Title: SH3 PROTEIN DOMAINS AND THEIR LIGANDS

Abstract: The present invention relates generally to molecules capable of interaction with one or more domains within a proteinaceous molecule such as a peptide, polypeptide, protein or a macromolecule comprising a proteinaceous molecule. More particularly, the present invention relates to molecules including ligands which are capable of interacting with, and more particularly, binding to, SH3 protein domains or homologs thereof and even more particularly to molecules including ligands which are capable of binding to SH3 domains having a three-dimensional ligand-binding site comprising a negatively charged residue and a hydrophobic residue linearly separated by at least five amino acid residues. The subject invention is preferably directed to the use of 2-aminopyrididine, 2-aminquinoline, 1-aminooquinoline und derivatives, homologs, analogs and mimetics thereof or pharmaceutically acceptable salts thereof which interact with SH3 domains, and more particularly to the binding of 2-aminopyrididine, 2-aminquinoline, 1-aminooquinoline and derivatives analogs and mimetics to SH3 domains as defined above. The present invention contemplates the use of a three dimensional structure of the subject SH3 domain to identify, screen and design amino-substituted and amino-substituted pyridines and aminooquinolines capable of binding to an SH3 domain. The present invention is also useful for the in silico selection of derivatives homologs, analogs and mimetics of 2-aminopyrididine, 2-aminquinoline, 1-aminooquinoline capable of binding to SH3 domains. The ligands of the present invention are useful in the development of a range of therapeutic and diagnostic agents.
FIELD OF THE INVENTION

The present invention relates generally to molecules capable of interaction with one or more domains within a proteinaceous molecule such as a peptide, polypeptide, protein or a macromolecule comprising a proteinaceous molecule. More particularly the present invention relates to molecules including ligands which are capable of interacting with, and more particularly, binding to, SH3 protein domains or homologs thereof and even more particularly to molecules including ligands which are capable of binding to SH3 domains having a three-dimensional ligand-binding site comprising a negatively charged residue and a hydrophobic residue linearly separated by at least five amino acid residues. The subject invention is preferably directed to the use of 2-aminopyridine, 2-aminoquinoline, 1-aminoisoquinoline and derivatives, homologs, analogs and mimetics thereof or pharmaceutically acceptable salts thereof which interact with SH3 domains, and more particularly to the binding of 2-aminopyridine, 2-aminoquinoline, 1-aminoisoquinoline and derivatives analogs and mimetics to SH3 domains as defined above. The present invention contemplates the use of a three dimensional structure of the subject SH3 domain to identify, screen and design amino-substituted and amino-substituted pyridines and aminquinolines capable of binding to an SH3 domain. The present invention is also useful for the in silico selection of derivatives homologs, analogs and mimetics of 2-aminopyridine, 2-aminoquinoline, 1-aminoisoquinoline capable of binding to SH3 domains. The ligands of the present invention are useful in the development of a range of therapeutic and diagnostic agents.

BACKGROUND OF THE INVENTION

Bibliographic details of references provided in the subject specification are listed at the end of the specification.
Reference to any prior art in this specification is not and should not be taken as an acknowledgment or any form of suggestion that this prior art forms part of the general knowledge or any country.

SH3 domains are present on many functionally diverse proteins that are involved in the response of cells to external stimuli (Musacchio et al., Mol. Cell Biol. 14: 5495, 1994; Kuriyan and Cowburn, Curr. Op. Struct. Biol. 3: 828-837, 1993). There are many known versions of this sequence motif in human proteins. While it is likely that each of these will have a specific binding partner, the mechanism of binding of protein ligands is essentially mediated by interaction with the conserved ligand-binding surface present on the SH3 domain. The ability of the SH3 domains to bind to short, specific, linear, proline-rich sequences (Cicchetti et al., Science 257: 803, 1992) within their binding partners has important functional consequences. SH3 domains may control the cellular localization of their binding partners (Bar-Sagi et al., Cell 74: 83-91, 1993; Rotin et al., EMBO J. 13: 4440, 1994) determine the substrate specificity of enzymes (Feller et al., EMBO J. 13: 2341-2351, 1994) or modulate the catalytic activity of SH3-containing (Liu et al., Mol. Cell Biol. 13: 5225, 1993; Mayer and Baltimore, Mol. Cell Biol. 14: 2883, 1994), as well as SH3-binding proteins (Pleiman et al., Science 263: 1609, 1994). SH3 domains are abundant within a range of proteins including signaling proteins and, hence, have the potential to be biologically important to physiological or pathological processes. It is known for example that two human diseases involve loss of function mutations of SH3 domains (Rawlings et al., Science 261: 358, 1993) or their binding sequences (Cheng et al., Proc. Natl. Acad. Sci. USA 91: 8152, 1994).

Crystal structures of several SH3 protein domains reveal that the overall structure of the SH3 domain is formed by two β sheets formed by five β strands. The sheets form a compact structure consisting of anti-parallel β strands. A speculative theory based on the structure of the SH3 domains present in Src- kinases, purports that regulation of the kinase activity of the enzyme is mediated through the SH3 domain. The SH3 domain interacts with the upper lobe of the kinase through a linker that connects the SH2 domain with the kinase domain. The intra-molecular protein-protein interactions stabilise the kinase in an
inactive conformation. These structures suggest that one way of activating the kinase may be through the use of high affinity ligands which bind to the SH3 domain. This type of interaction could convert the kinase from a closed or inactive conformation to an open or active conformation.

Current protein structure-based drug design efforts rely heavily on crystal structure information of the target-binding site. A number of crystal structures of SH3 domains have been produced. Whilst there are several structures for the protein ligands in complex with SH3 domains, the mode of binding of other molecules and ligands to the surface of the SH3 domain remains to be determined. Thus, there is a vast lack of structural data necessary to elucidate the many potential modes of binding of molecules and ligands to SH3 domains.

Given the lack of structural information, researchers must rely on other design procedures for preparing active inhibitors of proteins having particular SH3 domains. Thus, the inclusion of structural information in the drug design process should lead to more efficient identification of promising protein inhibitors.

Hence, there remains a need to identify molecules capable of binding selectively to particular SH3 domains. Furthermore, there is a need to identify particular molecules having much greater binding affinities for specific members having particular SH3 domains. In this respect, general and/or more selective binding of molecules specific for particular SH3 domains remain to be identified. Molecules with selective binding capacity specific for a particular SH3 domain are useful, for example, in modulating the activity of a particular SH3 domain-containing protein, while leaving others bearing a structurally related but distinct SH3 domain unaffected. Still, the more promiscuous general binding molecules are useful for the modulation of a broad spectrum of SH3 domain-containing proteins.
SUMMARY OF THE INVENTION

Throughout this specification, unless the context requires otherwise, the word “comprise”, or variations such as “comprises” or “comprising”, will be understood to imply the inclusion of a stated element or integer or group of elements or integers but not the exclusion of any other element or integer or group of elements or integers.

Nucleotide and amino acid sequences are referred to by a sequence identifier number (SEQ ID NO:). The SEQ ID NOs: correspond numerically to the sequence identifiers <400>1 (SEQ ID NO:1), <400>2 (SEQ ID NO:2), etc. A sequence listing is provided after the claims.

In work leading up to the present invention, a three-dimensional structure of an SH3 domain was employed in the molecular analysis of compounds that are potentially capable of binding to an SH3 domain comprising a three-dimensional ligand-binding site comprising a negatively charged amino acid residue and a hydrophobic amino acid residue linearly separated by at least five amino acid residues. The instant invention provides several classes of known compounds which are capable of binding to such an SH3 domain. These SH3 domains are in molecules such as Tec, Fyn, Nck1, Src, Grb2, p85α, Lyn, Lck, Fgr and Hck amongst many others. Preferably, the negatively charged amino acid residue is aspartic acid (D) and the hydrophobic amino acid is tryptophan (W) and both residues are linearly separated by 18 residues, not inclusive of D or W. 2-Aminopyridine, 2-aminquinoline and 1-aminooquinoline are shown to bind to these amino acid residues within the SH3 domain. A method of identifying derivatives and analogs of 2-aminopyridine, 2-aminquinoline and 1-aminooquinoline that can bind or have the potential to bind to the conserved amino acid residues present in the SH3 domains has also been developed in accordance with the present invention.

Accordingly, one embodiment of the present invention provides a method for modulating the activity of a protein comprising an SH3 domain having a three-dimensional ligand-binding site comprising a negatively charged amino acid residue and a hydrophobic amino
acid residue linearly separated by at least five amino acid residues, said method comprising the administration of an effective amount of a compound of the Formula I:-

\[
\text{(I)}
\]

or a pharmaceutically acceptable salt, hydrate, solvent, crystal form and/or individual diastereo isomer thereof for a time and under conditions sufficient for said compound to modulate the activity of said protein.

In another embodiment, the present invention provides a method for modulating the activity of a protein comprising an SH3 domain having a three-dimensional ligand-binding site comprising a negatively charged amino acid residue and a hydrophobic amino acid residue linearly separated by at least five amino acid residues, said method comprising the administration of an effective amount of a compound of the Formula II:-

\[
\text{(II)}
\]

or a pharmaceutically acceptable salt, hydrate, solvent, crystal form and/or individual diastereo isomer thereof for a time and under conditions sufficient for said compound to modulate the activity of said protein.

In a further embodiment, the present invention provides a method for modulating the activity of a protein comprising an SH3 domain having a three-dimensional ligand-binding
site comprising a negatively charged amino acid residue and a hydrophobic amino acid residue linearly separated by at least five amino acid residues, said method comprising the administration of an effective amount of a compound of the Formula III:-

![Chemical Structure](image)

(III)

or a pharmaceutically acceptable salt, hydrate, solvent, crystal form and/or individual diastere isomer thereof for a time and under conditions sufficient for said compound to modulate the activity of said protein.

5

The preferred compounds are 2-aminopyridine, 2-aminoquinoline and 1-aminoisquinoline.

10

The preferred SH3 domains comprise the consensus domain:

15

```
hsxbbsax(x)_{10}-lsbp(x)_{4}G-(x)_{3}1b(x)_{16}wxbbt(x)_{19}G(x)_{3}bhpxsbv
```

wherein:-

20

- **h** = hydrophobic (A, C, F, G, H, I, L, M, T, V, W or Y);
- **s** = small (A, C, D, G, N, P, S, T or V);
- **a** = aromatic (F, H, W or Y);
- **b** = big (E, F, H, I, K, L, M, Q, R, W or Y);
- **-** = negatively charged (D or E);
- **l** = aliphatic (I, L or V); and
- **t** = tiny (A or G);
using the single amino acid code (see Table 1 at the end of the Summary).

In a related aspect, the present invention provides a method for the prophylaxis and/or treatment of a disease state or pre-disease state that results from, or is associated with inappropriate activity or expression of a protein comprising an SH3 domain having a three-dimensional ligand-binding site comprising a negatively charged amino acid residue and a hydrophobic amino acid residue linearly separated by at least five amino acid residues, said method comprising the step of administering to a subject an effective amount of a compound of the Formula I or a derivative or analog or mimetic thereof or a pharmaceutically acceptable salt hydrate, solvent crystal form and/or diastereom isomer thereof for a time and under conditions sufficient for said compound to provide a treatment and/or a prophylactic response in said subject with a disease state or pre-disease state that results from, or is associated with an inappropriate activity or expression of said protein.

In another related aspect, the present invention provides a method for the prophylaxis and/or treatment of a disease state or pre-disease state that results from, or is associated with inappropriate activity or expression of a protein comprising an SH3 domain having a three-dimensional ligand-binding site comprising a negatively charged amino acid residue and a hydrophobic amino acid residue linearly separated by at least five amino acid residues, said method comprising the step of administering to a subject an effective amount of a compound of the Formula II or a derivative or analog or mimetic thereof or a pharmaceutically acceptable salt hydrate, solvent crystal form and/or diastereom isomer thereof for a time and under conditions sufficient for said compound to provide a treatment and/or a prophylactic response in said subject with a disease state or pre-disease state that results from, or is associated with an inappropriate activity or expression of said protein.

In still yet a further related aspect, the present invention provides a method for the prophylaxis and/or treatment of a disease state or pre-disease state that results from, or is associated with inappropriate activity or expression of a protein comprising an SH3 domain having a three-dimensional ligand-binding site comprising a negatively charged
amino acid residue and a hydrophobic amino acid residue linearly separated by at least five amino acid residues, said method comprising the step of administering to a subject an effective amount of a compound of the Formula III or a derivative or analog or mimetic thereof or a pharmaceutically acceptable salt hydrate, solvent crystal form and/or diastereoisomer thereof for a time and under conditions sufficient for said compound to provide a treatment and/or a prophylactic response in said subject with a disease state or pre-disease state that results from, or is associated with an inappropriate activity or expression of said protein.

Another embodiment of the present invention provides a compound of the Formula II or a pharmaceutically acceptable salt, hydrate, solvent, crystal form and individual diastereoisomer thereof capable of binding to the SH3 domain of a protein comprising an SH3 domain having a three-dimensional ligand-binding site comprising a negatively charged amino acid residue and a hydrophobic amino acid residue linearly separated by at least five amino acid residues.

A further embodiment of the present invention provides a compound of the Formula III or a pharmaceutically acceptable salt, hydrate, solvent, crystal form and individual diastereoisomer thereof capable of binding to the SH3 domain of a protein comprising an SH3 domain having a three-dimensional ligand-binding site comprising a negatively charged amino acid residue and a hydrophobic amino acid residue linearly separated by at least five amino acid residues.

Even yet another embodiment of the present invention contemplates a method of using the three-dimensional structure of a protein in a molecular screening assay to identify molecules capable of interacting with a peptide, polypeptide or protein, said method comprising subjecting the three-dimensional structure of a peptide, polypeptide or protein and a molecule to in silico molecular modelling means to determine gap space regions including a functional moiety or moieties present on said molecule that do not demonstrate optimum close contacts between the molecule and the amino acids of the interaction surface region or pocket present on said peptide, polypeptide or protein, and subjecting
said molecule to *in silico* manipulation means to optimize close contacts between the molecule and the selected amino acids of the interaction surface, region or pocket of said peptide, polypeptide or protein, thereby identifying a molecule with the same or altered capacity to interact with the surface, region or pocket of said peptide, polypeptide or protein.

The preferred proteins of the present invention having an SH3 domain comprising a protein comprising an SH3 domain having a three-dimensional ligand-binding site comprising a negatively charge amino acid residue and a hydrophobic amino acid residue linearly separated by at least five amino acid residues are Tec, Fyn, Nck1, Src, Grb2, p85α, Lyn, Lck, Fgr and Hck.
Single and three letter abbreviations used throughout the specification are defined in Table 1.

**TABLE 1**

*Single and three letter amino acid abbreviations*

<table>
<thead>
<tr>
<th>AMINO ACID</th>
<th>THREE-LETTER ABBREVIATION</th>
<th>ONE-LETTER SYMBOL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alanine</td>
<td>Ala</td>
<td>A</td>
</tr>
<tr>
<td>Arginine</td>
<td>Arg</td>
<td>R</td>
</tr>
<tr>
<td>Asparagine</td>
<td>Asn</td>
<td>N</td>
</tr>
<tr>
<td>Aspartic acid</td>
<td>Asp</td>
<td>D</td>
</tr>
<tr>
<td>Cysteine</td>
<td>Cys</td>
<td>C</td>
</tr>
<tr>
<td>Glutamine</td>
<td>Gln</td>
<td>Q</td>
</tr>
<tr>
<td>Glutamic acid</td>
<td>Glu</td>
<td>E</td>
</tr>
<tr>
<td>Glycine</td>
<td>Gly</td>
<td>G</td>
</tr>
<tr>
<td>Histidine</td>
<td>His</td>
<td>H</td>
</tr>
<tr>
<td>Isoleucine</td>
<td>Ile</td>
<td>I</td>
</tr>
<tr>
<td>Leucine</td>
<td>Leu</td>
<td>L</td>
</tr>
<tr>
<td>Lysine</td>
<td>Lys</td>
<td>K</td>
</tr>
<tr>
<td>Methionine</td>
<td>Met</td>
<td>M</td>
</tr>
<tr>
<td>Phenylalanine</td>
<td>Phe</td>
<td>F</td>
</tr>
<tr>
<td>Proline</td>
<td>Pro</td>
<td>P</td>
</tr>
<tr>
<td>Serine</td>
<td>Ser</td>
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</tr>
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<td>Threonine</td>
<td>Thr</td>
<td>T</td>
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<td>Tryptophan</td>
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<td>W</td>
</tr>
<tr>
<td>Tyrosine</td>
<td>Tyr</td>
<td>Y</td>
</tr>
<tr>
<td>Valine</td>
<td>Val</td>
<td>V</td>
</tr>
<tr>
<td>Any residue</td>
<td>Xaa</td>
<td>X</td>
</tr>
</tbody>
</table>
A summary of sequence identifiers used throughout the subject specification is provided in Table 2.

**TABLE 2**

*Summary of sequence identifiers*

<table>
<thead>
<tr>
<th>SEQUENCE ID NO.</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Tec-human (182-238) [Figure 3]</td>
</tr>
<tr>
<td>2</td>
<td>Fyn human (84-141) [Figure 3]</td>
</tr>
<tr>
<td>3</td>
<td>Nck1 human (109-164) [Figure 3]</td>
</tr>
<tr>
<td>4</td>
<td>Src human (86-143) [Figure 3]</td>
</tr>
<tr>
<td>5</td>
<td>Grb2 human (1-57) [Figure 3]</td>
</tr>
<tr>
<td>6</td>
<td>Grb2 human (159-214) [Figure 3]</td>
</tr>
<tr>
<td>7</td>
<td>p85α human (6-78) [Figure 3]</td>
</tr>
<tr>
<td>8</td>
<td>Lyn human (85-121) [Figure 3]</td>
</tr>
<tr>
<td>9</td>
<td>Lck human (63-119) [Figure 3]</td>
</tr>
<tr>
<td>10</td>
<td>Fgr human (80-137) [Figure 3]</td>
</tr>
<tr>
<td>11</td>
<td>Hck human (81-137) [Figure 3]</td>
</tr>
</tbody>
</table>
BRIEF DESCRIPTION OF THE FIGURES

**Figure 1** is a computer generated representation of a molecular structure of the SH3 domain from the murine Tec IV protein indicating the region on the surface where the ligands bind.

**Figure 2A** is three-dimensional view of a molecular model of 2-aminoquinoline docked into the ligand-binding site of the murine Tec SH3 domain structure (Pursglove *et al.*, *J. Biol. Chem.* 277: 755-762, 2002).

**Figure 2B** is a schematic diagram showing the spatial relationship of the side chain negative charged of aspartate 196 of the murine Tec SH3 structure and the delocalized positive charge of the bound 2-aminoquinoline ligand. Also indicated is the pi-pi stacking arrangement of the aromatic side chain of tryptophan 215 of the murine Tec SH3 structure and the aromatic ring structure of the bound 2-aminoquinoline ligand.

**Figure 3** is a representation showing an alignment of a selection of human SH3 domain sequences together with a consensus evaluation. The name of each protein is shown together with the range of amino acid numbers for the SH3 domain. The amino acids are represented by the one-letter code. The legend for the consensus: h = hydrophobic (A, C, F,G H, I, L, M, T, V, W or Y), s = small (A, C, D, G, N, P, S, T or V), a = aromatic (F, H, W or Y), b = big (E, F, H, I, K, L, M, Q, R, W or Y), - = negatively charged (D or E), l = aliphatic (I, L or V), t = tiny (A and G). Examples of absolute conservation are shown in upper case as one-letter code. (i.e. G, W, P, V). The analysis was undertaken using the simple modular architecture research tool (Schultz *et al.*, *Nucleic Acids Res* 28: 231-234, 2000). The asterisks highlight the highly conserved negatively charged residue and the tryptophan residue that together constitute the core three-dimensional binding site for the disclosed ligand compounds.

**Figure 4** is a diagrammatic representation showing examples of chemical shift titration data used to determine the equilibrium dissociation constant for 2-aminoquinoline binding
to the murine Tec SH3 domain. The absolute $^1$H chemical shift change in ppm is shown versus ligand concentration in micromolar for tryptophan 215 indole NH (▲) and backbone NH (■) and threonine 192 (▼) and glutamate 193 (♦) backbone NH.
DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention is predicated in part on the finding that 2-aminopyridine, 2-aminoquinoline and 1-aminoisoquinoline interact with an SH3 domain of a protein wherein the SH3 domain comprises a protein comprising an SH3 domain having a three-dimensional ligand-binding site comprising a negatively charged amino acid residue and a hydrophobic amino acid residue linearly separated by at least five amino acid residues.

The negatively charged amino acid residue may be a D or E residue and is preferably a D residue. The hydrophobic residue may be one of A, C, F, G, H, I, L, M, T, V, W and Y and is most preferably W.

The linear separation between the negatively charged residue and the hydrophobic residue may be 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 or 18 residues and is most preferably 18 residues (not inclusive of the two residues in question).

Most preferably, the SH3 domain comprises the consensus sequence:

\[ \text{hsbbsaxs(x)_{10}-lsbp(x)_{3}G-(x)_{3}lb(x)_{16}wxbbt(x)_{19}G(x)_{3}bhpxsby} \]

wherein:-

\[ h = \text{hydrophobic (A, C, F, G, H, I, L, M, T, V, W or Y)}; \]
\[ s = \text{small (A, C, D, G, N, P, S, T or V)}; \]
\[ a = \text{aromatic (F, H, W or Y)}; \]
\[ b = \text{big (E, F, H, I, K, L, M, Q, R, W or Y) [SEQ ID NO:]}; \]
\[ - = \text{negatively charged (D or E)}; \]
\[ l = \text{aliphatic (I, L or V)}; \]
\[ t = \text{tiny (A or G)}; \] and
x = any amino acid residue with the number of contiguous amino acid residues given after the parenthesis where there are two or more x residues.

The preferred SH3 domain-containing proteins include Tec, Fyn, Nck1, Src, Grb2, p85α, Lyn, Lck, Fgr and Hck. The present invention extends, however, to any protein comprising an SH3 domain as defined above.

Accordingly, one embodiment of the present invention provides a method for modulating the activity of a protein comprising an SH3 domain having a three-dimensional ligand-binding site comprising a negatively charged amino acid residue and a hydrophobic amino acid residue linearly separated by at least five amino acid residues, said method comprising the administration of a an effective amount of a compound of the Formula I:-

\[
\begin{align*}
R_1 & \\
R_2 & \\
R_3 & \\
R_4 & \\
R_5 & \\
\end{align*}
\]

or a pharmaceutically acceptable salt, hydrate, solvent, crystal form and/or individual diastereoisomers thereof for a time and under conditions sufficient for said compound to modulate the activity of said protein, wherein: R₁, R₂, R₃, R₄ and R₅ may be the same or different and each is selected from the group comprising of:-

(a) hydrogen,
(b) hydroxy,
(c) amino,
(d) carboxyl,
(e) aminocarbonyl,
(f) cyano,
(g) nitro,
(h) halo, where halo is selected from fluoro, chloro, bromo, and iodo,
(i) trifluoromethyl,
(j) C₁₋₁₂ alkyl,
(k) C₂₋₁₂ alkenyl,
(l) C₂₋₁₂ alkynyl,
(m) C₁₋₁₂ alkoxy,
(n) C₁₋₁₂ alkylcarbonyl,
(o) C₁₋₁₂ alkoxy carbonyl,
(p) C₁₋₁₂ alkylaminocarbonyl,
(q) mono- and di-C₁₋₁₂ alkylamino,
(r) C₁₋₁₂ alkylthio,
(s) aryl, where aryl is selected from phenyl and naphthyl,
(t) aryloxy, where aryl is selected from phenyl and naphthyl,
(u) arylthio, where aryl is selected from phenyl and naphthyl,
(v) aryl C₁₋₆ alkyl, where aryl is selected from phenyl and naphthyl,
(w) cycloalkyl, wherein the cycloalkyl is a 5- to 10-membered monocyclic ring which optionally contains 1 or 2 heteroatoms selected from S, O, and N,
(x) heteroaryl, wherein heteroaryl is selected from the group consisting of:
  (l) pyridyl,
  (2) pyrrolyl,
  (3) furanyl,
  (4) thienyl,
  (5) isothiazolyl,
  (6) imidazolyl,
  (7) benzimidazolyl,
  (8) tetrazolyl,
  (9) pyrazinyl,
  (10) pyrimidyl,
  (11) quinolyl,
  (12) isoquinolyl,
  (13) benzofuranyl,
(14) isobenzofuryl,
(15) benzothienyl,
(16) pyrazolyl,
(17) pyrazinyl,
(18) indolyl,
(19) isoindolyl,
(20) purinyl,
(21) carazolyl,
(22) isoxazolyl,
(23) thiazolyl,
(24) triazolyl
(25) oxazolyl,
(26) oxadiazolyl,
(27) thiadiazolyl
(28) benzthiazolyl; and
(29) benzoazolyl,
(y) heteroaryl C₁₋₆ alkyl, where heteroaryl is defined above in item (x),

each of (j) to (y) being optionally mono- or di- substituted, the substituents being

(1) hydroxy,
(2) C₁₋₆ alkyl,
(3) C₁₋₆ alkoxy,
(4) amino,
(5) mono- and di-C₁₋₆ alkylamino,
(6) carboxyl,
(7) C₁₋₆ alkylthio,
(8) --S(O)ₖ-C₁₋₃ alkyl, where k is 1 or 2,
(9) C₁₋₆ alkoxy carbonyl,
(10) halo selected from fluoro, chloro, bromo, and iodo,
(11) oxo,
(12) amidino, and
(13) guanidino,

wherein R₁ and R₂, or R₂ and R₃ or R₃ and R₄ may be joined together to form a 5- to 10-membered saturated or unsaturated ring containing 0 to 2 heteroatoms which together with the atoms to which R₁ and R₂, or R₂ and R₃, or R₃ and R₄ are attached there is formed a ring system according to Formulae I-I to I-III, the heteroatoms being selected from the group consisting of O, S and N,

wherein R₅ is selected from the group consisting of:

(a) hydrogen,
(b) amino,
(c) $C_{1-12}$ alkyl,
(d) $C_{2-12}$ alkenyl,
(e) $C_{2-12}$ alkynyl,
(f) aryl, wherein the aryl group is as defined above,
(g) aryl $C_{1-6}$ alkyl, wherein the aryl group is as defined above,
(h) heteroaryl, wherein heteroaryl is as defined above,
(i) heteroaryl $C_{1-6}$ alkyl, wherein heteroaryl is as defined above,
(j) an alkyl containing an aryl or heteroaryl substituent, and
(k) cycloalkyl, wherein the cycloalkyl is a 5- to 10-membered monocyclic ring which optionally contains 1 or 2 heteroatoms selected from the group consisting of S, O and N,

each of (b) to (k) being optionally mono- or di- substituted, the substituents being independently selected from:-

15
(1) hydroxy,
(2) $C_{1-6}$ alkyl,
(3) $C_{1-6}$ alkoxy,
(4) amino,

20
(5) mono- and di-$C_{1-6}$ alkylamino,
(6) carboxyl,
(7) $C_{1-6}$ alkylthio,
(8) --$S(O)_k$-$C_{1-3}$ alkyl, where k is 1 or 2,
(9) $C_{1-6}$ alkoxy carbonyl,

25
(10) halo selected from fluoro, chloro, bromo, and iodo,
(11) oxo,
(12) amidino, and
(13) guanidino.

30 In an alternative aspect, this embodiment includes compounds wherein $R_1$, $R_2$, $R_3$, $R_4$ may be aryl-$S(O)_k$ or heteroaryl-$S(O)_k$. 
Within this embodiment, there is the genus of compounds,

wherein R₁, R₂, R₃ and R₄ are each independently selected from the group comprising:-

5
(a) hydrogen,
(b) hydroxy,
(c) amino,
(d) cyano,
10 (e) fluoro, chloro, bromo, and iodo,
(f) trifluoromethyl,
(g) C₁₋₆ alkyl,
(h) C₁₋₆ alkoxy,
(i) C₁₋₆ alkylthio,
(j) C₁₋₆ alkylcarbonyl,
(k) mono- and di- C₁₋₆ alkylamino,
(l) aryl, where aryl is phenyl and naphthyl,
(m) aryloxy, where aryl is phenyl and naphthyl,
(n) cycloalkyl, wherein the cycloalkyl is a 5-, 6-, or 7-membered monocyclic ring
20 which optionally contains 1 or 2 heteroatoms selected from S, O, and N,
(o) heteroaryl, wherein heteroaryl is selected from the group comprising:-
1
(1) pyridyl,
(2) furanyl,
(3) thienyl,
25 (4) pyrazinyl,
(5) pyrimidyl,
(6) thiazolyl, and
(7) triazolyl,

30 each of (g) to (o) being optionally mono- or di- substituted, the substituents being independently selected from:-
(1) hydroxy,
(2) C$_{1-4}$ alkyl,
(3) C$_{1-3}$ alkoxy,
(4) C$_{1-3}$ alkylthio,
(5) mono- and di-C$_{1-3}$ alkylamino,
(6) --S(O)$_k$ -C$_{1-3}$ alkyl, where $k$ is 1 or 2,
(7) --C(O)-O-C$_{1-3}$ alkyl,
(8) halo selected from fluoro, chloro and bromo,
(9) amino, and
(10) carboxyl,

wherein $R_1$ and $R_2$, or $R_2$ and $R_3$, or $R_3$ and $R_4$ may be joined together to form a 5-, 6- or 7-membered saturated monocyclic ring containing 0, 1 or 2 heteroatoms which together with the atoms to which $R_1$ and $R_2$, or $R_2$ and $R_3$, or $R_3$ and $R_4$ are attached there is formed a ring system according to Formulae I-I to I-III the heteroatoms being selected from the group consisting of O, S and N,
wherein \( R_5 \) is selected from the group comprising:

5  (a) hydrogen,
   (b) amino,
   (c) \( C_{1-6} \) alkyl,
   (d) aryl, wherein the aryl group is phenyl and naphthyl,
   (e) aryl \( C_{1-6} \) alkyl, wherein the aryl group is phenyl and naphthyl,
10  (f) heteroaryl, wherein heteroaryl is as defined above,
   (g) heteroaryl \( C_{1-6} \) alkyl, wherein heteroaryl is as defined above,
   (h) cycloalkyl wherein the cycloalkyl is a 5-, 6-, or 7-membered monocyclic ring
      which optionally contains 1 or 2 heteroatoms selected from S, O, and N,
   (i) an alkyl containing an aryl or heteroaryl substituent, and
15  (j) any combination of (a) to (h),

each of (b) to (j) being optionally mono- or di- substituted, the substituents being
independently selected from:-

20  (1) hydroxy,
   (2) \( C_{1-4} \) alkyl,
   (3) \( C_{1-3} \) alkoxy,
   (4) \( C_{1-3} \) alkylthio,
   (5) mono- and di-\( C_{1-3} \) alkyamino,
25  (6) --S(O)\(^k\)-\( C_{1-3} \) alkyl, where \( k \) is 1 or 2,
   (7) --C(O)-O-\( C_{1-3} \) alkyl,
   (8) halo selected from fluoro, chloro and bromo.
Within this genus, there is a class of compounds,

wherein $R_1$, $R_2$, $R_3$ and $R_4$ are each independently selected from the group comprising:-

5
(a) hydrogen,
(b) hydroxy,
(c) amino,
(d) cyano,
10 (e) fluoro, chloro or bromo,
(f) trifluoromethyl,
(g) $C_{1-6}$ alkyl,
(h) $C_{1-6}$ alkoxy,
(i) $C_{1-6}$ alkylthio,
15 (j) mono- and di-$C_{1-4}$ alkylamino,

wherein $R_1$ and $R_2$, or $R_2$ and $R_3$, or $R_3$ and $R_4$ may be joined together to form a 5-, 6- or 7-membered saturated monocyclic ring containing 0, 1 or 2 heteroatoms which together with the atoms to which $R_1$ and $R_2$, or $R_2$ and $R_3$, or $R_3$ and $R_4$ are attached there is formed a ring system according to Formulae I-I to I-III, the heteroatoms being selected from the group consisting of O, S and N,
wherein $R_5$ is selected from the group comprising:

5

(a) hydrogen,
(b) amino,
(c) C$_{1-4}$ alkyl,
(d) phenyl,
10 (e) phenyl C$_{1-4}$ alkyl,
(f) heteroaryl, wherein heteroaryl is selected from,
(1) pyridyl,
(2) furanyl,
(3) thienyl,
15 (4) pyrazinyl,
(5) pyrimidyl,
(6) thiazolyl, and
(7) triazolyl,
(g) heteroaryl C$_{1-6}$ alkyl, wherein heteroaryl is defined as above,
20 (h) an alkyl containing an aryl or heteroaryl substituent, and
(i) cycloalkyl, wherein the cycloalkyl is a 5-, 6-, or 7-membered monocyclic ring which optionally contains 1 or 2 heteroatoms selected from S, O, and N,
each of (b) to (i) being optionally mono- or di- substituted, the substituents being independently selected from:-

(1) hydroxy,
(2) C\textsubscript{1-4} alkyl,
(3) C\textsubscript{1-3} alkoxy,
(4) C\textsubscript{1-3} alkylthio,
(5) mono- and di-C\textsubscript{1-3} alkylamino,
(6) \(\text{--S(O)}\textsubscript{k} -\text{C}_{1-3}\) alkyl, where \(k\) is 1 or 2,
(7) \(\text{--C(O)}\text{-O-} -\text{C}_{1-3}\) alkyl,
(8) halo selected from fluoro, chloro and bromo.

Within this class is the subclass of compounds wherein the rings of Formulae I-I, I-II and I-III are selected from the group comprising:-

(i)

(ii)

(iii)
wherein this subclass of compounds may be saturated or unsaturated. Preferably the compounds of the above subclass are unsaturated compounds.
Within the above subclass of compounds are the compounds of Formulae I-I, I-II, and I-III wherein R₁, R₂, R₃ and R₄, as explicitly shown, are each independently selected from the group comprising:

5
(a) hydrogen,
(b) hydroxy,
(c) amino,
(d) cyano,
(e) fluoro, chloro or bromo,
(f) trifluoromethyl,
(g) C₄ alkyl,
(h) C₄ alkoxy,
(i) C₄ alkylthio,
(j) mono- and di-C₄ alkylamino,

R₅ is selected from the group comprising:

20
(a) hydrogen,
(b) amino,
(c) C₄ alkyl,
(d) phenyl,
(e) phenyl C₄ alkyl,
(f) heteroaryl, wherein heteroaryl is selected from:-

25
(1) pyridyl,
(2) furanyl,
(3) thieryl,
(4) pyrazinyl,
(5) pyrimidyl,
(6) thiazolyl, and
(7) triazolyl,
heteroaryl C\textsubscript{1-6} alkyl, wherein heteroaryl is defined as above,

an alkyl containing an aryl or heteroaryl substituent, and
cycloalkyl, wherein the cycloalkyl is a 5-, 6-, or 7-membered monocyclic ring which optionally contains 1 or 2 heteroatoms selected from S, O, and N,

each of (b) to (i) being optionally mono- or di- substituted, the substituents being independently selected from:-

(1) hydroxy,
(2) C\textsubscript{1-4} alkyl,
(3) C\textsubscript{1-3} alkoxy,
(4) C\textsubscript{1-3} alkylthio,
(5) mono- and di-C\textsubscript{1-3} alkyamino,
(6) --S(O)	extsubscript{k} -C\textsubscript{1-3} alkyl, where k is 1 or 2,
(7) --C(O)-O-C\textsubscript{1-3} alkyl, and
(8) halo selected from fluoro, chloro and bromo.

The present invention is particularly exemplified by the following compounds, each of which is encompassed by the present invention:

(a) 2-amino-3-benzylurea-4-picoline,
(b) 2-amino-3-methoxypyridine,
(c) 2-amino-3-methylthio-4-picoline,
(d) 2-amino-4-methylthiomethylpyridine,
(e) 2-amino-3-hydroxymethyl-4-picoline,
(f) 2-amino-3-ethyl-4-picoline dihydrochloride,
(g) 2-amino-3-methoxymethyl-4-picoline dihydrochloride,
(h) 2-amino-3-n-propyl-4-picoline dihydrochloride,
(i) 2-amino-3-dimethylamino-4-picoline trihydrochloride,
(j) 2-amino-3-chloro-4-picoline,
(k) 2-amino-5-chloro-4-picoline,
(l) 2,5-diamino-4-picoline,
(m) 5-acetylamino-2-amino-4-picoline,
(n) 2-amino-5-ethynyl-4-methylpyridine,
(o) 2-amino-4-methyl-5-pentylpyridine,
(p) 4-methylthio-2-aminopyridine,
(q) 4-chloro-6-methoxycarbonyl-2-aminopyridine,
(r) 4,6-dimethyl-5-ethenyl-2-aminopyridine,
(s) 2,4-diaminopyridine dihydrochloride,
(t) 2-amino-5-phenylpyridine,
(u) 2-amino-4-methyl-5-phenylpyridine,
(v) 2-amino-5-bromo-4-methylpyridine,
(w) 2-amino-5-cyano-4-methylpyridine,
(x) 2-amino-5-carboxy-4-methylpyridine,
(y) 2-amino-5-methoxycarbonyl-4-methylpyridine,
(z) 2-amino-5-aminomethyl-4-methylpyridine dihydrochloride,
(aa) 2-amino-5-acetamidomethyl-4-methylpyridine,
(ab) 2-amino-5-hydroxymethyl-4-methylpyridine,
(ac) 2-(2-amino-3-pyridinoxy)-ethyl-(S)-glycine dihydrochloride,
(ad) 2-amino-4,5-dimethylpyridine hydrochloride,

(20) 2-amino-6-(3-buten-1-yl)-4-methylpyridine,
(21) 2-amino-6-ethyl-4-methylpyridine,
(22) 2-amino-4-methyl-6-(1-methylethyl)pyridine,
(23) 2-amino-6-(4-aminobutyl)-methylpyridine,
(24) 6-(4-acetamidobutyl)-2-amino-4-methylpyridine,
(25) 2-amino-6-hydroxymethyl-4-methylpyridine,
(ak) α-[2-(6-amino-4-methylpyrid-2-yl)ethyl]glycine dihydrochloride,
(a1) 2-amino-5-ethylpyridine,
(am) 2-amino-6-benzylpyridine,
(an) 2-amino-6,7-dihydro-(5H)-pyridine,

(30) 2-amino-6-(3-aminopropyl)-4-methylpyridine,
(ap) 2-amino-6-(2-aminoethyl)-4-methylpyridine,
(aq) 2-amino-4-methyl-6-propylpyridine,
(ar) 2-amino-4-methyl-6-(3-phenylpropyl)pyridine,
(as) 2-amino-4-methyl-6-(4-phenylbutyl)pyridine,
(at) 2-amino-4-methyl-6-(3-methylbutyl)pyridine,
5 (au) 2-amino-4-methyl-6-(2-methylpropyl)pyridine,
(av) 2-amino-4-methyl-6-(2-phenylethyl)pyridine,
(aw) 5-(6-amino-4-methyl-2-pyridyl)pentanoic acid hydrochloride,
(ax) 4-(6-amino-4-methyl-2-pyridyl)butanoic acid hydrochloride,
(ay) (S)-2-amino-6-(3-aminobutyl)-4-methylpyridine,
10 (az) (R)-2-amino-6-(3-aminobutyl)-4-methylpyridine, or
(ba) 2-aminopyridine.

or a pharmaceutically acceptable salt thereof.

15 A particularly preferred compound is 2-aminopyridine.

In another embodiment, the present invention provides a method for modulating the activity of a protein comprising an SH3 domain comprising a protein comprising an SH3 domain having a three-dimensional ligand-binding site comprising a negatively charged amino acid residue and a hydrophobic amino acid residue linearly separated by at least five amino acid residues, said method comprising the administration of an effective amount of a compound of the Formula II,
or a pharmaceutically acceptable salt, hydrate, solvent, crystal form and individual diastereoisomer thereof for a time and under conditions sufficient for said compound to modulate the activity of said protein wherein \( R_1, R_2, R_3, R_4, R_5 \) and \( R_6 \) are each independently selected from the group comprising:

5
(a) hydrogen,
(b) hydroxy,
(c) amino,
(d) carboxyl,
(e) aminocarbonyl,
(f) cyano,
(g) nitro,
(h) halo, where halo is selected from fluoro, chloro, bromo, and iodo,
(i) trifluoromethyl,
(j) \( \text{C}_{1-12} \) alkyl,
(k) \( \text{C}_{2-12} \) alkenyl,
(l) \( \text{C}_{2-12} \) alkynyl,
(m) \( \text{C}_{1-12} \) alkoxy,
(n) \( \text{C}_{1-12} \) alkylcarbonyl,
(o) \( \text{C}_{1-12} \) alkoxy carbonyl,
(p) \( \text{C}_{1-12} \) alkylaminocarbonyl,
(q) mono- and di-\( \text{C}_{1-12} \) alkylamino,
(r) \( \text{C}_{1-12} \) alkylthio,
(s) aryl, where aryl is selected from phenyl and naphthyl,
(t) aryloxy, where aryl is selected from phenyl and naphthyl,
(u) arylthio, where aryl is selected from phenyl and naphthyl,
(v) aryl \( \text{C}_{1-4} \) alkyl, where aryl is selected from phenyl and naphthyl,
(w) cycloalkyl, wherein the cycloalkyl is a 5- to 10-membered monocyclic ring which optionally contains 1 or 2 heteroatoms selected from S, O, and N,
(x) heteroaryl, wherein heteroaryl is selected from the group comprising:-
(l) pyridyl,
(2) pyrrolyl,
(3) furanyl,
(4) thiényl,
(5) isothiazolyl,
(6) imidazolyl,
(7) benzimidazolyl,
(8) tetrazolyl,
(9) pyraziny1,
(10) pyrimidyl,
(11) quinolyl,
(12) isoquinolyl,
(13) benzofuranyl,
(14) isobenzofuranyl,
(15) benzothienyl,
(16) pyrazolyl,
(17) pyraziny1,
(18) indolyl,
(19) isoindolyl,
(20) purinyl,
(21) carbazolyl,
(22) isoxazolyl,
(23) thiazolyl,
(24) triazolyl
(25) oxazolyl,
(26) oxadiazolyl,
(27) thiadiazolyl,
(28) benzthiazolyl; and
(29) benzoazolyl,
(y) heteroarylC_{1-6} alkyl, where heteroaryl is defined above in item (x),
each of (j) to (y) being optionally mono- or di- substituted, the substituents being independently selected from:

- hydroxy, 
- C<sub>1-6</sub> alkyl, 
- C<sub>1-6</sub> alkoxy, 
- amino, 
- mono-and di-C<sub>1-6</sub> alkylamino, 
- carboxyl, 
- C<sub>1-6</sub> alkylthio, 
- --S(O)<sub>k</sub>-C<sub>1-3</sub> alkyl, where k is 1 or 2, 
- C<sub>1-6</sub> alkoxy carbonyl, 
- halo selected from fluoro, chloro, bromo, and iodo, 
- oxo, 
- amidino, and 
- guanidino,

wherein R<sub>1</sub> and R<sub>2</sub>, or R<sub>2</sub> and R<sub>3</sub>, or R<sub>3</sub> and R<sub>4</sub>, or R<sub>4</sub> and R<sub>5</sub>, or R<sub>5</sub> and R<sub>6</sub> may be joined together to form a 5- to 10-membered saturated or unsaturated ring containing 0 to 2 heteroatoms which together with the atoms to which R<sub>1</sub> and R<sub>2</sub>, or R<sub>2</sub> and R<sub>3</sub>, or R<sub>3</sub> and R<sub>4</sub>, or R<sub>4</sub> and R<sub>5</sub>, or R<sub>5</sub> and R<sub>6</sub> are attached there is formed a ring system according to Formulae II-I to II-V, the heteroatoms being selected from the group consisting of O, S and N,
wherein R₇ is selected from the group comprising:

(a) hydrogen,
(b) amino,
(c) C₁₋₁₂ alkyl,
(d) C₂₋₁₂ alkenyl,
(e) C_{2-12} alkynyl,
(f) aryl, wherein the aryl group is as defined above,
(g) aryl C_{1-6} alkyl, wherein the aryl group is as defined above,
(h) heteroaryl, wherein heteroaryl is as defined above,
(i) heteroaryl C_{1-6} alkyl, wherein heteroaryl is as defined above,
(j) an alkyl containing an aryl or heteroaryl substituent,
(k) cycloalkyl, wherein the cycloalkyl is a 5- to 10-membered monocyclic ring which optionally contains 1 or 2 heteroatoms selected from the group consisting of S, O and N,

each of (b) to (k) being optionally mono- or di- substituted, the substituents being independently selected from:-

(1) hydroxy,
(2) C_{1-6} alkyl,
(3) C_{1-6} alkoxy,
(4) amino,
(5) mono- and di-C_{1-6} alkylamino,
(6) carboxyl,
(7) C_{1-6} alkylthio,
(8) \text{--S(O)}_k \text{-C}_{1-3} alkyl, where k is 1 or 2,
(9) C_{1-6} alkoxy carbonyl,
(10) halo selected from fluoro, chloro, bromo, and iodo,
(11) oxo,
(12) amidino, and
(13) guanidino.

In an alternative aspect, this embodiment includes compounds wherein R_1, R_2, R_3, R_4, R_5 and R_6 may be aryl-S(O)_k or heteroaryl-S(O)_k.

Within this embodiment, there is the genus of compounds,
wherein $R_1$, $R_2$, $R_3$, $R_4$, $R_5$ and $R_6$ are each independently selected from the group comprising:

5 (a) hydrogen,
(b) hydroxy,
(c) amino,
(d) cyano,
(e) fluoro, chloro, bromo, and iodo,
10 (f) trifluoromethyl,
(g) $C_{1-6}$ alkyl,
(h) $C_{1-6}$ alkoxy,
(i) $C_{1-6}$ alkylthio,
(j) $C_{1-6}$ alkylcarbonyl,
15 (k) mono- and di-$C_{1-6}$ alkylamino,
(l) aryl, where aryl is phenyl and naphthyl,
(m) arylxy, where aryl is phenyl and naphthyl,
(n) cycloalkyl, wherein the cycloalkyl is a 5-, 6-, or 7-membered monocyclic ring which optionally contains 1 or 2 heteroatoms selected from S, O, and N,
20 (o) heteroaryl, wherein heteroaryl is selected from the group comprising:
   (1) pyridyl,
   (2) furany1,
   (3) thiency1,
   (4) pyrazinyl,
25 (5) pyrimidyl,
   (6) thiazoly1, and
   (7) triazoly1,

wherein each of (g) to (o) being optionally mono- or di- substituted, the substituents being

30 independently selected from:
(1) hydroxy,
(2) C_{1-4} alkyl,
(3) C_{1-3} alkoxy,
(4) C_{1-3} alkylthio,
(5) mono- and di-C_{1-3} alkylamino,
(6) --S(O)_k-C_{1-3} alkyl, where k is 1 or 2,
(7) --C(O)-O-C_{1-3} alkyl,
(8) halo selected from fluoro, chloro and bromo,
(9) amino, and
(10) carboxyl,

wherein R_1 and R_2, or R_2 and R_3, or R_3 and R_4, or R_4 and R_5, or R_5 and R_6 may be joined together to form a 5-, 6- or 7-membered saturated monocyclic ring containing 0, 1 or 2 heteroatoms which together with the atoms to which R_1 and R_2, or R_2 and R_3, or R_3 and R_4, or R_4 and R_5, or R_5 and R_6 are attached there is formed a ring system according to Formulae II-I – to II-V the heteroatoms being selected from the group consisting of O, S and N,
wherein $R_7$ is selected from the group comprising:

(a) hydrogen,
(b) amino
(c) C$_{1-6}$ alkyl,
(d) aryl, wherein the aryl group is phenyl and naphthyl,
(e) aryl C$_{1-6}$ alkyl, wherein the aryl group is phenyl and naphthyl,
(f) heteroaryl, wherein heteroaryl is as defined above,
(g) heteroaryl C$_{1-6}$ alkyl, wherein heteroaryl is as defined above,
(h) cycloalkyl wherein the cycloalkyl is a 5-, 6-, or 7-membered monocyclic ring which optionally contains 1 or 2 heteroatoms selected from S, O, and N,
(i) an alkyl containing an aryl or heteroaryl substituent,
(j) any combination of (a) to (h),

each of (b) to (j) being optionally mono- or di- substituted, the substituents being independently selected from:

5

(1) hydroxy,
(2) C_{1-4} alkyl,
(3) C_{1-3} alkoxy,
(4) C_{1-3} alkylthio,
(5) mono- and di-C_{1-3} alkylamino,
(7) \text{--S(O)}_k\text{-C}_{1-3} \text{alkyl, where } k \text{ is 1 or 2,}
(8) \text{--C(O)-O-C}_{1-3} \text{alkyl,}
(9) halo selected from fluoro, chloro and bromo.

15 Within this genus, there is a class of compounds,

wherein \( R_1, R_2, R_3, R_4, R_5, \) and \( R_6 \) are each independently selected from the group comprising:

20 (a) hydrogen,
(b) hydroxy,
(c) amino,
(d) cyano,
(e) fluoro, chloro or bromo,
(f) trifluoromethyl,
(g) C_{1-6} alkyl,
(h) C_{1-6} alkoxy,
(i) C_{1-6} alkylthio, and
(j) mono- and di-C_{1-4} alkylamino.
wherein R₁ and R₂, or R₂ and R₃, or R₃ and R₄, or R₄ and R₅, or R₅ and R₆ may be joined together to form a 5-, 6- or 7-membered saturated monocyclic ring containing 0, 1 or 2 heteroatoms which together with the atoms to which R₁ and R₂, or R₂ and R₃ or R₃ and R₄ or R₄ and R₅, or R₅ and R₆ are attached, there is formed a ring system according to Formulae II-I to II-V, the heteroatoms being selected from the group consisting of O, S and N,
wherein \( R_7 \) is selected from the group comprising:

(a) hydrogen,
(b) amino,
(c) \( C_{1-4} \) alkyl,
(d) phenyl,
(e) phenyl \( C_{1-4} \) alkyl,
(f) heteroaryl, wherein heteroaryl is selected from,
   (1) pyridyl,
   (2) furanyl,
   (3) thienyl,
   (4) pyrazinyl,
   (5) pyrimidyl,
   (6) thiazolyl, and
   (7) triazolyl,
(g) heteroaryl \( C_{1-6} \) alkyl, wherein heteroaryl is defined as above,
(h) an alkyl containing an aryl or heteroaryl substituent, and
(i) cycloalkyl, wherein the cycloalkyl is a 5-, 6-, or 7-membered monocyclic ring which optionally contains 1 or 2 heteroatoms selected from \( S, O, \) and \( N \),

each of (b) to (i) being optionally mono- or di- substituted, the substituents being independently selected from:

(1) hydroxy,
(2) \( C_{1-4} \) alkyl,
(3) \( C_{1-3} \) alkoxy,
(4) \( C_{1-3} \) alkylthio,
(5) mono- and di-\( C_{1-3} \) alkylamino,
(7) \(--S(O)_{k}\) -\( C_{1-3} \) alkyl, where \( k \) is 1 or 2,
(8) \(--C(O)-O-C_{1-3} \) alkyl,
(9) halo selected from fluoro, chloro and bromo.

Within this class is the subclass of compounds wherein the rings of Formulae II-I, II-II, II-
III, II-IV and II-V are selected from the group comprising:-

(i)

(ii)

(iii)

(iv)
wherein this sub-class of compounds may be saturated or unsaturated. Preferably the compounds of the above subclass are unsaturated compounds.

Within the above subclass of compounds are the compounds of Formulae II-I, II-II, II-III, II-IV and II-V wherein \( R_1, R_2, R_3, R_4, R_5 \) and \( R_6 \), as explicitly shown, are each independently selected from the group comprising:-

(a) hydrogen,
(b) hydroxy,
(c) amino,
(d) cyano,
(e) fluoro, chloro or bromo,
(f) trifluoromethyl,
(g) \( C_{1-4} \) alkyl,
(h) \( C_{1-4} \) alkoxy,
(i) \( C_{1-4} \) alkylthio,
(j) mono- and di-\( C_{1-4} \) alkylamino,

\( R_7 \) is selected from the group comprising:-

(a) hydrogen,
(b) amino,
(c) \( C_{1-4} \) alkyl,
(d) phenyl,
(e) phenyl \( C_{1-4} \) alkyl,
(f) heteroaryl, wherein heteroaryl is selected from:-

(1) pyridyl,
(2) furanyl,
(3) thienyl,
(4) pyrazinyl,
(5) pyrimidyl,
(6) thiazolyl, and
(7) triazolyl,
(g) heteroaryl C_{1-6} alkyl, wherein heteroaryl is defined as above,
(h) an alkyl containing an aryl or heteroaryl substituent, and
(i) cycloalkyl, wherein the cycloalkyl is a 5-, 6-, or 7-membered monocyclic ring which optionally contains 1 or 2 heteroatoms selected from S, O, and N,

each of (b) to (i) being optionally mono- or di- substituted, the substituents being independently selected from:-

10
(1) hydroxy,
(2) C_{1-4} alkyl,
(3) C_{1-3} alkoxy,
(4) C_{1-3} alkylthio,
(5) mono- and di-C_{1-3} alkylamino,
(6) -S(O)\_k -C\_{1-3} alkyl, where \(k\) is 1 or 2,
(7) -C(O)-O-C\_{1-3} alkyl, and
(8) halo selected from fluoro, chloro and bromo.

20 The present invention is particularly exemplified by the following compounds, each of which is encompassed by the present invention:-

(a) 4-methyl-2-aminoquinoline,
(b) 6-methyl-2-aminoquinoline,
(c) 7-methyl-2-aminoquinoline,
(d) 8-methyl-2-aminoquinoline,
(e) 3-ethyl-2-aminoquinoline,
(f) 4-ethyl-2-aminoquinoline,
(g) 7-ethyl-2-aminoquinoline,
(h) 8-ethyl-2-aminoquinoline,
(i) 7-nitro-2-aminoquinoline,
(j) 3-methoxy-2-aminoquinoline
(k) 4-methoxy-2-aminoquinoline,
(l) 3-chloro-2-aminoquinoline,
(m) 2-aminoquinoline,

or a pharmaceutical acceptable salt thereof.

A particularly preferred compound is 2-aminopyridine.

In yet a further embodiment, the present invention provides a method for modulating the activity of a protein comprising an SH3 domain having a three-dimensional ligand-binding site comprising a negatively charged amino acid residue and a hydrophobic amino acid residue linearly separated by at least five amino acid residues, said method comprising the administration of an effective amount of a compound of the Formula III:

![Formula III](image)

or a pharmaceutically acceptable salt, hydrate, solvent, crystal form and individual diastereom isomer thereof for a time and under conditions sufficient for said compound to modulate the activity of said protein wherein R₁, R₂, R₃, R₄, R₅ and R₆ are each independently selected from the group comprising:

(a) hydrogen,
(b) hydroxy,
(c) amino,
(d) carboxyl,
(e) aminocarbonyl,
(f) cyano,
5  (g) nitro,
(h) halo, where halo is selected from fluoro, chloro, bromo, and iodo,
(i) trifluoromethyl,
(j) C₁₋₁₂ alkyl,
(k) C₂₋₁₂ alkenyl,
10  (l) C₂₋₁₂ alkyne,
(m) C₁₋₁₂ alkoxy,
(n) C₁₋₁₂ alkylcarbonyl,
(o) C₁₋₁₂ alkoxy carbonyl,
(p) C₁₋₁₂ alkylaminocarbonyl,
15  (q) mono- and di-C₁₋₁₂ alkylamino,
(r) C₁₋₁₂ alkylthio,
(s) aryl, where aryl is selected from phenyl and naphthyl,
(t) aryloxy, where aryl is selected from phenyl and naphthyl,
(u) arylthio, where aryl is selected from phenyl and naphthyl,
20  (v) aryl C₁₋₆ alkyl, where aryl is selected from phenyl and naphthyl,
(w) cycloalkyl, wherein the cycloalkyl is a 5- to 10-membered monocyclic ring which optionally contains 1 or 2 heteroatoms selected from S, O, and N,
(x) heteroaryl, wherein heteroaryl is selected from the group comprising:

(l) pyridyl,
25  (2) pyrrolyl,
(3) furanyl,
(4) thienyl,
(5) isothiazolyl,
(6) imidazolyl,
30  (7) benzimidazolyl,
(8) tetrazolyl,
(9) pyrazinyl,
(10) pyrimidyl,
(11) quinolyl,
(12) isoquinolyl,
5  (13) benzofuranyl,
    (14) isobenzofuryl,
    (15) benzothienyl,
    (16) pyrazolyl,
    (17) pyrazinyl,
10  (18) indolyl,
    (19) isoindolyl,
    (20) purinyl,
    (21) carbazolyl,
    (22) isoxazolyl,
15  (23) thiazolyl,
    (24) triazolyl
    (25) oxazolyl,
    (26) oxadiazolyl,
    (27) thiadiazolyl
20  (28) benzothiazolyl; and
    (29) benzoazolyl,
(y) heteroaryl C₁₋₆ alkyl, where heteroaryl is defined above in item (x),

each of (j) to (y) being optionally mono- or di- substituted, the substituents being
25 independently selected from:

(l) hydroxy,
    (2) C₁₋₆ alkyl,
    (3) C₁₋₆ alkoxy,
30  (4) amino,
    (5) mono- and di-C₁₋₆ alkylamino,
(6) carboxyl,
(7) $C_{1-6}$ alkylthio,
(8) $-S(O)_k-C_{1-3}$ alkyl, where $k$ is 1 or 2,
(9) $C_{1-6}$ alkoxycarbonyl,
(10) halo selected from fluoro, chloro, bromo, and iodo,
(11) oxo,
(12) amidino, and
(13) guanidino,

wherein $R_1$ and $R_2$, or $R_2$ and $R_3$, or $R_3$ and $R_4$, or $R_4$ and $R_5$, or $R_5$ and $R_6$ may be joined together to form a 5- to 10-membered saturated or unsaturated ring containing 0 to 2 heteroatoms which together with the atoms to which $R_1$ and $R_2$, or $R_2$ and $R_3$, or $R_3$ and $R_4$, or $R_4$ and $R_5$, or $R_5$ and $R_6$ are attached there is formed a ring system according to Formulae III-I to III-V, the heteroatoms being selected from the group consisting of O, S and N,
wherein \( R_7 \) is selected from the group comprising:

(a) hydrogen,
(b) amino,
(c) \( C_{1-12} \) alkyl,
(d) \( C_{2-12} \) alkenyl,
(e) \( C_{2-12} \) alkynyl,
(f) aryl, wherein the aryl group is as defined above,
(g) aryl \( C_{1-6} \) alkyl, wherein the aryl group is as defined above,
(h) heteroaryl, wherein heteroaryl is as defined above,
(i) heteroaryl \( C_{1-6} \) alkyl, wherein heteroaryl is as defined above,
(j) an alkyl containing an aryl or heteroaryl substituent, and
(k) cycloalkyl, wherein the cycloalkyl is a 5- to 10-membered monocyclic ring which optionally contains 1 or 2 heteroatoms selected from the group consisting of S, O and N,

5 each of (b) to (k) being optionally mono- or di- substituted, the substituents being independently selected from:

(1) hydroxy,
(2) C<sub>1-6</sub> alkyl,
(3) C<sub>1-6</sub> alkoxy,
(4) amino,
(5) mono- and di-C<sub>1-6</sub> alkylamino,
(6) carboxyl,
(7) C<sub>1-6</sub> alkylthio,
(8) --S(O)<sub>k</sub>-C<sub>13</sub> alkyl, where k is 1 or 2,
(9) C<sub>1-6</sub> alkoxy carbonyl,
(10) halo selected from fluoro, chloro, bromo, and iodo,
(11) oxo,
(12) amidino, and
(13) guanidino.

In an alternative aspect, this embodiment includes compounds wherein R₁, R₂, R₃, R₄, R₅ and R₆ may be aryl-S(O)<sub>k</sub> or heteroaryl-S(O)<sub>k</sub>.

25 Within this embodiment, there is the genus of compounds,

wherein R₁, R₂, R₃, R₄, R₅ and R₆ are each independently selected from the group comprising:

30 (a) hydrogen,
(b) hydroxy,
(c) amino,
(d) cyano,
(e) fluoro, chloro, bromo, and iodo,
(f) trifluoromethyl,
5  (g) C_{1-6} alkyl,
(h) C_{1-6} alkoxy,
(i) C_{1-6} alkylthio,
(j) C_{1-6} alkylcarbonyl,
(k) mono- and di-C_{1-6} alkylamino,
10 (l) aryl, where aryl is phenyl and naphthyl,
(m) aryloxy, where aryl is phenyl and naphthyl,
(n) cycloalkyl, wherein the cycloalkyl is a 5-, 6-, or 7-membered monocyclic ring
which optionally contains 1 or 2 heteroatoms selected from S, O, and N,
(o) heteroaryl, wherein heteroaryl is selected from the group comprising:
15  (1) pyridyl,
(2) furanyl,
(3) thiroyl,
(4) pyrazinyl,
(5) pyrimidyl,
20  (6) thiazolyl, and
(7) triazolyl,

each of (g) to (o) being optionally mono- or di- substituted, the substituents being
independently selected from:
25  (1) hydroxy,
(2) C_{1-4} alkyl,
(3) C_{1-3} alkoxy,
(4) C_{1-3} alkylthio,
30  (5) mono- and di-C_{1-3} alkylamino,
(6) --S(O)\text{$_{k}$}-C_{1-3} alkyl, where $k$ is 1 or 2, .
(7) --C(O)-O-C_{1-3} alkyl,
(8) halo selected from fluoro, chloro and bromo,
(9) amino, and
(10) carboxyl,

wherein R₁ and R₂, or R₂ and R₃, or R₃ and R₄, or R₄ and R₅, or R₅ and R₆ may be joined together to form a 5-, 6- or 7-membered saturated monocyclic ring containing 0, 1 or 2 heteroatoms which together with the atoms to which R₁ and R₂, or R₂ and R₃, or R₃ and R₄, or R₄ and R₅, or R₅ and R₆ are attached there is formed a ring system according to Formulae III-I to III-V, the heteroatoms being selected from the group consisting of O, S and N,
wherein $R_7$ is selected from the group consisting of

(a) hydrogen,
(b) amino,
(c) C$_{1-6}$ alkyl,
(d) aryl, wherein the aryl group is phenyl and naphthyl,
(e) aryl C$_{1-6}$ alkyl, wherein the aryl group is phenyl and naphthyl,
(f) heteroaryl, wherein heteroaryl is as defined above,
(g) heteroaryl C$_{1-6}$ alkyl, wherein heteroaryl is as defined above,
(h) cycloalkyl wherein the cycloalkyl is a 5-, 6-, or 7-membered monocyclic ring which optionally contains 1 or 2 heteroatoms selected from S, O, and N,
(i) an alkyl containing an aryl or heteroaryl substituent, and
(j) any combination of (a) to (h),

each of (b) to (j) being optionally mono- or di- substituted, the substituents being independently selected from:
(1)hydroxy,
(2)C_{1-4} alkyl,
(3)C_{1-3} alkoxy,
(4)C_{1-3} alkylthio,
(5)mono- and di-C_{1-3} alkylamino,
(6)\text{--S(O)}_k\text{-C}_{1-3} alkyl, where k is 1 or 2,
(7)\text{--C(O)-O-C}_{1-3} alkyl,
(8)halo selected from fluoro, chloro and bromo.

Within this genus, there is a class of compounds,

wherein R_1, R_2, R_3, R_4, R_5 and R_6 are each independently selected from the group comprising:-

(a)hydrogen,
(b)hydroxy,
(c)amino,
(d)cyano,
(e)fluoro, chloro or bromo,
(f)trifluoromethyl,
(g)C_{1-6} alkyl,
(h)C_{1-6} alkoxy,
(i)C_{1-6} alkylthio, and
(j)mono- and di-C_{1-4} alkylamino.

wherein R_1 and R_2, or R_2 and R_3, or R_3 and R_4, or R_4 and R_5, or R_5 and R_6 may be joined together to form a 5-, 6- or 7-membered saturated monocyclic ring containing 0, 1 or 2 heteroatoms which together with the atoms to which R_1 and R_2, or R_2 and R_3, or R_3 and R_4, or R_4 and R_5, or R_5 and R_6 are attached, there is formed a ring system according to
Formulae III-I to III-V, the heteroatoms being selected from the group consisting of O, S and N:-

(III-I)

(III-II)

(III-III)

(III-IV)
wherein \( R_7 \) is selected from the group comprising:

5. (a) hydrogen,
(b) amino,
(c) \( C_{1-4} \) alkyl,
(d) phenyl,
(e) phenyl \( C_{1-4} \) alkyl,
10. (f) heteroaryl, wherein heteroaryl is selected from:
   (1) pyridyl,
   (2) furanyl,
   (3) thienyl,
   (4) pyrazinyl,
15. (5) pyrimidyl,
   (6) thiazolyl, and
   (7) triazolyl,
(g) heteroaryl \( C_{1-6} \) alkyl, wherein heteroaryl is defined as above,
(h) an alkyl containing an aryl or heteroaryl substituent, and
20. (i) cycloalkyl, wherein the cycloalkyl is a 5-, 6-, or 7-membered monocyclic ring
    which optionally contains 1 or 2 heteroatoms selected from S, O, and N,

each of (b) to (i) being optionally mono- or di- substituted, the substituents being
independently selected from:

25. (1) hydroxy,
Within this class is the sub-class of compounds wherein the rings of Formulae III-I, III-II, III-III, III-IV and III-V are selected from the group comprising:

(i) [Chemical structure image]

(ii) [Chemical structure image]

(iii) [Chemical structure image]

(iv) [Chemical structure image]
wherein this sub-class of compounds may be saturated or unsaturated. Preferably the compounds of the above sub-class are unsaturated compounds.

Within the above subclass of compounds are the compounds of Formulae III-I, III-II, III-III, III-IV and III-V wherein R₁, R₂, R₃, R₄, R₅ and R₆, as explicitly shown, are each independently selected from the group comprising: -
(a) hydrogen,
(b) hydroxy,
(c) amino,
(d) cyano,
(e) fluoro, chloro or bromo,
(f) trifluoromethyl,
(g) C\(_{1-4}\) alkyl,
(h) C\(_{1-4}\) alkoxy,
(i) C\(_{1-4}\) alkylthio,
(j) mono- and di-C\(_{1-4}\) alkylamino,

R\(_7\) is selected from the group comprising:-

(a) hydrogen,
(b) amino,
(c) C\(_{1-4}\) alkyl,
(d) phenyl,
(e) phenyl C\(_{1-4}\) alkyl,
(f) heteroaryl, wherein heteroaryl is selected from:-
    (1) pyridyl,
    (2) furanyl,
    (3) thienyl,
    (4) pyrazinyl,
    (5) pyrimidyl,
    (6) thiazolyl, and
    (7) triazolyl,
(g) heteroaryl C\(_{1-6}\) alkyl, wherein heteroaryl is defined as above,
(h) an alkyl containing an aryl or heteroaryl substituent, and
(i) cycloalkyl, wherein the cycloalkyl is a 5-, 6-, or 7-membered monocyclic ring
which optionally contains 1 or 2 heteroatoms selected from S, O, and N,
each of (b) to (i) being optionally mono- or di- substituted, the substituents being independently selected from:-

(1) hydroxy,
(2) C_{1-4} alkyl,
(3) C_{1-3} alkoxy,
(4) C_{1-3} alkylthio,
(5) mono- and di-C_{1-3} alkylamino,
(6) \(\text{--S(O)}_k\text{-C}_{1-3}\) alkyl, where \(k\) is 1 or 2,
(7) \(\text{--C(O)}\text{-O-C}_{1-3}\) alkyl, and
(8) halo selected from fluoro, chloro and bromo.

The present invention is exemplified by the following compounds, each of which is encompassed by the present invention:-

(a) tert-butyl 2-\{[(4-chloro-1-guanidino-7-isoquinolinyl)sulphonyl]amino\}benzoate;
(b) tert-butyl 3-\{[(4-chloro-1-guanidino-7-isoquinolinyl)sulphonyl]amino\}benzoate;
(c) methyl-3-\{[(4-chloro-1-guanidino-7-isoquinolinyl)sulphonyl]amino\}-4-methoxybenzoate;
(d) \(N\)-[(4-chloro-1-guanidino-7-isoquinolinyl)sulphonyl]glycine tert-butyl ester hydrochloride;
(e) \(N\)-[(4-chloro-1-guanidino-7-isoquinolinyl)sulphonyl]-\(\beta\)-alanine tert-butyl ester;
(f) \(N\)-[(4-chloro-1-guanidino-7-isoquinolinyl)sulphonyl]-N-methylglycine tert-butyl ester;
(g) \(N\)-[(4-chloro-1-guanidino-7-isoquinolinyl)sulphonyl]-N-phenylglycine tert-butyl ester;
(h) \(N\)-[(4-chloro-1-guanidino-7-isoquinolinyl)sulphonyl]-N-(cyclopentylmethyl)-glycine tert-butyl ester;
(i) \(N\)-[(4-chloro-1-guanidino-7-isoquinolinyl)sulphonyl]-N-(cyclohexylmethyl)glycine tert-butyl ester;
(j) \( N-[(4\text{-chloro}-1\text{-guanidino}-7\text{-isoquinolinyl})\text{ sulphonyl}]\text{-N-benzylglycine tert-butyl ester;} \)

(k) \( N-[(4\text{-chloro}-1\text{-guanidino}-7\text{-isoquinolinyl})\text{ sulphonyl}]\text{-N-(2-methylbenzyl)glycine tert-butyl ester;} \)

(l) 1-aminoisoquinoline.

A particularly preferred compound is 2-aminopyridine.

For purposes of this specification, alkyl is defined to include linear, branched, and cyclic structures, with \( C_{1-6} \) alkyl including methyl, ethyl, propyl, 2-propyl, sec-butyl and tert-butyl, butyl, pentyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. Similarly, \( C_{1-6} \) alkoxy is intended to include alkoxy groups of from 1 to 6 carbon atoms of a straight, branched, or cyclic configuration. Examples of lower alkoxy groups include methoxy, ethoxy, propoxy, isopropanoxy, cyclopropyloxy, cyclohexyloxy, and the like. Likewise, \( C_{1-6} \) alkylthio is intended to include alkylthio groups of from 1 to 6 carbon atoms of a straight, branched or cyclic configuration. Examples of lower alkylthio groups include methylthio, propylthio, isopropylthio, cycloheptylthio, etc. By way of illustration, the propylthio group signifies \( \text{--SCH}_2 \text{CH}_2 \text{CH}_3 \).

Heteroaryl includes but is not limited to, pyridyl, pyrrolyl, furanyl, thienyl, isothiazolyl, imidazolyl, benzimidazolyl, tetrazolyl, pyrazinyl, pyrimidyl, quinolyl, isoquinolyl, benzo[\text{furan}yl, isobenzofuryl, benzothienyl, pyrazolyl, pyridazinyl, indolyl, isoindolyl, purinyl, carboxazolyl, isoxazolyl, thiazolyl, triazolyl, oxazolyl, oxadiazolyl, thiadiazolyl, benzthiazolyl and benzoxazolyl.

Reference herein to a protein includes reference to a peptide or polypeptide.

Without limiting the present invention to one theory or mode of action, the compounds of the present invention can bind to the surface of an SH3 domain present in a peptide, polypeptide or protein. It is thought that the binding of the compounds of the present invention to the surface of the SH3 domain as herein defined can modulate the activity of
the protein. The SH3 domain binding compounds of the present invention exhibit a wide range of biological activities which include the enhancement (or inhibition, depending on the particular molecule and the nature of the interaction of the molecule with the target SH3 domain, in this case, a peptide, polypeptide or protein bearing an SH3 domain) of the natural function or biological activity of the target molecule. For example, the interaction of the compounds of the present invention can result in the modulation of the oncogenic activity of a peptide, polypeptide or protein bearing an SH3 domain or the ability of a peptide, polypeptide or protein to signal an immune response. Therefore, modulating the activity of a protein facilitates the prophylaxis and treatment of disease conditions which are associated with or result from elevated or decreased levels of the proteins in question.

By "modulating" is meant an alteration in the activity or expression of a protein when compared with wild type activity of the protein. By "wild-type" is meant protein activity in a subject which is not inappropriately expressed. The term includes up-regulating and down-regulating the activity or expression of the protein. A compound capable of up-regulating the expression of the protein provides prophylaxis or therapeutic benefit when the activity of a protein is below that of wild-type activity. Conversely, a compound capable of down regulating the expression of the protein provides a therapeutic benefit when the activity of the protein is above that of wild-type activity.

The term "subject" includes primates, livestock animals (e.g. horse, cattle, sheep, pigs, donkeys), laboratory test animals (e.g. mice, rats, rabbits, guinea pigs), companion animals (e.g. dogs, cats), captive wild animals (e.g. kangaroos, deer, foxes) and birds (e.g. chickens, ducks, bantams, pheasants). Preferably, the subject is a human or a laboratory test animal. Even more preferably, the subject is a human.

"Inappropriate activity" or "inappropriate expression" should be understood as activity or expression of proteins that can be substantially greater than or substantially less than the wild-type activity of the protein. The inappropriate activity or expression is preferably between 100 and 1000 times greater than or less than wild-type activity or expression of a protein comprising the SH3 domain. Still more preferably, the inappropriate activity is
between 50 and 500 times greater than or less than wild-type activity of the protein. Even more preferably, the inappropriate activity is between 5 and 100 times greater than or less than wild-type activity of the protein. Most preferably, the inappropriate activity is between 1 and 10 times greater than or less than wild-type expression of the protein.

The compounds of the present invention are useful for the treatment and prophylaxis of inappropriate expression of proteins including but not limited to Tec, Btk, Itk, Tec, Rlk, and Bmx kinases, as well as Src, Lyn, Hck, Fgr, Fyn, Lck, Nck, Grb2 and p85α. Inappropriate activity or expression of such a protein can result in a disease state or pre-disease state, or be associated with a disease state and/or a pre-disease state. Disease states contemplated herein include but are not limited to proliferative disorders such as cancer. Cancers contemplated herein include but are not limited to lymphosarcoma, osteosarcoma, mammary tumors, mastocytoma, brain tumor, melanoma, adenosquamous carcinoma, carcinoid lung tumor, bronchial gland tumor, bronchiolar adenocarcinoma, fibroma, myxochondroma, pulmonary sarcoma, neurosarcoma, osteoma, papilloma, retinoblastoma, Ewing’s sarcoma, Wilms tumor, Burkitt’s lymphoma, microglioma, neuroblastoma, osteoclastoma, oral neoplasia, fibrosarcoma, osteosarcoma and rhabdomyosarcoma.

The compounds of the present invention are further useful in the treatment and prophylaxis of inflammatory conditions that result from, or are associated with, inappropriate protein activity or expression. Inflammatory conditions and disorders contemplated herein include but are not limited to osteoarthritis, tissue and/or organ transplant rejection, sepsis, ARDS, asthma, trauma, oxidative stress, cell death, irradiation damage, ischemia, reperfusion, cancer, viral infection, autoimmune disease, rheumatoid arthritis, psoriasis, inflammatory bowel disease, glomerulonephritis, lupus, uveitis, chronic hepatitis, juvenile diabetes, chronic non-suppurative thyroiditis, tuberculosis, syphilis, actinomycosis, sarcoidosis, amyloidosis, granulomatous thyroiditis, lymphocytic thyroiditis, Hashimoto’s thyroiditis, invasive fibrous thyroiditis, Grave’s disease, regional enteritis, Crohn’s Disease, granulomatous ileitis, ulcerative colitis, chorioretinal inflammatory syndrome, pancreatitis, Paget’s Disease, synovitis of the hip, odynophagia, dysphagia, viral and bacterial pharyngitis, infectious mononucleosis, acute tonsillitis, peritonsillar abscess, ulcerative
tonsillitis, lingual tonsillitis, Candidiasis, Epiglottitis, tracheobronchial inflammation, Ludwig’s angina, idiopathic pulmonary fibrosis, interstitial lung disease, lichen planus, lichen sclerosus, squamous hyperplasia, abscess, meningitis, encephalitis, vasculitis, progressive multifocal leukoencephalopathy, urticaria, spongiotic dermatitis, allergic contact dermatitis, dermatitis, chronic contact dermatitis, lichen simplex chronicus, atopic dermatitis, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, discoid lupus erythematosus, acne vulgaris and atherosclerosis.

The present invention, therefore, provides a method for the treatment and prophylaxis of a disease state or pre-disease state that results from, or is associated with inappropriate protein activity or expression in proliferative disorders including cancer.

Other conditions contemplated herein to be treated include stroke, osteoporosis, HIV infection, immunosuppression and cardiac dysfunction.

Preferably, compounds of Formula I are useful for the prophylaxis and/or treatment of a disease state or pre-disease state that results from, or is associated with, inappropriate activity or expression of a protein comprising an SH3 domain having a three-dimensional ligand-binding site comprising a negatively charged amino acid residue and a hydrophobic amino acid residue linearly separated by at least five amino acid residues.

Accordingly, the present invention provides a method for the prophylaxis and/or treatment of a disease state or pre-disease state that results from, or is associated with, inappropriate activity or expression of the protein, said method comprising the step of administering to a subject an effective amount of a compound of the Formula I or a derivative or analog or mimetic thereof or a pharmaceutically acceptable salt hydrate, solvent crystal form and/or diastereoisomer thereof for a time and under conditions sufficient for said compound to provide a treatment and/or a prophylactic response in said subject with a disease state or pre-disease state that results from, or is associated with, an inappropriate activity or expression of the protein.
Reference to "administering" a compound should be understood to include all routes of administration including but not limited to injection, inhalation and ingestion.

In a related aspect, compounds of Formula II are useful for the prophylaxis and/or treatment of a disease state or pre-disease state that results from, or is associated with, inappropriate activity or expression of a protein comprising an SH3 domain having a three-dimensional ligand-binding site comprising a negatively charged amino acid residue and a hydrophobic amino acid residue linearly separated by at least five amino acid residues.

Accordingly, the present invention provides a method for the prophylaxis and/or treatment of a disease state or pre-disease state that results from, or is associated with, inappropriate activity or expression of a protein comprising an SH3 domain having a three-dimensional ligand-binding site comprising a negatively charged amino acid residue and a hydrophobic amino acid residue linearly separated by at least five amino acid residues, said method comprising the step of administering to a subject an effective amount of a compound of the Formula II or a derivative or analog or mimetic thereof or a pharmaceutically acceptable salt hydrate, solvent crystal form and/or diastereoisomer thereof for a time and under conditions sufficient for said compound to provide a treatment and/or a prophylactic response in said subject with a disease state or pre-disease state that results from, or is associated with, an inappropriate activity or expression of said protein.

Compounds of Formula III are useful for the prophylaxis and/or treatment of a disease state or pre-disease state that results from, or is associated with, inappropriate activity or expression of a protein comprising an SH3 domain having a three-dimensional ligand-binding site comprising a negatively charged amino acid residue and a hydrophobic amino acid residue linearly separated by at least five amino acid residues.

In still yet a further embodiment, the present invention provides a method for the prophylaxis and/or treatment of a disease state or pre-disease state that results from, or is associated with, inappropriate activity or expression of a protein comprising an SH3 domain having a three-dimensional ligand-binding site comprising a negatively charged
amino acid residue and a hydrophobic amino acid residue linearly separated by at least five amino acid residues, said method comprising the step of administering to a subject an effective amount of a compound of the Formula III or a derivative or analog or mimetic thereof or a pharmaceutically acceptable salt hydrate, solvent crystal form and/or diastereoisomer thereof for a time and under conditions sufficient for said compound to provide a treatment and/or a prophylactic response in said subject with a disease state or pre-disease state that results from, or is associated with, an inappropriate activity or expression of said protein.

Without limiting the application of the present invention in any way, the present invention provides a method for facilitating the analysis, design and/or modification of compounds capable of binding the SH3 domain present in a peptide, polypeptide or protein. The conserved nature of the SH3 domain, such as in human, is highlighted in Table 3. As a consequence, a ligand identified and generated in accordance with the present invention with respect to one particular SH3 domain, is likely to act as a ligand for SH3 domains in other proteins. Preferably the SH3 domain is present in a protein selected from Tec, Src, Lyn, Hck, Fgr, Fyn, Lck, Nck, Grb2 and p85α. In this regard, reference to “analysis, design and/or modification” of a compound should be understood in its broadest sense to include all screening strategies (for example, high throughput screening technology) to identify members of the compounds of Formulae I, II and III which exhibit a preferred modulatory capacity with respect to SH3 domain functional activity. Screening methods for the determination of the biological and pharmaceutical activity of compounds and molecules are well known in the art. In this aspect, the present invention provides a molecular model of the three dimensional structure of an SH3 domain from a protein. The model provides a means for determining the potential interaction of compounds of the Formulae I, II or III with an SH3 domain. In a particularly preferred aspect, the present invention provides a binding site present on the SH3 domain to which compounds of the Formulae I, II and III bind. In a related aspect, the present invention, therefore, provides a method for the analysis design and/or modification of the compounds of the Formulae I, II or III, for the purpose of increasing or decreasing the binding capacity of the compounds.
Accordingly, the present invention provides a method of using the three-dimensional structure of a protein in a molecular screening assay to identify molecules capable of interacting with a peptide, polypeptide or protein, said method comprising subjecting the three dimensional structure of a peptide, polypeptide or protein and a molecule to \textit{in silico} molecular modelling means to determine gap space regions including a functional moiety or moieties present on said molecule that do not demonstrate optimum close contacts between the molecule and the amino acids of the interaction surface region or pocket present on said peptide polypeptide or protein, and subjecting said molecule to \textit{in silico} manipulation means to optimize close contacts between the molecule and the selected amino acids of the interaction surface, region or pocket of said peptide polypeptide or protein, thereby identifying a molecule with the same or altered capacity to interact with the surface, region or pocket of the a peptide polypeptide or protein.

As used herein, reference to a three-dimensional structure means a model of the three-dimensional structure of a SH3 domain. Methods for the production of a three-dimensional structure include but are not limited to x-ray crystallography, nuclear magnetic resonance, neutron scattering, chemical probing and the like. All such methods are contemplated herein.

As used herein, "gap space" means unoccupied space between the van der Waals surface of a compound positioned within the binding pocket and the surface of the binding pocket defined by residues in the binding site. This gap space between atoms represents volume that could be occupied by new functional groups on a modified version of the compound positioned within the binding pocket. Reference herein to a "pocket", "binding pocket" or "composite binding pocket" means a site on a three-dimensional structure of a SH3 domain binding site to which a compound with the structure of Formulae I, II or III can bind. The binding pocket represents a molecular surface which reveals regions within the binding site on the SH3 domain to which compounds of the present invention bind.

Reference herein to "\textit{in silico}" or "\textit{in silico} molecular modelling means" or "\textit{in silico} manipulation means" refers to the process in which a molecule or molecules such as an
(antagonist or agonist) can be examined through the use of a computer and a computer program such as but not limited to GRAM, DOCK, or AUTODOCK to determine the potential fit of a molecule or molecules to a given binding site present on another molecule such as but not limited to a peptide, polypeptide or protein. The term includes the virtual or "in silico" removal or addition of functional chemical groups by computational methods to provide a molecule with different chemical substituents or functional moieties, that may be examined for its potential fit to the molecule in question. Such "in silico" manipulation of molecular structure or computer based molecular methods for fitting of a molecule or molecules into a binding site or pocket present on a protein may also be used to estimate the attraction, repulsion and steric hindrance of the molecule or molecules to the binding site of the protein. Generally, the tighter the fit (e.g. the lower the steric hindrance, and/or the greater the attractive force), the greater the potential for the molecule or molecules to act as an agonist or antagonist as such properties are consistent with a tighter binding constraint. Furthermore, the more specificity in the design of the molecule or molecules, the more likely that the molecule or molecules will not interfere with closely related proteins. Therefore "in silico" manipulation of a molecule can be used to design molecules that can minimize side-effects by abolishing interactions with other proteins. The computer simulation of "docking" a compound in a binding pocket achieved by positioning a model of a compound in a model of the binding pocket. The model of the binding pocket can be, for example, based on coordinates obtained from the NMR structure of an SH3 domain and computer software can be used to simulate the docking interaction. Docking permits the identification of positions of the compound within the binding pocket that are favored, for example, due to minimization of energy.

As used herein, "minimization of energy" means achieving an atomic geometry of a molecule or molecular complex via systematic alteration such that any further minor perturbation of the atomic geometry would cause the total energy of the system as measured by a molecular mechanics force-field to increase. Minimization and molecular mechanics force-fields are well understood in computational chemistry.

Preferably, the peptide, polypeptide or protein to which a binding molecule or molecules is
sought comprising an SH3 domain comprising a protein comprising an SH3 domain having a three-dimensional ligand-binding site comprising a negatively charged amino acid residue and a hydrophobic amino acid residue linearly separated by at least five amino acid residues, and, even more preferably the molecule is Tec, Src, Lyn, Hck, Fgr, Fyn, Lck, Nck, Grb2 and p85α.

Accordingly, the present invention provides a method of using the three dimensional structure of a SH3 domain in a molecular screening assay to identify molecules capable of interacting with a SH3 domain, said method comprising subjecting the three dimensional structure of a SH3 domain and a molecule to \textit{in silico} molecular modelling means to determine gap space regions including a functional moiety or moieties present on said molecule that do not demonstrate optimum close contacts between the molecule and the amino acids of the interaction surface region or pocket present on said SH3 domain, and subjecting said molecule to \textit{in silico} manipulation means to optimize close contacts between the molecule and the selected amino acids of the interaction surface, region or pocket of SH3 domain, thereby identifying a molecule with the same or altered capacity to interact with the surface, region or pocket of the SH3 domain.

Preferably, the molecules capable of binding to such an SH3 domain are 2-aminopyridine, 2-aminoquinoline or 1-aminooisoquinoline or derivatives, homologs, analogs and mimetics.

In still another related embodiment, the present invention provides a method of using the three-dimensional structure of a SH3 domain comprising an SH3 domain having a three-dimensional ligand-binding site comprising a negatively charged amino acid residue and a hydrophobic amino acid residue linearly separated by at least five amino acid residues in a molecular screening assay to identify derivatives, homologs, analogs or mimetics of 2-aminopyridine, 2-aminoquinoline and 1-aminooisoquinoline capable of interacting with a SH3 domain of a said protein, said method comprising subjecting the three-dimensional structure of a SH3 domain of a said protein or a derivative, homolog, analog or mimetic of 2-aminopyridine, 2-aminoquinoline and 1-aminooisoquinoline to \textit{in silico} molecular modelling means to determine gap space regions including a functional moiety or moieties.
present on said derivative, homolog, analog or mimetic of 2-aminopyridine, 2-aminooquinoline and 1-aminooisoquinoline that do not demonstrate optimum close contacts between the derivative, homolog, analog or mimetic of 2-aminopyridine, 2-aminooquinoline and 1-aminooisoquinoline and the amino acids of the interaction surface region or pocket present on said SH3 domain of said protein and subjecting said derivative, homolog, analog or mimetic of 2-aminopyridine, 2-aminooquinoline and 1-aminooisoquinoline to in silico manipulation means to optimize close contacts between the derivative, homolog, analog or mimetic of 2-aminopyridine, 2-aminooquinoline and 1-aminooisoquinoline and the selected amino acids of the interaction surface, region or pocket of SH3 domain of said protein, thereby identifying a derivative, homolog, analog or mimetic of 2-aminopyridine, 2-aminooquinoline and 1-aminooisoquinoline with the same or altered capacity to interact with the surface, region or pocket of the SH3 domain of said protein.

In the present invention, the terms “derivative”, “homolog”, “analog” or “mimetic” are used interchangeably to mean a chemical substance that is related structurally and functionally to another substance. An analog or derivative contains a modified structure from the other substance, and maintains the function of the other substance, in this instance, maintaining the ability to interact with an SH3 binding site. The analog or derivative need not, but can be synthesized from the other substance. For example, a 2-aminooquinoline analog means a compound structurally related to 2-aminooquinoline, but not necessarily made from 2-aminooquinoline.

It is particularly preferred that the derivatives, homologs, analogs and mimetics of 2-aminopyridine, 2-aminooquinoline and 1-aminooisoquinoline make close contacts between tryptophan and optionally glutamate or aspartic acid amino acid residues present on the interaction surface, region or pocket of an SH3 domain of said protein.

In still another related embodiment, the present invention provides a method of using the three dimensional structure of a SH3 domain comprising a protein comprising an SH3 domain having a three-dimensional ligand-binding site comprising a negatively charged amino acid residue and a hydrophobic amino acid residue linearly separated by at least five
amino acid residues in a molecular screening assay to identify derivatives, homologs, analogs or mimetics of 2-aminopyridine, 2-aminoquinoline and 1-aminoisooquinoline capable of interacting with a SH3 domain of said protein, said method comprising subjecting the three dimensional structure of a SH3 domain of said protein or a derivative, homolog, analog or mimetic of 2-aminopyridine, 2-aminoquinoline and 1-aminoisooquinoline to in silico molecular modelling means to determine gap space regions including a functional moiety or moieties present on said derivative, homolog, analog or mimetic of 2-aminopyridine, 2-aminoquinoline and 1-aminoisooquinoline that do not demonstrate optimum close contacts between the derivative, homolog, analog or mimetic of 2-aminopyridine, 2-aminoquinoline and 1-aminoisooquinoline and the tryptophan and optionally glutamate or aspartic acid amino acid residues of the interaction surface region or pocket present on said SH3 domain of said protein, and subjecting said derivative, homolog, analog or mimetic of 2-aminopyridine, 2-aminoquinoline and 1-aminoisooquinoline to in silico manipulation means to optimize close contacts between the derivative, homolog, analog or mimetic of 2-aminopyridine, 2-aminoquinoline and 1-aminoisooquinoline and the selected tryptophan and optionally glutamate or aspartic acid amino acid residues of the interaction surface, region or pocket of SH3 domain of said protein, thereby identifying a derivative, homolog, analog or mimetic of 2-aminopyridine, 2-aminoquinoline and 1-aminoisooquinoline with the same or altered capacity to interact with the surface, region or pocket of the SH3 domain of said protein.

The compounds of the present invention are useful for the treatment of disorders associated with B-cells and B-cell precursors expressing a protein comprising an SH3 domain comprising an SH3 domain having a three-dimensional ligand-binding site comprising a negatively charged amino acid residue and a hydrophobic amino acid residue linearly separated by at least five amino acid residues which are implicated in the pathology of a number of diseases and conditions including B-cell malignancies such as acute lymphoblastic leukemia, chronic lymphocytic leukemia, non-Hodgkin's lymphoma, EBV lymphoma, and myeloma, and other cancers, including B-cell lymphoproliferative disorders/autoimmune diseases, lupus, Crohn's disease, and chronic myelogenous leukemia or graft-versus-host disease, mast cell disorders such as allergies and
anaphylactic shock. Tec kinase, for example, is also implicated in disease conditions that relate to improper platelet aggregation, and rejection of xenotransplants such as pig to human heart transplants. The compounds of the present invention are further useful in treating disorders in which Tec kinase activity plays a role in the aetiology of the disorder. Such disorders include but are not limited to, organ transplant, or heterograft or homograft (such as employed in burn treatment) rejection, or for the protection from ischemic or perfusion injury such as ischemic or perfusion injury incurred during organ transplantation, myocardial infarction, stroke or other causes. The compounds of the present invention are further useful in the treatment of arthritis, such as rheumatoid arthritis, psoriatic arthritis or osteoarthritis, multiple sclerosis, inflammatory bowel disease, including ulcerative colitis, T cell-mediated hypersensitivity diseases, including contact hypersensitivity diseases, delayed and type sensitivity, type 1 diabetes, psoriasis, dermatitis, Hashimoto’s thyroiditis, Sjogens Syndrome, auto-immune hyperthyroidism, autoimmune polyglandular syndrome, alopecia, pernicious anaemia, vitiligo, colon carcinoma and thymoma or cancers where the expression of the protein facilitates tumour growth such as mesothelioma, leukemia, and Karposi’s sarcoma. The compounds of the present invention are further useful in the treatment of a range of disorders including osteoporosis, allergic diseases such as asthma, hay-fever, scleracierma, mycosis fungoides, acute inflammatory responses such as respiratory distress syndrome, dermatomyositis, chronic actinic dermatitis, systemic sclerosis, Brechts disease, Pustulosis palmoplanteris, polydermagangrenum, Sezary’s syndrome, apoptotic dermatitis, systemic sclerosis and morphea. The present invention also provides for a method for treating the aforementioned disorders such as mesothelioma by the administration of a therapeutically effective amount of a compound of the present invention, which is a modulator of protein activity, to a patient or subject in need of such treatment.

It will be understood that in the discussion of methods of treatment which follows, references to the compounds of Formulae I, II and III are meant to also include the pharmaceutically acceptable salts.
The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example, magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the technique described in the U.S. Patent Nos. 4,256,108, 4,166,452 and 4,265,874 to form osmotic therapeutic tablets for control release.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active material in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethyl-cellulose, methylcellulose, hydroxy-propylmethyl-cellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example
polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethylene-oxyctanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose, saccharin or aspartame.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of an oil-in-water emulsion. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring phosphatides, for example soy beans, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene
oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavouring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Compounds of Formulae I, II and III may also be administered in the form of a suppository for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will, therefore, melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compounds of Formulae I, II and III are employed. (For purposes of this application, topical application shall include mouth washes and gargles.)

Dosage levels of the order of from about 0.01 mg to about 140 mg/kg of body weight per day are useful in the treatment of the above-indicated conditions, or alternatively about 0.5 mg to about 7 g per patient per day. For example, inflammation may be effectively treated by the administration of from about 0.01 to 50 mg of the compound per kilogram of body
weight per day, or alternatively about 0.5 mg to about 3.5 g per patient per day, preferably 2.5 mg to 1 g per patient per day.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration of humans may contain from 0.5 mg to 5 g of active agent compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Dosage unit forms will generally contain between from about 1 mg to about 500 mg of an active ingredient, typically 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 800 mg, or 1000 mg.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

The present invention is further described by the following non-limiting Examples.
EXAMPLE 1

Protein preparation

Definitions of Terminology

Names of Chemicals

IPTG: Isopropyl-β-D-thiogalactopyranoside
PMSF: Phenylmethylsulfonyl fluoride

Bacterial Growth Media

LB (Luria Broth): 1.0% w/v bacto-tryptone, 0.5% w/v yeast extract, 1% w/v NaCl. Made in double distilled autoclaved water. Adjusted to pH 7.0.

Min A (Minimal A Medium): 1.05% w/v K₂HPO₄, 0.45% w/v KH₂PO₄, 0.05% w/v Na₃Citrate, 0.081% w/v ¹⁵NH₄Cl, 0.8 mM MgSO₄, 0.2% w/v glucose, 5 x 10⁻⁴% w/v thiamine. Adjusted to pH 7.0.
**Buffers**

20 x TBS (Tris Buffered Saline): 500 mM H₂N-C(CH₂OH)₃, 3.0 M NaCl, pH adjusted to 8.0 with HCl.

1 x TTB: 0.1% v/v Triton X-100, in 1 x TBS.

**Procedure**

10 *Murine Tec* IV SH3 protein was prepared according to accepted protein preparation procedures (Pursglove et al., *J. Biomol. NMR* 12: 461-462, 1998). In brief, *Eschericia coli* strain BL21-DE3 was transfected with the p-Gex 4T-2 expression vector containing regions of cDNA encoding Glutathione S Transferase (GST), connected by a thrombin site to amino acids 181-245 of the *Murine Tec* IV sequence (representing the SH3 domain).

An overnight culture of *E.coli* BL21-DE3 p-GEK 4T-2 in LB + ampicillin (0.1 mg/ml) was diluted 1/100 into freshly prepared Min A media + ampicillin (0.1 mg/ml). These were grown at 37°C until they reached an OD₆₀₀ of 0.6, at which point fusion protein expression was induced by the addition of 100 mM IPTG such that the final concentration of IPTG was 0.1 mM. Incubation of cultures was continued for a further 3 hours, before being spun at 5000 rpm at 4°C for 30 minutes, and the supernatants were discarded. The pellets were then resuspended in 1 x TTBS, before lysing the cells under pressure three times, with 0.1 mM PMSF added each time such that the final concentration of PMSF was 1.0% w/v. The lysis mixture was then spun at 10,000 rpm at 4°C for 20 minutes, and the supernatant was filtered using a 1.0 μm prefiltter followed by a 0.45 μm nitrocellulose membrane. This sample was then chromatographed on an agarose/glutathione affinity column using 1 x TBS as the mobile phase, and the fusion protein was eluted with reduced glutathione (10 mM in 1 x TBS, pH 8). Thrombin (Sigma T 9681) (2.5 units/mg protein) was then used to cleave the fusion protein, in the presence of 2.5 mM CaCl₂, and 0.01% w/v NaN₃ as an antibacterial agent. This sample was incubated at 37°C for 2.5 hours. The cleaved protein products were then concentrated using an ultrafiltration system, before being separated by
size exclusion chromatography with 1 x TBS as mobile phase. The appropriate fractions containing the SH3 protein were combined and concentrated to approximately 1.5 ml by ultrafiltration and the concentration of protein was determined by a Bradford dye-binding assay (Rylatt and Parish, *Anal. Biochem.* 121: 213-214, 1982) to be 12.0 mg/ml. This 1.5 ml fraction was loaded onto a PD10 sepharose buffer exchange column that had been equilibrated with 10 mM Na₂HPO₄ buffer (pH 6, 0.01% w/v NaN₃) (40 ml). Of the several fractions collected, a 1.0 ml fraction determined to contain 5 mg/ml of the 8 KDa SH3 protein was used as the major stock supply for NMR samples.

EXAMPLE 2

Protein titration experiments

Samples of uniformly ^15^N labelled *Murine Tec* IV SH3 protein were prepared at a concentration of 0.125 mM (10% v/v D₂O, 10% v/v d₆-DMSO, 0.01% w/v NaN₃, made up to 600 µL with 10 mM Na₂HPO₄, pH adjusted to 6.60). Protein NMR experiments were recorded on a Varian Inova 600 Spectrometer (3 RF channels), using a 5 mm ^1^H(^13^C/^15^N) inverse triple resonance PFG probe. Sensitivity enhanced ^15^N/^1^H HSQC spectra (Kay et al., *J. Am. Chem. Soc.* 114: 10663-10665, 1992) were recorded at 20°C with spectral widths of 8000 Hz and 2000 Hz in F1 and F2, respectively, with 128 t₁ increments. The Fourier Transformed data resulted in a matrix size of 1024 x 512 data points, for F1 and F2, respectively.

Control ^15^N/^1^H HSQC spectra were first recorded on samples of the free protein. Candidate ligands were then titrated into the sample at an initial concentration of 0.125 mM (1 molar equivalent) in 2 µL of d₆-DMSO and the pH was readjusted, before a new HSQC spectrum was recorded. The titration step was then repeated several times, eventually increasing the concentration of candidate ligand introduced into the sample in each step, until saturation binding was observed. If by the stage when [candidate ligand] = 1.25 mM (10 x molar excess) no marked changes in chemical shift were observed, then the titration was ceased for that compound, and the compound was eliminated as a potential ligand.
Prior to using any compounds in ligand binding assays, they were all tested for solubility in a 10% v/v DMSO/Na₂HPO₄ buffer solution (pH 6.6) at a concentration of 1.25 mM which represented a ten times molar excess of the Tec SH3 protein (0.125 mM). This was considered the minimum criterion for solubility of all compounds that were included in ligand binding studies. Similarly, this was also considered the maximum concentration that a titration should be extended to if it became apparent that no changes in chemical shift were occurring, (i.e. no binding).

Processed NMR data were then analyzed using the package XEASY (Bartels et al., J. Biomol. NMR 6: 1-10, 1995). The spectra were centred about 4.85 ppm and 120 ppm for F1 and F2, respectively. Chemical shift change versus ligand concentration for peaks that moved significantly upon ligand addition were fitted using non-linear regression analysis with the program Prism3 (GraphPad Software Inc), to the relationship \( Y = B_{\text{max}} \cdot X / [K_d + X] \), where \( B_{\text{max}} \) is the maximal binding and \( K_d \) is the equilibrium dissociation constant and is representative of the concentration of ligand required to reach half maximal binding. Representative isotherms for four residues are undergoing chemical shift changes upon binding 2-aminoquinoline are shown in Figure 4. Mapping of the magnitude and sign (upfield or downfield shifts) of the chemical shift for each residue onto the SH3 protein structure was done using the package InsightII - (Molecular Simulations Incorporated) to indicate the location of the binding site of the ligand on the surface of the Tec SH3 domain.

**EXAMPLE 3**

**Biological analysis**

The influence of these compounds on the *in vitro* kinase activity of Tec is tested by immunoprecipitating endogenous Tec from cultured cells, or over expressed versions including mutant proteins, and incubating the isolated kinase with a peptide substrate and \(^{32}\text{P}-\text{labelled} \gamma-\text{ATP*} (Machide et al., Oncogene 11: 619-625, 1995). The effects of these compounds on cells in tissue culture is investigated, measuring indicators such as the
phosphorylation status of specific proteins, cell proliferation, differentiation, apoptosis and cell cycle regulation.

**EXAMPLE 4**

*Binding specificity*

Comparison of the amino acid sequence of human SH3 domains indicates that some regions of sequence are strongly conserved whereas other regions are not well conserved (Figure 3). The residues undergoing chemical shift changes upon compound binding, described in Example 2, include aspartate 196 and tryptophan 215. The corresponding residues are indicated by * in the last line of the Figure. The position corresponding to Trp 215 is conserved in all examples shown. The position corresponding to Asp 196 is represented in eight examples shown. The requirement for a negative residue at this position is tested by substitution with glutamate, alanine and threonine using site directed mutagenesis (Quikchange (trademark), Stratagene, La Jolla, CA, USA) and measurement of ligand binding as described in Example 3.

**EXAMPLE 5**

*Inhibiting osteoclast activity*


Human osteoclasts are prepared from 20 mL of heparinized peripheral blood by mixing with an equal volume of α-MEM (α-Minimal Essential Medium, Gibco-BRL) split into 5 tubes (8 ml each) and add 5 ml of histopaque (Sigma). After centrifugation for 30 minutes at 450 xg, the buffy coat layer is decanted into a fresh tube and washed in 10 mL of
α–MEM. Resuspend the cells in 4 mL of αMEM plus 10% v/v fetal calf serum (FCS) and count using a haemocytometer.

500,000 cells, in a volume of 20 μL are added to each well of 96 well tissue culture plate. After 1 hr at 37°C, the cells are washed 3 times and treated with 100 μL of α–MEM/10% v/v FCS containing 30 ng/mL RANK ligand and 25 ng/mL M-CSF.

In order to test resorption activities of the osteoclasts, the cells are allowed to adhere to sterile dentine discs (Immunodiagnostic Systems Ltd, UK) for 30 minutes at 37°C at 5% v/v CO₂. The discs are washed and treated with fresh media containing compounds or vehicle controls for 24-48 hrs at 37°C and 5% v/v CO₂. The discs are then washed briefly in 0.5% hypochlorite and stained in 1% w/v toluidine blue. The extent of resorption is quantified by reflective light microscopy.

This aspect of the invention is predicated on the use of 2-aminopyridine, 2-aminoquinoline and 1-aminooisoquinoline as inhibitors of Src in the treatment of osteoporosis (Violetta et al., Bone 28: 54-64, 2001).

EXAMPLE 6

*Preventing bone resorption activity*

The influence of 2-aminopyridine, 2-aminoquinoline and 1-aminooisoquinoline on the resorption of bone *in vivo* is measured using rat model systems. Surgical removal of the thyroid and parathyroid glands of rats can be used to induce a model of osteoporosis [Shakespear et al., Proc. Natl. Acad. Sci. USA 97: 9373-9378, 2000; Lark et al., Bone 30: 746-753, 2000]. The animals are allowed to recover from surgery for at least 2 days or until their serum calcium levels to drop to below 7 mg/100 mL. The effects of administration of compounds or vehicle control on serum calcium levels are monitored over a 21 day period using a colourimetric Arsenazo III complexation assay (Sigma).
EXAMPLE 7

Effect of 2-aminopyridine, 2-aminoquinoline and 1-aminoisoquinoline on Src proteins

Mammalian Src proteins may be generated by any number of means. For example, human Src proteins carrying an SH3 domain may be produced and purified as described by Lynch et al., Anal. Biochem. 247: 77-82, 1997; Vu et al., J. Med. Chem. 42: 4088-4098, 1999.

Methods similar to those described in Example 2 are then performed to analyze the extent of binding to the Src protein. It is expected that since Scr<sup>−/−</sup> mice are osteoprototic, i.e. inhibition of Src increases numbers of osteoblasts over osteoclasts, binding of the subject compound or their analogs or their derivatives to the Src SH3 domain will be useful treatment for osteoporosis.

Similarly, Src<sup>−/−</sup> mice also decreased infarct volumes after stroke. Consequently, an inhibitor of the Src SH3 domain may be indicated for stroke victims.

EXAMPLE 8

Inhibition of Lyn in the treatment of atherosclerosis

Similar protein titration studies are conducted on Lyn as described in the aforementioned Examples. As Lyn<sup>−/−</sup> mice shows reduced atherosclerosis, inhibition of the Lyn SH3 domain is proposed to be indicated in the treatment of atherosclerosis.

Compounds such as 2-aminopyridine, 2-aminoquinoline and 1-aminoisoquinoline are tested.
EXAMPLE 9

Inhibition of HIV infection

HIV infection is dependent on the interaction between the viral protein Nef and the SH3 domain of Hck. Similar binding studies as described above are preferred on Hck. Inhibition of the Hck SH3 domain such as by 1-aminopyridine, 2-aminoquinoline and/or 1-aminoquinoline or their derivatives is proposed to be useful in the prophylaxis of HIV infection.

EXAMPLE 10

Treatment of endotoxic shock

Hck\textsuperscript{−/−} and Fgr\textsuperscript{−/−} mice are resistant to endotoxic shock due to defects in neutrophil migration and activation. It is proposed, therefore, that inhibition of the Hck and/or Fgr SH3 domains by the compounds of the present invention will be useful in the treatment or prophylaxis of endotoxic shock.

EXAMPLE 11

Induction of immunosuppression

Lck is required for T-cell signaling. Consequently, inhibitors of Lck are proposed to act as T-cell specific immunosuppressants. This is particularly efficacious since expression of Lck is limited to lymphocytes.

EXAMPLE 12

Inhibition of tumor growth

The N- and C-terminal domains of Grb2 comprise SH3 domains. Grb2 is involved in signal cascade for a number of graft factor receptors including the EGF receptor family (e.g. ErbB-2, hepatocyte growth factor receptor (Met) and BCR/Ab1. Consequently,
inhibition of the SH3 domains of Grb2 is proposed to be useful in the treatment of aberrant cell growth such as tumor growth.

Those skilled in the art will appreciate that the invention described herein is susceptible to variations and modifications other than those specifically described. It is to be understood that the invention includes all such variations and modifications. The invention also includes all of the steps, features, compositions and compounds referred to or indicated in this specification, individually or collectively, and any and all combinations of any two or more of said steps or features.
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<td><img src="image1" alt="化合物1" /></td>
<td>Binds with $K_D = 135 \mu M$</td>
<td><img src="image2" alt="化合物2" /></td>
<td>NB</td>
</tr>
<tr>
<td><img src="image3" alt="化合物3" /></td>
<td>Binds with $K_D = 746 \mu M$</td>
<td><img src="image4" alt="化合物4" /></td>
<td>NB</td>
</tr>
<tr>
<td><img src="image5" alt="化合物5" /></td>
<td>Binds with $K_D = 4100 \mu M$</td>
<td><img src="image6" alt="化合物6" /></td>
<td>NB</td>
</tr>
<tr>
<td><img src="image7" alt="化合物7" /></td>
<td>Binds with $K_D = 368 \mu M$</td>
<td><img src="image8" alt="化合物8" /></td>
<td>NB</td>
</tr>
<tr>
<td><img src="image9" alt="化合物9" /></td>
<td>Binds with $K_D = 193 \mu M$</td>
<td><img src="image10" alt="化合物10" /></td>
<td>NB</td>
</tr>
<tr>
<td><img src="image11" alt="化合物11" /></td>
<td>NB</td>
<td><img src="image12" alt="化合物12" /></td>
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</tr>
<tr>
<td><img src="image13" alt="化合物13" /></td>
<td>NB</td>
<td><img src="image14" alt="化合物14" /></td>
<td>NB</td>
</tr>
</tbody>
</table>

**NB** = no binding observed
BIBLIOGRAPHY

CLAMS

1. A method for modulating the activity of a protein comprising an SH3 domain having a three-dimensional ligand-binding site comprising a negatively charged amino acid residue and a hydrophobic amino acid residue linearly separated by at least five amino acid residues, said method comprising the administration of an effective amount of a compound selected from a compound of Formulae I, II and III:

![Chemical Structures](image1)

(I)

![Chemical Structures](image2)

(II)

![Chemical Structures](image3)

(III)
or a pharmaceutically acceptable salt, hydrate, solvent, crystal form and/or individual diastereo isomers thereof for a time and under conditions sufficient for said compound to modulate the activity of said protein

wherein in relation to Formula I, R₁, R₂, R₃, R₄ and R₅ may be the same or different and each is selected from the group comprising of:-

(a) hydrogen,
(b) hydroxy,
(c) amino,
(d) carboxyl,
(e) aminocarbonyl,
(f) cyano,
(g) nitro,
(h) halo, where halo is selected from fluoro, chloro, bromo, and iodo,
(i) trifluoromethyl,
(j) C₁₋₁₂ alkyl,
(k) C₂₋₁₂ alkenyl,
(l) C₂₋₁₂ alkynyl,
(m) C₁₋₁₂ alkoxy,
(n) C₁₋₁₂ alkylcarbonyl,
(o) C₁₋₁₂ alkoxy carbonyl,
(p) C₁₋₁₂ alkylaminocarbonyl,
(q) mono-and di-C₁₋₁₂ alkylamino,
(r) C₁₋₁₂ alkylthio,
(s) aryl, where aryl is selected from phenyl and naphthyl,
(t) aryloxy, where aryl is selected from phenyl and naphthyl,
(u) arylthio, where aryl is selected from phenyl and naphthyl,
(v) aryl C₁₋₁₂ alkyl, where aryl is selected from phenyl and naphthyl,
(w) cycloalkyl, wherein the cycloalkyl is a 5- to 10-membered monocyclic ring which optionally contains 1 or 2 heteroatoms selected from S, O, and N,
(x) heteroaryl, wherein heteroaryl is selected from the group consisting of:

(1) pyridyl,
(2) pyrrolyl,
(3) furanyl,
(4) thietyl,
(5) isothiazolyl,
(6) imidazolyl,
(7) benzimidazolyl,
(8) tetrazolyl,
(9) pyrazinyl,
(10) pyrimidyl,
(11) quinolyl,
(12) isoquinolyl,
(13) benzofurany1,
(14) isobenzofurany1,
(15) benzothienyl,
(16) pyrazolyl,
(17) pyrazinyl,
(18) indolyl,
(19) isoindolyl,
(20) purinyl,
(21) carbazoly1,
(22) isoxazoly1,
(23) thiazoly1,
(24) triazolyl
(25) oxazoly1,
(26) oxadiazoly1,
(27) thiadiazoly1,
(28) benzthiazoly1; and
(29) benzoxazoly1,
(z) heteroaryl C₁₋₆ alkyl, where heteroaryl is defined above in item (x),
each of (j) to (y) being optionally mono- or di- substituted, the substituents being
independently selected from:-

(1) hydroxy,
(2) C₁₋₆ alkyl,
(3) C₁₋₆ alkoxy,
(4) amino,
(5) mono- and di-C₁₋₆ alkylamino,
(6) carboxyl,
(10) C₁₋₆ alkylthio,
(11) --S(O)ₓ-C₁₋₃ alkyl, where k is 1 or 2,
(12) C₁₋₆ alkoxy carbonyl,
(10) halo selected from fluoro, chloro, bromo, and iodo,
(11) oxo,
(12) amidino, and
(13) guanidino,

wherein R₁ and R₂, or R₂ and R₃ or R₃ and R₄ may be joined together to form a 5- to 10-
membered saturated or unsaturated ring containing 0 to 2 heteroatoms which together with
the atoms to which R₁ and R₂, or R₂ and R₃, or R₃ and R₄ are attached there is formed a
ring system according to Formulae I-I to I-III, the heteroatoms being selected from the
group consisting of O, S and N,
wherein \( R_5 \) is selected from the group consisting of:

(c) hydrogen,
(d) amino,
(c) \( C_{1-12} \) alkyl,
(d) \( C_{2-12} \) alkenyl,
(e) \( C_{2-12} \) alkynyl,
(f) aryl, wherein the aryl group is as defined above,
(g) aryl \( C_{1-6} \) alkyl, wherein the aryl group is as defined above,
(h) heteroaryl, wherein heteroaryl is as defined above,
(ii) heteroaryl \( C_{1-6} \) alkyl, wherein heteroaryl is as defined above,
(l) an alkyl containing an aryl or heteroaryl substituent, and
(m) cycloalkyl, wherein the cycloalkyl is a 5- to 10-membered monocyclic ring which optionally contains 1 or 2 heteroatoms selected from the group consisting of S, O and N,

each of (b) to (k) being optionally mono- or di-substituted, the substituents being independently selected from:-
(1) hydroxy,
(2) C_{1-6} alkyl,
(3) C_{1-6} alkoxy,
(4) amino,
(5) mono- and di-C_{1-6} alkyamino,
(6) carboxyl,
(7) C_{1-6} alkylthio,
(8) \text{--S(O)}_k\text{-C}_{1-3} alkyl, where \( k \) is 1 or 2,
(9) C_{1-6} alkoxy carbonyl,
(10) halo selected from fluoro, chloro, bromo, and iodo,
(11) oxo,
(12) amidino, and
(13) guanidino;

wherein in relation to Formula II, \( R_1, R_2, R_3, R_4, R_5 \) and \( R_6 \) are each independently selected from the group comprising:

(a) hydrogen,
(b) hydroxy,
(c) amino,
(d) carboxyl,
(e) aminocarbonyl,
(f) cyano,
(g) nitro,
(h) halo, where halo is selected from fluoro, chloro, bromo, and iodo,
(i) trifluoromethyl,
(j) C_{1-12} alkyl,
(k) C_{2-12} alkenyl,
(l) C_{2-12} alkynyl,
(m) C_{1-12} alkoxy,
(n) C_{1-12} alkylcarbonyl,
(o) C<sub>1</sub>-C<sub>12</sub> alkoxy carbonyl,
(p) C<sub>1</sub>-C<sub>12</sub> alkyaminocarbonyl,
(q) mono- and di-C<sub>1</sub>-C<sub>12</sub> alkylamino,
(r) C<sub>1</sub>-C<sub>12</sub> alkylthio,
(s) aryl, where aryl is selected from phenyl and naphthyl,
(t) arylxy, where aryl is selected from phenyl and naphthyl,
(u) arylthio, where aryl is selected from phenyl and naphthyl,
(v) aryl C<sub>1</sub>-C<sub>4</sub> alkyl, where aryl is selected from phenyl and naphthyl,
(w) cycloalkyl, wherein the cycloalkyl is a 5- to 10-membered monocyclic ring which optionally contains 1 or 2 heteroatoms selected from S, O, and N,
(x) heteroaryl, wherein heteroaryl is selected from the group comprising:-

(l) pyridyl,
(2) pyrrolyl,
(3) furanyl,
(4) thienyl,
(5) isothiazolyl,
(6) imidazolyl,
(7) benzimidazolyl,
(8) tetrazolyl,
(9) pyrazinyl,
(10) pyrimidyl,
(11) quinolyl,
(12) isoquinolyl,
(13) benzofuranyl,
(14) isobenzofuranyl,
(15) benzothienyl,
(16) pyrazolyl,
(17) pyrazinyl,
(18) indolyl,
(19) isoindolyl,
(20) purinyl,
(21) carbazolyl,
(22) isoxazolyl,
(23) thiazolyl,
(24) triazolyl
(25) oxazolyl,
(26) oxadiazolyl,
(27) thiadiazolyl,
(28) benzthiazolyl; and
(29) benzoazolyl,

(z) heteroarylC₁₋₆ alkyl, where heteroaryl is defined above in item (x),

each of (j) to (y) being optionally mono- or di- substituted, the substituents being independently selected from:-

(l) hydroxy,
(2) C₁₋₆ alkyl,
(3) C₁₋₆ alkoxy,
(4) amino,
(5) mono- and di-C₁₋₆ alkylamino,
(6) carboxyl,
(10) C₁₋₆ alkylthio,
(11) --S(O)ₓ-C₁₋₃ alkyl, where k is 1 or 2,
(12) C₁₋₆ alkoxycarbonyl,
(13) halo selected from fluoro, chloro, bromo, and iodo,
(11) oxo,
(12) amidino, and
(13) guanidino,
wherein R₁ and R₂, or R₃ and R₄, or R₅ and R₆ may be joined together to form a 5- to 10-membered saturated or unsaturated ring containing 0 to 2 heteroatoms which together with the atoms to which R₁ and R₂, or R₃ and R₄, or R₅ and R₆ are attached there is formed a ring system according to Formulae II-I to II-V, the heteroatoms being selected from the group consisting of O, S and N,
wherein $R_7$ is selected from the group comprising:

(c) hydrogen,
(d) amino,
(e) $C_{1-12}$ alkyl,
(f) $C_{2-12}$ alkenyl,
(g) $C_{2-12}$ alkynyl,
(h) aryl, wherein the aryl group is as defined above,
(i) aryl $C_{1-6}$ alkyl, wherein the aryl group is as defined above,
(j) heteroaryl, wherein heteroaryl is as defined above,
(k) heteroaryl $C_{1-6}$ alkyl, wherein heteroaryl is as defined above,

each of (b) to (k) being optionally mono- or di-substituted, the substituents being independently selected from:

(1) hydroxy,
(2) $C_{1-6}$ alkyl,
(3) $C_{1-6}$ alkoxy,
(4) amino,
(5) mono- and di-$C_{1-6}$ alkylamino,
(6) carboxyl,
(7) C_{1-6} alkylthio,
(8) \text{-S(O)}_k \text{-} C_{1-3} \text{ alkyl, where } k \text{ is 1 or 2},
(9) C_{1-6} alkoxy carbonyl,
(10) halo selected from fluoro, chloro, bromo, and iodo,
(11) oxo,
(12) amidino, and
(13) guanidin;

and in relation to Formula III, R_1, R_2, R_3, R_4, R_5 and R_6 are each independently selected from the group comprising:

(a) hydrogen,
(b) hydroxy,
(c) amino,
(d) carboxyl,
(e) aminocarbonyl,
(f) cyano,
(g) nitro,
(h) halo, where halo is selected from fluoro, chloro, bromo, and iodo,
(i) trifluoromethyl,
(j) C_{1-12} alkyl,
(k) C_{2-12} alkenyl,
(l) C_{2-12} alkynyl,
(m) C_{1-12} alkoxy,
(n) C_{1-12} alkylcarbonyl,
(o) C_{1-12} alkoxy carbonyl,
(p) C_{1-12} alkylaminocarbonyl,
(q) mono- and di-C_{1-12} alkylamino,
(r) C_{1-12} alkylthio,
(s) aryl, where aryl is selected from phenyl and naphthyl,
(t) aryloxy, where aryl is selected from phenyl and naphthyl,
(u) arylthio, where aryl is selected from phenyl and naphthyl,
(v) aryl C₆₋₆ alkyl, where aryl is selected from phenyl and naphthyl,
(w) cycloalkyl, wherein the cycloalkyl is a 5- to 10-membered monocyclic ring which optionally contains 1 or 2 heteroatoms selected from S, O, and N,
(x) heteroaryl, wherein heteroaryl is selected from the group comprising:

(1) pyridyl,
(2) pyrrolyl,
(3) furanyl,
(4) thiényl,
(5) isothiazolyl,
(6) imidazolyl,
(7) benzimidazolyl,
(8) tetrazolyl,
(9) pyrazinyl,
(10) pyrimidyl,
(11) quinolyl,
(12) isoquinolyl,
(13) benzofuranyl,
(14) isobenzofuryl,
(15) benzothienyl,
(16) pyrazolyl,
(17) pyrazinyl,
(18) indolyl,
(19) isoindolyl,
(20) purinyl,
(21) carbazolyl,
(22) isoxazolyl,
(23) thiazolyl,
(24) triazolyl
(25) oxazolyl,
(26) oxadiazolyl,
(27) thiadiazolyl
(28) benzthiazolyl; and
(29) benzoxazolyl,

(z) heteroaryl C<sub>1-6</sub> alkyl, where heteroaryl is defined above in item (x),

each of (j) to (y) being optionally mono- or di- substituted, the substituents being independently selected from:

(1) hydroxy,
(2) C<sub>1-6</sub> alkyl,
(11) C<sub>1-6</sub> alkoxy,
(12) amino,
(5) mono- and di-C<sub>1-6</sub> alkylamino,
(6) carboxyl,
(10) C<sub>1-6</sub> alkylthio,
(11) --S(O)<sub>k</sub>-C<sub>1-3</sub> alkyl, where k is 1 or 2,
(12) C<sub>1-6</sub> alkoxy carbonyl,
(10) halo selected from fluoro, chloro, bromo, and iodo,
(11) oxo,
(12) amidino, and
(13) guanidino,

wherein R<sub>1</sub> and R<sub>2</sub>, or R<sub>2</sub> and R<sub>3</sub>, or R<sub>3</sub> and R<sub>4</sub>, or R<sub>4</sub> and R<sub>5</sub>, or R<sub>5</sub> and R<sub>6</sub> may be joined together to form a 5- to 10-membered saturated or unsaturated ring containing 0 to 2 heteroatoms which together with the atoms to which R<sub>1</sub> and R<sub>2</sub>, or R<sub>2</sub> and R<sub>3</sub>, or R<sub>3</sub> and R<sub>4</sub>, or R<sub>4</sub> and R<sub>5</sub>, or R<sub>5</sub> and R<sub>6</sub> are attached there is formed a ring system according to Formulae III-I to III-V, the heteroatoms being selected from the group consisting of O, S and N,
wherein \( R_7 \) is selected from the group comprising:

(a) hydrogen,
(b) amino,
(c) \( C_{1-12} \) alkyl,
(d) \( C_{2-12} \) alkenyl,
(e) \( C_{2-12} \) alkynyl,
(f) aryl, wherein the aryl group is as defined above,
(g) aryl \( C_{1-6} \) alkyl, wherein the aryl group is as defined above,
(h) heteroaryl, wherein heteroaryl is as defined above,
(i) heteroaryl \( C_{1-6} \) alkyl, wherein heteroaryl is as defined above,
(j) an alkyl containing an aryl or heteroaryl substituent, and
(k) cycloalkyl, wherein the cycloalkyl is a 5- to 10-membered monocyclic ring which optionally contains 1 or 2 heteroatoms selected from the group consisting of S, O and N,

each of (b) to (k) being optionally mono- or di- substituted, the substituents being independently selected from:

(1) hydroxy,
(2) \( C_{1-6} \) alkyl,
(3) \( C_{1-6} \) alkoxy,
(4) amino,
(5) mono- and di-\( C_{1-6} \) alkylamino,
(6) carboxyl,
(7) C_{1-6} alkylthio,
(8) --S(O)\(_k\)-C\(_{13}\) alkyl, where \(k\) is 1 or 2,
(9) C\(_{1-6}\) alkoxy carbonyl,
(10) halo selected from fluoro, chloro, bromo, and iodo,
(11) oxo,
(12) amidino, and
(13) guanidino.

2. The method of Claim 1 wherein \(R_1, R_2, R_3\) and \(R_4\) of Formulae I to III, and in respect of Formulae II and III, additionally \(R_5\) and \(R_6\), are alternatively aryl-S(O)\(_k\) or heteroaryl-S(O)\(_k\).

3. The method of Claim 1 or 2 wherein \(R_1, R_2, R_3\) and \(R_4\) of Formulae I are each independently selected from the group comprising:

(a) hydrogen,
(b) hydroxy,
(c) amino,
(d) cyano,
(e) fluoro, chloro, bromo, and iodo,
(f) trifluoromethyl,
(g) C\(_{1-6}\) alkyl,
(h) C\(_{1-6}\) alkoxy,
(i) C\(_{1-6}\) alkylthio,
(j) C\(_{1-6}\) alkyl carbonyl,
(k) mono- and di- C\(_{1-6}\) alkyl amino,
(l) aryl, where aryl is phenyl and naphthyl,
(m) aryloxy, where aryl is phenyl and naphthyl,
(n) cycloalkyl, wherein the cycloalkyl is a 5-, 6-, or 7-membered monocyclic ring which optionally contains 1 or 2 heteroatoms selected from S, O, and N,
(o) heteroaryl, wherein heteroaryl is selected from the group comprising:-

(1) pyridyl,
(2) furanyl,
(3) thieryl,
(4) pyrazinyl,
(5) pyrimidyl,
(6) thiazolyl, and
(7) triazolyl,

each of (g) to (o) being optionally mono- or di- substituted, the substituents being independently selected from:-

(1) hydroxy,
(2) C<sub>1-4</sub> alkyl,
(3) C<sub>1-3</sub> alkoxy,
(4) C<sub>1-3</sub> alkylthio,
(5) mono- and di-C<sub>1-3</sub> alkylamino,
(6) -S(O)<sub>k</sub> -C<sub>1-3</sub> alkyl, where k is 1 or 2,
(7) -C(O)-O-C<sub>1-3</sub> alkyl,
(8) halo selected from fluoro, chloro and bromo,
(9) amino, and
(10) carboxyl,

wherein R<sub>1</sub> and R<sub>2</sub>, or R<sub>2</sub> and R<sub>3</sub>, or R<sub>3</sub> and R<sub>4</sub> may be joined together to form a 5-, 6- or 7-membered saturated monocyclic ring containing 0, 1 or 2 heteroatoms which together with the atoms to which R<sub>1</sub> and R<sub>2</sub>, or R<sub>2</sub> and R<sub>3</sub>, or R<sub>3</sub> and R<sub>4</sub> are attached there is formed a ring system according to Formulae I-I to I-III the heteroatoms being selected from the group consisting of O, S and N,
wherein $R_5$ is selected from the group comprising:

(c) hydrogen,
(d) amino,
(c) $C_{1-6}$ alkyl,
(d) aryl, wherein the aryl group is phenyl and naphthyl,
(e) aryl $C_{1-6}$ alkyl, wherein the aryl group is phenyl and naphthyl,
(f) heteroaryl, wherein heteroaryl is as defined above,
(g) heteroaryl $C_{1-6}$ alkyl, wherein heteroaryl is as defined above,
(h) cycloalkyl wherein the cycloalkyl is a 5-, 6-, or 7-membered monocyclic ring which optionally contains 1 or 2 heteroatoms selected from S, O, and N,
(i) an alkyl containing an aryl or heteroaryl substituent, and
(j) any combination of (a) to (h),
each of (b) to (j) being optionally mono- or di- substituted, the substituents being independently selected from:-

(1)  hydroxy,
(2)  C$_{1-4}$ alkyl,
(3)  C$_{1-3}$ alkoxy,
(4)  C$_{1-3}$ alkylthio,
(5)  mono- and di-C$_{1-3}$ alkylamino,
(6)  --S(O)$_k$ -C$_{1-3}$ alkyl, where $k$ is 1 or 2,
(7)  --C(O)-O-C$_{1-3}$ alkyl,
(8)  halo selected from fluoro, chloro and bromo.

4. The method of Claim 1 or 2 wherein $R_1$, $R_2$, $R_3$, $R_4$, $R_5$ and $R_6$ of Formula II are each independently selected from the group comprising:

(a)  hydrogen,
(b)  hydroxy,
(c)  amino,
(d)  cyano,
(e)  fluoro, chloro, bromo, and iodo,
(f)  trifluoromethyl,
(g)  C$_{1-6}$ alkyl,
(h)  C$_{1-6}$ alkoxy,
(i)  C$_{1-6}$ alkylthio,
(j)  C$_{1-6}$ alky carbonyl,
(k)  mono- and di-C$_{1-6}$ alky lamino,
(l)  aryl, where aryl is phenyl and naphthyl,
(m)  aryloxy, where aryl is phenyl and naphthyl,
(n)  cycloalkyl, wherein the cycloalkyl is a 5-, 6-, or 7-membered monocyclic ring which optionally contains 1 or 2 heteroatoms selected from S, O, and N,
(o) heteroaryl, wherein heteroaryl is selected from the group comprising:

(1) pyridyl,
(2) furanyl,
(3) thiptyl,
(4) pyrazinyl,
(5) pyrimidyl,
(6) thiazolyl, and
(7) triazolyl,

wherein each of (g) to (o) being optionally mono- or di- substituted, the substituents being independently selected from:

(1) hydroxy,
(2) C\textsubscript{1-4} alkyl,
(3) C\textsubscript{1-3} alkoxy,
(4) C\textsubscript{1-3} alkylthio,
(11) mono- and di-C\textsubscript{1-3} alkylamino,
(12) --S(O)\textsubscript{k}-C\textsubscript{1-3} alkyl, where k is 1 or 2,
(13) --C(O)-O-C\textsubscript{1-3} alkyl,
(14) halo selected from fluoro, chloro and bromo,
(15) amino, and
(16) carboxyl,

wherein R\textsubscript{1} and R\textsubscript{2}, or R\textsubscript{2} and R\textsubscript{3}, or R\textsubscript{3} and R\textsubscript{4}, or R\textsubscript{4} and R\textsubscript{5}, or R\textsubscript{5} and R\textsubscript{6} may be joined together to form a 5-, 6- or 7-membered saturated monocyclic ring containing 0, 1 or 2 heteroatoms which together with the atoms to which R\textsubscript{1} and R\textsubscript{2}, or R\textsubscript{2} and R\textsubscript{3}, or R\textsubscript{3} and R\textsubscript{4}, or R\textsubscript{4} and R\textsubscript{5}, or R\textsubscript{5} and R\textsubscript{6} are attached there is formed a ring system according to Formulae II-I – to II-V the heteroatoms being selected from the group consisting of O, S and N,
(II-I)

(II-II)

(II-III)

(II-IV)

(II-V)
wherein R7 is selected from the group comprising:

(c) hydrogen,
(d) amino
(e) C1-6 alkyl,
(d) aryl, wherein the aryl group is phenyl and naphthyl,
(e) aryl C1-6 alkyl, wherein the aryl group is phenyl and naphthyl,
(f) heteroaryl, wherein heteroaryl is as defined above,
(g) heteroaryl C1-6 alkyl, wherein heteroaryl is as defined above,
(h) cycloalkyl wherein the cycloalkyl is a 5-, 6-, or 7-membered monocyclic ring
    which optionally contains 1 or 2 heteroatoms selected from S, O, and N,
(ii) an alkyl containing an aryl or heteroaryl substituent,
(j) any combination of (a) to (h),

each of (b) to (j) being optionally mono- or di- substituted, the substituents being
independently selected from:

(1) hydroxy,
(2) C1-4 alkyl,
(3) C1-3 alkoxy,
(4) C1-3 alkylthio,
(5) mono- and di-C1-3 alkyaminio,
(7) --S(O)k-C1-3 alkyl, where k is 1 or 2,
(9) --C(O)-O-C1-3 alkyl,
(10) halo selected from fluoro, chloro and bromo.

5. The method of Claim 1 or 2 wherein R1, R2, R3, R4, R5 and R6 of Formula III are
each independently selected from the group comprising:

(a) hydrogen,
(b) hydroxy,
(c) amino,
(d) cyano,
(e) fluoro, chloro, bromo, and iodo,
(f) trifluoromethyl,
(g) C\textsubscript{1-6} alkyl,
(h) C\textsubscript{1-6} alkoxy,
(i) C\textsubscript{1-6} alkylthio,
(j) C\textsubscript{1-6} alkylcarbonyl,
(k) mono- and di-C\textsubscript{1-6} alkylamino,
(l) aryl, where aryl is phenyl and naphthyl,
(m) aryloxy, where aryl is phenyl and naphthyl,
(n) cycloalkyl, wherein the cycloalkyl is a 5-, 6-, or 7-membered monocyclic ring which optionally contains 1 or 2 heteroatoms selected from S, O, and N,
(o) heteroaryl, wherein heteroaryl is selected from the group comprising:

(1) pyridyl,
(2) furanyl,
(3) thiényl,
(4) pyrazinyl,
(5) pyrimidyl,
(6) thiazolyl, and
(7) triazolyl,

each of (g) to (o) being optionally mono- or di- substituted, the substituents being independently selected from:

(1) hydroxy,
(2) C\textsubscript{1-4} alkyl,
(3) C\textsubscript{1-3} alkoxy,
(4) C\textsubscript{1-3} alkylthio,
(13) mono- and di-C\textsubscript{1-3} alkylamino,
(14) \(-\text{S(O)}_k\text{-C}_{1-3}\) alkyl, where \(k\) is 1 or 2,
(15) \(-\text{C(0)}\text{-O-C}_{1-3}\) alkyl,
(16) halo selected from fluoro, chloro and bromo,
(17) amino, and
(18) carboxyl,

wherein \(R_1\) and \(R_2\), or \(R_2\) and \(R_3\), or \(R_3\) and \(R_4\), or \(R_4\) and \(R_5\), or \(R_5\) and \(R_6\) may be joined together to form a 5-, 6- or 7-membered saturated monocyclic ring containing 0, 1 or 2 heteroatoms which together with the atoms to which \(R_1\) and \(R_2\), or \(R_2\) and \(R_3\), or \(R_3\) and \(R_4\), or \(R_4\) and \(R_5\), or \(R_5\) and \(R_6\) are attached there is formed a ring system according to Formulae III-I to III-V, the heteroatoms being selected from the group consisting of O, S and N,
wherein $R_7$ is selected from the group consisting of

(a) hydrogen,
(b) amino,
(c) C$_{1-6}$ alkyl,
(d) aryl, wherein the aryl group is phenyl and naphthyl,
(e) aryl C$_{1-6}$ alkyl, wherein the aryl group is phenyl and naphthyl,
(f) heteroaryl, wherein heteroaryl is as defined above,
(g) heteroaryl C$_{1-6}$ alkyl, wherein heteroaryl is as defined above,
(h) cycloalkyl wherein the cycloalkyl is a 5-, 6-, or 7-membered monocyclic ring which optionally contains 1 or 2 heteroatoms selected from S, O, and N,
(ii) an alkyl containing an aryl or heteroaryl substituent, and
(j) any combination of (a) to (h),

each of (b) to (j) being optionally mono- or di- substituted, the substituents being independently selected from:

(1) hydroxy,
(2) C_{1-4} alkyl,
(3) C_{1-3} alkoxy,
(4) C_{1-3} alkylthio, \]
(9) mono- and di-C_{1-3} alkylamino,
(10) --S(O)_{k} \cdot C_{1-3} alkyl, where k is 1 or 2,
(11) --C(O)-O-C_{1-3} alkyl,
(12) halo selected from fluoro, chloro and bromo.

wherein R_{1}, R_{2}, R_{3}, R_{4}, R_{5} and R_{6} are each independently selected from the group comprising:-

(a) hydrogen,
(b) hydroxy,
(c) amino,
(d) cyano,
(e) fluoro, chloro or bromo,
(f) trifluoromethyl,
(g) C_{1-6} alkyl,
(h) C_{1-6} alkoxy,
(i) C_{1-6} alkylthio, and
(j) mono- and di-C_{1-4} alkylamino.

wherein R_{1} and R_{2}, or R_{2} and R_{3}, or R_{3} and R_{4}, or R_{4} and R_{5}, or R_{5} and R_{6} may be joined together to form a 5-, 6- or 7-membered saturated monocyclic ring containing 0, 1 or 2
heteroatoms which together with the atoms to which R₁ and R₂, or R₂ and R₃, or R₃ and R₄, or R₄ and R₅, or R₅ and R₆ are attached, there is formed a ring system according to Formulae III-I to III-V, the heteroatoms being selected from the group consisting of O, S and N:-

(III-I)

(III-II)

(III-III)

(III-IV)
wherein \( R_7 \) is selected from the group comprising:-

(c) hydrogen,
(d) amino,
(e) \( C_{1-4} \) alkyl,
(f) heteroaryl, wherein heteroaryl is selected from:-

(1) pyridyl,
(2) furanyl,
(3) thienyl,
(4) pyrazinyl,
(5) pyrimidyl,
(6) thiazolyl,
(7) triazolyl,

(g) heteroaryl \( C_{1-6} \) alkyl, wherein heteroaryl is defined as above,
(h) an alkyl containing an aryl or heteroaryl substituent, and
(i) cycloalkyl, wherein the cycloalkyl is a 5-, 6-, or 7-membered monocyclic ring which optionally contains 1 or 2 heteroatoms selected from S, O, and N,

each of (b) to (i) being optionally mono- or di- substituted, the substituents being independently selected from:-
(1) hydroxy,
(2) C_{1-4} alkyl,
(3) C_{1-3} alkoxy,
(4) C_{1-3} alkylthio,
(9) mono- and di-C_{1-3} alkylamino,
(10) --S(O)_k -C_{1-3} alkyl, where k is 1 or 2,
(11) --C(O)-O-C_{1-3} alkyl,
(12) halo selected from fluoro, chloro and bromo.

6. The method of Claim 3 wherein R_1, R_2, R_3 and R_4 are each independently selected from the group comprising:

(a) hydrogen,
(b) hydroxy,
(c) amino,
(d) cyano,
(e) fluoro, chloro or bromo,
(f) trifluoromethyl,
(g) C_{1-6} alkyl,
(h) C_{1-6} alkoxy,
(i) C_{1-6} alkylthio,
(j) mono- and di-C_{1-4} alkylamino,

wherein R_1 and R_2, or R_2 and R_3, or R_3 and R_4 may be joined together to form a 5-, 6- or 7-membered saturated monocyclic ring containing 0, 1 or 2 heteroatoms which together with the atoms to which R_1 and R_2, or R_2 and R_3, or R_3 and R_4 are attached there is formed a ring system according to Formulae I-I to I-III, the heteroatoms being selected from the group consisting of O, S and N,
wherein $R_5$ is selected from the group comprising:

(c) hydrogen,
(d) amino,
(e) $C_{1-4}$ alkyl,
(f) heteroaryl, wherein heteroaryl is selected from,
  (1) pyridyl,
  (2) furanyl,
  (3) thienyl,
  (4) pyrazinyl,
  (5) pyrimidyl,
  (6) thiazolyl, and
(8) triazolyl,
(g) heteroaryl C₆₋₆ alkyl, wherein heteroaryl is defined as above,
(h) an alkyl containing an aryl or heteroaryl substituent, and
(i) cycloalkyl, wherein the cycloalkyl is a 5-, 6-, or 7-membered monocyclic ring
   which optionally contains 1 or 2 heteroatoms selected from S, O, and N,

each of (b) to (i) being optionally mono- or di-substituted, the substituents being
independently selected from:-

(1) hydroxy,
(2) C₄₋₄ alkyl,
(3) C₃₋₃ alkoxy,
(4) C₃₋₃ alkylthio,
(9) mono- and di-C₃₋₃ alkylamino,
(10) --S(O)ₖ-C₃₋₃ alkyl, where k is 1 or 2,
(11) --C(O)-O-C₃₋₃ alkyl,
(12) halo selected from fluoro, chloro and bromo.

7. The method of Claim 6 wherein the rings of Formulae I-I, I-II and I-III are selected
   from the group comprising:-

![Chemical Structure](image-url)
wherein this subclass of compounds may be saturated or unsaturated.

8. The method of Claim 7 wherein the sub-class of compounds is unsaturated.

9. The method of Claim 7 or 8 wherein the sub-class of compounds are compounds of Formulae I-I, I-II and I-III wherein R₁, R₂, R₃ and R₄ are each independently selected from the group comprising:

(a) hydrogen,
(b) hydroxy,
(c) amino,
(d) cyano,
(e) fluoro, chloro or bromo,
(f) trifluoromethyl,
(g) C₁-₄ alkyl,
(h) C₁-₄ alkoxy,
(i) C₁-₄ alkylthio,
(k) mono- and di-C₁-₄ alkylamino,

and R₅ is selected from the group comprising:

(g) hydrogen,
(h) amino,
(i) C₁-₄ alkyl,
(j) phenyl,
(k) phenyl C$_{1-4}$ alkyl,
(l) heteroaryl, wherein heteroaryl is selected from:
   (8) pyridyl,
   (9) furanyl,
   (10) thieryl,
   (11) pyrazinyl,
   (12) pyrimidyl,
   (13) thiazolyl, and
   (14) triazolyl,
(g) heteroaryl C$_{1-6}$ alkyl, wherein heteroaryl is defined as above,
(h) an alkyl containing an aryl or heteroaryl substituent, and
(i) cycloalkyl, wherein the cycloalkyl is a 5-, 6-, or 7-membered monocyclic ring
     which optionally contains 1 or 2 heteroatoms selected from S, O, and N,

each of (b) to (i) being optionally mono- or di- substituted, the substituents being
independently selected from:

   (1) hydroxy,
   (2) C$_{1-4}$ alkyl,
   (3) C$_{1-3}$ alkoxy,
   (4) C$_{1-3}$ alkylthio,
   (9) mono- and di-C$_{1-3}$ alkylamino,
   (10) $\text{--S(O)}$_k -C$_{1-3}$ alkyl, where k is 1 or 2,
   (11) $\text{--C(O)-O-C}_1$ -C$_{1-3}$ alkyl, and
   (12) halo selected from fluoro, chloro and bromo.

10. The method of Claim 1 or 7 or 8 or 9 wherein the compound is selected from the
    group comprising:

   (a) 2-amino-3-benzylurea-4-picoline,
(b) 2-amino-3-methoxypyridine,
(c) 2-amino-3-methylthio-4-picoline,
(d) 2-amino-4-methylthiomethylpyridine,
(e) 2-amino-3-hydroxymethyl-4-picoline,
(f) 2-amino-3-ethyl-4-picoline dihydrochloride,
(g) 2-amino-3-methoxymethyl-4-picoline dihydrochloride,
(h) 2-amino-3-n-propyl-4-picoline dihydrochloride,
(i) 2-amino-3-dimethylamino-4-picoline trihydrochloride,
(j) 2-amino-3-chloro-4-picoline,
(k) 2-amino-5-chloro-4-picoline,
(l) 2,5-diamino-4-picoline,
(m) 5-acetylamino-2-amino-4-picoline,
(n) 2-amino-5-ethynyl-4-methylpyridine,
(o) 2-amino-4-methyl-5-pentylpyridine,
(p) 4-methylthio-2-aminopyridine,
(q) 4-chloro-6-methoxycarbonyl-2-aminopyridine,
(r) 4,6-dimethyl-5-ethenyl-2-aminopyridine,
(s) 2,4-diaminopyridine dihydrochloride,
(t) 2-amino-5-phenylpyridine,
(u) 2-amino-4-methyl-5-phenylpyridine,
(v) 2-amino-5-bromo-4-methylpyridine,
(w) 2-amino-5-cyano-4-methylpyridine,
(x) 2-amino-5-carboxy-4-methylpyridine,
(y) 2-amino-5-methoxycarbonyl-4-methylpyridine,
(z) 2-amino-5-aminomethyl-4-methylpyridine dihydrochloride,
(aa) 2-amino-5-acetamidomethyl-4-methylpyridine,
(ab) 2-amino-5-hydroxymethyl-4-methylpyridine,
(ac) 2-(2-amino-3-pyridinoxy)-ethyl-(S)-glycine dihydrochloride,
(ad) 2-amino-4,5-dimethylpyridine hydrochloride,
(ae) 2-amino-6-(3-buten-1-yl)-4-methylpyridine,
(f) 2-amino-6-ethyl-4-methylpyridine,
(ag) 2-amino-4-methyl-6-(1-methylethyl)pyridine,
(ah) 2-amino-6-(4-aminobutyl)-methylpyridine,
(ai) 6-(4-acetamidobutyl)-2-amino-4-methylpyridine,
(aj) 2-amino-6-hydroxymethyl-4-methylpyridine,
(ak) α-[2-(6-amino-4-methylpyridin-2-yl)ethyl]glycine dihydrochloride,
(al) 2-amino-5-ethylypyridine,
(am) 2-amino-6-benzylpyridine,
(an) 2-amino-6,7-dihydro-(5H)-pyridine,
(ao) 2-amino-6-(3-aminopropyl)-4-methylpyridine,
(ap) 2-amino-6-(2-aminoethyl)-4-methylpyridine,
(aq) 2-amino-4-methyl-6-propylpyridine,
(ar) 2-amino-4-methyl-6-(3-phenylpropyl)pyridine,
(as) 2-amino-4-methyl-6-(4-phenylbutyl)pyridine,
(at) 2-amino-4-methyl-6-(3-methylbutyl)pyridine,
(au) 2-amino-4-methyl-6-(2-methylpropyl)pyridine,
(av) 2-amino-4-methyl-6-(2-phenylethyl)pyridine,
(aw) 5-(6-amino-4-methyl-2-pyridyl)pentanoic acid hydrochloride,
(ax) 4-(6-amino-4-methyl-2-pyridyl)butanoic acid hydrochloride,
(ay) (S)-2-amino-6-(3-aminobutyl)-4-methylpyridine,
(az) (R)-2-amino-6-(3-aminobutyl)-4-methylpyridine,
(ba) 2-aminopyridine; or

a pharmaceutically acceptable salt thereof.

11. The method of Claim 10 wherein the compound is 2-aminopyridine.

12. The method Claim 4 wherein R₁, R₂, R₃, R₄, R₅, and R₆ of Formula II are each independently selected from the group comprising:

(a) hydrogen,
(b) hydroxy,
(c) amino,
(d) cyano,
(e) fluoro, chloro or bromo,
(f) trifluoromethyl,
(g) \( \text{C}_{1-6} \) alkyl,
(h) \( \text{C}_{1-6} \) alkoxy,
(i) \( \text{C}_{1-6} \) alkylthio, and
(k) mono- and di-\( \text{C}_{1-4} \) alkylamino.

wherein \( \text{R}_1 \) and \( \text{R}_2 \), or \( \text{R}_2 \) and \( \text{R}_3 \), or \( \text{R}_3 \) and \( \text{R}_4 \), or \( \text{R}_4 \) and \( \text{R}_5 \), or \( \text{R}_5 \) and \( \text{R}_6 \) may be joined together to form a 5-, 6- or 7-membered saturated monocyclic ring containing 0, 1 or 2 heteroatoms which together with the atoms to which \( \text{R}_1 \) and \( \text{R}_2 \), or \( \text{R}_2 \) and \( \text{R}_3 \) or \( \text{R}_3 \) and \( \text{R}_4 \) or \( \text{R}_4 \) and \( \text{R}_5 \), or \( \text{R}_5 \) and \( \text{R}_6 \) are attached, there is formed a ring system according to Formulae (II-I to II-V), the heteroatoms being selected from the group consisting of O, S and N,
wherein $R_7$ is selected from the group comprising:

(d) hydrogen,
(e) amino,
(f) $C_{1-4}$ alkyl,
(d) phenyl,
(e) phenyl $C_{1-4}$ alkyl,
(f) heteroaryl, wherein heteroaryl is selected from,
   (1) pyridyl,
   (2) furanyl,
   (3) thienyl,
   (4) pyrazinyl,
(5) pyrimidyl,
(10) thiazolyl, and
(11) triazolyl,
(g) heteroaryl C₁₋₆ alkyl, wherein heteroaryl is defined as above,
(h) an alkyl containing an aryl or heteroaryl substituent, and
(i) cycloalkyl, wherein the cycloalkyl is a 5-, 6-, or 7-membered monocyclic ring
which optionally contains 1 or 2 heteroatoms selected from S, O, and N,

each of (b) to (i) being optionally mono- or di- substituted, the substituents being
independently selected from:-

(1) hydroxy,
(2) C₃₋₄ alkyl,
(3) C₁₋₃ alkoxy,
(4) C₁₋₃ alkylthio,
(5) mono- and di-C₁₋₃ alkylamino,
(7) --S(O)ₓ₋₁₋₃ alkyl, where k is 1 or 2,
(12) --C(O)-O-C₁₋₃ alkyl,
(13) halo selected from fluoro, chloro and bromo.

13. The method of Claim 12 wherein the rings of Formula II-I, II-II, II-III, II-IV and II-
V are selected from the group comprising:-

(i)

(ii)
wherein this sub-class of compounds may be saturated or unsaturated.

14. The method of Claim 13 wherein the sub-class of compounds is unsaturated.

15. The method of Claim 13 or 14 wherein the sub-class of compounds are compounds of Formulae II-I, II-II, II-III, II-IV and II-V wherein R₁, R₂, R₃, R₄, R₅ and R₆, as explicitly shown, are each independently selected from the group comprising:-

(a) hydrogen,
(b) hydroxy,
(c) amino,
(d) cyano,
(e) fluoro, chloro or bromo,
(f) trifluoromethyl,
(g) C₁-4 alkyl,
(h) C₁-4 alkoxy,
(ii) \( \text{C}_{1-4} \) alkylthio,

(k) mono- and di-\( \text{C}_{1-4} \) alkyaminio,

\( R_7 \) is selected from the group comprising:-

(g) hydrogen,
(h) amino,
(i) \( \text{C}_{1-4} \) alkyl,
(j) phenyl,
(k) phenyl \( \text{C}_{1-4} \) alkyl,
(l) heteroaryl, wherein heteroaryl is selected from:-
   (8) pyridyl,
   (9) furanyl,
   (10) thiethyl,
   (11) pyrazinyl,
   (12) pyrimidyl,
   (13) thiazolyl, and
   (14) triazolyl,

(g) heteroaryl \( \text{C}_{1-6} \) alkyl, wherein heteroaryl is defined as above,
(h) an alkyl containing an aryl or heteroaryl substituent, and
(i) cycloalkyl, wherein the cycloalkyl is a 5-, 6-, or 7-membered monocyclic ring
    which optionally contains 1 or 2 heteroatoms selected from S, O, and N,

each of (b) to (i) being optionally mono- or di- substituted, the substituents being
independently selected from:-

(1) hydroxy,
(2) \( \text{C}_{1-4} \) alkyl,
(3) \( \text{C}_{1-3} \) alkoxy,
(4) \( \text{C}_{1-3} \) alkylthio,
(9) mono- and di-\( \text{C}_{1-3} \) alkyaminio,
(10) \(-\text{S(O)}_k\text{-C}_{1,3}\) alkyl, where \(k\) is 1 or 2,
(11) \(-\text{C(O)}\text{-O-C}_{1,3}\) alkyl, and
(12) halo selected from fluoro, chloro and bromo.

16. The method of Claim 1 or 13 or 14 or 15 wherein the compound is selected from the group comprising:

(a) 4-methyl-2-aminoquinoline,
(b) 6-methyl-2-aminoquinoline,
(c) 7-methyl-2-aminoquinoline,
(d) 8-methyl-2-aminoquinoline,
(e) 3-ethyl-2-aminoquinoline,
(f) 4-ethyl-2-aminoquinoline,
(g) 7-ethyl-2-aminostroquinoline,
(h) 8-ethyl-2-aminostroquinoline,
(i) 7-nitro-2-aminostroquinoline,
(j) 3-methoxy-2-aminostroquinoline
(k) 4-methoxy-2-aminostroquinoline,
(l) 3-chloro-2-aminostroquinoline,
(m) 2-aminostroquinoline, or

a pharmaceutical acceptable salt thereof.

17. The method of Claim 16 wherein the compound is 2-aminostroquinoline or a pharmaceutically acceptable salt thereof.

18. The method of Claim 5 wherein \(R_1, R_2, R_3, R_4, R_5\) and \(R_6\) are each independently selected from the group comprising:

(a) hydrogen,
(b) hydroxy,
(c) amino,
(d) cyano,
(e) fluoro, chloro, bromo, and iodo,
(f) trifluoromethyl,
(g) C<sub>1-6</sub> alkyl,
(h) C<sub>1-6</sub> alkoxy,
(i) C<sub>1-6</sub> alkylthio,
(j) C<sub>1-6</sub> alkylcarbonyl,
(k) mono- and di-C<sub>1-6</sub> alkylamino,
(l) aryl, where aryl is phenyl and naphthyl,
(m) aryloxy, where aryl is phenyl and naphthyl,
(n) cycloalkyl, wherein the cycloalkyl is a 5-, 6-, or 7-membered monocyclic ring which optionally contains 1 or 2 heteroatoms selected from S, O, and N,
(o) heteroaryl, wherein heteroaryl is selected from the group comprising:
   (1) pyridyl,
   (2) furanyl,
   (3) thieryl,
   (4) pyrazinyl,
   (5) pyrimidyl,
   (6) thiazolyl, and
   (7) triazolyl,

each of (g) to (o) being optionally mono- or di- substituted, the substituents being independently selected from:

   (1) hydroxy,
   (2) C<sub>1-4</sub> alkyl,
   (3) C<sub>1-3</sub> alkoxy,
   (4) C<sub>1-3</sub> alkylthio,
   (19) mono- and di-C<sub>1-3</sub> alkylamino,
   (20) --S(O)<sub>k</sub>-C<sub>1-3</sub> alkyl, where k is 1 or 2.
(21) -C(O)-O-C<sub>1-3</sub> alkyl,
(22) halo selected from fluoro, chloro and bromo,
(23) amino, and
(24) carboxyl,

wherein R<sub>1</sub> and R<sub>2</sub>, or R<sub>2</sub> and R<sub>3</sub>, or R<sub>3</sub> and R<sub>4</sub>, or R<sub>4</sub> and R<sub>5</sub>, or R<sub>5</sub> and R<sub>6</sub> may be joined together to form a 5-, 6- or 7-membered saturated monocyclic ring containing 0, 1 or 2 heteroatoms which together with the atoms to which R<sub>1</sub> and R<sub>2</sub>, or R<sub>2</sub> and R<sub>3</sub>, or R<sub>3</sub> and R<sub>4</sub>, or R<sub>4</sub> and R<sub>5</sub>, or R<sub>5</sub> and R<sub>6</sub> are attached there is formed a ring system according to Formulae III-I to III-V, the heteroatoms being selected from the group consisting of O, S and N,
wherein \( R_7 \) is selected from the group consisting of

(a) hydrogen,
(b) amino,
(c) \( \text{C}_{1-6} \) alkyl,
(d) aryl, wherein the aryl group is phenyl and napthyl,
(e) aryl \( \text{C}_{1-6} \) alkyl, wherein the aryl group is phenyl and napthyl,
(f) heteroaryl, wherein heteroaryl is as defined above,
(g) heteroaryl \( \text{C}_{1-6} \) alkyl, wherein heteroaryl is as defined above,
(h) cycloalkyl wherein the cycloalkyl is a 5-, 6-, or 7-membered monocyclic ring which optionally contains 1 or 2 heteroatoms selected from S, O, and N,
(iii) an alkyl containing an aryl or heteroaryl substituent, and
(j) any combination of (a) to (h),

each of (b) to (j) being optionally mono- or di- substituted, the substituents being independently selected from:
(1) hydroxy,
(2) C<sub>1-4</sub> alkyl,
(3) C<sub>1-3</sub> alkoxy,
(4) C<sub>1-3</sub> alkylthio,
(13) mono- and di-C<sub>1-3</sub> alkylamino,
(14) --S(O)<sub>k</sub>-C<sub>1-3</sub> alkyl, where k is 1 or 2,
(15) --C(O)-O-C<sub>1-3</sub> alkyl,
(16) halo selected from fluoro, chloro and bromo.

19. The method of Claim 18 wherein the rings of Formulae III-I, III-II, III-III, III-IV and III-V are selected from the group comprising:-
(xvi)  

(xvii)  

(xviii)  

(xix)  

(xx)  

(xxi)  

(xxii)  

(xxiii)
wherein this sub-class of compounds may be saturated or unsaturated.

20. The method Claim 19 wherein the sub-class of compounds is unsaturated.

21. The method of Claim 20 wherein the sub-class of compounds are compounds of Formulae III-I, III-II, III-III, III-IV and III-V wherein \( R_1, R_2, R_3, R_4, R_5 \) and \( R_6 \), as explicitly shown, are each independently selected from the group comprising:-
(a) hydrogen,
(b) hydroxy,
(c) amino,
(d) cyano,
(e) fluoro, chloro or bromo,
(f) trifluoromethyl,
(g) C₁₋₄ alkyl,
(h) C₁₋₄ alkoxy,
(i) C₁₋₄ alkylthio,
(k) mono- and di-C₁₋₄ alkylamino,

R₇ is selected from the group comprising:-

(g) hydrogen,
(h) amino,
(i) C₁₋₄ alkyl,
(j) phenyl,
(k) phenyl C₁₋₄ alkyl,
(l) heteroaryl, wherein heteroaryl is selected from:-
   (1) pyridyl,
   (2) furanyl,
   (3) thiienyl,
   (4) pyrazinyl,
   (5) pyrimidyl,
   (6) thiazolyl, and
   (7) triazolyl,
(g) heteroaryl C₁₋₆ alkyl, wherein heteroaryl is defined as above,
(h) an alkyl containing an aryl or heteroaryl substituent, and
(i) cycloalkyl, wherein the cycloalkyl is a 5-, 6-, or 7-membered monocyclic ring which optionally contains 1 or 2 heteroatoms selected from S, O, and N,
each of (b) to (i) being optionally mono- or di- substituted, the substituents being independently selected from:-

(1) hydroxy,
(2) C\textsubscript{1-4} alkyl,
(3) C\textsubscript{1-3} alkoxy,
(4) C\textsubscript{1-3} alkylthio,
(9) mono- and di-C\textsubscript{1-3} alkylamino,
(10) --S(O)\textsubscript{k} -C\textsubscript{1-3} alkyl, where k is 1 or 2,
(11) --C(O)-O-C\textsubscript{1-3} alkyl, and
(12) halo selected from fluoro, chloro and bromo.

22. The method of Claim 1 or 19 or 20 or 21 wherein the compound is selected from the list comprising:

(a) \textit{tert}-butyl 2-\{[(4-chloro-1-guanidino-7-isoquinolinyl)sulphonyl]amino\} benzoate;
(b) \textit{tert}-butyl 3-\{[(4-chloro-1-guanidino-7-isoquinolinyl)sulphonyl]amino\} benzoate;
(c) methyl-3-\{[(4-chloro-1-guanidino-7-isoquinolinyl)sulphonyl]amino\}-4-methoxybenzoate;
(d) N-[(4-chloro-1-guanidino-7-isoquinolinyl)sulphonyl]glycine \textit{tert}-butyl ester hydrochloride;
(e) N-[(4-chloro-1-guanidino-7-isoquinolinyl)sulphonyl]-\beta\text{-alanine \textit{tert}-butyl ester;
(f) N-[(4-chloro-1-guanidino-7-isoquinolinyl)sulphonyl]-N-methylglycine \textit{tert}-butyl ester;
(g) N-[(4-chloro-1-guanidino-7-isoquinolinyl)sulphonyl]-N-phenylglycine \textit{tert}-butyl ester;
(h) N-[(4-chloro-1-guanidino-7-isoquinolinyl)sulphonyl]-N-(cyclopentylmethyl)-glycine \textit{tert}-butyl ester;
(i) N-[(4-chloro-1-guanidino-7-isoquinolinyl)sulphonyl]-N-(cyclohexylmethyl)glycine \textit{tert}-butyl ester;
(j) \( N-[(4\text{-chloro}-1\text{-guanidino}-7\text{-isoquinolinyl})\text{ sulphonyl}]\text{-N-benzylglycine} \text{ tert-butyl ester; } \)

(l) \( N-[(4\text{-chloro}-1\text{-guanidino}-7\text{-isoquinolinyl})\text{ sulphonyl}]\text{-N-(2-methylbenzyl)glycine} \text{ tert-butyl ester; } \)

(m) 1-aminooisoquinoline.

23. The method Claim 22 wherein the compound is 1-aminooisoquinoline.

24. The method of Claim 1 or 11 or 16 or 23 wherein the SH3 domain comprising the consensus sequence:

\[
\text{hxsbsaxs(x)_{10}-lsbp(x)_{4}G-(x)_{3}1b(x)_{16}wxbbt(x)_{19}G(x)_{3}bhpxsbv}
\]

wherein:-

\[
\begin{align*}
\text{h} & = \text{hydrophobic (A, C, F, G, H, I, L, M, T, V, W or Y);} \\
\text{s} & = \text{small (A, C, D, G, N, P, S, T or V);} \\
\text{a} & = \text{aromatic (F, H, Wor Y);} \\
\text{b} & = \text{big (E, F, H, I, K, L, M, Q, R, W or Y);} \\
\text{-} & = \text{negatively charged (D or E);} \\
\text{l} & = \text{aliphatic (I, L or V); and} \\
\text{t} & = \text{tiny (A or G).}
\end{align*}
\]

25. The method of Claim 1 or 24 wherein the SH3 domain is from a protein selected from Tec, Fyn, Nck1, Src, Grb2, p85α, Lyn, Lck, Fgr and Hck.

26. The method of Claim 25 wherein the protein is Src.

27. A method for modulating the activity of a protein comprising an SH3 domain having a three-dimensional ligand-binding site comprising a negatively charged amino acid residue and a hydrophobic amino acid residue linearly separated by at least five amino
acid residues, said method comprising the administration of a an effective amount of a compound selected from 2-aminopyridine, 2-aminoquinoline and 1-aminooisoquinoline or a pharmaceutically acceptable salt thereof.

28. The method of Claim 27 wherein the SH3 domain comprising the consensus sequence:

$$\text{hxsbsbsaxs(x)}_{10}-\text{lsbp(x)}_{4}G-(x)_{3}1b(x)_{16}wxbbt(x)_{19}G(x)_{3}bhpxs\text{bv}$$

wherein:

- \( h \) = hydrophobic (A, C, F, G, H, I, L, M, T, V, W or Y);
- \( s \) = small (A, C, D, G, N, P, S, T or V);
- \( a \) = aromatic (F, H, W or Y);
- \( b \) = big (E, F, H, I, K, L, M, Q, R, W or Y);
- \( - \) = negatively charged (D or E);
- \( l \) = aliphatic (I, L or V); and
- \( t \) = tiny (A or G).

29. The method of Claim 28 wherein the SH3 domain is from a protein selected from Tec, Fyn, Nck1, Src, Grb2, p85α, Lyn, Lck, Fgr and Hck.

30. The method Claim 29 wherein the protein is Src.

31. A method for modulating the activity of a protein comprising an SH3 domain comprising the consensus sequence:

$$\text{hxsbsbsaxs(x)}_{10}-\text{lsbp(x)}_{4}G-(x)_{3}1b(x)_{16}wxbbt(x)_{19}G(x)_{3}bhpxs\text{bv}$$

wherein:-
h = hydrophobic (A, C, F, G, H, I, L, M, T, V, W or Y);
s = small (A, C, D, G, N, P, S, T or V);
a = aromatic (F, H, W or Y);
b = big (E, F, H, I, K, L, M, Q, R, W or Y);
- = negatively charged (D or E);
l = aliphatic (I, L or V); and

and said SH3 domain having a three-dimensional ligand-binding site comprising a negatively charged amino acid residue and a hydrophobic amino acid residue linearly separated by at least five amino acid residues, said method comprising the administration of a an effective amount of a compound selected from 2-aminopyridine, 2-aminoquinoline and 1-aminoisoquinoline or a pharmaceutically acceptable salt thereof.

32. The method of Claim 31 wherein the SH3 domain is from a protein selected from Tec, Fyn, Nck1, Src, Grb2, p85α, Lyn, Lck, Fgr and Hek.

33. The method Claim 32 wherein the protein is Src.

34. A method for the prophylaxis and/or treatment of a disease state or pre-disease state that results from, or is associated with inappropriate activity or expression of a protein comprising an SH3 domain having a three-dimensional ligand-binding site comprising a negatively charged amino acid residue and a hydrophobic amino acid residue linearly separated by at least five amino acid residues, said method comprising the step of administering to a subject an effective amount of a compound selected from a compound of Formula I or II or III or a derivative or analog or mimetic thereof or a pharmaceutically acceptable salt hydrate, solvent crystal form and/or diastereo isomer thereof for a time and under conditions sufficient for said compound to provide a treatment and/or a prophylactic response in said subject with a disease state or pre-disease state that results from, or is associated with an inappropriate activity or expression of said protein.
35. The method of Claim 34 wherein the SH3 domain comprises the consensus sequence:

\[ \text{hxsbsaxs}(x)_{10}\text{-lsbp}(x)_{4}\text{-}(x)_{3}\text{lb}(x)_{16}\text{wxbbt}(x)_{19}\text{G}(x)_{3}\text{bhpxsbv} \]

wherein:-

\( h = \) hydrophobic (A, C, F, G, H, I, L, M, T, V, W or Y);
\( s = \) small (A, C, D, G, N, P, S, T or V);
\( a = \) aromatic (F, H, W or Y);
\( b = \) big (E, F, H, I, K, L, M, Q, R, W or Y);
\( - = \) negatively charged (D or E);
\( l = \) aliphatic (I, L or V); and
\( t = \) tiny (A or G).

36. The method of Claim 35 wherein the SH3 domain is from a protein selected from Tec, Fyn, Nck1, Src, Grb2, p85\( \alpha \), Lyn, Lck, Fgr and Hck.

37. The method Claim 36 wherein the protein is Src.

38. The method of any one of Claims 34 to 37 wherein the compound is selected from 2-aminopyridine, 2-aminoquinoline and 1-aminoisoquinoline or a pharmaceutically acceptable salt thereof.

39. The method of Claim 34 or 38 wherein the disease condition is selected from osteoarthritis, tissue and/or organ transplant rejection, sepsis, ARDS, asthma, trauma, oxidative stress, cell death, irradiation damage, ischemia, reperfusion, cancer, viral infection, autoimmune disease, rheumatoid arthritis, psoriasis, inflammatory bowel disease, glomerulonephritis, lupus, uveitis, chronic hepatitis, juvenile diabetes, chronic non-suppurative thyroiditis, tuberculosis, syphilis, actinomycosis, sarcoidosis, amyloidosis, granulomatous thyroiditis, lymphocytic thyroiditis, Hashimoto’s thyroiditis, invasive fibrous thyroiditis, Grave’s disease, regional enteritis, Crohn’s Disease, granulomatous
ileitis, ulcerative colitis, chorioretinal inflammatory syndrome, pancreatitis, Paget’s Disease, synovitis of the hip, odynophagia, dysphagia, viral and bacterial pharyngitis, infectious mononucleosis, acute tonsillitis, peritonsillar abscess, ulcerative tonsillitis, lingual tonsillitis, Candidiasis, Epiglottitis, tracheobronchial inflammation, Ludwig’s angina, idiopathic pulmonary fibrosis, interstitial lung disease, lichen planus, lichen sclerosus, squamous hyperplasia, abscess, meningitis, encephalitis, vasculitis, progressive multifocal leukoencephalopathy, urticaria, spongiotic dermatitis, allergic contact dermatitis, dermatitis, chronic contact dermatitis, lichen simplex chronicus, atopic dermatitis, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, discoid lupus erythematosus, acne vulgaris and atherosclerosis.

40. The method of Claim 34 or 38 wherein the disease condition is cancer.

41. The method of Claim 40 wherein the cancer is selected from the list comprising lymphosarcoma, osteosarcoma, mammary tumors, mastocytoma, brain tumor, melanoma, adenocarcinoma, squamous cell carcinoma, carcinoid lung tumor, bronchial gland tumor, bronchiolar adenocarcinoma, fibroma, myxochondroma, pulmonary sarcoma, neurosarcoma, osteoma, papilloma, retinoblastoma, Ewing’s sarcoma, Wilms tumor, Burkitt’s lymphoma, microglioma, neuroblastoma, osteoclastoma, oral neoplasia, fibrosarcoma, osteosarcoma and rhabdomyosarcoma.

42. The method of Claim any one of Claims 34 to 38 wherein the disease condition is selected from a stroke, osteoporosis, HIV infection, immunosuppression and cardiac dysfunction.

43. Use of a compound of Formula I or II or III as herein defined in the manufacture of a medicament for treating a condition associated with a protein having an SH3 domain which comprises a three-dimensional ligand-binding site comprising a negatively charged amino acid residue and a hydrophobic amino acid residue linearly separated by at least five amino acid residues.
44. Use of Claim 43 wherein the compound is selected from the list comprising 2-aminopyridine, 2-aminoquinoline and 1-aminoisoquinoline or a pharmaceutically acceptable salt thereof.

45. Use of Claim 44 wherein the SH3 domain comprises a consensus sequence:-

\[ \text{hxsbsaxs(x)_{10}-lsbp(x)_{4}G-(x)_{2}1b(x)_{16}wxbbt(x)_{19}G(x)_{3}bhpxsbv} \]

wherein:-

\[ \begin{align*}
h &= \text{hydrophobic (A, C, F, G, H, I, L, M, T, V, W or Y);} \\
s &= \text{small (A, C, D, G, N, P, S, T or V);} \\
a &= \text{aromatic (F, H, W or Y);} \\
b &= \text{big (E, F, H, I, K, L, M, Q, R, W or Y);} \\
- &= \text{negatively charged (D or E);} \\
l &= \text{aliphatic (I, L or V); and} \\
t &= \text{tiny (A or G).}
\end{align*} \]

46. Use of Claim 43 wherein the disease condition is selected from osteoarthritis, tissue and/or organ transplant rejection, sepsis, ARDS, asthma, trauma, oxidative stress, cell death, irradiation damage, ischemia, reperfusion, cancer, viral infection, autoimmune disease, rheumatoid arthritis, psoriasis, inflammatory bowel disease, glomerulonephritis, lupus, uveitis, chronic hepatitis, juvenile diabetes, chronic non-suppurative thyroiditis, tuberculosis, syphilis, actinomycosis, sarcoidosis, amyloidosis, granulomatous thyroiditis, lymphocytic thyroiditis, Hashimoto's thyroiditis, invasive fibrous thyroiditis, Grave's disease, regional enteritis, Crohn's Disease, granulomatous ileitis, ulcerative colitis, chorioretinal inflammatory syndrome, pancreatitis, Paget's Disease, synovitis of the hip, odynophagia, dysphagia, viral and bacterial pharyngitis, infectious mononucleosis, acute tonsillitis, peritonsillar abscess, ulcerative tonsillitis, lingual tonsillitis, Candidiasis, Epiglottitis, tracheobronchial inflammation, Ludwig's angina, idiopathic pulmonary fibrosis, interstitial lung disease, lichen planus, lichen sclerosus, squamous hyperplasia,
abscess, meningitis, encephalitis, vasculitis, progressive multifocal leukoencephalopathy, urticaria, spongiotic dermatitis, allergic contact dermatitis, dermatitis, chronic contact dermatitis, lichen simplex chronicus, atopic dermatitis, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, discoid lupus erythematosus, acne vulgaris and atherosclerosis.

47. The method of Claim 46 wherein the disease condition is cancer.

48. The method of Claim 47 wherein the cancer is selected from the list comprising lymphosarcoma, osteosarcoma, mammary tumors, mastocytoma, brain tumor, melanoma, adenosquamous carcinoma, carcinoid lung tumor, bronchial gland tumor, bronchiolar adenocarcinoma, fibroma, myxochondroma, pulmonary sarcoma, neurosarcoma, osteoma, papilloma, retinoblastoma, Ewing’s sarcoma, Wilms tumor, Burkitt’s lymphoma, microglioma, neuroblastoma, osteoclastoma, oral neoplasia, fibrosarcoma, osteosarcoma and rhabdomyosarcoma.

49. The method of Claim any one of Claims 43 to 49 wherein the disease condition is selected from a stroke, osteoporosis, HIV infection, immunosuppression and cardiac dysfunction.

50. A method of using the three-dimensional structure of a protein in a molecular screening assay to identify molecules capable of interacting with a peptide, polypeptide or protein, said method comprising subjecting the three dimensional structure of a peptide, polypeptide or protein and a molecule to in silico molecular modelling means to determine gap space regions including a functional moiety or moieties present on said molecule that do not demonstrate optimum close contacts between the molecule and the amino acids of the interaction surface region or pocket present on said peptide polypeptide or protein, and subjecting said molecule to in silico manipulation means to optimize close contacts between the molecule and the selected amino acids of the interaction surface, region or pocket of said peptide polypeptide or protein, thereby identifying a molecule with the same
or altered capacity to interact with the surface, region or pocket of the a peptide polypeptide or protein.

51. A method of using the three dimensional structure of a SH3 domain in a molecular screening assay to identify molecules capable of interacting with a SH3 domain, said method comprising subjecting the three dimensional structure of a SH3 domain and a molecule to in silico molecular modelling means to determine gap space regions including a functional moiety or moieties present on said molecule that do not demonstrate optimum close contacts between the molecule and the amino acids of the interaction surface region or pocket present on said SH3 domain, and subjecting said molecule to in silico manipulation means to optimize close contacts between the molecule and the selected amino acids of the interaction surface, region or pocket of SH3 domain, thereby identifying a molecule with the same or altered capacity to interact with the surface, region or pocket of the SH3 domain.

52. A method of using the three-dimensional structure of a SH3 domain comprising an SH3 domain having a three-dimensional ligand-binding site comprising a negatively charged amino acid residue and a hydrophobic amino acid residue linearly separated by at least five amino acid residues in a molecular screening assay to identify derivatives, homologs, analogs or mimetics of 2-aminopyridine, 2-aminquinoline and 1-aminoisoquinoline capable of interacting with a SH3 domain of a said protein, said method comprising subjecting the three-dimensional structure of a SH3 domain of a said protein or a derivative, homolog, analog or mimic of 2-aminopyridine, 2-aminquinoline and 1-aminoisoquinoline to in silico molecular modelling means to determine gap space regions including a functional moiety or moieties present on said derivative, homolog, analog or mimic of 2-aminopyridine, 2-aminquinoline and 1-aminoisoquinoline that do not demonstrate optimum close contacts between the derivative, homolog, analog or mimic of 2-aminopyridine, 2-aminquinoline and 1-aminoisoquinoline and the amino acids of the interaction surface region or pocket present on said SH3 domain of said protein and subjecting said derivative, homolog, analog or mimic of 2-aminopyridine, 2-aminquinoline and 1-aminoisoquinoline to in silico manipulation means to optimize close
contacts between the derivative, homolog, analog or mimetic of 2-aminopyridine, 2-aminooquinoline and 1-aminoisoquinoline and the selected amino acids of the interaction surface, region or pocket of SH3 domain of said protein, thereby identifying a derivative, homolog, analog or mimetic of 2-aminopyridine, 2-aminooquinoline and 1-aminoisoquinoline with the same or altered capacity to interact with the surface, region or pocket of the SH3 domain of said protein.

53. A method of using the three dimensional structure of a SH3 domain comprising a protein comprising an SH3 domain having a three-dimensional ligand-binding site comprising a negatively charged amino acid residue and a hydrophobic amino acid residue linearly separated by at least five amino acid residues in a molecular screening assay to identify derivatives, homologs, analogs or mimetics of 2-aminopyridine, 2-aminooquinoline and 1-aminoisoquinoline capable of interacting with a SH3 domain of said protein, said method comprising subjecting the three dimensional structure of a SH3 domain of said protein or a derivative, homolog, analog or mimetic of 2-aminopyridine, 2-aminooquinoline and 1-aminoisoquinoline to in silico molecular modelling means to determine gap space regions including a functional moiety or moieties present on said derivative, homolog, analog or mimetic of 2-aminopyridine, 2-aminooquinoline and 1-aminoisoquinoline that do not demonstrate optimum close contacts between the derivative, homolog, analog or mimetic of 2-aminopyridine, 2-aminooquinoline and 1-aminoisoquinoline and the tryptophan and optionally glutamate or aspartic acid amino acid residues of the interaction surface region or pocket present on said SH3 domain of said protein, and subjecting said derivative, homolog, analog or mimetic of 2-aminopyridine, 2-aminooquinoline and 1-aminoisoquinoline to in silico manipulation means to optimize close contacts between the derivative, homolog, analog or mimetic of 2-aminopyridine, 2-aminooquinoline and 1-aminoisoquinoline and the selected tryptophan and optionally glutamate or aspartic acid amino acid residues of the interaction surface, region or pocket of SH3 domain of said protein, thereby identifying a derivative, homolog, analog or mimetic of 2-aminopyridine, 2-aminooquinoline and 1-aminoisoquinoline with the same or altered capacity to interact with the surface, region or pocket of the SH3 domain of said protein.
**Figure 2A**

**Figure 2B**
Figure 4

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- $E193$
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Branson, Kim (US only) M
Inglis, Steven (US only) R

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INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl. 7: A61K 31/44, 31/47 A61P 19/02, 31/18, 35/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols):

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used):

Derwent, Chemical Abstracts, Medline and Keywords

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
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<td>WO 00/62778 A (BRISTOL-MYERS SQUIBB CO.) 26 October 2000 Compound 373 at p 143, comp. 539 at p 198 and comp. 551 at p 200-201. Pages 40-43</td>
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☐ Further documents are listed in the continuation of Box C

X See patent family annex

* Special categories of cited documents:
  "A" document defining the general state of the art which is not considered to be of particular relevance
  "E" earlier application or patent but published on or after the international filing date
  "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
  "O" document referring to an oral disclosure, use, exhibition or other means
  "P" document published prior to the international filing date but later than the priority date claimed
  "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
  "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
  "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
  "&" document member of the same patent family

Date of the actual completion of the international search: 10 October 2002

Date of mailing of the international search report: 15 NOV 2002

Name and mailing address of the ISA/AU

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Authorized officer

ANDREW ACHILLEOS
Telephone No: (02) 6283 2280

Form PCT/ISA/210 (second sheet) (July 1998)
INTERNATIONAL SEARCH REPORT

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

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This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

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

2. Claims Nos: 1-53
   because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
   A complete search was not feasible for economic reasons. Consequently, the search was limited to the compounds as exemplified in the specification.

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

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

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

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

2. Claims Nos:
   because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
   A complete search was not feasible for economic reasons. Consequently, the search was limited to the compounds as exemplified in the specification.

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

4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims, it is covered by claims Nos.:

    Remark on Protest
    |   |   |
    | 4. |   |   |

   No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims, it is covered by claims Nos.:

   The additional search fees were accompanied by the applicant’s protest.

   No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet(1)) (July 1998)
This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

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