, hydroxy, oxo, thiocarbonyl, carboxy, -COOR<sub>3</sub> wherein R<sub>3</sub> is the same as defined earlier, arylthio, thiol, alkylthio, aryl, aralkyl, 20 aryloxy, aminosulfonyl, nitro, heterocyclyl, heteroaryl, heterocyclyl alkyl, heteroarylalkyl, -NHC(=O)R<sub>x</sub>, -NR<sub>x</sub>R<sub>y</sub>, -NHC(=O)NR<sub>x</sub>R<sub>y</sub>, -C(=O)NR<sub>x</sub>R<sub>y</sub>, -O-C(=O)NR<sub>x</sub>R<sub>y</sub> (wherein R<sub>x</sub> and R<sub>y</sub> are the same as defined earlier), -S(O)<sub>m</sub>R<sub>4</sub> (wherein R<sub>4</sub> and m are the same as defined earlier). Unless otherwise constrained by the definition, all substituents may optionally be further substituted by 1-3 substituents chosen from alkyl, carboxy, -COOR<sub>3</sub> (wherein R<sub>3</sub> is 25 the same as defined earlier), hydroxy, alkoxy, halogen, CF<sub>3</sub>, -NR<sub>x</sub>R<sub>y</sub>, -C(=O)NR<sub>x</sub>R<sub>y</sub>, -NHC(=O)NR<sub>x</sub>R<sub>y</sub>, -C(=O)NR<sub>x</sub>R<sub>y</sub> (wherein R<sub>x</sub> and R<sub>y</sub> are the same as defined earlier), cyano, and -S(O)<sub>m</sub>R<sub>4</sub> (where R<sub>4</sub> and m are the same as defined earlier).

The term "alkynylene," unless otherwise specified, refers to a diradical of an unsaturated hydrocarbon, preferably having from 2 to 6 carbon atoms. In the event that 30 alkynylene is attached to a heteroatom, any triple bond cannot be alpha to the heteroatom. The alkenylene group is connected by two bonds to the rest of the structure of compound of Formula Ia. Alkynylene may further be substituted with one or more substituents

selected from the group consisting of alkyl, alkenyl, alkoxy, cycloalkyl, acyl, acylamino, acyloxy, alkoxycarbonylamino, azido, cyano, halogen, hydroxy, oxo, thiocarbonyl, carboxy, arylthio, thiol, alkylthio, aryl, aralkyl, aryloxy, aminosulfonyl, nitro, heterocyclyl, heteroaryl, heterocyclyl alkyl, heteroarylalkyl, -NHC(=O)R<sub>x</sub> -NR<sub>x</sub>R<sub>y</sub>, -NHC(=O)NR<sub>x</sub>R<sub>y</sub>, -C(=O)NR<sub>x</sub>R<sub>y</sub>, -OC(=O)NR<sub>x</sub>R<sub>y</sub> (wherein R<sub>x</sub> and R<sub>y</sub> are the same as defined earlier), -S(O)<sub>m</sub>R<sub>4</sub> (wherein R<sub>4</sub> and m are the same as defined earlier). Unless otherwise constrained by the definition, all substituents may optionally be further substituted by 1-3 substituents chosen from alkyl, carboxy, -COOR<sub>3</sub> (wherein R<sub>3</sub> is the same as defined earlier), hydroxy, alkoxy, halogen, CF<sub>3</sub>, -NR<sub>x</sub>R<sub>y</sub>, -C(=O)NR<sub>x</sub>R<sub>y</sub>, -NHC(=O)NR<sub>x</sub>R<sub>y</sub>, -C(=O)NR<sub>x</sub>R<sub>y</sub> (wherein R<sub>x</sub> and R<sub>y</sub> are the same as defined earlier), cyano, and -S(O)<sub>m</sub>R<sub>4</sub> (where R<sub>4</sub> and m are the same as defined earlier).

The term "cycloalkyl" 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 or otherwise constrained by the definition. The cycloalkyl group may optionally contain 1-3 heteroatoms selected from the group consisting of O, N or S such as oxazoline, isoxazoline, thiazoline, and the like. Such cycloalkyl groups include, by way of example, single ring structures such as cyclopropyl, cyclobutyl, cyclooctyl, cyclopentenyl, and the like, or multiple ring structures such as adamantanyl, and bicyclo (2.2.1) heptane, or cyclic alkyl groups to which is fused an aryl group, for example indane, and the like. Fused or spiro rings are also contemplated. Cycloalkyl may further be substituted with one or more substituents selected from alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, acyl, acylamino, acyloxy, alkoxycarbonylamino, azido, cyano, halogen, hydroxy, oxo, thiocarbonyl, carboxy, -COOR<sub>3</sub> (wherein R<sub>3</sub> is the same as defined earlier), arylthio, thiol, alkylthio, aryl, aralkyl, aryloxy, aminosulfonyl, -NR<sub>x</sub>R<sub>y</sub>, -NHC(=O)NR<sub>x</sub>R<sub>y</sub>, -NHC(=O)R<sub>x</sub>, -C(=O)NR<sub>x</sub>R<sub>y</sub>, -OC(=O)NR<sub>x</sub>R<sub>y</sub> (wherein R<sub>x</sub> and R<sub>y</sub> are the same as defined earlier), nitro, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl, -S(O)<sub>m</sub>R<sub>4</sub> (wherein R<sub>4</sub> and m are the same as defined earlier). Unless otherwise constrained by the definition, all substituents may optionally be further substituted by 1-3 substituents chosen from alkyl, carboxy, hydroxy, alkoxy, halogen, CF<sub>3</sub>, -NR<sub>x</sub>R<sub>y</sub>, -C(=O)NR<sub>x</sub>R<sub>y</sub>, -NHC(=O)NR<sub>x</sub>R<sub>y</sub>, -OC(=O)NR<sub>x</sub>R<sub>y</sub> (wherein R<sub>x</sub> and R<sub>y</sub> are the same as defined earlier), cyano, and -S(O)<sub>m</sub>R<sub>4</sub> (where R<sub>4</sub> and m are the same as defined earlier).

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

The term "aralkyl" refers to alkyl-aryl linked through alkyl (wherein alkyl is the same as defined above) portion and the alkyl portion contains carbon atoms from 1-6 and aryl is as defined below. The examples of aralkyl groups are benzyl and the like.

The term "aryl" herein refers to a carbocyclic aromatic group, for example phenyl, biphenyl or naphthyl ring and the like optionally substituted with 1 to 3 substituents selected from halogen (F, Cl, Br, I), hydroxy, carboxy,  $-\text{COOR}_3$  (wherein  $R_3$  is the same as defined earlier), alkyl, alkenyl, alkynyl, cycloalkyl, alkoxy, acyl, aryloxy, cyano, nitro,  $-\text{NHC}(=\text{O})\text{R}_x$ ,  $-\text{NR}_x\text{R}_y$ ,  $-\text{C}(=\text{O})\text{NR}_x\text{R}_y$ ,  $-\text{NHC}(=\text{O})\text{NR}_x\text{R}_y$ ,  $-(\text{SO})_m\text{R}_4$  (wherein  $R_4$ ,  $R_x$ ,  $R_y$  and  $m$  are the same as defined earlier), carboxy, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl. The aryl group may optionally be fused with cycloalkyl group, wherein the cycloalkyl group may optionally contain heteroatoms selected from the group consisting of O, N, S.

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

The term "aralkyloxy" denotes the group O-aralkyl wherein aralkyl is the same as defined above.

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

The term "heteroaryl" unless and otherwise specified refers to an aromatic ring structure containing 5 or 6 ring atoms, or a bicyclic aromatic group having 8 to 10 ring atoms, with one or more heteroatom(s) independently selected from the group consisting of N, O and S optionally substituted with 1 to 3 substituent(s) selected from the group consisting of halogen (F, Cl, Br, I), hydroxy, alkyl, alkenyl, alkynyl, cycloalkyl, acyl, carboxy,  $-\text{COOR}_3$  (wherein  $R_3$  is the same as defined earlier), aryl, alkoxy, aralkyl, cyano, nitro,  $-\text{NR}_x\text{R}_y$ ,  $-\text{C}(=\text{O})\text{NR}_x\text{R}_y$  and  $-\text{NHC}(=\text{O})\text{NR}_x\text{R}_y$ ,  $-\text{S}(\text{O})_m\text{R}_4$ ,  $-\text{OC}(=\text{O})\text{NR}_x\text{R}_y$  (wherein  $m$ ,  $R_4$ ,  $R_x$  and  $R_y$  are the same as defined earlier). Unless otherwise constrained by the definition, the substituents are attached to the ring atom, be it carbon or heteroatom. Examples of heteroaryl groups are pyridinyl, pyridazinyl, pyrimidinyl, pyrrolyl, pyrazolyl, tetrazolyl, oxazolyl, thiazolyl, thienyl, isoxazolyl, triazinyl, furanyl, benzofuranyl, indolyl, benzothiazolyl, benzoxazolyl, and the like.

The term "heterocyclyl" unless and otherwise specified, refers to a non-aromatic monocyclic or bicyclic cycloalkyl group having 5 to 10 atoms in which 1 to 3 carbon atoms in a ring are replaced by heteroatoms selected from O, S or N, and are optionally benzofused or fused heteroaryl of 5-6 ring members and/or are optionally substituted wherein the substituents are selected from halogen (F, Cl, Br, I), hydroxy, alkyl, alkenyl, alkynyl, cycloalkyl, acyl, aryl, alkoxy, alkaryl, cyano, nitro, oxo, carboxy, -COOR<sub>3</sub> (wherein R<sub>3</sub> is the same as defined earlier), -C(=O)NR<sub>x</sub>R<sub>y</sub>, -S(O)<sub>m</sub>R<sub>4</sub>, -OC(=O)NR<sub>x</sub>R<sub>y</sub>, -NHC(=O)NR<sub>x</sub>R<sub>y</sub> -NR<sub>x</sub>R<sub>y</sub> (wherein m, R<sub>4</sub>, R<sub>x</sub> and R<sub>y</sub> are the same as defined earlier). Unless otherwise constrained by the definition, the substituents are attached to the ring atom, be it carbon or heteroatom. Also unless or otherwise constrained by the definition the heterocyclyl ring may optionally contain one or more olefinic bond(s). Examples of heterocyclyl groups are tetrahydrofuranyl, dihydrofuranyl, dihydropyridinyl, dihydrobenzofuranyl, azabicyclohexyl, dihydroindolyl, piperidinyl, pyrrolidinyl, morpholinyl or piperazinyl.

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

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

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

"Substituted amino" unless and otherwise specified refers to a group -N(R<sub>k</sub>)<sub>2</sub> wherein each R<sub>k</sub> is independently selected from hydrogen (provided that both R<sub>k</sub> groups are not hydrogen (defined as "amino")), alkyl, alkenyl, alkynyl, aralkyl, carboxy, -COOR<sub>3</sub> wherein R<sub>3</sub> is the same as defined earlier, cycloalkyl, aryl, heteroaryl, heterocyclyl, heterocyclylalkyl, heteroarylalkyl, acyl, -S(O)<sub>m</sub>R<sub>4</sub> (wherein m and R<sub>4</sub> is the same as defined above), -C(=R<sub>v</sub>)NR<sub>x</sub>R<sub>y</sub> (wherein R<sub>v</sub> is O or S, R<sub>x</sub> and R<sub>y</sub> are the same as defined earlier) or -NHC(=R<sub>v</sub>)NR<sub>x</sub>R<sub>y</sub> (wherein R<sub>v</sub>, R<sub>x</sub> and R<sub>y</sub> are the same as defined earlier).

Unless otherwise constrained by the definition, all substituents may optionally be further substituted by 1-3 substituents chosen from alkyl, aralkyl, cycloalkyl, aryl, carboxy, -COOR<sub>3</sub> wherein R<sub>3</sub> is the same as defined earlier heteroaryl, heterocyclyl, carboxy, hydroxy, alkoxy, halogen, CF<sub>3</sub>, cyano, -C(=R<sub>v</sub>)NR<sub>x</sub>R<sub>y</sub>, -OC(=O)NR<sub>x</sub>R<sub>y</sub> (wherein

$R_x$ ,  $R_y$  and  $R_v$  are the same as defined earlier) and  $-OC(=R_v)NR_xR_y$ ,  $-S(O)_mR_4$  (where  $m$  and  $R_4$  are the same as defined above).

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

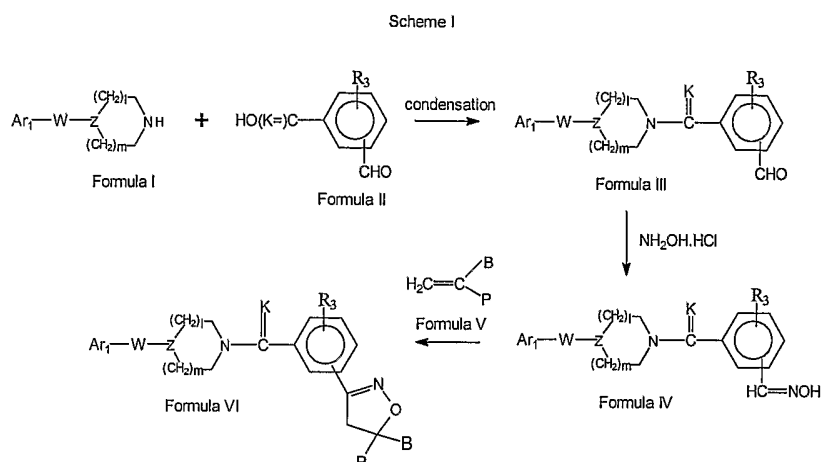
The compounds provided herein can contain one or more asymmetric carbon atoms and thus occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. All such isomeric forms of these compounds are expressly included in the present invention. Each stereogenic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

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

The salt forms differ from the compound described herein in certain physical properties such as solubility, but the salts are otherwise equivalent for the purpose of this invention.

### Detailed Description of the Invention

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



The compounds of Formula VI can be prepared by Scheme I. Thus a compound of Formula I (wherein  $l$  is an integer from 0-2 and  $\text{Ar}_1$ ,  $W$ ,  $Z$  and  $m$  are the same as defined earlier) is reacted with a compound of Formula II (wherein  $K$  and  $R_3$  are the same as defined earlier) to furnish a compound of Formula III, which is reacted with hydroxylamine hydrochloride to furnish a compound of Formula IV, which is reacted with a compound of Formula V (wherein  $B$  is hydrogen or alkyl and  $P$  is cyano,  $-\text{COOR}_3$  (wherein  $R_3$  is same as defined earlier) or  $-\text{CH}_2\text{OH}$ ) to furnish a compound of Formula VI.

The compound of Formula I can be reacted with a compound of Formula II to give a compound of Formula III in an organic solvent, such as tetrahydrofuran, dimethylformamide or dioxane, with a condensing agent, such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride or dicyclohexylcarbodiimide, in the presence of an organic base, such as  $N$ -methylmorpholine, diisopropylethylamine or triethylamine. Alternatively, a compound of Formula I can be reacted with an "activated derivative of carboxylic acid" to furnish a compound of Formula III (when  $k$  is  $O$ ).

The compound of Formula III can be reacted with hydroxylamine hydrochloride to give a compound of Formula IV in an organic solvent, such as ethanol, methanol, propanol or isopropylalcohol, in the presence of an organic base, such as pyridine, N-methylmorpholine or diisopropylethylamine.

- 5           The compound of Formula IV can be reacted with a compound of Formula V to give a compound of Formula VI in an organic solvent such as tetrahydrofuran, dimethylformamide, chloroform, carbon tetrachloride or dioxane with oxidants such as, sodium hypochlorite, N-chlorosuccinimide or tert-butoxychloride in the presence of an optional base such as, pyridine, butyl lithium, N-methylmorpholine,  
10       diisopropylethylamine or triethylamine.

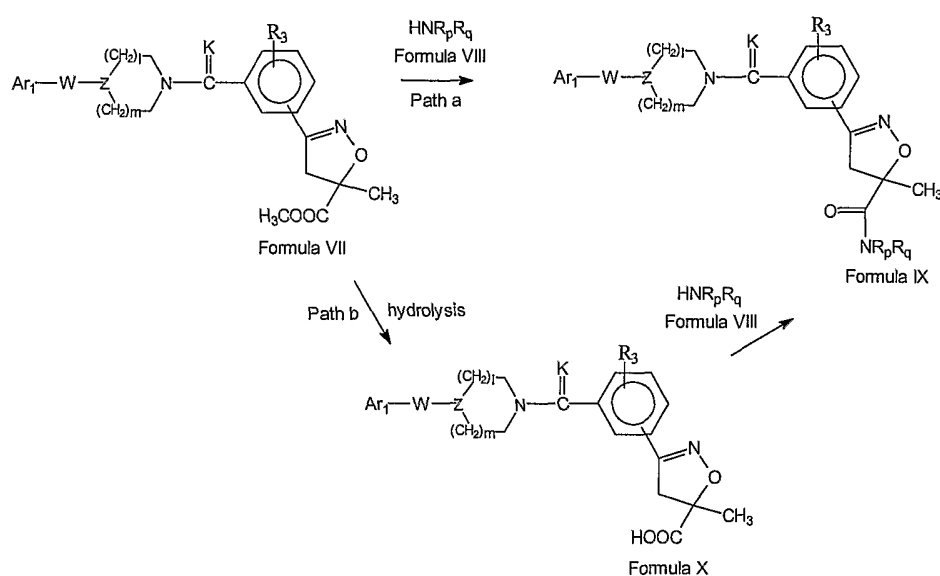
Representative compounds prepared following Scheme I are:

- 3-[4-(4-Benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid methyl ester (Compound No. 1);
- 15   3-[3-(4-Benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid methyl ester (Compound No. 6);
- (4-Benzylpiperidin-1-yl)-[4-(5-hydroxymethyl-4,5-dihydroisoxazole-3-yl)phenyl]methanone (Compound No. 23);
- 20   (4-Benzylpiperidin-1-yl)-[4-(5-hydroxymethyl-5-methyl-4,5-dihydroisoxazol-3-yl)phenyl]methanone (Compound No. 24);
- 3-[2-(4-Benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid methyl ester (Compound No. 30);
- 25   4-{4-[(4-Benzylpiperidin-1-yl)carbonyl]phenyl}-5-methyl-4,5-dihydroisoxazole-5-carbonitrile (compound No. 43);
- 30   Ethyl 4-{4-[(4-benzylpiperidin-1-yl)carbonyl]phenyl}-4,5-dihydroisoxazole-5-carboxylate (Compound No. 44);
- Methyl 3-{3-[(4-benzylpiperidin-1-yl)carbonyl]-4-methoxyphenyl}-5-methyl-4,5-dihydroisoxazole-5-carboxylate (Compound No. 65);
- 35   Methyl 3-(3-{[4-(4-fluorobenzyl)piperidin-1-yl]carbonyl}-4-methoxyphenyl)-5-methyl-4,5-dihydroisoxazole-5-carboxylate (Compound No. 70).

- Also, in all the above representative examples wherever esters are specified one skilled in the art would optionally hydrolyze them to their respective acids, for example  
40   hydrolysis of alkyl esters (such as ethyl, methyl or benzyl ester) to their corresponding

acids can be carried out in the presence of a base for example lithium hydroxide, sodium hydroxide or potassium hydroxide. Alternatively hydrolysis of benzyl ester can be carried out hydrogenatically using catalysts for example palladium on carbon or platinum on carbon. The esters such as tert-butyl can be hydrolyzed to their corresponding acids in the presence of acid for example trifluoroacetic acid or hydrochloric acid.

Scheme II



The compound of Formula IX can be prepared, for example, by Scheme II, thus

**Path a:** The compound of Formula VII (wherein  $Ar_1$ ,  $R_3$ ,  $W$ ,  $Z$ ,  $l$ ,  $m$  and  $k$  are the same as defined earlier) reacts with a compound of Formula VIII (wherein  $R_p$  and  $R_q$  are the same as defined earlier) to give a compound of Formula IX.

**Path b:** The compound of Formula VII undergoes hydrolysis to give a compound of Formula X, which is reacted with a compound of Formula VIII to give a compound of Formula IX.

The compound of Formula VII (Path a) can be reacted with a compound of Formula VIII to furnish a compound of Formula IX in an organic solvent, such as tetrahydrofuran, dimethylformamide, diethyl ether or dioxane.

The compound of Formula VII (Path b) can be hydrolyzed to furnish a compound of Formula X in an organic solvent, such as tetrahydrofuran, dimethylformamide,

methanol or ethanol, in the presence of base, such as lithium hydroxide, potassium hydroxide or sodium hydroxide.

The compound of Formula X can be reacted with a compound of Formula VIII to furnish a compound of Formula IX in an organic solvent, such as tetrahydrofuran,  
5 dimethylformamide, diethylether or dioxane, with condensing agent, such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride or dicyclohexyl carbodiimide, in the presence of base, such as N-methylmorpholine, diisopropylethylamine or triethylamine.

Representative compounds prepared following Scheme II, Path *a* are:

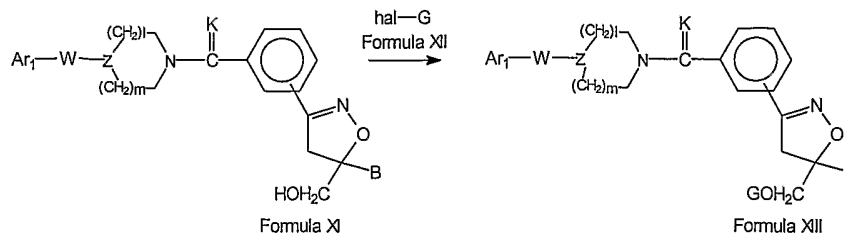
- 10 3-[4-(4-Benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid amide (Compound No. 3);
- 3-[4-(4-Benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid methylamide (Compound No. 4);
- 15 3-[3-(4-Benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid methylamide (Compound No. 5);
- 20 3-[3-(4-Benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid amide (Compound No. 8);
- 3-[3-(4-Benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid cyclopropylamide (Compound No. 9);
- 25 3-[3-(4-Benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid propylamide (Compound No. 10);
- 3-[3-(4-Benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid cyclohexylamide (Compound No. 11);
- 30 3-[3-(4-Benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid (2-hydroxy-ethyl)amide (Compound No. 12);
- 35 3-[3-(4-Benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid benzylamide (Compound No. 13);
- 3-[3-(4-Benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid isopropylamide (Compound No. 14);
- 40 3-[3-(4-Benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid ethylamide (Compound No. 15);

- 3-[3-(4-Benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-yl}pyrrolidin-1-ylmethanone (Compound No. 16);
- 5 3-[4-(4-Benzyl-piperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid butylamide (Compound No. 22);
- 3-[4-(4-Benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid prop-2-ynylamide (Compound No. 26);
- 10 3-[2-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid methylamide (Compound No. 31);
- 3-[4-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid isopropylamide (Compound No. 32);
- 15 3-[4-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid cyclopropylamide (Compound No. 33);
- 3-[4-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid benzylamide (Compound No. 34);
- 20 3-[4-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid (2-hydroxy-ethyl)-amide (Compound No. 35);
- 25 3-[4-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid cyclohexylamide (Compound No. 37);
- 3-[4-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid ethylamide (Compound No. 38);
- 30 3-[4-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid propylamide (Compound No. 39);
- 3-[4-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid cyclopentylamide (Compound No. 42);
- 35 3-[4-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid (3-methyl-butyl)-amide (Compound No. 45);
- 40 3-[4-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid allylamide (Compound No. 46);
- (4-Benzyl-piperidin-1-yl)-{2-[5-methyl-5-(pyrrolidine-1-carbonyl)-4,5-dihydro-isoxazol-3-yl]-phenyl}-methanone (Compound No. 55);
- 45 3-[2-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid propylamide (Compound No. 56);

- 3-[2-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid (2-hydroxy-ethyl)-amide (Compound No. 57);
- 5 3-[2-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid ethylamide (Compound No. 58);
- 3-[2-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid cyclopropylamide (Compound No. 59);
- 10 (4-Benzyl-piperidin-1-yl)-{3-[5-(2-hydroxymethyl-pyrrolidine-1-carbonyl)-5-methyl-4,5-dihydro-isoxazol-3-yl]-phenyl}-methanone (Compound No. 61);
- 3-[3-(4-Benzyl-piperidine-1-carbonyl)-2-methoxy-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid cyclopropylamide (Compound No. 64);
- 15 (4-Benzyl-piperidin-1-yl)-{2-methoxy-5-[5-methyl-5-(pyrrolidine-1-carbonyl)-4,5-dihydro-isoxazol-3-yl]-phenyl}-methanone (Compound No. 66);
- (4-Benzyl-piperidin-1-yl)-{5-[5-(2-hydroxymethyl-pyrrolidine-1-carbonyl)-5-methyl-4,5-dihydro-isoxazol-3-yl]-2-methoxy-phenyl}-methanone (Compound No. 67);
- 20 [4-(4-Fluoro-benzyl)-piperidin-1-yl]-{5-[5-(2-hydroxymethyl-pyrrolidine-1-carbonyl)-5-methyl-4,5-dihydro-isoxazol-3-yl]-2-methoxy-phenyl}-methanone (Compound No. 68);
- 25 3-{3-[4-(4-Fluoro-benzyl)-piperidine-1-carbonyl]-4-methoxy-phenyl}-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid methylamide (Compound No. 69);
- 4-{3-[4-(4-Fluoro-benzyl)-piperidine-1-carbonyl]-4-methoxy-phenyl}-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid amide (Compound No. 71);
- 30 4-{3-[4-(4-Fluoro-benzyl)-piperidine-1-carbonyl]-4-methoxy-phenyl}-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid ethylamide (Compound No. 72);
- 35 3-[4-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid (2-pyrrolidin-1-yl-ethyl)-amide (Compound No. 73);
- 3-[4-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid (3-morpholin-4-yl-propyl)-amide (Compound No. 74).
- 40 Representative compounds prepared following Scheme II, Path *b* are:
- 3-[4-(4-Benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid (Compound No. 2);
- 45 3-[3-(4-Benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid (Compound No. 7);

- 3-[4-(4-Benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid hydroxyamide (Compound No. 17);
- 5 3-[4-(4-Benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid (2-methylene-pent-3-enyloxy)amide (Compound No. 18);
- 3-[4-(4-Benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid methoxyamide (Compound No. 19);
- 10 3-[4-(4-Benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid dimethylamide (Compound No. 20);
- 3-[4-(4-Benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid diisopropylamide (Compound No. 21);
- 15 3-[4-(4-Benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid tert-butylamide (Compound No. 25);
- 20 3-{2-[(4-Benzylpiperidin-1-yl)carbonyl]phenyl}-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid (Compound No. 29);
- (4-Benzyl-piperidin-1-yl)-{4-[5-methyl-5-(pyrrolidine-1-carbonyl)-4,5-dihydro-isoxazol-3-yl]-phenyl}-methanone (Compound No. 36);
- 25 (4-Benzyl-piperidin-1-yl)-{4-[5-methyl-5-(morpholine-4-carbonyl)-4,5-dihydro-isoxazol-3-yl]-phenyl}-methanone (Compound No. 40);
- 3-[4-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid diethylamide (Compound No. 41);
- 30 (4-Benzyl-piperidin-1-yl)-{4-[5-(2-hydroxymethyl-pyrrolidine-1-carbonyl)-5-methyl-4,5-dihydro-isoxazol-3-yl]-phenyl}-methanone (Compound No. 53);
- 1-{3-[4-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonyl}-pyrrolidine-2-carboxylic acid methyl ester (Compound No. 54);
- 35 (4-Benzyl-piperidine-1-yl)-{4-[5-methyl-5-(piperidine-1-carbonyl)-4,5-dihydro-isoxazole-3-yl]-phenyl}-methanone (Compound No. 75);
- 40 3-[4-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid phenylamide (Compound No. 76).

Scheme III



The compound of Formula XIII can be prepared, for example, by Scheme III, thus a compound of Formula XI (wherein Ar, Z, W, l, m and K same as defined earlier and B is H or alkyl) is reacted with a compound of Formula XII (wherein hal is Cl, Br or I and G is alkyl or aralkyl) to give a compound of Formula XIII.

10

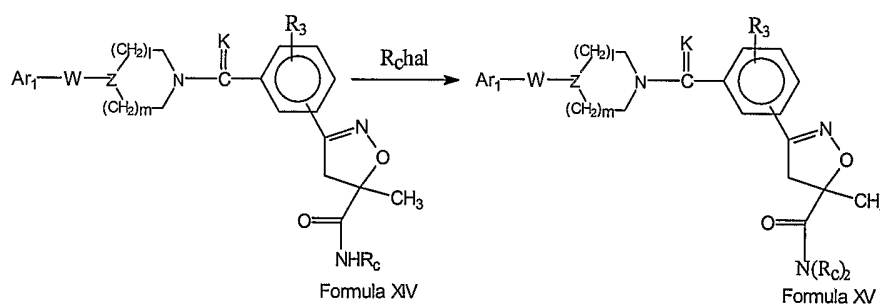
The compound of Formula XI can be reacted with a compound of Formula XII to give a compound of Formula XIII in an organic solvent, such as tetrahydrofuran, dimethylformamide, acetonitrile, acetone or dioxane, in the presence of a base such as sodium hydride, lithium hydride, potassium carbonate or calcium hydride.

15 Representative compounds prepared following Scheme III are:

(4-Benzylpiperidin-1-yl)-[4-(5-hydroxymethyl-5-methyl-4,5-dihydroisoxazol-3-yl)phenyl]methanone (Compound No. 24);

20 [4-(5-Benzyloxymethyl-5-methyl-4,5-dihydroisoxazol-3-yl)phenyl]-(4-benzylpiperidin-1-yl)methanone (Compound No. 28).

Scheme IV



The compound of Formula XV can be prepared by following the procedure as depicted in Scheme IV. Thus a compound of Formula XIV can be reacted with a compound of Formula R<sub>c</sub>-hal (wherein R<sub>c</sub> is alkyl, aryl, cycloalkyl, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl or heterocyclylalkyl and hal are the same as defined earlier) to give a compound of Formula XV.

25

The reaction of a compound of Formula XIV with a compound of Formula R<sub>c</sub>-hal to give a compound of Formula XV can be carried out in an organic solvent such as, dimethylformamide, tetrahydrofuran, diethyl ether or dioxane in the presence of a base such as, sodium hydride, potassium *tert*-butoxide, potassium carbonate or cesium carbonate.

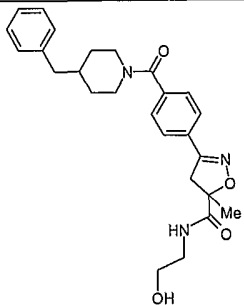
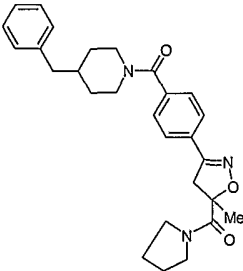
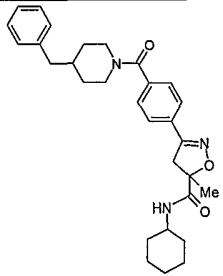
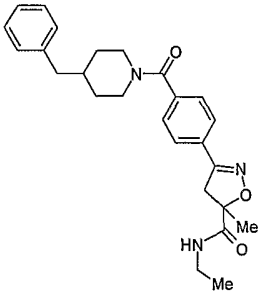
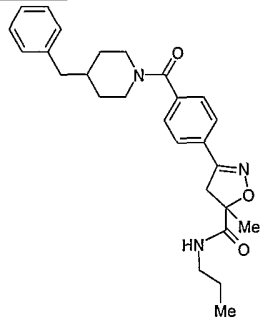
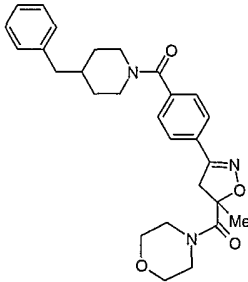
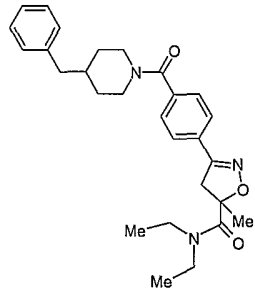
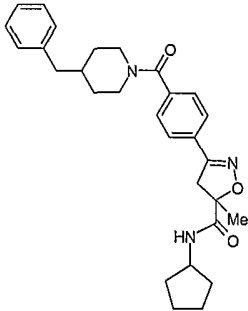
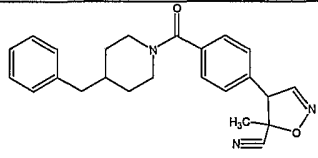
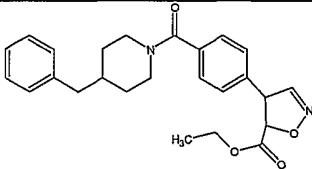
Representative compounds prepared following Scheme IV are:

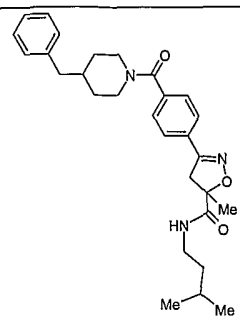
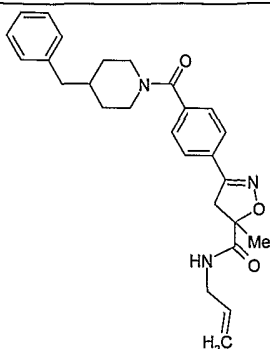
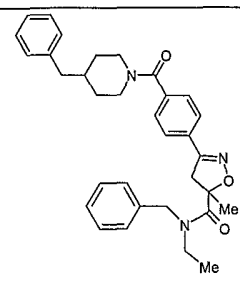
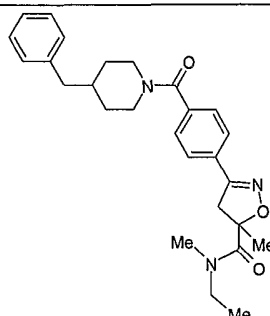
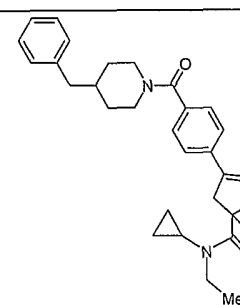
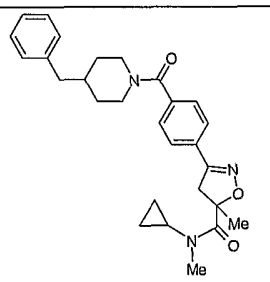
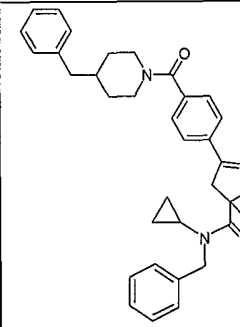
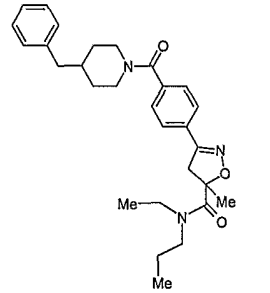
- 3-[4-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid benzyl-ethyl-amide (Compound No. 47);
- 10 3-[4-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid ethyl-methyl-amide (Compound No. 48);
- 3-[4-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid cyclopropyl-ethyl-amide (Compound No. 49);
- 15 3-[4-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid cyclopropyl-methyl-amide (Compound No. 50);
- 3-[4-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid benzyl-cyclopropyl-amide (Compound No. 51);
- 20 3-[4-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid ethyl-propyl-amide (Compound No. 52);
- 25 3-[3-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-2,5-dihydro-isoxazole-5-carboxylic acid benzyl-methyl-amide (Compound No. 60);
- 3-[3-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid cyclopropyl-methyl-amide (Compound No. 62);
- 30 3-[3-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid ethyl-methyl-amide (Compound No. 63).

Particular compounds which can be produced by Scheme I, are listed in the Table below:

| Compound No. | Structure | Compound No. | Structure |
|--------------|-----------|--------------|-----------|
| 1.           |           | 9.           |           |
| 2.           |           | 10.          |           |
| 3.           |           | 11.          |           |
| 4.           |           | 12.          |           |
| 5.           |           | 13.          |           |
| 6.           |           | 14.          |           |
| 7.           |           | 15.          |           |
| 8.           |           | 16.          |           |
| 17.          |           | 18.          |           |

| Compound No. | Structure | Compound No. | Structure |
|--------------|-----------|--------------|-----------|
| 19.          |           | 20.          |           |
| 21.          |           | 22           |           |
| 23.          |           | 24.          |           |
| 25.          |           | 26.          |           |
| 27.          |           | 28.          |           |
| 29.          |           | 30.          |           |
| 31.          |           | 32.          |           |
| 33.          |           | 34.          |           |

| Compound No. | Structure                                                                           | Compound No. | Structure                                                                             |
|--------------|-------------------------------------------------------------------------------------|--------------|---------------------------------------------------------------------------------------|
| 35.          |    | 36.          |    |
| 37.          |    | 38.          |    |
| 39.          |   | 40.          |   |
| 41.          |  | 42.          |  |
| 43           |  | 44.          |  |

| Compound No. | Structure                                                                           | Compound No. | Structure                                                                            |
|--------------|-------------------------------------------------------------------------------------|--------------|--------------------------------------------------------------------------------------|
| 45.          |    | 46.          |    |
| 47.          |    | 48.          |   |
| 49.          |  | 50.          |  |
| 51.          |  | 52.          |  |

| Compound No. | Structure | Compound No. | Structure |
|--------------|-----------|--------------|-----------|
| 53.          |           | 54.          |           |
| 55.          |           | 56.          |           |
| 57.          |           | 58.          |           |
| 59.          |           | 60.          |           |
| 61.          |           | 62.          |           |
| 63.          |           | 64.          |           |
| 65.          |           | 66.          |           |

| Compound No. | Structure | Compound No. | Structure |
|--------------|-----------|--------------|-----------|
| 67.          |           | 68.          |           |
| 69.          |           | 70.          |           |
| 71.          |           | 72.          |           |
| 73.          |           | 74.          |           |
| 75.          |           | 76.          |           |

The compounds described herein have pharmacological activity, and therefore may be administered to an animal for treatment orally, parenterally, topically, rectally, intranasally, subcutaneously or transdermally. The pharmaceutical compositions of the present invention comprise a pharmaceutically effective amount of a compound described herein formulated together with one or more pharmaceutically acceptable carriers. The term "pharmaceutically acceptable carriers" is intended to include non-toxic, inert solid,

semi-solid or liquid filter, diluent, encapsulating material or formulation auxiliary of any type. Solid form preparation for oral administrations, include capsules, tablets, pills, powders, granules, and suppositories. For solid form preparations, the active compound can be mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate, dicalcium phosphate and/or a filler or extenders such as starch, lactose, sucrose, glucose, mannitol and silicic acid; binders such as carboxymethylcellulose, alginates, gelatins, polyvinylpyrrolidinone, sucrose, acacia; disintegrating agents such as a agar-agar, calcium carbonate, potato starch, alginic acid, certain silicates and sodium carbonate, absorption accelerators such as quaternary ammonium compounds; wetting agents such as cetyl alcohol, glycerol, monostearate; adsorbents such as kaolin; lubricants such as talc, calcium stearate, magnesium stearate, solid polyethyleneglycol, sodium lauryl sulphate and mixtures thereof.

In case of capsules, tablets, or pills the dosage form may also comprise buffering agents. Solid preparations of tablets, capsules, pills, granules can be prepared with coating and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art.

Liquid form preparations for oral administration can include pharmaceutically acceptable emulsions, solution, suspensions, syrups and elixirs. For liquid form preparations, the active compound can be mixed with water or other solvent, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (such as cottonseed, groundnut, corn, germ, olive, castor and Sesame oil), glycerol, and fatty acid esters of sorbitan and mixtures thereof. Besides inert diluents, oral compositions can also include adjuvants such as wetting agents, emulsifying agents, suspending agents, sweetening agents, flavoring agents and perfuming agents.

Injectable preparations such as sterile injections, aqueous or oleaginous suspensions may be formulated according to the art using suitable dispersing or wetting and suspending agents. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride.

Dosage forms for topical or transdermal administration of compounds described herein include ointments, pastes, creams, lotions, gel, powders, solutions, spray, inhalants or patches. The active compound can be admixed under sterile conditions with pharmaceutically acceptable carriers and any preservatives or buffers as may be desired.

Ophthalmic formulation, eardrops, eye ointments, powders and solutions are also included herein.

The pharmaceutical preparation may be in unit dosage form. In such forms, the preparation may be subdivided into unit doses containing appropriate quantities of active component. Unit dosage forms can be packaged preparations, the package containing discrete capsules, powders, in vials or ampoules and ointments, capsules, cachets, tablets, gel creams or it can be the appropriate number of any packaged forms.

Formulations disclosed herein may be formulated so as to provide quick, sustained, or delayed release of the active ingredient after administration to the patient by employing procedures well known to the art.

### **EXPERIMENTAL**

#### **Synthesis of 4-(4-fluorobenzyl)piperidine**

##### **Step a: Synthesis of diethyl (4-fluorobenzyl)phosphonate**

A mixture of the compound 4-fluorobenzyl bromide (1.50 g, 8.4 mmol) and triethylphosphite (1.20 g, 9.32 mmol) was stirred at 150 °C for 8 hours to furnish the title compound (2.2 g). This compound was used as such in the next step without purification.

##### **Step b: Synthesis of 1-benzyl-4-(4-fluorobenzylidene)piperidine**

To a solution of the compound obtained from step *a* above (0.38 g, 1.72 mmol) and N-benzyl-4-piperidone (0.326 g, 1.72 mmol) in dimethylformamide (3 ml) was added sodium hydride (0.10 g, 4.3 mol) at 0°C and stirred for overnight. The reaction mixture was quenched with ice-cold water followed by the addition of ethyl acetate. The organic layer was separated, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to furnish the title compound (0.40 g).

##### **Step c: synthesis of 4-(4-fluorobenzyl)piperidine**

To a solution of the compound obtained from step *b* above (0.280 g, 1mol) in methanol (20 ml) was added ammonium formate (0.63 g, 10.0 mmol) and palladium on carbon (0.3 g) under nitrogen atmosphere. The mixture was refluxed for 3 hours and subsequently cooled to room temperature. The mixture was filtered through celite pad and washed with methanol. The filtrate was concentrated under reduced pressure to furnish the title compound (0.07 g).

*Scheme I:***Example 1: Synthesis of 3-[4-(4-benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid methyl ester (Compound No. 1)****Step a: Synthesis of 3-(4-benzylpiperidine-1-carbonyl)benzaldehyde**

5 To a solution of 3-carboxaldehyde (1.5 g, 10 mmol) in dry tetrahydrofuran (10 ml) under argon atmosphere, was added N-methylmorpholine (2.52 g, 25 mmol) and 4-benzyl piperidine (1.75 g, 10 mmol). The reaction mixture was stirred for 30 minutes at 0-5 °C followed by the addition of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.9 g, 10 mmol). The resulting reaction mixture was stirred for 10 minutes  
10 at same temperature and thereafter warmed up to room temperature and stirred overnight. The solvent was removed under reduced pressure and the residue thus obtained was collected in ethyl acetate and extracted with water. The organic layer was collected, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The residue was purified by column chromatography using 30% ethyl acetate in hexane as eluent to  
15 furnish the title compound (2.4 g).

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300MHz) δ: 10.04 (s, 1H, CHO), 7.94-7.90 (d, 2H, *J*=12.0Hz, Ar-H), 7.68-7.56 (m, 2H, Ar-H), 7.31-7.13 (m, 5H, Ar-H), 4.73 (brs, 1H), 3.66 (s, 1H), 2.98 (brs, 1H), 2.84 (brs, 1H), 2.75 (s, 2H), 1.85-1.80 (brs, 2H) and 1.28-1.23 (m, 3H).

**Step b: Synthesis of 3-(4-benzylpiperidine-1-carbonyl)benzaldehyde oxime.**

20 To a solution of the compound obtained from step a above (1.90 g, 6.18 mmol) in ethanol and pyridine solution (1:1, 5 ml), was added hydroxyl amine hydrochloride (0.64 g, 9.28 mmol) under nitrogen atmosphere. The reaction mixture was stirred for overnight followed by removal of solvent under reduced pressure. The residue was diluted with ice-cold water and extracted with ethyl acetate. The organic layer was collected, dried over  
25 anhydrous sodium sulphate and concentrated to furnish the title compound (1.78 g).

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300MHz) δ: 8.10 (s, 1H), 7.69 (s, 1H), 7.57-7.54 (m, 1H, Ar-H), 7.40-7.12 (m, 8H, Ar-H), 4.69 (brs, 1H), 3.68 (brs, 1H), 2.94 (brs, 1H), 2.73 (brs, 1H), 2.56 (brs, 2H), 1.80-1.77 (m, 2H) and 1.25 (m, 3H).

**Step c: Synthesis of 3-[4-(4-benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazol-5-carboxylic acid methyl ester.**  
30

To a solution of the compound obtained from step *b* above (1.0 g, 3.11 mmol) in dry tetrahydrofuran (5 ml), was added methyl methacrylate (0.534 g, 6.22 mmol) and stirred at room temperature under nitrogen atmosphere. To the reaction mixture thus obtained, was added aqueous solution of sodium hypochlorite (4%, 5 ml) dropwise and stirred for 36 hours. The reaction mixture was concentrated under reduced pressure and the residue thus obtained was collected in ethyl acetate. The organic layer was extracted with water and dried over anhydrous sodium sulphate. The organic layer was concentrated under reduced pressure and the residue thus obtained was purified by column chromatography using 20% ethyl acetate in hexane as eluent to furnish the title compound (0.7 g).

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300MHz) δ: 7.64-7.62 (d, *J*=6.0 Hz, 2H, Ar-H), 7.38-7.36 (d, *J*=6.0Hz, 2H, Ar-H), 7.26-7.07 (m, 5H, Ar-H), 4.62 (brs, 1H), 3.86-3.81 (d, *J*=15.0Hz, 1H), 3.76 (s, 3H), 3.69-3.60 (m, 1H), 3.19-3.13 (d, *J*=18.0Hz, 1H), 2.89 (m, 1H), 2.69-2.67 (m, 1H), 2.51 (brs, 2H), 1.75-1.73 (m, 2H) and 1.68-1.59 (m, 6H).

IR (DCM): 2929, 1740, 1629, 1440, 1286, 1105 and 966 cm<sup>-1</sup>

Analogues of 3-[4-(4-benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid methyl ester (Compound No. 1) described below, can be prepared by using appropriate carboxaldehyde in place of 3-carboxaldehyde and acrylate in place of methylmethacrylate, respectively, as applicable in each case.

3-[3-(4-Benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid methyl ester (Compound No. 6)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300MHz) δ: 7.72-7.65 (m, 2H, Ar-H), 7.46-7.42 (m, 2H, Ar-H), 7.31-7.12 (m, 5H, Ar-H), 4.67 (brs, 1H), 3.91-3.86 (d, 1H), 3.81 (s, 3H), 3.68 (brs, 1H), 3.24-3.18 (d, 1H), 2.76 (brs, 1H), 2.76-2.72 (m, 1H), 2.59-2.56 (m, 2H), 1.81-1.77 (m, 2H), 1.72 (s, 3H) and 1.32-1.25 (m, 3H).

IR (DCM): 3447, 2929, 2361, 1740, 1630, 1447, 1286, 1107 and 967cm<sup>-1</sup>

(4-Benzylpiperidin-1-yl)-[4-(5-hydroxymethyl-4,5-dihydroisoxazol-3-yl)phenyl]methanone (Compound No. 23)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300MHz) δ: 7.78-7.71 (m, 2H, Ar-H), 7.48-7.46 (d, 2H, *J*=6.3Hz, Ar-H), 7.48-7.17 (m, 5H, Ar-H), 4.95-4.92 (m, 2H), 3.95-3.90 (m, 2H), 3.76-3.70 (m, 2H),

3.53-3.31 (m, 1H), 2.50-2.30 (m, 2H), 2.63-2.61 (d, 2H,  $J=6.0\text{Hz}$ ), 1.86-1.82 (m, 6H) and 1.30 (m, 1H).

IR (DCM): 3396, 2921, 1616 and  $1450\text{ cm}^{-1}$

(4-Benzylpiperidin-1-yl)-[4-(5-hydroxymethyl-5-methyl-4,5-dihydroisoxazol-3-yl)-phenyl]methanone (Compound No. 24)

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300MHz)  $\delta$ : 7.64-7.62 (d, 2H,  $J=6.0\text{Hz}$ , Ar-H), 7.39-7.36 (d, 2H,  $J=9.0\text{Hz}$ , Ar-H), 7.27-7.08 (m, 5H, Ar-H), 4.70 (brs, 1H), 3.73-3.68 (m, 2H), 3.57-3.42 (m, 2H), 2.99-2.94 (d, 2H,  $J=15.0\text{Hz}$ ), 2.68 (brm, 1H), 2.52 (s, 2H), 2.02-1.96 (dd, 1H,  $J=6.0\text{Hz}$  each), 1.75-1.74 (d, 2H,  $J=3.0\text{Hz}$ ), 1.58 (s, 3H) and 1.24-1.21 (brm, 2H).

3-[2-(4-Benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid methyl ester (Compound No. 30)

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300MHz)  $\delta$ : 7.45-7.37 (m, 3H, Ar-H), 7.29-7.11 (m, 6H, Ar-H), 4.72-4.68 (d, 1H,  $J=12.0\text{Hz}$ ,  $-\text{CH}_2\text{Ph}$ ), 3.80 (brs, 4H,  $-\text{OCH}_3$  &  $-\text{CH}$ ), 3.38-3.34 (d, 1H,  $J=12.0\text{Hz}$ ,  $-\text{CH}_2\text{Ph}$ ), 3.15 (brm, 1H), 2.92-2.84 (t, 1H,  $J=12.0\text{Hz}$ ), 2.71-2.67 (t, 1H,  $J=12.0\text{Hz}$ ), 2.57-2.55 (brs, 2H), 1.79-1.75 (m, 2H), 1.68-1.25 (m, 4H), and 1.17-1.11 (m, 2H).

IR (DCM): 3464, 2931, 1740, 1632, 1435, 1200, 1108, 913 and  $750\text{ cm}^{-1}$ .

Mass (positive ion mode)  $m/z$ : 421 [ $\text{M}^+ + 1$ ].

4-{4-[(4-Benzylpiperidin-1-yl)carbonyl]phenyl}-5-methyl-4,5-dihydroisoxazole-5-carbonitrile (compound No. 43)

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300MHz)  $\delta$ : 7.67-7.65 (d, 2H,  $J=6.0\text{Hz}$ , Ar-H), 7.46-7.44 (d, 2H,  $J=6.0\text{Hz}$ , Ar-H), 7.28-7.12 (m, 5H, Ar-H), 4.68 (m, 1H,  $-\text{CH}_2\text{Ph}$ ), 3.88-3.82 (d, 1H,  $J=18.0\text{Hz}$ ), 3.65 (m, 1H,  $-\text{CH}_2\text{Ph}$ ), 3.44-3.38 (d, 1H,  $J=18.0\text{Hz}$ ), 2.95 (m, 1H), 2.73 (m, 1H), 2.57 (brs, 2H), 1.91 (s, 3H,  $-\text{CH}_3$ ), 1.80 (m, 2H) and 1.37-1.26 (m, 3H).

Mass (positive ion mode)  $m/z$ : 388 [ $\text{M}^+ + 1$ ].

Ethyl 4-{4-[(4-benzylpiperidin-1-yl)carbonyl]phenyl}-4,5-dihydroisoxazole-5-carboxylate (Compound No. 44)

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300MHz)  $\delta$ : 7.72-7.69 (d, 2H,  $J=9.0\text{Hz}$ , Ar-H), 7.44-7.42 (d, 2H,  $J=6.0\text{Hz}$ , Ar-H), 7.36-7.12 (m, 5H, Ar-H), 5.21-5.15 (m, 1H), 4.67 (m, 1H,  $-\text{CH}_2\text{Ph}$ ), 4.31-

4.24 (m, 2H), 4.11-4.07 (m, 1H), 3.65-3.61 (m, 3H), 2.90 (m, 1H), 2.7 (m, 1H), 2.56 (brs, 2H), 2.05-2.04 (m, 2H), 1.35-1.25 (m, 3H) and 0.97-0.88 (m, 3H).

Mass (positive ion mode)  $m/z$ : 421  $[M^+ + 1]$ .

Methyl 3-{3-[(4-benzylpiperidin-1-yl)carbonyl]-4-methoxyphenyl}-5-methyl-4,5-dihydroisoxazole-5-carboxylate (Compound No. 65)

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300MHz)  $\delta$ : 7.54-7.48 (m, 2H, Ar-H), 7.22-7.19 (m, 5H, Ar-H), 6.94-6.90 (m, 1H, Ar-H), 4.76-4.72 (d, 1H,  $J=12.0\text{Hz}$ ), 4.13-4.11 (m, 1H), 3.89-3.79 (m, 6H), 3.40-3.44 (d, 1H,  $J=12.0\text{Hz}$ ), 3.2-3.1 (m, 1H), 2.9-2.8 (m, 1H), 2.72-2.69 (m, 1H), 2.56 (brs, 2H), 1.77-1.69 (m, 5H) and 1.33-1.23 (m, 3H).

Mass (positive ion mode)  $m/z$ : 451  $[M^+ + 1]$ .

Methyl 3-(3-{[4-(4-fluorobenzyl)piperidin-1-yl]carbonyl}-4-methoxyphenyl)-5-methyl-4,5-dihydroisoxazole-5-carboxylate (Compound No. 70)

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300MHz)  $\delta$ : 7.88-7.39 (m, 2H, Ar-H), 7.08-6.90 (m, 5H, Ar-H), 4.77-4.73 (m, 1H), 3.92-3.80 (m, 6H), 3.45-3.41 (d, 1H,  $J=12.0\text{Hz}$ ), 2.72-2.64 (m, 2H), 2.66-2.64 (m, 2H), 2.56-2.54 (m, 2H), 2.08-2.05 (m, 2H), 1.72 (s, 3H) and 1.15-0.88 (m, 3H).

Mass (positive ion mode)  $m/z$ : 469  $[M + 1]$ .

Scheme II, path a:

**Example 2: Synthesis of 3-[3-(4-benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazol-5-yl)pyrrolidin-1-ylmethanone (Compound No. 16)**

To a solution of the Compound No. 1 (0.12 g, 0.28 mmol) in tetrahydrofuran (1 ml), was added pyrrolidine (0.45 g, 5.71 mmol). The reaction mixture was stirred at 40 °C for overnight. The reaction mixture was diluted with ethyl acetate and extracted with water. The organic layer was collected and concentrated under reduced pressure. The residue thus obtained was purified by column chromatography using 80% ethyl acetate in hexane as eluent to furnish the title compound (0.128 g).

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300MHz)  $\delta$ : 7.70-7.67 (m, 2H, Ar-H), 7.46-7.41 (m, 2H, Ar-H), 7.31-7.13 (m, 5H, Ar-H), 4.69 (brs, 1H), 4.27-4.22 (d, 1H,  $J=15.0\text{Hz}$ ), 3.87-3.76 (m, 3H), 3.53-3.49 (m, 2H), 3.18-3.12 (d, 1H,  $J=18.0\text{Hz}$ ), 2.95 (brs, 1H), 2.72 (bs, 1H), 2.57 (brs, 2H), 2.04-1.75 (m, 6H), 1.7 (brs, 3H) and 1.70 (brs, 3H).

IR (DCM): 3455, 2926, 1630, 1430, 1287 and 921 cm<sup>-1</sup>

Analogues of 3-[3-(4-benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazol-5-yl)pyrrolidin-1-ylmethanone (Compound No. 16) described below, can be prepared by using appropriate amine in place of pyrrolidine, respectively, as applicable in each case.

- 5 3-[4-(4-Benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazol-5-carboxylic acid amide (Compound No. 3)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300MHz) δ: 7.72-7.69 (d, 2H, *J*=9.0Hz, Ar-H), 7.41-7.38 (d, 2H, *J*=9.0Hz, Ar-H), 7.20-7.10 (m, 5H, Ar-H), 4.54 (brs, 1H), 3.75-3.58 (m, 2H), 3.00 (m, 1H), 2.78-2.75 (m, 1H), 2.54-2.52 (m, 2H), 1.81-1.53 (m, 6H) and 1.23-1.16 (m, 3H).

- 10 IR: (DCM): 3471, 2929, 1736, 1688, 1456, 1356, 1286, 1103 and 966 cm<sup>-1</sup>

3-[4-(4-Benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid methylamide (Compound No. 4)

- <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300MHz) δ: 7.67-7.64 (d, 2H, *J*=9.0Hz, Ar-H), 7.44-7.41 (d, 2H, *J*=9.0Hz, Ar-H), 7.31-7.12 (m, 5H, Ar-H), 6.88-6.86 (brs, 1H, -NH), 4.67 (brs, 1H), 3.86-3.80 (d, 1H, *J*=18.0Hz), 3.72 (brs, 1H), 3.26-3.20 (d, 1H, *J*=18.0Hz), 2.84-2.82 (brs, 3H), 2.72 (brs, 1H), 2.57 (brs, 2H), 1.81-1.73 (m, 5H) and 1.25-1.11 (m, 4H).

IR (DCM): 3854, 3424, 2954, 2364, 1626, 1539, 1442, 1356, 1208 and 966 cm<sup>-1</sup>

3-[3-(4-Benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid methylamide (Compound No. 5)

- 20 <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300MHz) δ: 7.67-7.64 (m, 2H, Ar-H), 7.44-7.42 (m, 2H, Ar-H), 7.31-7.13 (m, 5H, Ar-H), 6.86 (brs, 1H, -NH), 4.67 (brs, 1H), 3.86-3.80 (d, 1H, *J*=18.0Hz), 3.76 (brs, 1H), 3.25-3.19 (d, 1H, *J*=18.0Hz), 2.97 (brs, 1H), 2.84 (brs, 3H), 2.72 (brs, 1H), 2.59-2.57 (m, 2H), 1.83-1.72 (m, 4H), 1.72-1.64 (brs, 3H) and 1.29-1.21 (m, 1H).

IR (KBr): 3422, 2928, 1672, 1534, 1287, 1054 and 967 cm<sup>-1</sup>

- 25 3-[3-(4-Benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid amide (Compound No. 8)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300MHz) δ: 7.67-7.65 (m, 2H, Ar-H), 7.44-7.43 (m, 2H, Ar-H), 7.31-7.12 (m, 5H, Ar-H), 6.78 (brs, 1H, -NH), 5.35 (brs, 1H, -NH), 4.67 (brs, 1H), 3.87-3.81 (d,

1H,  $J=18.0\text{Hz}$ ), 3.66 (brs, 1H), 3.26-3.21 (d, 1H,  $J=18.0\text{Hz}$ ) 2.95 (brs, 1H), 2.72 (brs, 1H), 2.58-2.56 (m, 2H), 1.83-1.75 (m, 5H) and 1.30-1.25 (m, 3H).

IR (DCM): 3471, 2927, 1686, 1625, 1450, 1287, 1098 and  $966\text{ cm}^{-1}$

3-[3-(4-Benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid cyclopropylamide (Compound No. 9)

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300MHz)  $\delta$ : 7.65-7.64 (m, 2H, Ar-H), 7.44-7.42 (m, 2H, Ar-H), 7.31-7.13 (m, 5H, Ar-H), 6.86 (brs, 1H, -NH), 4.67 (brs, 1H), 3.86-3.80 (d, 1H,  $J=18.0\text{Hz}$ ), 3.67 (brs, 1H), 3.24-3.19 (d, 1H,  $J=18.0\text{Hz}$ ), 2.98 (brs, 1H), 2.77-2.71 (m, 1H), 2.57 (m, 2H), 1.81-1.77 (m, 2H), 1.70 (brs, 4H), 1.61 (brs, 3H), 0.80-0.77 (m, 2H) and 0.53-0.51 (m, 2H).

IR (DCM): 3314, 2928, 2361, 1629, 1515, 1364, 1199 and  $967\text{ cm}^{-1}$

3-[3-(4-Benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid propylamide (Compound No. 10)

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300MHz)  $\delta$ : 7.68-7.64 (m, 2H, Ar-H), 7.46-7.42 (m, 2H, Ar-H), 7.30-7.12 (m, 5H, Ar-H), 6.86 (brs, 1H, -NH), 4.69 (brs, 1H), 3.85-3.79 (d, 1H,  $J=18.0\text{Hz}$ ), 3.72 (brs, 1H), 3.28-3.15 (m, 3H), 2.97 (brs, 1H), 2.72 (brs, 1H), 2.57 (brs, 2H), 1.81-1.72 (m, 5H), 1.65 (brs, 2H), 1.59-1.50 (m, 3H) and 1.28-1.23 (m, 3H).

IR (DCM): 3337, 2931, 2361, 1669, 1525, 1365, 1286, 1054 and  $966\text{ cm}^{-1}$

3-[3-(4-Benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid cyclohexylamide (Compound No. 11)

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300MHz)  $\delta$ : 7.68-7.65 (d, 2H,  $J=9.0\text{Hz}$  Ar-H), 7.44-7.42 (d, 2H,  $J=9.0\text{Hz}$ , Ar-H), 7.31-7.12 (m, 5H, Ar-H), 6.73-6.70 (d, 1H,  $J=9.0\text{Hz}$ , -NH), 4.67 (brs, 1H), 3.84-3.78 (d, 1H,  $J=18.0\text{Hz}$ ), 3.72-3.66 (m, 1H), 3.24-3.18 (d, 1H,  $J=18.0\text{Hz}$ ), 2.97 (brs, 1H), 2.77 (brs, 1H), 2.57 (brs, 2H), 1.90-1.58 (m, 13H) and 1.35-1.28 (m, 5H).

IR (DCM): 3854, 3413, 2930, 2361, 1633, 1519, 1365, 1286 and  $966\text{ cm}^{-1}$

3-[3-(4-Benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid (2-hydroxyethyl)amide (Compound No. 12)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300MHz) δ: 7.64 (brs, 2H, Ar-H), 7.43-7.42 (m, 2H, Ar-H), 7.30-7.12 (m, 5H, Ar-H), 3.85-3.70 (m, 3H), 3.50-3.35 (m, 2H), 3.27-3.21 (d, 1H, *J*=18.0Hz), 2.95-2.73 (brs, 2H), 2.57 (brs, 2H), 1.73-1.40 (m, 8H) and 1.28-1.23 (m, 2H).

IR: 3416, 2930, 2361, 1624, 1287 and 1056 cm<sup>-1</sup>

- 5 3-[3-(4-Benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid benzylamide (Compound No. 13)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300MHz) δ: 4.67-7.65 (m, 2H, Ar-H), 7.44-7.42 (m, 2H, Ar-H), 7.33-7.12 (m, 10H, Ar-H), 4.70 (brs, 1H), 4.56-4.49 (m, 1H), 4.38-4.32 (m, 1H), 3.89-3.83 (d, 1H, *J*=18.0Hz), 3.67 (brs, 1H), 3.28-3.22 (d, 1H, *J*=18.0Hz), 2.95 (brs, 1H), 2.73 (brs, 1H), 2.57 (brs, 2H), 1.75 (brs, 4H), 1.63 (brs, 3H) and 1.27-1.23 (m, 1H).

10 IR (DCM): 3336, 2926, 2361, 1670, 1522, 1363, 1286, 1054 and 966 cm<sup>-1</sup>

IR (DCM): 3336, 2926, 2361, 1670, 1522, 1363, 1286, 1054 and 966 cm<sup>-1</sup>

3-[3-(4-Benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid isopropylamide (Compound No. 14)

- <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300MHz) δ: 7.67-7.65 (d, 2H, *J*=6.0Hz Ar-H), 7.44-7.42 (d, 2H, *J*=6.0Hz, Ar-H), 7.31-6.65 (m, 5H, Ar-H), 4.69 (brs, 1H), 4.06-3.99 (m, 1H), 3.84-3.78 (d, 1H, *J*=18.0Hz), 3.79 (brs, 1H), 3.24-3.18 (d, 1H, *J*=18.0Hz), 2.99 (brs, 1H), 2.72 (brs, 1H), 2.59-2.57 (brs, 2H), 1.81-1.66 (m, 7H) and 1.32-1.12 (m, 7H).

IR (DCM): 3414, 2973, 2929, 1630, 1518, 1450, 1367, 1287, 1205, 1085 and 967 cm<sup>-1</sup>

- 3-[3-(4-Benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid ethylamide (Compound No. 15)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300MHz) δ: 7.83-7.64 (m, 2H, Ar-H), 7.44-7.42 (m, 2H, Ar-H), 7.31-7.12 (m, 5H, Ar-H), 6.82 (brs, 1H, -NH), 4.69 (brs, 1H), 3.85-3.79 (d, 1H, *J*=18.0Hz), 3.65 (brs, 1H), 3.37-3.19 (m, 3H), 2.97 (brs, 1H), 2.72 (brs, 1H), 2.57 (brs, 2H), 1.81-1.65 (m, 8H) and 1.28-1.13 (m, 3H).

- 25 IR (DCM): 3421, 2937, 1629, 1528, 1448, 1366, 1287, 1266, 1098 and 913 cm<sup>-1</sup>

3-[3-(4-Benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-yl}pyrrolidin-1-ylmethanone (Compound No. 16)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300MHz) δ: 7.70-7.67 (m, 2H, Ar-H), 7.46-7.41 (m, 2H, Ar-H), 7.31-7.13 (m, 5H, Ar-H), 4.69 (brs, 1H), 4.27-4.22 (d, 1H, *J*=15.0Hz), 3.87-3.76 (m, 3H), 3.53-

3.49 (m, 2H), 3.18-3.12 (d, 1H,  $J=18.0\text{Hz}$ ), 2.95 (brs, 1H), 2.72 (brs, 1H), 2.57 (brs, 2H), 2.04-1.75 (m, 6H), 1.7 (brs, 3H) and 1.70 (brs, 3H).

IR (DCM): 3455, 2926, 1630, 1430, 1287 and  $921\text{ cm}^{-1}$

5 3-[4-(4-Benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid butylamide (Compound No. 22)

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300MHz)  $\delta$ : 7.67-7.65 (d, 2H,  $J=9.0\text{Hz}$ , Ar-H), 7.41-7.44 (d, 2H,  $J=9.0\text{Hz}$ , Ar-H), 7.31-7.12 (m, 5H, Ar-H), 6.86-6.82 (brs, 1H, N-H), 4.7 (brs, 1H), 3.85-3.80 (d, 1H), 3.70 (brs, 1H), 3.32-3.19 (m, 3H), 2.94 (brs, 1H), 2.71 (brs, 1H), 2.57 (brs, 2H), 1.72 (m, 5H), 1.37-1.26 (m, 6H) and 0.96-0.86 (m, 5H).

10 IR: 3421, 2928, 2857, 1628, 1529, 1443, 1285 and  $1099\text{ cm}^{-1}$

3-[4-(4-Benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid prop-2-ynylamide (Compound No. 26)

15  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300MHz)  $\delta$ : 7.66-7.64 (d, 2H,  $J=6.0\text{Hz}$ , Ar-H), 7.43-7.40 (d, 2H,  $J=9.0\text{Hz}$ , Ar-H), 7.30-7.11 (m, 4H, Ar-H), 7.06-7.03 (m, 3H), 4.70 (brs, 1H), 4.08-3.99 (m, 2H), 3.84-3.78 (d, 1H,  $J=18.0\text{Hz}$ ), 3.64 (brs, 1H), 3.26-3.20 (d, 1H,  $J=18.0\text{Hz}$ ), 3.00-2.56 (m, 2H), 2.56 (s, 2H), 2.24-2.22 (t, 1H,  $J=3.0\text{Hz}$ ), 1.80-1.73 (m, 5H) and 1.24-1.16 (m, 3H).

IR (DCM): 3302, 2921, 2361, 1673, 1624, 1516 and  $1445\text{ cm}^{-1}$

20 3-[2-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid methylamide (Compound No. 31)

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300MHz)  $\delta$ : 7.40-7.35 (m, 3H, Ar-H), 7.23-7.07 (m, 6H, Ar-H), 4.69-4.65 (m, 1H,  $-\text{CH}_2\text{Ph}$ ), 3.80 (m, 1H), 3.38-3.34 (m, 1H,  $-\text{CH}_2\text{Ph}$ ), 3.15 (m, 1H), 2.84-2.73 (m, 5H,  $-\text{NCH}_3$  &  $2\times\text{-CH}$ ), 2.52-2.50 (brs, 2H), 1.93 (m, 2H), 1.63 (s, 3H) and 1.25-1.20 (m, 3H).

25 Mass (positive ion mode)  $m/z$ : 421 [ $\text{M}^++1$ ].

3-[4-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid isopropylamide (Compound No. 32)

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300MHz)  $\delta$ : 7.69-7.65 (m, 2H, Ar-H), 7.43-7.41 (m, 2H, Ar-H), 7.28-7.1 (m, 5H, Ar-H), 7.28-7.1 (m, 1H,  $-\text{NH}$  &  $\text{D}_2\text{O}$  exchangeable), 4.67-4.64 (m, 1H, -

CH<sub>2</sub>Ph), 4.03-4.01 (m, 1H), 3.91 (m, 2H), 3.84-3.79 (m, 1H), 3.24-3.18 (m, 1H), 2.93-2.85 (m, 1H), 2.76-2.68 (m, 1H), 2.58-2.56 (brs, 2H), 1.8-1.71 (m, 4H) and 1.19-1.14 (m, 9H).

Mass (positive ion mode) m/z: 448 [M<sup>+</sup>+1].

m.pt.: 95-96.4 °C.

- 5 3-[4-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid cyclopropylamide (Compound No. 33)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300MHz) δ: 7.67-7.64 (d, 2H, J=9.0Hz, Ar-H), 7.43-7.41 (d, 2H, J=6.0Hz, Ar-H), 7.31-7.12 (m, 5H, Ar-H), 6.87-6.86 (brs, 1H, Ar-H), 4.67-4.63 (m, 1H, -CH<sub>2</sub>Ph), 3.86-3.80 (d, J=18.0Hz, 1H), 3.64 (m, 1H), 3.24-3.18 (d, J=18.0Hz, 1H), 2.93-2.85 (m, 1H), 2.76-2.70 (m, 2H), 2.58-2.56 (brs, 2H), 1.80-1.78 (m, 2H), 1.70 (s, 3H), 1.29-1.25 (m, 3H), 0.80-0.75 (m, 2H) and 0.53-0.52 (m, 2H).

Mass (positive ion mode) m/z: 446 [M<sup>+</sup>+1].

m.pt: 60-62.4 °C

- 15 3-[4-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid benzylamide (Compound No. 34)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300MHz) δ: 7.67-7.65 (d, 2H, J=6.0Hz, Ar-H), 7.44-7.41 (d, 2H, J=9.0Hz, Ar-H), 7.32-7.12 (m, 11H, Ar-H & -NH), 4.67 (m, 1H, -CH<sub>2</sub>Ph), 4.56-4.49 (m, 1H, -CH<sub>2</sub>Ph), 4.39-4.32 (m, 1H, -CH<sub>2</sub>Ph), 3.90-3.84 (d, 1H, J=18.0Hz), 3.66 (m, 1H, -CH<sub>2</sub>Ph), 3.28-3.23 (d, 1H, J=18.0Hz), 2.93-7.0 (m, 2H), 2.57 (brs, 2H), 1.84-1.76 (m, 5H) and 1.29-1.25 (m, 3H).

Mass (positive ion mode) m/z: 496 [M<sup>+</sup>+1].

m.pt: 61-63 °C.

3-[4-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid (2-hydroxy-ethyl)-amide (Compound No. 35)

- 25 <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300MHz) δ: 7.68-7.65 (d, 2H, J=9.0Hz, Ar-H), 7.44-7.41 (d, 2H, J=9.0Hz, Ar-H), 7.31-7.12 (m, 6H, Ar-H & -NH), 6.20 (m, 1H, -OH), 4.67 (m, 1H, -CH<sub>2</sub>Ph), 3.86-3.80 (d, J=18.0Hz, 1H), 3.72-3.69 (m, 3H, -CH<sub>2</sub>Ph & -OCH<sub>2</sub>), 3.48-3.38 (m, 2H, -NCH<sub>2</sub>), 3.27-3.22 (d, 1H, J=15.0Hz), 2.60 (m, 1H), 2.73 (m, 1H), 2.57 (brs, 2H), 1.82-1.60 (m, 5H) and 1.29-1.26 (m, 3H).

- 30 Mass (positive ion mode) m/z: 450 [M<sup>+</sup>+1].

3-[4-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid cyclohexylamide (Compound No. 37)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300MHz) δ: 7.67-7.64 (d, 2H, *J*=9.0Hz, Ar-H), 7.43-7.41 (d, 2H, *J*=6.0Hz, Ar-H), 7.35-7.12 (m, 4H, Ar-H), 6.73-6.71 (d, 1H, *J*=6.0Hz, Ar-H), 4.70 (m, 1H, -CH<sub>2</sub>Ph), 3.84-3.78 (d, 1H, *J*=18.0Hz), 3.75-3.69 (m, 2H), 3.24-3.18 (d, 1H, *J*=18.0Hz), 2.94-2.72 (m, 2H), 2.58 (brs, 2H), 1.93-1.59 (m, 9H) and 1.42-1.12(m, 9H).

Mass (positive ion mode) *m/z*: 488 [M<sup>+</sup>+1].

m.pt: 133.4-134.2 °C

3-[4-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid ethylamide (Compound No. 38)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300MHz) δ: 7.66 (m, 2H, Ar-H), 7.43 (m, 2H, Ar-H), 7.28-7.12 (m, 5H, Ar-H & 1NH), 6.83 (s, 1H, Ar-H), 4.69 (m, 1H, -CH<sub>2</sub>Ph), 3.85-3.80 (d, 1H, *J*=18.0Hz), 3.66 (m, 1H, -CH<sub>2</sub>Ph), 3.34-3.19 (m, 3H), 2.94 (m, 1H), 2.74 (m, 1H), 2.57 (brs, 2H), 1.79-1.72 (m, 5H), 1.42-1.12 (m, 3H) and 1.17-1.13 (m, 3H, -CH<sub>3</sub>).

Mass (positive ion mode) *m/z*: 434 [M<sup>+</sup>+1].

m.pt: 112-115.4 °C

3-[4-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid propylamide (Compound No. 39)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300MHz) δ: 7.67-7.64 (d, 2H, Ar-H), 7.43-7.41 (d, 2H, Ar-H), 7.31-7.12 (m, 5H, Ar-H & NH), 6.88-6.85 (m, 1H, Ar-H), 4.68 (m, 1H, -CH<sub>2</sub>Ph), 3.85-3.80 (d, 1H), 3.64 (m, 1H, -CH<sub>2</sub>Ph), 3.28-3.1 (m, 3H), 2.90-2.70 (m, 2H), 2.58-2.57 (brs, 2H), 1.80-1.72 (m, 5H), 1.62-1.49 (m, 2H), 1.28-1.25 (m, 3H) and 0.93-0.88 (m, 3H, -CH<sub>3</sub>).

Mass (positive ion mode) *m/z*: 448 [M<sup>+</sup>+1].

m.pt.: 75-77 °C.

3-[4-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid cyclopentylamide (Compound No. 42)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300MHz) δ: 7.68-7.65 (d, 2H, *J*=9.0Hz, Ar-H), 7.44-7.41 (d, 2H, *J*=9.0Hz, Ar-H), 7.31-7.12 (m, 4H, Ar-H & 1NH), 6.79-6.76 (d, 1H, *J*=9.0Hz, Ar-H), 4.67 (m, 1H, -CH<sub>2</sub>Ph), 4.19-4.12 (m, 1H), 3.85-3.80 (d, 1H, *J*=18.0Hz), 3.66 (m, 1H), 3.24-3.18

(d, 1H,  $J=18.0\text{Hz}$ ), 2.94 (m, 1H), 2.73 (m, 1H), 2.57 (brs, 2H), 2.00-1.94 (m, 2H), 1.78-1.61 (m, 10H) and 1.46-1.26 (m, 4H).

Mass (positive ion mode)  $m/z$ : 474 [ $M^+ + 1$ ].

m.pt: 135.3 -135.9 °C

- 5 3-[4-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid (3-methyl-butyl)-amide (Compound No. 45)

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300MHz)  $\delta$ : 7.63-7.60 (d, 2H,  $J=9.0\text{Hz}$ , Ar-H), 7.39-7.37 (d, 2H,  $J=6.0\text{Hz}$ , Ar-H), 7.26-7.08 (m, 5H, Ar-H & -NH), 6.76 (m, 1H, Ar-H), 4.70 (m, 1H, - $\text{CH}_2\text{Ph}$ ), 3.81-3.75 (d, 1H,  $J=18.0\text{Hz}$ ), 3.69 (m, 1H, - $\text{CH}_2\text{Ph}$ ), 3.29-3.15 (m, 3H), 2.90 (m, 10  
1H), 2.70 (m, 1H), 2.54 (brs, 2H), 1.76-1.68 (m, 5H), 1.58-1.54 (m, 2H), 1.39-1.32 (m, 2H), 1.21 (m, 2H) and 0.87-0.84 (m, 6H).

Mass (positive ion mode)  $m/z$ : 476 [ $M^+ + 1$ ].

m.pt: 116.3-117.4 °C.

- 15 3-[4-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid allylamide (Compound No. 46)

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300MHz)  $\delta$ : 7.67-7.65 (d, 2H,  $J=9.0\text{Hz}$ , Ar-H), 7.44-7.41 (d, 2H,  $J=9.0\text{Hz}$ , Ar-H), 7.31-7.12 (m, 5H, Ar-H & -NH) 6.96 (m, 1H, Ar-H), 5.80 (m, 1H), 5.19-5.11 (m, 2H), 4.70 (m, 1H), 3.90-3.81 (m, 3H), 3.73 (m, 1H), 3.26-3.21 (d, 1H,  $J=18.0\text{Hz}$ ), 2.90 (m, 1H), 2.70(m, 1H), 2.57 (brs, 2H), 1.80-1.74 (m, 5H) and 1.25 (m, 3H).

- 20 Mass (positive ion mode)  $m/z$ : 446 [ $M^+ + 1$ ].

m.pt.: 128.7-130.1 °C.

(4-Benzyl-piperidin-1-yl)-{2-[5-methyl-5-(pyrrolidine-1-carbonyl)-4,5-dihydro-isoxazol-3-yl]-phenyl}-methanone (Compound No. 55)

- $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300MHz)  $\delta$ : 7.60-7.36 (m, 3H, Ar-H), 7.21-7.13 (m, 6H, Ar-H), 4.73-4.69 (d, 1H,  $J=12.0\text{Hz}$ ), 4.21-4.15 (d, 1H,  $J=18.0\text{Hz}$ ), 3.83-3.64 (m, 2H), 3.49-3.10 (m, 4H), 2.87-2.74 (m, 2H), 2.57-2.54 (m, 2H), 1.96-1.80 (m, 2H), 1.78 (s, 3H) and 1.28-1.25 (m, 7H).

Mass (positive ion mode)  $m/z$ : 460 [ $M^+ + 1$ ].

3-[2-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid propylamide (Compound No. 56)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300MHz) δ: 7.47-7.37 (m, 3H, Ar-H), 7.21-7.19 (m, 4H, Ar-H), 7.13-7.11 (m, 2H, Ar-H), 6.8 (brs, 1H, Ar-H), 4.73-4.69 (m, 1H, *J*=12.0Hz), 3.83-3.77 (d, 1H, *J*=18.0Hz), 3.38-3.14 (m, 4H), 2.72-2.55 (m, 2H), 2.54-2.50 (m, 2H), 1.76-1.68 (m, 2H), 1.59 (s, 3H), 1.25 (s, 4H) and 0.97-0.85 (m, 4H).

Mass (positive ion mode) *m/z*: 448 [*M*<sup>+</sup>+1].

3-[2-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid (2-hydroxy-ethyl)-amide (Compound No. 57)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300MHz) δ: 7.42-7.16 (m, 10H, Ar-H), 4.6-4.5 (m, 1H), 3.72-3.44 (m, 3H), 3.42-3.36 (m, 4H), 2.94-2.92 (m, 1H), 2.75-2.73 (m, 1H), 2.61-2.54 (m, 2H), 2.08-2.05 (m, 2H), 2.00 (s, 3H) and 1.90-1.21 (m, 3H).

Mass (positive ion mode) *m/z*: 450 [*M*<sup>+</sup>+1].

3-[2-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid ethylamide (Compound No. 58)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300MHz) δ: 7.42 (brs, 3H, Ar-H), 7.21-7.11 (m, 6H, Ar-H), 6.80 (brs, 1H, Ar-H), 4.73 (brs, 1H), 3.83-3.77 (m, 1H), 3.34-3.18 (m, 4H), 2.86-2.74 (m, 2H), 2.56 (brs, 2H), 1.53-1.49 (m, 2H), 1.30 (3H, s), 1.25-1.15 (5H, m) and 1.00-0.87 (1H, m).

Mass (positive ion mode) *m/z*: 434 [*M*<sup>+</sup>+1].

3-[2-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid cyclopropylamide (Compound No. 59)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300MHz) δ: 7.46-7.37 (m, 3H, Ar-H), 7.21-7.11 (m, 6H, Ar-H), 6.86 (brs, 1H, Ar-H), 4.73-4.68 (d, 1H, *J*=15.0Hz), 3.83-3.77 (m, 1H), 3.39-3.34 (d, 1H, *J*=15.0Hz), 3.23-3.17 (d, 1H, *J*=18.0Hz), 2.88-2.82 (m, 1H), 2.73-2.72 (m, 2H), 2.60-2.56 (m, 2H), 1.73 (brs, 2H), 1.66 (s, 3H), 1.29-1.25 (m, 3H), 0.87-0.76 (m, 2H) and 0.53 (brs, 2H).

Mass (positive ion mode) *m/z*: 446 [*M*<sup>+</sup>+1].

(4-Benzyl-piperidin-1-yl)-{3-[5-(2-hydroxymethyl-pyrrolidine-1-carbonyl)-5-methyl-4,5-dihydro-isoxazol-3-yl]-phenyl}-methanone (Compound No. 61)

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300MHz)  $\delta$ : 7.72-7.67 (m, 2H, Ar-H), 7.54-7.52 (m, 1H, Ar-H), 7.44-7.42 (2H, m, Ar-H), 7.19-7.12 (m, 4H, Ar-H), 4.4 (brs, 1H), 4.28-4.2 (m, 4H), 4.1-3.9 (m, 1H), 3.68-3.61 (m, 2H), 3.16-3.12 (m, 1H), 2.70-2.60 (m, 2H), 2.58-2.56 (m, 2H), 1.74-1.66 (m, 5H), 1.41-1.32 (m, 3H) and 0.94-0.88 (m, 4H).

5 Mass (positive ion mode)  $m/z$ : 490 [ $\text{M}^+ + 1$ ].

3-[3-(4-Benzyl-piperidine-1-carbonyl)-2-methoxy-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid cyclopropylamide (Compound No. 64)

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300MHz)  $\delta$ : 7.67-7.62 (m, 1H, Ar-H), 7.34-7.14 (m, 6H, Ar-H), 6.9 (brs, 1H, Ar-H), 4.78-4.74 (d, 1H,  $J=12.0\text{Hz}$ ), 3.8 (s, 3H), 3.48-3.36 (m, 2H), 3.10-2.90 (m, 1H), 2.73 (brs, 2H), 2.57 (brs, 1H), 2.32-2.20 (m, 1H), 1.42-1.33 (m, 5H), 0.88 (m, 3H) and 0.52 (brs, 2H).

Mass (positive ion mode)  $m/z$ : 476 [ $\text{M}^+ + 1$ ].

(4-Benzyl-piperidin-1-yl)-{2-methoxy-5-[5-methyl-5-(pyrrolidine-1-carbonyl)-4,5-dihydro-isoxazol-3-yl]-phenyl}-methanone (Compound No. 66)

15  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300MHz)  $\delta$ : 7.68-7.52 (m, 2H, Ar-H), 7.21-7.12 (m, 5H, Ar-H), 6.92-6.89 (m, 1H, Ar-H), 4.76-4.72 (d, 1H,  $J=12.0\text{Hz}$ ), 4.40-4.30 (m, 1H), 3.85 (s, 3H), 3.83 (m, 1H), 3.51-3.39 (m, 4H), 2.90-2.80 (m, 1H), 2.79-2.65 (m, 1H), 2.60-2.59 (m, 1H), 2.58-2.56 (m, 2H), 2.56 (s, 2H), 2.05-1.77 (m, 4H), 1.69 (s, 3H) and 1.28-1.25 (m, 3H).

Mass (positive ion mode)  $m/z$ : 490 [ $\text{M}^+ + 1$ ].

20 (4-Benzyl-piperidin-1-yl)-{5-[5-(2-hydroxymethyl-pyrrolidine-1-carbonyl)-5-methyl-4,5-dihydro-isoxazol-3-yl]-2-methoxy-phenyl}-methanone (Compound No. 67)

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300MHz)  $\delta$ : 7.71-7.59 (m, 2H, Ar-H), 7.21-7.12 (m, 5H, Ar-H), 6.90-6.89 (1H, m, Ar-H), 4.76-4.72 (d, 1H,  $J=12.0\text{Hz}$ , -CHPh), 4.28-4.18 (m, 3H), 4.15 (brs, 1H), 3.80 (s, 3H, -OCH<sub>3</sub>), 3.68-3.60 (m, 3H), 3.40-2.70 (m, 3H), 2.58-2.56 (d, 2H,  $J=6.00\text{Hz}$ ), 2.06-2.04 (m, 2H), 1.92-1.90 (m, 2H), 1.77-1.65 (m, 6H) and 1.60-1.53 (m, 2H).

Mass (positive ion mode)  $m/z$ : 520 [ $\text{M}^+ + 1$ ].

[4-(4-Fluoro-benzyl)-piperidin-1-yl]-{5-[5-(2-hydroxymethyl-pyrrolidine-1-carbonyl)-5-methyl-4,5-dihydro-isoxazol-3-yl]-2-methoxy-phenyl}-methanone (Compound No. 68)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300MHz) δ: 7.71-7.36 (m, 2H, Ar-H), 7.08-6.94 (m, 5H, Ar-H), 4.77-4.73 (d, 1H, *J*=12.0Hz), 4.28-4.14, (m, 3H), 3.86 (s, 3H), 3.66-3.59 (m, 3H), 3.45-3.41 (m, 2H), 3.20-3.10 (m, 1H), 3.00-2.90 (m, 1H), 2.55-2.53 (m, 2H), 2.04-1.9 (m, 2H), 1.73-1.42 (m, 7H) and 1.25 (m, 3H).

5 Mass (positive ion mode) *m/z*: 538 [*M*<sup>+</sup>+1].

3-{3-[4-(4-Fluoro-benzyl)-piperidine-1-carbonyl]-4-methoxy-phenyl}-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid methylamide (Compound No. 69)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300MHz) δ: 7.66-7.36 (m, 2H, Ar-H), 7.08-6.93 (m, 6H, Ar-H), 4.77-4.73 (d, 1H, *J*=12.0Hz), 3.86-3.78 (m, 5H), 3.43-3.39 (d, 1H, *J*=12.0Hz), 2.84-2.54 (m, 10 5H), 2.08-2.05 (m, 2H), 1.72-1.33 (m, 5H) and 1.26-1.06 (m, 3H).

Mass (positive ion mode) *m/z*: 468 [*M*<sup>+</sup>+1].

4-{3-[4-(4-Fluoro-benzyl)-piperidine-1-carbonyl]-4-methoxy-phenyl}-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid amide (Compound No. 71)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300MHz) δ: 7.64-7.42 (m, 3H, Ar-H), 7.08-6.81 (m, 4H, Ar-H), 5.59 15 (brs, -1H, -NH<sub>2</sub>), 4.77-4.73 (d, 1H, *J*=12.0Hz, -NCH), 3.92-3.80 (d, 4H, -OCH<sub>3</sub> & -NCH), 3.59 (brs, 2H, -NCH<sub>2</sub>), 3.43-3.39 (d, 2H, -CH<sub>2</sub>Ph), 3.00 (brs, 1H, -CH), 2.71-2.68 (d, 2H, *J*=9.00, -CH<sub>2</sub>), 2.55-2.53 (d, 4H, *J*=6.0Hz, 2x-CH<sub>2</sub>) and 1.74 (s, 3H, -CH<sub>3</sub>).

Mass (positive ion mode) *m/z*: 454 [*M*<sup>+</sup>+1].

4-{3-[4-(4-Fluoro-benzyl)-piperidine-1-carbonyl]-4-methoxy-phenyl}-5-methyl-4,5- 20 dihydro-isoxazole-5-carboxylic acid ethylamide (Compound No. 72)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300MHz) δ: 7.63-7.49 (m, 2H, Ar-H), 7.11-6.85 (m, 5H, Ar-H), 4.77-4.73 (d, 1H, *J*=12.0Hz, -NCH), 3.86-3.84 (d, 1H, *J*=6.0Hz, -NCH), 3.79 (s, 3H, -OCH<sub>3</sub>), 3.60 (brs, 1H, -NCH), 3.49-3.20 (m, 3H, -NCH & -NCH<sub>2</sub>), 2.56-2.51 (t, 2H, *J*=9.0Hz, -CH<sub>2</sub>Ph), 2.08-2.04 (t, 2H, *J*=6.0Hz), 1.72-1.69 (m, 6H, -CH<sub>3</sub>, -CH<sub>2</sub> & -CH), 1.23 (t, 3H, - 25 CH<sub>3</sub>)

Mass (positive ion mode) *m/z*: 482 [*M*<sup>+</sup>+1].

3-[4-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid (2-pyrrolidin-1-yl-ethyl)-amide (Compound No. 73)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)δ: 7.67-7.65 (d, *J*=6.0Hz, 2H, Ar-H), 7.43-7.40 (d, *J*=9.0Hz, 2H, Ar-H), 7.31-7.12 (m, 5H, Ar-H), 4.8 (brs, 1H, -CHPh), 3.86-3.80 (d, *J*=18.0Hz, 1H), 3.70 (brs, 1H, -CHPh), 3.40-3.38 (m, 2H), 3.25-3.19 (d, *J*=18.0Hz, 1H), 2.85 (m, 2H), 2.65-2.50 (m, 8H) and 1.80-1.12 (m, 12H).

5 Mass (positive ion mode) *m/z*: 503 [*M*<sup>+</sup>+1]

IR (DCM): 3418, 2931, 1629, 1528, 1444, 1287 and 752 cm<sup>-1</sup>

3-[4-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid (3-morpholin-4-yl-propyl)-amide (Compound No. 74)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)δ: 8.08 (s, 1H, -NH), 7.67-7.64 (d, *J*=9.0Hz, 2H, Ar-H), 7.43-7.40 (d, *J*=9.0Hz, 2H, Ar-H), 7.31-7.12 (m, 6H, Ar-H), 4.7 (brs, 1H, -CHPh), 3.84-3.78 (m, 5H, 2x-OCH<sub>2</sub> & -CH), 3.71 (m, 2H), 3.42-3.18 (m, 3H), 2.90 (brs, 1H), 2.70 (brs, 1H), 2.56 (s, 2H), 2.45-2.41 (m, 6H, 3x-NCH<sub>2</sub>), 1.96 (m, 1H), 1.79-1.68 (m, 5H) and 1.25-1.11 (m, 3H).

Mass (positive ion mode) *m/z*: 533 [*M*<sup>+</sup>+1].

15 IR (DCM): 3422, 2933, 1625, 1524, 1445, 1116, 910 and 752 cm<sup>-1</sup>.

Scheme II, Path b:

Example 3: Synthesis of 3-[4-(4-benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid (Compound No. 2)

To a solution of the Compound No. 1 in tetrahydrofuran (5 ml), was added aqueous lithium hydroxide (4.5 equiv.) at 0 °C and the resulting reaction mixture was stirred at room temperature for about 30 minutes. The reaction mixture was allowed to warm up to room temperature for 2-3 hours. The solvent was removed under reduced pressure and the aqueous layer was cooled at 0 °C. To the reaction mixture was added hydrochloric acid drop wise (10 ml, 2 N). The white precipitate thus obtained was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure to furnish the title compound.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300MHz) δ: 7.66-7.63 (d, 2H, *J*=9.0Hz, Ar-H), 7.44-7.41 (d, 2H, *J*=9.0Hz, Ar-H), 7.31-7.12 (m, 5H, Ar-H), 4.72-4.69 (m, 1H), 3.75-3.69 (d, 1H,

$J=18.0\text{Hz}$ ), 3.64 (m, 1H), 3.23-3.17 (d, 1H,  $J=18.0\text{Hz}$ ), 2.96 (m, 1H), 2.74 (m, 4H) and 1.63-1.60 (brs, 2H).

IR (KBr): 3486, 2921, 2366, 1735, 1601, 1357, 1285, 1184 and  $967\text{ cm}^{-1}$

The analogs of 3-[4-(4-benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid (Compound No. 2) described below, can be prepared by replacing Compound No. 6 in place of compound No. 1, respectively, as applicable in each case.

3-[3-(4-Benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid (Compound No. 7)

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300MHz)  $\delta$ : 7.73-7.64 (m, 2H, Ar-H), 7.43-7.38 (m, 2H, Ar-H), 7.29-7.10 (m, 5H, Ar-H), 4.70-4.67 (d, 1H,  $J=9.0\text{Hz}$ ), 3.84-3.78 (d, 1H,  $J=18.0\text{Hz}$ ), 3.70-3.66 (d, 1H,  $J=12.0\text{Hz}$ ), 3.22-3.16 (d, 1H,  $J=18.0\text{Hz}$ ), 2.95 (brs, 1H), 2.77-2.70 (m, 1H), 2.55 (brs, 2H), 1.80-1.77 (brs, 2H), 1.69 (brs, 3H) and 1.30-1.16 (m, 3H).

IR (KBr): 3447, 2926, 2364, 1735, 1602, 1452, 1287, 1190 and  $966\text{ cm}^{-1}$ .

3-{2-[(4-Benzylpiperidin-1-yl)carbonyl]phenyl}-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid (Compound No. 29)

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300MHz)  $\delta$ : 7.48-7.37 (m, 3H, Ar-H), 7.28-7.10 (m, 6H, Ar-H), 4.70-4.66 (d, 1H,  $J=12.0\text{Hz}$ ,  $-\text{CH}_2\text{Ph}$ ), 3.85-3.79 (d, 1H,  $J=18.0\text{Hz}$ ), 3.39-3.35 (d, 1H,  $J=12.0\text{Hz}$ ,  $-\text{CH}_2\text{Ph}$ ), 3.26-3.20 (d, 1H,  $J=18.0\text{Hz}$ ), 2.93-2.85 (m, 1H), 2.76-2.68 (m, 1H), 2.57-2.55 (brs, 2H), 1.68 (m, 3H), 1.52-1.43 (m, 1H) and 1.28-1.12 (m, 2H).

IR (DCM): 3447, 2930, 2535, 1946, 1733, 1588, 1453, 1269, 1192 and  $917\text{ cm}^{-1}$ .

Mass (positive ion mode)  $m/z$ : 407 [ $\text{M}^+ + 1$ ].

m.pt.: 68.7-70.4 °C

**Example 4: Synthesis of 3-[4-(4-benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid methoxyamide (Compound No. 19)**

To a solution of the compound No.2 (0.1 g, 0.246 mmol) in dry tetrahydrofuran (5.0 ml), was added methoxylamine hydrochloride (0.020 g, 0.258 mmol), N-methylmorpholine (0.069 g, 0.61 mmol) and hydroxybenzotriazole (0.033 g, 0.24 mmol) at room temperature under nitrogen atmosphere. The reaction mixture was stirred for 20

minutes followed by the addition of 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (0.049 g, 0.0248 mmol) and the reaction mixture was allowed to stir for overnight. The solvent was evaporated under reduced pressure and the residue was collected in ethylacetate. The organic layer was extracted with water, collected, dried over anhydrous sodium sulphate and concentrated under reduced pressure to furnish the little compound (0.078 g).

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300MHz) δ: 9.29 (brs, 1H, -NH), 7.67-7.64 (d, 2H, *J*=9.0Hz, Ar-H), 7.45-7.42 (d, 2H, *J*=9.0Hz, Ar-H), 7.31-7.12 (m, 5H, Ar-H), 4.7 (brs, 1H), 3.89-3.83 (d, 1H, *J*=18.0Hz), 3.78 (s, 3H), 3.68 (brs, 1H), 3.29-3.23 (d, 1H, *J*=18.0Hz), 2.92 (brs, 1H), 2.68 (brs, 1H), 2.57 (brs, 2H), 1.63 (s, 3H), 1.43 (s, 1H) and 1.28-1.17 (m, 4H).

IR (DCM): 3453, 1658 and 1443 cm<sup>-1</sup>

The analogs of 3-[4-(4-benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid methoxyamide (Compound No. 19) described below, can be prepared by replacing appropriate amine in place of methoxylamine hydrochloride, respectively as applicable in each case.

3-[4-(4-Benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid hydroxyamide (Compound No. 17)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300MHz) δ: 7.62-7.59 (d, 2H, *J*=9.0Hz, Ar-H), 7.41-7.38 (d, 2H, *J*=9.0Hz, Ar-H), 7.30-6.97 (m, 5H), 4.66 (brs, 1H), 3.83-3.77 (d, 1H, *J*=18.0Hz), 3.65 (brs, 1H), 3.28-3.22 (d, 1H, *J*=18.0Hz), 2.94 (brs, 1H), 2.75 (brs, 2H), 2.57 (brs, 2H), 1.82-1.61 (m, 3H), 1.43 (s, 1H) and 1.28-1.11 (m, 4H).

IR (DCM): 3443, 2921, 2851, 1626, 1448, 1358, 1286, 1100 and 910 cm<sup>-1</sup>

3-[4-(4-Benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid (2-methylene-pent-3-enyloxy)amide (Compound No. 18)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300MHz) δ: 9.10 (brs, 1H, -NH), 7.65-7.62 (d, 2H, *J*=9.0Hz, Ar-H), 7.44-7.20 (m, 10H, Ar-H), 7.15-7.12 (d, 2H, *J*=9.0Hz, Ar-H), 4.91 (s, 2H), 4.69 (s, 2H), 3.84-3.78 (d, 1H, *J*=18.0Hz), 3.65 (brs, 1H), 3.25-3.19 (d, 1H, *J*=18.0Hz), 3.06 (brs, 1H), 2.57 (brs, 2H), 2.27 (brs, 1H), 1.89-1.63 (m, 4H), 1.43 (s, 1H) and 1.25-1.10 (m, 2H).

IR (DCM): 3451, 2929, 1626, 1449, 1359, 1286 and 908 cm<sup>-1</sup>

3-[4-(4-Benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid methoxyamide (Compound No. 20)

- <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300MHz) δ: 7.59-7.57 (d, 2H, *J*=9.0Hz, Ar-H), 7.39-7.36 (d, 2H, *J*=9.0Hz, Ar-H), 7.34-7.12 (m, 5H, Ar-H), 4.78 (brs, 1H), 4.38-4.32 (d, 1H, *J*=18.0Hz),  
5 3.63-3.60 (m, 1H), 3.31 (s, 3H, -NCH<sub>3</sub>), 3.14-3.08 (d, 1H, *J*=18.0Hz), 3.01-2.99 (s, 3H), 2.76 (brs, 3H), 2.58-2.56 (d, 2H, *J*=4.0Hz), 1.80-1.60 (m, 5H) and 1.28-1.41 (m, 4H).

IR (DCM): 3447, 2921, 1631 and 1446 cm<sup>-1</sup>

3-[4-(4-Benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid diisopropylamide (Compound No. 21)

- 10 <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300MHz) δ: 7.67-7.65 (d, 2H, *J*=8.4Hz, Ar-H), 7.43-7.41 (d, 2H, *J*=8.4Hz, Ar-H), 7.31-7.12 (m, 5H, Ar-H), 4.70 (brs, 1H), 4.8 (m, 1H), 3.84-3.59 (m, 3H), 3.24-3.18 (d, 1H, *J*=18.0Hz), 2.90 (brs, 1H), 2.74 (brs, 1H), 2.56 (brs, 2H) and 1.81-1.02 (m, 19H).

- 15 3-[4-(4-Benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid tertbutyl amide (Compound No. 25)

- <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300MHz) δ: 7.68-7.65 (d, 2H, *J*=9.0Hz, Ar-H), 7.43-7.40 (d, 2H, *J*=9.0Hz, Ar-H), 7.35-7.17 (m, 3H, Ar-H), 7.14-7.11 (d, 2H, *J*=9.0Hz), 4.75 (m, 1H), 3.77-3.63 (m, 1H), 3.63-3.59 (m, 2H), 3.20-3.14 (d, 2H, *J*=18.0Hz), 2.80-2.77 (m, 2H), 2.57-2.56 (d, 2H, *J*=3.0Hz), 1.90 (s, 1H), 1.80 (s, 2H), 1.72-1.40 (m, 4H, -CH<sub>3</sub> & -CH) and  
20 1.28-1.25 (m, 13H).

IR (DCM): 2925, 1734, 1631 and 1517 cm<sup>-1</sup>.

(4-Benzyl-piperidin-1-yl)-{4-[5-methyl-5-(pyrrolidine-1-carbonyl)-4,5-dihydro-isoxazol-3-yl]-phenyl}-methanone (Compound No. 36)

- <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300MHz) δ: 7.70-7.67 (d, 2H, *J*=9.0Hz, Ar-H), 7.43-7.40 (d, 2H, *J*=9.0Hz, Ar-H), 7.31-7.12 (m, 5H, Ar-H), 4.69 (m, 1H, -CH<sub>2</sub>Ph), 4.28-4.22 (d, 1H, *J*=18.0Hz), 3.87-3.74 (m, 2H, -NCH<sub>2</sub>), 3.53-3.48 (m, 2H, -NCH<sub>2</sub>), 3.17-3.11 (d, 1H, *J*=18.0Hz), 2.90-2.70 (m, 2H), 2.58-2.56 (brs, 2H), 1.99-1.77 (m, 6H), 1.64 (s, 3H) and 1.25 (m, 3H).

Mass (positive ion mode) *m/z*: 460 [M<sup>+</sup>+1].

m.pt.: 80-82.6 °C.

(4-Benzyl-piperidin-1-yl)-{4-[5-methyl-5-(morpholine-4-carbonyl)-4,5-dihydro-isoxazol-3-yl]-phenyl}-methanone (Compound No. 40)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300MHz) δ: 7.68-7.14 (m, 9H, Ar-H), 4.70 (m, 1H, -CH<sub>2</sub>Ph), 4.42-4.37 (d, 1H), 4.10 (m, 1H, -CH<sub>2</sub>Ph), 3.74-3.60 (m, 8H), 3.15-3.09 (m, 1H), 2.93 (m, 1H), 2.72 (m, 1H), 2.57 (bs, 2H), 1.80-1.70 (m, 2H) and 1.25 (m, 6H).

Mass (positive ion mode) m/z: 476 [M<sup>+</sup>+1].

m.pt.: 105.3-106.6 °C.

3-[4-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid diethylamide (Compound No. 41)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300MHz) δ: 7.71-7.68 (d, 2H, *J*=9.0Hz, Ar-H), 7.43-7.40 (d, 2H, *J*=9.0Hz, Ar-H), 7.36-7.12 (m, 5H, Ar-H), 4.69 (brs, 1H, -CH<sub>2</sub>Ph), 4.40-4.34 (d, 4H, *J*=18.0Hz), 3.16-3.10 (d, 1H, *J*=18.0Hz), 2.95 (m, 1H), 2.80 (m, 1H), 2.57 (m, 2H), 2.04-2.01 (m, 2H), 1.80-1.60 (m, 3H) and 1.43-1.12 (m, 9H).

Mass (+ve ion mode, m/z): 462 [M<sup>+</sup>+1].

(4-Benzyl-piperidin-1-yl)-{4-[5-(2-hydroxymethyl-pyrrolidine-1-carbonyl)-5-methyl-4,5-dihydro-isoxazol-3-yl]-phenyl}-methanone (Compound No. 53)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300MHz) δ: 7.70-7.68 (d, 2H, *J*=6.0Hz, Ar-H), 7.44-7.41 (d, 2H, *J*=9.0Hz, Ar-H), 7.31-7.12 (m, 5H, Ar-H), 4.69 (m, 1H, -CH<sub>2</sub>Ph), 4.30-4.22 (m, 3H), 3.68-3.58 (m, 4H), 3.22-3.12 (m, 1H), 2.90 (m, 1H), 2.7 (m, 1H), 2.58-2.57 (brs, 2H), 2.01-1.91 (m, 4H), 1.80-1.56 (m, 5H) and 1.25-1.18 (m, 3H).

Mass (positive ion mode) m/z: 490 [M<sup>+</sup>+1].

1-{3-[4-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonyl}-pyrrolidine-2-carboxylic acid methyl ester (Compound No. 54)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300MHz) δ: 7.71-7.63 (m, 2H, Ar-H), 7.44-7.40 (m, 2H, Ar-H), 7.31-7.12 (m, 5H, Ar-H), 4.70 (m, 1H), 4.5 (m, 1H), 4.25 (m, 1H), 4.06 (m, 2H), 3.82-3.69 (m, 4H), 3.15 (m, 1H), 2.90 (m, 1H), 2.7 (m, 1H), 2.57 (brs, 2H), 2.10-1.88 (m, 4H), 1.80-1.68 (m, 5H) and 1.33-1.26 (m, 3H).

Mass (positive ion mode)  $m/z$ : 518  $[M^+ + 1]$ .

(4-Benzyl-piperidine-1-yl)-{4-[5-methyl-5-(piperidine-1-carbonyl)-4,5-dihydro-isoxazole-3-yl]-phenyl}-methanone (Compound No. 75)

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300MHz)  $\delta$ : 7.71-7.68 (d,  $J=9.0\text{Hz}$ , 2H, Ar-H), 7.43-7.40 (d,  $J=9.0\text{Hz}$ , 2H, Ar-H), 7.31-7.12 (m, 5H, Ar-H), 4.70 (brs, 1H, -CHPh), 4.46-4.40 (d,  $J=18.0\text{Hz}$ , 1H), 3.90 (m, 1H), 3.70 (m, 2H), 3.68 (m, 2H), 3.56-3.52 (m, 2H), 3.40-3.37 (d,  $J=9.0\text{Hz}$ , 1H), 3.13 (brs, 1H), 3.08 (brs, 1H), 2.57 (s, 2H), 2.08 (s, 2H, -CH<sub>3</sub>), 1.8-1.56 (m, 3H) and 1.43-1.22 (m, 10H).

Mass (positive ion mode)  $m/z$ : 474  $[M^+ + 1]$ .

IR (DCM): 3423, 2918, 2362, 1649, 1649, 1219, 1029 and 772  $\text{cm}^{-1}$

3-[4-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid phenylamide (Compound No. 76)

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300MHz)  $\delta$ : 8.61 (s, 1H, -NH), 7.69-7.66 (d,  $J=9.0\text{Hz}$ , 2H, Ar-H), 7.59-7.56 (d,  $J=9.0\text{Hz}$ , 2H, Ar-H), 7.36-7.11 (m, 8H, Ar-H), 4.66 (brs, 1H, -CHPh), 3.97-3.92 (d,  $J=15.0\text{Hz}$ , 1H, -CH), 3.6 (brs, 1H, -CHPh), 3.34-3.28 (d,  $J=18.0\text{Hz}$ , 1H, -CH), 2.90 (brs, 1H, -CH), 2.7 (brs, 1H, -CH), 2.57 (s, 2H), 1.82-1.77 (brs, 3H), 1.72-1.70 (brs, 2H) and 1.33-1.18 (m, 3H).

Mass (positive ion mode)  $m/z$ : 482  $[M^+ + 1]$ .

## 20 Scheme III:

Example 5: Synthesis of (4-benzylpiperidin-1-yl)-[4-(5-methoxymethyl-5-methyl-4,5-dihydroisoxazol-3-yl)phenyl]methanone (Compound No. 27)

To the solution of compound No. 24 (0.10 g, 0.25 mmol) in dry tetrahydrofuran (5.0 ml) at  $-15^\circ\text{C}$  under nitrogen atmosphere, was added sodium hydride (0.025 g, 0.50 mmol) and the reaction mixture was stirred at the same temperature for 3 hours. To the reaction mixture was added methyl iodide (0.072 g, 0.50 mmol) and reaction mixture was stirred at the same temperature for 30 minutes and then allowed to warm to room temp and stirred overnight. Excess of sodium hydride was decomposed carefully with chilled water and the reaction mixture was collected in ethyl acetate and extracted with water. The

organic layer was collected and dried over anhydrous sodium sulphate and concentrated under reduced pressure. The residue thus obtained was purified by column chromatography using 15% ethyl acetate in hexane as eluent to furnish the title compound (0.085 g).

- 5 <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300MHz) δ: 7.61-7.58 (d, 2H, *J*=8.1Hz, Ar-H), 7.34-7.31 (d, 2H, *J*=8.4Hz, Ar-H), 7.23-7.04 (m, 5H, Ar-H), 4.52-4.50 (m, 1H), 3.60-3.56 (m, 1H), 3.43-3.37 (m, 2H), 3.34-3.32 (brs, 3H, -OCH<sub>3</sub>), 2.92-2.86 (m, 2H), 2.62-2.60 (brm, 2H), 2.50-2.48 (m, 2H), 1.72-1.70 (brm, 2H), 1.54 (s, 4H) and 1.29-1.17 (m, 3H).

- Analogue of (4-benzylpiperidin-1-yl)-[4-(5-methoxymethyl-5-methyl-4,5-dihydroisoxazol-3-yl)phenyl]methanone (Compound No. 27) described below, can be prepared by replacing appropriate alkyl halide group in place of methyl iodide, respectively, as applicable in each case.

(4-Benzylpiperidin-1-yl)-[4-(5-benzylloxymethyl-5-methyl-4,5-dihydroisoxazol-3-yl)phenyl]methanone (Compound No. 28)

- 15 <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300MHz) δ: 7.61-7.59 (d, 2H, *J*=6.0Hz, Ar-H), 7.35-7.32 (d, 2H, *J*=9.0Hz, Ar-H), 7.28-7.05 (m, 13H, Ar-H), 4.59-4.49 (m, 3H), 3.59-3.54 (brm, 1H), 3.52-3.43 (m, 2H), 3.40-3.35 d, 1H, *J*=15.0Hz), 2.94-2.88 (d, 2H, *J*=18.0Hz), 2.73-2.71 (m, 2H), 2.51-2.49 (brm, 2H), 1.72-1.71 (brm, 2H), 1.18 (s, 3H, -CH<sub>3</sub>) and 1.09 (brs, 5H).

#### Scheme IV:

- 20 Example 6: Synthesis of 3-[4-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid benzyl-ethyl-amide (Compound No. 47)

- <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300MHz) δ: 7.72-7.70 (d, 3H, *J*=6.0Hz, Ar-H), 7.44-7.12 (m, 11H, Ar-H), 4.96-4.91 (d, 1H, *J*=15.0Hz, -CH<sub>2</sub>Ph), 4.72-4.67 (d, 1H, *J*=15.0Hz, -CH<sub>2</sub>Ph), 4.51-4.40 (d, 1H, *J*=18.0Hz, -CH<sub>2</sub>Ph), 4.30-4.25 (d, 1H, *J*=15.0Hz), 3.7 (m, 1H, -CH<sub>2</sub>Ph), 3.48 (m, 25 2H, -CH<sub>2</sub>N), 3.37-3.28 (m, 1H), 3.21-3.20 (m, 1H), 2.94 (m, 1H), 2.70 (m, 1H), 2.58-2.57 (brs, 2H), 1.77-1.67 (m, 5H), 1.32-1.25 (m, 3H) and 1.09-1.04 (m, 3H).

Mass (positive ion mode) *m/z*: 524 [M<sup>+</sup>+1].

Following compounds were prepared similarly,

- 3-[4-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid ethyl-methyl-amide (Compound No. 48)
- 30

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300MHz) δ: 7.74-7.71 (d, 2H, *J*=9.0Hz Ar-H), 7.46-7.44 (d, 2H, *J*=6.0Hz, Ar-H), 7.34-7.16 (m, 5H, Ar-H), 4.70 (m, 1H, -CH<sub>2</sub>Ph), 4.44-4.38 (d, 1H, *J*=18.0Hz), 3.67 (m, 1H), 3.52-3.42 (m, 2H), 3.30 (s, 1H), 3.19-3.13 (d, 1H, *J*=18.0Hz), 2.97 (s, 3H, -NCH<sub>3</sub>), 2.52-2.50 (m, 1H), 2.62-2.60 (brs, 2H), 1.83-1.73 (m, 5H), 1.19-1.14 (m, 3H) and 0.91-0.88 (m, 3H).

Mass (positive ion mode) *m/z*: 448 [M<sup>+</sup>+1].

3-[4-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid cyclopropyl-ethyl-amide (Compound No. 49)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300MHz) δ: 7.70-7.68 (d, 2H, *J*=6.0Hz, Ar-H), 7.43-7.40 (d, 2H, *J*=9.0Hz, Ar-H), 7.31-7.12 (m, 5H, Ar-H), 4.68 (m, 1H, -CH<sub>2</sub>Ph), 4.45 (m, 1H), 3.66 (m, 1H, -CH<sub>2</sub>Ph & 2H, -NCH<sub>2</sub>), 3.15-3.09 (m, 1H), 2.90 (m, 1H), 2.7 (m, 1H), 2.56 (brs, 2H), 1.77-1.56 (m, 5H), 1.32-1.25 (m, 6H), 0.88-0.85 (m, 2H) and 0.60 (m, 2H).

Mass (positive ion mode) *m/z*: 474 [M<sup>+</sup>+1].

3-[4-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid cyclopropyl-methyl-amide (Compound No. 50)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300MHz) δ: 7.70-7.67 (d, 2H, *J*=9.0Hz, Ar-H), 7.43-7.40 (d, 2H, *J*=9.0Hz, Ar-H), 7.31-7.12 (m, 5H, Ar-H), 4.70 (m, 1H, -CH<sub>2</sub>Ph), 4.28 (m, 1H), 3.70 (m, 1H, -CH<sub>2</sub>Ph), 3.19-3.13 (m, 3H), 2.93 (m, 1H), 2.74 (m, 1H), 2.58-2.57 (brs, 2H), 1.79-1.60 (m, 5H), 1.33-1.26 (m, 3H), 0.88-0.80 (m, 2H) and 0.64 (m, 2H).

Mass (positive ion mode) *m/z*: 460 [M<sup>+</sup>+1].

3-[4-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid benzyl-cyclopropyl-amide (Compound No. 51)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300MHz) δ: 7.70-7.68 (d, 2H, *J*=6.0Hz, Ar-H), 7.44-7.41 (d, 2H, *J*=9.0Hz, Ar-H), 7.35-7.12 (m, 10H, Ar-H), 4.89-4.70 (m, 3H), 4.30 (m, 1H), 3.67 (m, 1H), 3.22-3.17 (m, 1H), 2.94 (m, 1H), 2.72 (m, 1H), 2.56 (brs, 2H), 2.08-1.42 (m, 5H), 1.32-1.25 (m, 3H), 0.98 (m, 3H) and 0.87-0.74 (m, 4H).

Mass (positive ion mode) *m/z*: 556 [M<sup>+</sup>+1].

3-[4-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid ethyl-propyl-amide (Compound No. 52)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300MHz) δ: 7.71-7.68 (d, 2H, *J*=9.0Hz, Ar-H), 7.43-7.40 (d, 2H, *J*=9.0Hz, Ar-H), 7.31-7.12 (m, 5H, Ar-H), 4.70 (m, 1H, -CH<sub>2</sub>Ph), 4.40-4.34 (d, 1H, *J*=18.0Hz), 3.70-3.60 (m, 1H, -CH<sub>2</sub>Ph), 3.45-3.35 (m, 2H), 3.30 (m, 1H), 3.23-3.16 (m, 1H), 2.90 (m, 1H), 2.73 (m, 1H), 2.58-2.56 (brs, 2H), 1.78-1.70 (m, 5H), 1.32-1.25 (m, 3H), 1.16-1.14 (m, 3H) and 0.96-0.88 (m, 5H).

Mass (positive ion mode) *m/z*: 476 [M<sup>+</sup>+1].

10 3-[3-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-2,5-dihydro-isoxazole-5-carboxylic acid benzyl-methyl-amide (Compound No. 60)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300MHz) δ: 7.62 (s, 2H, Ar-H), 7.42-7.13 (m, 12H, Ar-H), 4.78-4.70 (m, 1H), 4.50-4.40 (m, 2H), 3.68 (brs, 1H), 3.15 (s, 3H), 2.95-2.73 (m, 4H), 2.58-2.57 (m, 2H), 1.75-1.74 (m, 5H) and 1.42-1.41 (m, 3H).

Mass (positive ion mode) *m/z*: 510 [M<sup>+</sup>+1].

15 3-[3-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid cyclopropyl-methyl-amide (Compound No. 62)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300MHz) δ: 7.71-7.67 (m, 2H, Ar-H), 7.52 (s, 2H, Ar-H), 7.20-7.13 (m, 5H, Ar-H), 4.40 (brs, 1H), 4.23-4.20 (m, 2H), 3.60 (brs, 1H), 3.19-3.13 (m, 3H), 2.96-2.87 (m, 2H), 2.70-2.60 (m, 1H), 2.59-2.57 (m, 2H), 1.72-1.56 (m, 5H), 0.95-0.92 (m, 5H) and 0.60 (m, 2H).

Mass (positive ion mode) *m/z*: 460 [M<sup>+</sup>+1].

3-[3-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid ethyl-methyl-amide (Compound No. 63)

25 <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300MHz) δ: 7.67 (s, 2H, Ar-H), 7.41 (s, 2H, Ar-H), 7.22-7.19 (m, 3H, Ar-H), 7.15-7.13 (m, 2H, Ar-H), 4.40 (brs, 1H), 4.35-4.34 (d, 1H, *J*=3.0Hz), 3.60 (brs, 1H), 3.48-3.41 (m, 2H), 3.26-3.16 (m, 1H), 2.90 (s, 3H), 2.58-2.56 (m, 2H), 2.40 (brs, 1H), 2.30-2.20 (m, 1H), 1.80-1.71 (m, 5H), 1.33-1.28 (m, 3H) and 1.6-1.11 (m, 3H).

Mass (positive ion mode) *m/z*: 448 [M<sup>+</sup>+1].

**Cell based Assay for TNF- $\alpha$  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<sup>-6</sup>-0.41 $\mu$ 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 was then removed and tested by ELISA for TNF- $\alpha$  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 results of in-vitro tests are listed in Table-II

| Compound No. | IC50 (micromolar) | Compound No. | IC50 (micromolar) |
|--------------|-------------------|--------------|-------------------|
| 1.           | 2.95              | 9.           | >100              |
| 2.           | >100              | 10.          | >100              |
| 3.           | 3                 | 11.          | >100              |
| 4.           | 1.8               | 12.          | 24                |
| 5.           | 2.3               | 13.          | >100              |
| 6.           | >100              | 14.          | >100              |
| 7.           | >100              | 15.          | >100              |
| 8.           | >100              | 16.          | 1                 |
| 17.          | 1.58              | 18.          | 100               |
| 19.          | 100               | 20.          | 39.81             |
| 21.          | >100              | 22.          | 15.84             |
| 23.          | >100              | 24.          | >100              |
| 25.          | ~100              | 26.          | 25.11             |
| 27.          | >100              | 28.          | 57.23             |

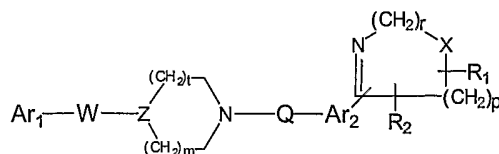
| Compound No. | IC50 (micromolar) | Compound No. | IC50 (micromolar) |
|--------------|-------------------|--------------|-------------------|
| 29.          | >100              | 30.          | >100              |
| 31.          | 100               | 32.          | 10                |
| 33.          | 0.691             | 34.          | 1.7               |
| 35.          | 1.12              | 36.          | 3.97              |
| 37.          | 4.09              | 38.          | 0.577             |
| 39.          | 3.23              | 40.          | 10                |
| 41.          | 39.81             | 42.          | 5.01              |
| 43.          | >100              | 44.          | 31.62             |
| 45.          | >100              | 46.          | >100              |
| 47.          | 1.125             | 48.          | 1.995             |
| 49.          | 0.964             | 50.          | 1.206             |
| 51.          | ~10               | 52.          | >100              |
| 53.          | 1.258             | 54.          | 10                |
| 55.          | >100              | 56.          | >100              |
| 57.          | >100              | 58.          | >100              |
| 59.          | >100              | 60.          | 17.78             |
| 61.          | 1                 | 62.          | 2.37              |

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| Compound No. | IC50 (micromolar) | Compound No. | IC50 (micromolar) |
|--------------|-------------------|--------------|-------------------|
| 63.          | 8.9               | 64.          | >100              |
| 65.          | 1                 | 66.          | 0.657             |
| 67.          | 0.566             | 68.          | 0.562             |
| 69.          | 2.51              | 70.          | 1.25              |
| 71.          | 1.77              | 72.          | 1.58              |

We Claim:

1. A compound having the structure of Formula Ia



Formula Ia

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

X can be oxygen, sulphur, or -NR (wherein R can be alkyl, or aryl).

Each of r and p represents an integer from 0-4, with the proviso that both r and p cannot be zero at the same time.

Q can be alkylene, alkenylene, alkynylene, or -C(=T) (wherein T can be oxygen, sulphur, -N(CN), -N(NO<sub>2</sub>), or -CH(NO<sub>2</sub>)) (wherein double bond of said alkenylene or triple bond of said alkynylene cannot be attached directly to N atom).

Z can be nitrogen, or -CH.

W can be alkylene, alkenylene, or alkynylene (wherein when Z is nitrogen double bond of said alkenylene or triple bond of said alkynylene cannot be attached directly to Z atom).

The subscript m is an integer from 0-3, and the subscript t is an integer from 0-4.

R<sub>1</sub> and R<sub>2</sub> can independently be hydrogen, cyano, alkyl, alkenyl, alkynyl, hydroxyalkyl, alkoxy, aryloxy, cycloalkyl, aryl, aralkyl, carboxy, -COOR<sub>3</sub> (wherein R<sub>3</sub> can be alkyl, alkenyl, alkynyl, aryl, aralkyl, cycloalkyl, heterocyclyl, heteroaryl, heterocyclylalkyl or heteroarylalkyl), -NR<sub>p</sub>R<sub>q</sub> (wherein R<sub>p</sub> and R<sub>q</sub> can independently be hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl or heterocyclylalkyl, or R<sub>p</sub> and R<sub>q</sub> may also together join to form a heterocyclic ring), -OC(=O)NR<sub>x</sub>R<sub>y</sub> [wherein R<sub>x</sub> and R<sub>y</sub> can independently be hydrogen, hydroxy (excepting that both R<sub>x</sub> and R<sub>y</sub> cannot be -OH at the same time), alkyl, cycloalkyl, alkoxy, hydroxyalkyl, aryloxy, aralkyloxy, aryl, aralkyl, or -SO<sub>2</sub>R<sub>4</sub> (wherein R<sub>4</sub> can be alkyl, alkenyl, alkynyl,

26 cycloalkyl,  $-NR_pR_q$  wherein  $R_p$  and  $R_q$  as defined above, aryl, aralkyl, heteroaryl,  
 27 heterocyclyl, heterocyclalkyl, or heteroarylalkyl), or  $R_x$  and  $R_y$  may also together  
 28 join to form a heterocyclyl or heteroaryl ring],  $-NR_J(C=O)OR_s$  (wherein  $R_s$  can be  
 29 alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heterocyclalkyl, or  
 30 heteroarylalkyl, and wherein  $R_J$  can be hydrogen, lower ( $C_1-C_6$ ) alkyl, lower ( $C_3-$   
 31  $C_6$ ) cycloalkyl, lower ( $C_1-C_3$ ) aralkyl, aryl, heteroaryl, heteroarylalkyl, or  
 32 heterocyclalkyl),  $NR_JYR_U$  (wherein  $Y$  can be  $-C(=O)$ ,  $-C(=S)$  or  $-SO_2$ ,  $R_J$  is as  
 33 defined above, and  $R_U$  can be alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl,  
 34 heteroaryl, heterocyclyl, or heterocyclalkyl),  $-NR_J(=T)NR_xR_y$  (wherein  $R_J$ ,  $T$ ,  $R_x$   
 35 and  $R_y$  are as defined above),  $-C(=K)NR_xR_y$  (wherein  $K$  is O or S),  $-CH_2OR_s$   
 36 (wherein  $R_s$  is the same as defined above), heteroaryl, heterocyclyl, heteroarylalkyl  
 37 or heterocyclalkyl.

38 'Ar<sub>1</sub> and Ar<sub>2</sub> can independently be aryl, heteroaryl, or heterocyclyl.

1 2. The compound of claim 1, wherein Ar<sub>1</sub> is phenyl, W is methylene, Z is  $-CH-$ , t and  
 2 m are 1, Q is carbonyl, Ar<sub>2</sub> is 1,2-, 1,3-, or 1,4-disubstituted phenyl, r is 0, p is 1,  
 3 and X is oxygen.

1 3. The compound of claim 2, wherein R<sub>1</sub> is alkyl.

1 4. The compound of claim 3, wherein R<sub>1</sub> is methyl and R<sub>2</sub> is COOR<sub>3</sub> or  $C(=K)NR_xR_y$ .

1 5. The compound of claim 1, wherein Ar<sub>2</sub> is trisubstituted phenyl.

1 6. The compound of claim 5, wherein Ar<sub>2</sub> is substituted with alkoxy.

1 7. A compound selected from

2 3-[4-(4-Benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-  
 3 carboxylic acid methyl ester (Compound No. 1),

4  
 5 3-[4-(4-benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-  
 6 carboxylic acid,

7  
 8 3-[4-(4-Benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-  
 9 carboxylic acid amide (Compound No. 3),

10  
 11 3-[4-(4-Benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-  
 12 carboxylic acid methylamide (Compound No. 4),

13  
 14 3-[3-(4-Benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-  
 15 carboxylic acid methylamide (Compound No. 5),

3-[3-(4-Benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid methyl ester (Compound No. 6),

3-[3-(4-Benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid (Compound No. 7),

3-[3-(4-Benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid amide (Compound No. 8),

3-[3-(4-Benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid cyclopropylamide (Compound No. 9),

3-[3-(4-Benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid propylamide (Compound No. 10),

3-[3-(4-Benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid cyclohexylamide (Compound No. 11),

3-[3-(4-Benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid (2-hydroxy-ethyl)amide (Compound No. 12),

3-[3-(4-Benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid benzylamide (Compound No. 13),

3-[3-(4-Benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid isopropylamide (Compound No. 14),

3-[3-(4-Benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid ethylamide (Compound No. 15),

3-[3-(4-Benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-yl}pyrrolidin-1-ylmethanone (Compound No. 16),

3-[4-(4-Benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid hydroxyamide (Compound No. 17),

3-[4-(4-Benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid (2-methylene-pent-3-enyloxy)amide (Compound No. 18),

3-[4-(4-Benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid methoxyamide (Compound No. 19),

3-[4-(4-Benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid dimethylamide (Compound No. 20),

3-[4-(4-Benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid diisopropylamide (Compound No. 21),

- 3-[4-(4-Benzyl-piperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid butylamide (Compound No. 22),
- (4-Benzylpiperidin-1-yl)-[4-(5-hydroxymethyl-4,5-dihydroisoxazole-3-yl)phenyl]methanone (Compound No. 23),
- (4-Benzylpiperidin-1-yl)-[4-(5-hydroxymethyl-5-methyl-4,5-dihydroisoxazol-3-yl)phenyl]methanone (Compound No. 24),
- 3-[4-(4-Benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid tert-butyl amide (Compound No. 25),
- 3-[4-(4-Benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid prop-2-ynylamide (Compound No. 26),
- (4-benzylpiperidin-1-yl)-[4-(5-methoxymethyl-5-methyl-4,5-dihydroisoxazol-3-yl)phenyl]methanone (Compound No. 27),
- [4-(5-Benzylloxymethyl-5-methyl-4,5-dihydroisoxazol-3-yl)phenyl]-(4-benzylpiperidin-1-yl)methanone (Compound No. 28),
- 3-{2-[(4-Benzylpiperidin-1-yl)carbonyl]phenyl}-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid (Compound No. 29),
- 3-[2-(4-Benzylpiperidine-1-carbonyl)phenyl]-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid methyl ester (Compound No. 30)
- 3-[2-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid methylamide (Compound No. 31),
- 3-[4-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid isopropylamide (Compound No. 32),
- 3-[4-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid cyclopropylamide (Compound No. 33),
- 3-[4-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid benzylamide (Compound No. 34),
- 3-[4-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid (2-hydroxy-ethyl)-amide (Compound No. 35),
- (4-Benzyl-piperidin-1-yl)-{4-[5-methyl-5-(pyrrolidine-1-carbonyl)-4,5-dihydro-isoxazol-3-yl]-phenyl}-methanone (Compound No. 36),
- 3-[4-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid cyclohexylamide (Compound No. 37),
- 3-[4-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid ethylamide (Compound No. 38),

- 114 3-[4-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-  
115 carboxylic acid propylamide (Compound No. 39),  
116  
117 (4-Benzyl-piperidin-1-yl)-{4-[5-methyl-5-(morpholine-4-carbonyl)-4,5-dihydro-  
118 isoxazol-3-yl]-phenyl}-methanone (Compound No. 40),  
119  
120 3-[4-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-  
121 carboxylic acid diethylamide (Compound No. 41),  
122  
123 3-[4-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-  
124 carboxylic acid cyclopentylamide (Compound No. 42),  
125  
126 4-{4-[(4-Benzylpiperidin-1-yl)carbonyl]phenyl}-5-methyl-4,5-dihydroisoxazole-5-  
127 carbonitrile (compound No. 43),  
128  
129 Ethyl 4-{4-[(4-benzylpiperidin-1-yl)carbonyl]phenyl}-4,5-dihydroisoxazole-5-  
130 carboxylate (Compound No. 44)  
131  
132 3-[4-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-  
133 carboxylic acid (3-methyl-butyl)-amide (Compound No. 45),  
134  
135 3-[4-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-  
136 carboxylic acid allylamide (Compound No. 46),  
137  
138 3-[4-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-  
139 carboxylic acid benzyl-ethyl-amide (Compound No. 47),  
140  
141 3-[4-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-  
142 carboxylic acid ethyl-methyl-amide (Compound No. 48),  
143  
144 3-[4-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-  
145 carboxylic acid cyclopropyl-ethyl-amide (Compound No. 49),  
146  
147 3-[4-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-  
148 carboxylic acid cyclopropyl-methyl-amide (Compound No. 50),  
149  
150 3-[4-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-  
151 carboxylic acid benzyl-cyclopropyl-amide (Compound No. 51),  
152  
153 3-[4-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-  
154 carboxylic acid ethyl-propyl-amide (Compound No. 52),  
155  
156 (4-Benzyl-piperidin-1-yl)-{4-[5-(2-hydroxymethyl-pyrrolidine-1-carbonyl)-5-  
157 methyl-4,5-dihydro-isoxazol-3-yl]-phenyl}-methanone (Compound No. 53),  
158  
159 1-{3-[4-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-  
160 isoxazole-5-carbonyl}-pyrrolidine-2-carboxylic acid methyl ester (Compound No.  
161 54),  
162

- 163 (4-Benzyl-piperidin-1-yl)-{2-[5-methyl-5-(pyrrolidine-1-carbonyl)-4,5-dihydro-  
164 isoxazol-3-yl]-phenyl}-methanone (Compound No. 55),  
165  
166 3-[2-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-  
167 carboxylic acid propylamide (Compound No. 56),  
168  
169 3-[2-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-  
170 carboxylic acid (2-hydroxy-ethyl)-amide (Compound No. 57),  
171  
172 3-[2-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-  
173 carboxylic acid ethylamide (Compound No. 58),  
174  
175 3-[2-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-  
176 carboxylic acid cyclopropylamide (Compound No. 59),  
177  
178 3-[3-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-2,5-dihydro-isoxazole-5-  
179 carboxylic acid benzyl-methyl-amide (Compound No. 60),  
180  
181 (4-Benzyl-piperidin-1-yl)-{3-[5-(2-hydroxymethyl-pyrrolidine-1-carbonyl)-5-  
182 methyl-4,5-dihydro-isoxazol-3-yl]-phenyl}-methanone (Compound No. 61),  
183  
184 3-[3-(4-Benzyl-piperidine-1-carbonyl)-phenyl]-5-methyl-4,5-dihydro-isoxazole-5-  
185 carboxylic acid ethyl-methyl-amide (Compound No. 63),  
186  
187 3-[3-(4-Benzyl-piperidine-1-carbonyl)-2-methoxy-phenyl]-5-methyl-4,5-dihydro-  
188 isoxazole-5-carboxylic acid cyclopropylamide (Compound No. 64),  
189  
190 Methyl 3-{3-[(4-benzylpiperidin-1-yl)carbonyl]-4-methoxyphenyl}-5-methyl-4,5-  
191 dihydroisoxazole-5-carboxylate (Compound No. 65),  
192  
193 (4-Benzyl-piperidin-1-yl)-{2-methoxy-5-[5-methyl-5-(pyrrolidine-1-carbonyl)-4,5-  
194 dihydro-isoxazol-3-yl]-phenyl}-methanone (Compound No. 66),  
195  
196 (4-Benzyl-piperidin-1-yl)-{5-[5-(2-hydroxymethyl-pyrrolidine-1-carbonyl)-5-  
197 methyl-4,5-dihydro-isoxazol-3-yl]-2-methoxy-phenyl}-methanone (Compound  
198 No. 67),  
199  
200 [4-(4-Fluoro-benzyl)-piperidin-1-yl]-{5-[5-(2-hydroxymethyl-pyrrolidine-1-  
201 carbonyl)-5-methyl-4,5-dihydro-isoxazol-3-yl]-2-methoxy-phenyl}-methanone  
202 (Compound No. 68),  
203  
204 3-{3-[4-(4-Fluoro-benzyl)-piperidine-1-carbonyl]-4-methoxy-phenyl}-5-methyl-  
205 4,5-dihydro-isoxazole-5-carboxylic acid methylamide (Compound No. 69),  
206  
207 Methyl 3-(3-{[4-(4-fluorobenzyl)piperidin-1-yl]carbonyl}-4-methoxyphenyl)-5-  
208 methyl-4,5-dihydroisoxazole-5-carboxylate (Compound No. 70),  
209  
210 4-{3-[4-(4-Fluoro-benzyl)-piperidine-1-carbonyl]-4-methoxy-phenyl}-5-methyl-  
211 4,5-dihydro-isoxazole-5-carboxylic acid amide (Compound No. 71),

212 4-{3-[4-(4-Fluoro-benzyl)-piperidine-1-carbonyl]-4-methoxy-phenyl}-5-methyl-  
213 4,5-dihydro-isoxazole-5-carboxylic acid ethylamide (Compound No. 72).

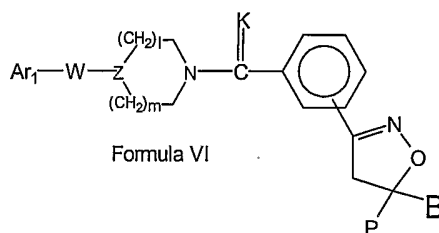
1 8. A method of treating a mammal suffering from inflammation or associated  
2 pathologies, the method comprising administration to the mammal a  
3 therapeutically effective amount of a compound of claim 1, or a pharmaceutically  
4 acceptable salt thereof.

1 9. The method of claim 8, further comprising administration of the compound of  
2 claim 1 or a pharmaceutically acceptable salt thereof in a pharmaceutical  
3 composition, comprising a pharmaceutically acceptable carrier.

1 10. A method of treating mammals suffering from inflammatory diseases and  
2 associated pathologies selected from sepsis, rheumatoid arthritis, inflammatory  
3 bowel disease, type-1 diabetes, asthma, chronic obstructive pulmonary disorder,  
4 organ transplant rejection and psoriasis, the method comprising administration to  
5 the mammal a therapeutically effective amount of a compound of claim 1, or a  
6 pharmaceutically acceptable salt thereof.

1 11. The method of claim 10, further comprising administration of the compound of  
2 claim 1 or a pharmaceutically acceptable salt thereof in a pharmaceutical  
3 composition, comprising a pharmaceutically acceptable carrier.

1 12. A method of preparing a compound of Formula VI,



6 wherein

7 Z is nitrogen, or -CH;

8 W is alkylene, alkenylene, or alkynylene;

9 the subscript m is an integer from 0-3, and the subscript l is an integer from 0-2;

10 Ar<sub>1</sub> is aryl, heteroaryl, or heterocyclyl;

11 K is O or S;

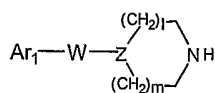
- 64 -

B is hydrogen or alkyl; and

P is  $-\text{COOR}_3$  (wherein  $\text{R}_3$  is alkyl, alkenyl, alkynyl, aryl, aralkyl, cycloalkyl, heterocyclyl, or heteroaryl) or  $\text{CH}_2\text{OH}$ ,

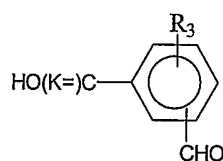
the method comprising:

a) reacting a compound of Formula I



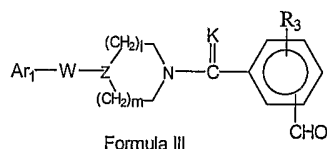
Formula I

(where  $\text{Ar}_1$ , W, Z, l and m are as defined) with a compound of Formula II  
(where K is as defined)



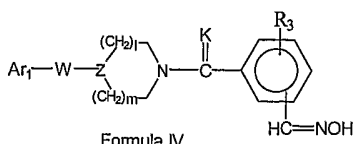
Formula II

to produce a compound of Formula III;



Formula III

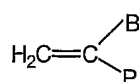
b) reacting the compound of Formula III with hydroxylamine hydrochloride to  
produce a compound of Formula IV;



Formula IV

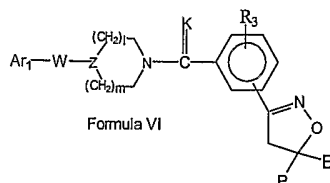
c) reacting the compound of Formula IV with a compound of Formula V  
(where B and P  
are the same as defined earlier)

- 65 -

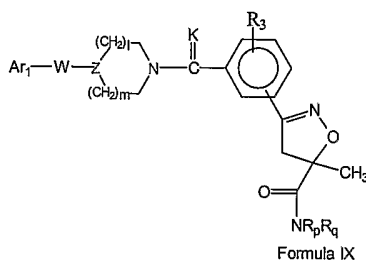


Formula V

to produce a compound of Formula VI.



13. A method of producing a compound of Formula IX



wherein

Z is nitrogen or -CH;

W is alkylene, alkenylene, or alkynylene;

the subscript m is an integer from 0-3, and the subscript l is an integer from 0-2;

Ar<sub>1</sub> is aryl, heteroaryl, or heterocyclyl;

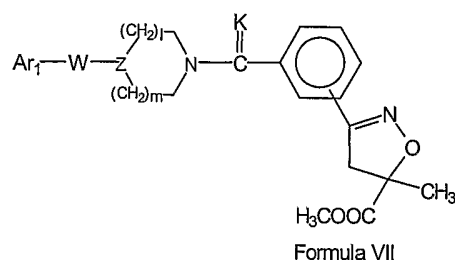
K is O or S;

R<sub>p</sub> and R<sub>q</sub> are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, heterocyclyl, or heterocyclylalkyl, or R<sub>p</sub> and R<sub>q</sub> may also

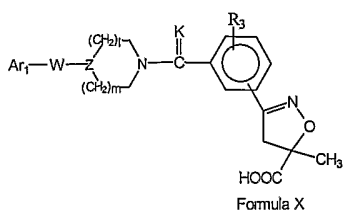
together join to form a heterocyclic ring;

the method comprising:

reacting a compound of Formula VII with a compound of Formula VIII ( $\text{NHR}_p\text{R}_q$ , wherein  $\text{R}_p$  and  $\text{R}_q$  are as defined) to produce the compound of Formula IX.



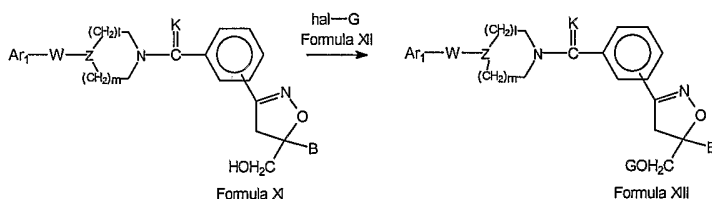
14. A method of producing a compound of Formula IX
- wherein Z is nitrogen or -CH;
- W is alkylene, alkenylene, or alkynylene;
- the subscript m is an integer from 0-3, and the subscript l is an integer from 0-2;
- Ar<sub>1</sub> is aryl, heteroaryl, or heterocyclyl;
- K is O or S;
- R<sub>p</sub> and R<sub>q</sub> are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, heterocyclyl, or heterocyclylalkyl, or R<sub>p</sub> and R<sub>q</sub> may also together join to form a heterocyclic ring;
- the method comprising:
- a) hydrolyzing a compound of Formula VII to give a compound of Formula X; and



b) reacting the compound of Formula X with a compound of Formula VIII (NHR<sub>p</sub>R<sub>q</sub>, wherein R<sub>p</sub> and R<sub>q</sub> are as defined) to produce the compound of Formula IX.

15. A method of making a compound of Formula XIII

Scheme III



wherein

Z is nitrogen or -CH;

W is alkylene, alkenylene, or alkynylene;

the subscript m is an integer from 0-3, and the subscript l is an integer from 0-2;

Ar<sub>1</sub> is aryl, heteroaryl, or heterocyclyl;

K is O or S;

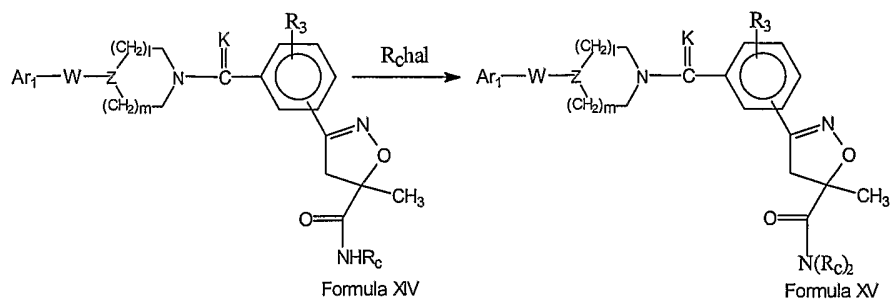
B is hydrogen or alkyl; and

G is alkyl or aralkyl,

the method comprising reacting a compound of Formula XI with a compound of Formula XII (hal-G, wherein hal is a halogen and G is as defined) to produce the compound of Formula XIII.

- 1 16. A method of making a compound of Formula XV

Scheme IV



2  
3 wherein

4 Z is nitrogen or -CH;

5 W is alkylene, alkenylene, or alkynylene;

6 the subscript m is an integer from 0-3, and the subscript l is an integer from 0-2;

7 Ar<sub>1</sub> is aryl, heteroaryl, or heterocyclyl;

8 K is O or S;

9 R<sub>c</sub> is alkyl, aryl, cycloalkyl, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl or  
10 heterocyclylalkyl;

11 hal is Cl, Br or I;

12 the method comprising reacting a compound of Formula XIV with a compound of  
13 Formula R<sub>c</sub>-hal to produce a compound of Formula XV.