Title: β-SULFONE DERIVATIVES AS INHIBITORS OF MATRIX METALLOPROTEINASES AND/OR TNF-α CONVERTING ENZYME (TACE)

Abstract: The present application describes novel β-sulfone derivatives of formula (I), or pharmaceutically acceptable salt or prodrug forms thereof, wherein R¹, R², R³, R⁴, X, Y, and Z are defined in the present specification, which are useful as inhibitors of matrix metalloproteinases (MMP), TNF-α converting enzyme (TACE), aggrecanase, or a combination thereof.
TITLE
β-SULFONE DERIVATIVES AS INHIBITORS OF MATRIX METALLOPROTEINASES AND/OR TNF-α CONVERTING ENZYME (TACE)

FIELD OF THE INVENTION
This invention relates generally to novel β-sulfone derivatives as inhibitors of matrix metalloproteinases (MMP), TNF-α converting enzyme (TACE), aggrecanase or a combination thereof, pharmaceutical compositions containing the same, and methods of using the same.

BACKGROUND OF THE INVENTION
There is now a body of evidence that metalloproteases (MP) are important in the uncontrolled breakdown of connective tissue, including proteoglycan and collagen, leading to resorption of the extracellular matrix. This is a feature of many pathological conditions, such as rheumatoid and osteoarthritis; corneal, epidermal or gastric ulceration; tumor metastasis or invasion; periodontal disease; and, bone disease. Normally these catabolic enzymes are tightly regulated at the level of their synthesis as well as at their level of extracellular activity through the action of specific inhibitors, such as alpha-2-macroglobulins and TIMPs (tissue inhibitors of metalloprotease), which form inactive complexes with the MP's.

Osteo- and Rheumatoid Arthritis (OA and RA respectively) are destructive diseases of articular cartilage characterized by localized erosion of the cartilage surface. Findings have shown that articular cartilage from the femoral heads of patients with OA, for
example, had a reduced incorporation of radiolabeled sulfate over controls, suggesting that there must be an enhanced rate of cartilage degradation in OA (Mankin et al. *J. Bone Joint Surg.* 1970, 52A, 424-434). There are four classes of protein degradative enzymes in mammalian cells: serine, cysteine, aspartic and metalloproteases. The available evidence supports that it is the metalloproteases that are responsible for the degradation of the extracellular matrix of articular cartilage in OA and RA.

Increased activities of collagenases and stromelysin have been found in OA cartilage and the activity correlates with severity of the lesion (Mankin et al. *Arthritis Rheum.* 1978, 21, 761-766, Woessner et al. *Arthritis Rheum.* 1983, 26, 63-68 and Woessner et al. *Arthritis Rheum.* 1984, 27, 305-312). In addition, aggrecanase has been identified as providing the specific cleavage product of proteoglycan found in RA and OA patients (Lohmander L.S. et al. *Arthritis Rheum.* 1993, 36, 1214-22).

Therefore, metalloproteases (MP) have been implicated as the key enzymes in the destruction of mammalian cartilage and bone. It can be expected that the pathogenesis of such diseases can be modified in a beneficial manner by the administration of MP inhibitors, and many compounds have been suggested for this purpose (see Wahl et al. *Ann. Rep. Med. Chem.* 1990, 25, 175-184, AP, San Diego).

Tumor necrosis factor-α (TNF-α) is a cell-associated cytokine that is processed from a 26kd precursor form to a 17kd active form. TNF-α has been shown to be a primary mediator in humans and in animals, of inflammation, fever, and acute phase responses, similar to those observed during acute infection and shock. Excess TNF-α has been shown to
be lethal. There is now considerable evidence that blocking the effects of TNF-\(\alpha\) with specific antibodies can be beneficial in a variety of circumstances including autoimmune diseases such as rheumatoid arthritis (Feldman et al, Lancet 1994, 344, 1105), non-insulin dependent diabetes melitus (Lohmander, L.S. et al. Arthritis Rheum. 1993, 36, 1214-22), and Crohn's disease (MacDonald et al. Clin. Exp. Immunol. 1990, 81, 301).

Compounds which inhibit the production of TNF are therefore of therapeutic importance for the treatment of inflammatory disorders. Recently, TNF-\(\alpha\) converting enzyme (TACE), the enzyme responsible for TNF-\(\alpha\) release from cells, were purified and sequenced (Black et al Nature 1997, 385, 729; Moss et al Nature 1997, 385, 733). This invention describes molecules that inhibit this enzyme and hence the secretion of active TNF-\(\alpha\) from cells. These novel molecules provide a means of mechanism based therapeutic intervention for diseases including but not restricted to septic shock, haemodynamic shock, sepsis syndrome, post ischemic reperfusion injury, malaria, Crohn's disease, inflammatory bowel diseases, mycobacterial infection, meningitis, psoriasis, congestive heart failure, fibrotic diseases, cachexia, graft rejection, cancer, diseases involving angiogenesis, autoimmune diseases, skin inflammatory diseases, OA, RA, multiple sclerosis, radiation damage, hyperoxic alveolar injury, periodontal disease, HIV, and non-insulin dependent diabetes melitus.

Since excessive TNF-\(\alpha\) production has been noted in several disease conditions also characterized by MMP-mediated tissue degradation, compounds which inhibit both MMPs and TNF-\(\alpha\) production may also have a particular advantage in diseases where both mechanisms are involved.
Prostaglandins (PG) play a major role in the inflammation process and the inhibition of PG production has been a common target of anti-inflammatory drug discovery. Many NSAIDS have been found to prevent the production of PG by inhibiting the enzyme cyclooxygenase (COX). Among the two isoforms of COXs, COX-1 is constitutively expressed. COX-2 is an inducible isozyme associated with inflammation. Selective COX-2 inhibitor was believed to maintain the efficacy of traditional NSAIDS, which inhibit both isozymes, and produce fewer and less drastic side effects. As a result, development of selective COX-2 inhibitors has attracted major interest in the pharmaceutical industry. Because of the significant roles of PGs and TNF-α in inflammation, combined use of COX-2 and TACE inhibitors may have superior efficacy to either therapy alone in some inflammatory diseases.

WO99/38843 describes hydroxamic and carboxylic acid derivatives of the formula:

\[ B - X - (CH_2)_m - (CR^1R^2)_n - W - COY \]

wherein B can be a substituted aryl or heteroaryl; X can be sulfonyl; and W-COY can be N(OH)C(O)H. These compounds are defined as being useful for treating diseases mediated by MMPs, TNF, and other receptors. WO99/38843 does not describe or disclose compounds of the presently claimed invention.

WO00/12478 and WO00/75108 illustrate aryl piperazines of the formula:
wherein B can be heteroaryl; P can be a variety of linkers; A is an aliphatic ring; Y can be sulfonyl; and Z can be N(OH)C(O)H. These compounds are defined as being useful for inhibiting MMPs. Neither publication describes or discloses compounds of the presently claimed invention.

WO01/62742 piperidine and piperazine substituted N-hydroxyformamides of the formula:

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B-X\[N-SO_2\]
   \[R_1\]
   \[N\]
   \[HO\]
   \[CHO\]
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wherein B represents phenyl, pyridyl or pyrimidinyl and X represents a carbon or nitrogen atom. These compounds are defined as being useful for inhibiting MMPs. WO01/62742 does not describe or disclose compounds of the presently claimed invention.

WO99/06361 discloses reverse hydroxamate MMP inhibitors of the formula:

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A\[N\]
\[OH\]
\[R_3\]
\[R_4\]
\[X\]
\[Ar_1\]
\[Ar_2\]
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wherein X can be sulfonyl; Y can be a linker such as alkylenone or oxygen; Ar₁ is optionally substituted phenyl; and Ar₂ is selected from a list of 5-6 membered aryl or heteroaryl groups. WO99/06361 does not describe or disclose compounds of the present invention.

WO00/44712 depicts MMP inhibitors of the formula:
wherein $X$ can be sulfonyl; $Y^1$ can be a linker such as alkylene or oxygen; and $Ar$ is selected from a list of 5-6 membered aryl or heteroaryl groups. WO00/44712 does not describe or disclose compounds of the present invention.

WO00/44739 depicts MMP inhibitors of the formula:

wherein $Y^1$ can be a linker such as alkylene or oxygen and $Ar$ is selected from a list of 5-6 membered aryl or heteroaryl groups. WO00/44739 does not describe or disclose compounds of the present invention.

The compounds of the present invention act as inhibitors of MPs, in particular TACE, MMPs, and/or aggreccanase. These novel molecules are provided as anti-inflammatory compounds and cartilage protecting therapeutics. The inhibition of aggreccanase, TACE, and other metalloproteases by molecules of the present invention indicates they are anti-inflammatory and should prevent the degradation of cartilage by these enzymes, thereby alleviating the pathological conditions of OA and RA.
SUMMARY OF THE INVENTION

Accordingly, the present invention provides novel β-sulfone derivatives useful as MMP, TACE and/or aggrecanase inhibitors or pharmaceutically acceptable salts or prodrugs thereof.

The present invention provides pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of at least one of the compounds of the present invention or a pharmaceutically acceptable salt or prodrug form thereof.

The present invention provides a method for treating inflammatory disorders, comprising: administering to a host, in need of such treatment, a therapeutically effective amount of at least one of the compounds of the present invention or a pharmaceutically acceptable salt or prodrug form thereof.

The present invention provides a method for treating a condition or disease mediated by MMPs, TACE, aggrecanase, or a combination thereof in a mammal, comprising: administering to the mammal in need of such treatment a therapeutically effective amount of a compound of the present invention or a pharmaceutically acceptable salt or prodrug form thereof.

The present invention provides a method comprising: administering a compound of the present invention or a pharmaceutically acceptable salt or prodrug form thereof in an amount effective to treat a condition or disease mediated by MMPs, TACE, aggrecanase, or a combination thereof.

The present invention provides a method for treating inflammatory disorders, comprising: administering, to a host in need of such treatment, a therapeutically effective
amount of one of the compounds of the present invention, in combination with one or more additional anti-inflammatory agents selected from selective COX-2 inhibitors, interleukin-1 antagonists, dihydroorotate synthase inhibitors, p38 MAP kinase inhibitors, TNF-α inhibitors, TNF-α sequestration agents, and methotrexate.

The present invention provides novel compounds of the present invention for use in therapy.

The present invention provides the use of novel compounds of the present invention for the manufacture of a medicament for the treatment of a condition or disease mediated by MMPs, TACE, aggrecanase, or a combination thereof.

These and other objects, which will become apparent during the following detailed description, have been achieved by the inventors' discovery that compounds of formula I:

\[
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{OH} \\
\text{R}^2 \\
\text{R}^1 \\
\text{S} \\
\text{Z} \\
\text{X} \\
\text{Y} \\
\text{Z}^a
\end{array}
\]

or pharmaceutically acceptable salt or prodrug forms thereof, wherein R\(^1\), R\(^2\), R\(^3\), R\(^4\), R\(^5\), X, Y, Z and Z\(^a\) are defined below, are effective MMP, TACE, and/or aggrecanase inhibitors.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

[1] Thus, in an embodiment, the present invention provides a novel compound of formula I:
or a stereoisomer or pharmaceutically acceptable salt form thereof, wherein;

R¹ is selected from: H, C₁₋₆ alkyl substituted with 0-1 Rᵇ, C₂₋₆ alkenyl substituted with 0-1 Rᵇ, and C₂₋₆ alkylnyl substituted with 0-1 Rᵇ;


-(CRᵃRᵃ₁)ᵣ₁NRᵃSO₂NRᵃ(CRᵃRᵃ₁)ᵣ₋Q;
Q, at each occurrence, is independently selected from: H, a C\textsubscript{3-13} carbocycle substituted with 0-5 R\textsuperscript{d}, and a 4-14 membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)\textsubscript{P}, and substituted with 0-5 R\textsuperscript{d};

R\textsuperscript{3} is selected from: Q\textsuperscript{1}, -C\textsubscript{1-6} alkyne-Q\textsuperscript{1}, -C\textsubscript{2-6} alkenylene-Q\textsuperscript{1}, -C\textsubscript{2-6} alkynylene-Q\textsuperscript{1}, -(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r1}O(CH\textsubscript{2})\textsubscript{r}-Q\textsuperscript{1}, -(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r1}NR\textsuperscript{a}(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r}-Q\textsuperscript{1}, -(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r1}NR\textsuperscript{a}C(O)(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r}-Q\textsuperscript{1}, -(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r1}C(O)NR\textsuperscript{a}(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r}-Q\textsuperscript{1}, -(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r1}C(O)(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r}-Q\textsuperscript{1}, -(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r1}C(O)O(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r}-Q\textsuperscript{1}, -(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r1}S(O)\textsubscript{P}(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r}-Q\textsuperscript{1}, and -(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r1}SO\textsubscript{2}NR\textsuperscript{a}(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r}-Q\textsuperscript{1};

Q\textsuperscript{1}, at each occurrence, is independently selected from: H, a C\textsubscript{3-13} carbocycle substituted with 0-5 R\textsuperscript{d}, and a 5-14 membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)\textsubscript{P}, and substituted with 0-5 R\textsuperscript{d};

R\textsuperscript{4} is selected from: H, C\textsubscript{1-6} alkyl substituted with 0-1 R\textsuperscript{b}, C\textsubscript{2-6} alkenyl substituted with 0-1 R\textsuperscript{b}, and C\textsubscript{2-6} alkynyl substituted with 0-1 R\textsuperscript{b};

alternatively, R\textsuperscript{3} and R\textsuperscript{4} together with the carbon atom to which they are attached combine to form a 3-10 membered carbocyclic or heterocyclic ring consisting
of carbon atoms and 0-2 ring heteroatoms selected from 0, N, NR, and S(O)p, and substituted with 0-3 RC;

R5 is selected from: H, and C1-4 alkyl;

R10, at each occurrence, is independently selected from: H, C1-6 alkyl substituted with 0-2 RC, C2-6 alkenyl substituted with 0-2 RC, C2-6 alkynyl substituted with 0-2 RC, -(CRaR1)sNRaR1, -(CRaR1)R1C(O)NRaOH,

- (CRaR1)R1C(O)Ra1, -(CRaR1)R1C(O)ORa1,
- (CRaR1)R1C(S)ORa1, -(CRaR1)R1C(O)NRaRa1,
- (CRaR1)sNRaC(O)Ra1, -(CRaR1)R1C(S)NRaRa1,
- (CRaR1)sOC(O)NRaRa1, -(CRaR1)sNRaC(O)ORa1,
- (CRaR1)sNRaC(O)NRaRa1, -(CRaR1)R1S(O)pRa3,

- (CRaR1)R1SO2NRaRa1, -(CRaR1)sNRaSO2Ra3,
- (CRaR1)sNRaSO2NRaRa1, -(CRaR1)R1-C3-10 carbocycle substituted with 0-2 RC, and -(CRaR1)R1-5-14 membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)p, and substituted with 0-2 RC;

X-Y is CH2, CH2O or OCH2;

Z is selected from: a C6-10 aryl substituted with 0-5 Rb, and a 5-14 membered heteroaryl consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)p, and substituted with 0-5 Rb;
provided that X, Y, and Z do not combine to form a N-O, O-O, or S(O)ₖ-O, group;

Z, is substituted with 0-5 R⁵ and is a 8-14 membered heterocycle consisting of carbon atoms, 1-3 N atoms, and 0-1 heteroatom selected from the group consisting of O, and S(O)ₖ;

R₆, at each occurrence, is independently selected from: H, C₁₋₆ alkyl, phenyl, and benzyl;

R₆₁, at each occurrence, is independently selected from: H, C₁₋₆ alkyl substituted with 0-1 R₅, C₂₋₆ alkenyl substituted with 0-1 R₅, C₂₋₆ alkynyl substituted with 0-1 R₅, and -(CH₂)₁₋₃₋₈ membered carbocyclic or heterocyclic ring consisting of carbon atoms and 0-2 ring heteroatoms selected from N, NR₆₂, O, and S(O)ₖ, and substituted with 0-3 R₅;

alternatively, R₆ and R₆₁ when attached to a nitrogen are taken together with the nitrogen to which they are attached form a 5 or 6 membered heterocycle consisting of carbon atoms and 0-1 additional heteroatoms selected from N, NR₆₂, O, and S(O)ₖ;

R₆₂, at each occurrence, is independently selected from: C₁₋₄ alkyl, phenyl, and benzyl;

R₆₃, at each occurrence, is independently selected from: H, C₁₋₆ alkyl substituted with 0-1 R₅, C₂₋₆ alkenyl substituted with 0-1 R₅, C₂₋₆ alkynyl substituted with
0-1 R<sup>cl</sup>, and -(CH<sub>2</sub>)<sub>r</sub>-3-8 membered carbocyclic or heterocyclic ring consisting of carbon atoms and 0-2 ring heteroatoms selected from N, NR<sup>2a</sup>, O, and S(O)<sub>p</sub>, and substituted with 0-3 R<sup>cl</sup>;

R<sub>b</sub>, at each occurrence, is independently selected from:

- C<sub>1-6</sub> alkyl substituted with 0-1 R<sup>cl</sup>, -OR<sup>a</sup>, Cl, F, Br, I, =O, -CN, NO<sub>2</sub>, -NR<sup>a</sup>R<sup>al</sup>, -C(O)R<sup>a</sup>, -C(O)OR<sup>a</sup>, -C(O)NR<sup>a</sup>R<sup>al</sup>, -C(S)NR<sup>a</sup>R<sup>al</sup>, -NR<sup>a</sup>C(O)NR<sup>a</sup>R<sup>al</sup>, -OC(O)NR<sup>a</sup>R<sup>al</sup>, -NR<sup>a</sup>CH(O)OR<sup>a</sup>, -S(O)<sub>2</sub>NR<sup>a</sup>R<sup>al</sup>, -NR<sup>a</sup>S(O)<sub>2</sub>R<sup>a</sup>, -NR<sup>a</sup>S(O)<sub>2</sub>R<sup>a</sup>R<sup>al</sup>, -OS(O)<sub>2</sub>NR<sup>a</sup>R<sup>al</sup>, -NR<sup>a</sup>S(O)<sub>2</sub>R<sup>a</sup>, -S(O)<sub>p</sub>R<sup>a</sup>, CF<sub>3</sub>, -CF<sub>2</sub>CF<sub>3</sub>, -CHF<sub>2</sub>, -CH<sub>2</sub>F, and phenyl;

R<sub>c</sub>, at each occurrence, is independently selected from: H, C<sub>1-6</sub> alkyl substituted with 0-2 R<sup>cl</sup>, C<sub>2-6</sub> alkenyl substituted with 0-2 R<sup>cl</sup>, C<sub>2-6</sub> alkynyl substituted with 0-2 R<sup>cl</sup>, -OR<sup>a</sup>, Cl, F, Br, I, =O, -CN, NO<sub>2</sub>, CF<sub>3</sub>, -OCF<sub>3</sub>, -CF<sub>2</sub>CF<sub>3</sub>, -CHF<sub>2</sub>, -CH<sub>2</sub>F, -(CR<sup>a</sup>R<sup>al</sup>)<sub>r</sub>NR<sup>a</sup>R<sup>al</sup>, -(CR<sup>a</sup>R<sup>al</sup>)<sub>r</sub>C(=NCN)NR<sup>a</sup>R<sup>al</sup>, -(CR<sup>a</sup>R<sup>al</sup>)<sub>r</sub>C(=NR<sup>a</sup>)NR<sup>a</sup>R<sup>al</sup>, -(CR<sup>a</sup>R<sup>al</sup>)<sub>r</sub>C(=NOR<sup>a</sup>)NR<sup>a</sup>R<sup>al</sup>, -(CR<sup>a</sup>R<sup>al</sup>)<sub>r</sub>C(=O)NR<sup>a</sup>R<sup>al</sup>, -(CR<sup>a</sup>R<sup>al</sup>)<sub>r</sub>C(=O)R<sup>a</sup>, -(CR<sup>a</sup>R<sup>al</sup>)<sub>r</sub>C(=O)OR<sup>a</sup>, -(CR<sup>a</sup>R<sup>al</sup>)<sub>r</sub>C(S)OR<sup>a</sup>, -(CR<sup>a</sup>R<sup>al</sup>)<sub>r</sub>C(=O)NR<sup>a</sup>R<sup>al</sup>, -(CR<sup>a</sup>R<sup>al</sup>)<sub>r</sub>C(=O)NR<sup>a</sup>R<sup>al</sup>, -(CR<sup>a</sup>R<sup>al</sup>)<sub>r</sub>C(=O)NR<sup>a</sup>R<sup>al</sup>, -(CR<sup>a</sup>R<sup>al</sup>)<sub>r</sub>C(=O)R<sup>a</sup>, -(CR<sup>a</sup>R<sup>al</sup>)<sub>r</sub>OC(O)NR<sup>a</sup>R<sup>al</sup>, -(CR<sup>a</sup>R<sup>al</sup>)<sub>r</sub>OC(O)R<sup>a</sup>, -(CR<sup>a</sup>R<sup>al</sup>)<sub>r</sub>SO<sub>2</sub>NR<sup>a</sup>R<sup>al</sup>, -(CR<sup>a</sup>R<sup>al</sup>)<sub>r</sub>SO<sub>2</sub>NR<sup>a</sup>R<sup>al</sup>, -(CR<sup>a</sup>R<sup>al</sup>)<sub>r</sub>SO<sub>2</sub>NR<sup>a</sup>R<sup>al</sup>, -(CR<sup>a</sup>R<sup>al</sup>)<sub>r</sub>S(O)<sub>p</sub>R<sup>a</sup>, -(CR<sup>a</sup>R<sup>al</sup>)<sub>r</sub>S(O)<sub>p</sub>R<sup>a</sup>, -(CR<sup>a</sup>R<sup>al</sup>)<sub>r</sub>S(O)<sub>p</sub>R<sup>a</sup>, -(CR<sup>a</sup>R<sup>al</sup>)<sub>r</sub>-C<sub>3-10</sub> carbocycle substituted with 0-2 R<sup>cl</sup>, and -(CR<sup>a</sup>R<sup>al</sup>)<sub>r</sub>-5-14 membered heterocycle consisting of carbon atoms and 1-4
heteroatoms selected from the group consisting of N, 0, and S(O)ₚ, and substituted with 0-2 Rᵪ₁;

alternatively, when two Rᵦ groups are attached to the same carbon atom they form a spiro ring C that is a 3-11 membered carbocycle substituted with 0-2 Rᵪ₁ or a 3-13 membered heterocycle consisting of: carbon atoms, 0-3 carbonyl groups, 0-4 double bonds, and from 1-5 ring heteroatoms selected from O, N, and S(O)ₚ, and substituted with 0-2 Rᵪ₁, provided that ring C contains other than a S-S, O-O, or S-O bond;

alternatively, when two Rᵦ groups are attached to adjacent carbon atoms, together with the carbon atoms to which they are attached they form a 5-7 membered carbocyclic or heterocyclic ring consisting of: carbon atoms, 0-2 heteroatoms selected from the group consisting of N, O, and S(O)ₚ, and 0-3 double bonds, and substituted with 0-2 Rᵪ₁;

Rᵪ₁, at each occurrence, is independently selected from: H, C₁₋₆ alkyl, -ORᵃ, Cl, F, Br, I, =O, -CN, NO₂, -NRᵃRᵃ¹, -C(O)Rᵃ⁻², -C(O)ORᵃ⁻², -C(O)NRᵃ⁻², -NRᵃC(O)NRᵃ⁻², -OC(O)NRᵃ⁻², -NRᵃC(O)ORᵃ⁻², -S(O)₂NRᵃ⁻², -NRᵃS(O)₂Ra², -NRᵃS(O)₂NRᵃ⁻², -OS(O)₂NRᵃ⁻², -NRᵃS(O)₂Ra², -S(O)ₚRa², CF₃, -OCF₃, -CF₂CF₃, -CH₂F, and -CHF₂;

Rᵈ, at each occurrence, is independently selected from:
C₁₋₆ alkyl, -ORᵃ, Cl, F, Br, I, =O, -CN, NO₂, -NRᵃRᵃ¹, -C(O)Rᵃ⁻², -C(O)ORᵃ⁻², -C(O)NRᵃ⁻², -C(S)NRᵃ⁻², -NRᵃC(O)NRᵃ⁻², -OC(O)NRᵃ⁻², -NRᵃC(O)ORᵃ⁻²,
-S(O)\(_2\)NR\(_a\)Ra\(_1\), -NR\(_a\)S(O)\(_2\)Ra\(_3\), -NR\(_a\)S(O)\(_2\)NR\(_a\)Ra\(_1\),
-OS(O)\(_2\)NR\(_a\)Ra\(_1\), -NR\(_a\)S(O)\(_2\)Ra\(_3\), -S(O)\(_p\)Ra\(_3\), CF\(_3\), -CF\(_2\)CF\(_3\),
C\(_3\)-\(_10\) carbocycle, and a 5-14 membered heterocycle
consisting of carbon atoms and 1-4 heteroatoms
selected from the group consisting of N, O, and S(O)\(_p\);

R\(_a\), at each occurrence, is independently selected from: H,
C\(_1\)-\(_6\) alkyl, -OR\(_a\), Cl, F, Br, I, =O, -CN, NO\(_2\), -NR\(_a\)Ra,
-C(O)Ra, -C(O)OR\(_a\), -C(O)NR\(_a\)Ra, -NR\(_a\)C(O)NR\(_a\)Ra,
-OC(O)NR\(_a\)Ra, -NR\(_a\)C(O)OR\(_a\), -S(O)\(_2\)NR\(_a\)Ra, -NR\(_a\)S(O)\(_2\)Ra\(_2\),
-NR\(_a\)S(O)\(_2\)NR\(_a\)Ra, -OS(O)\(_2\)NR\(_a\)Ra, -NR\(_a\)S(O)\(_2\)Ra\(_2\), -S(O)\(_p\)Ra\(_2\),
CF\(_3\), -OCF\(_3\), -CF\(_2\)CF\(_3\), -CH\(_2\)F, and -CHF\(_2\);

p, at each occurrence, is selected from 0, 1, and 2;

r, at each occurrence, is selected from 0, 1, 2, 3, and 4;

r\(_1\), at each occurrence, is selected from 0, 1, 2, 3, and 4;

and,

s, at each occurrence, is selected from 1, 2, 3, and 4.

[2] In a preferred embodiment, the present invention
provides a novel compound, wherein;

Z\(_a\) is substituted with 0-4 R\(_c\) and is selected from the
group:
W is S, SO, SO₂, O, or NR₁¹;

R₁¹, at each occurrence, is independently selected from: H, C₁-₄ alkyl, phenyl, and benzyl;

Rₖ, at each occurrence, is independently selected from: H, C₁-₆ alkyl substituted with 0-2 R₁¹, C₂-₆ alkenyl substituted with 0-2 R₁¹, C₂-₆ alkynyl substituted with 0-2 R₁¹, -ORₐ, Cl, F, Br, I, =O, -CN, NO₂, CF₃, -OCF₃, -CF₂CF₃, -CH₂F, -CHF₂, -(CRₐRₐ¹)ᵣ₁NRₐRₐ¹, -(CRₐRₐ¹)ᵣ₁C(O)Rₐ¹, -(CRₐRₐ¹)ᵣ₁C(O)ORₐ¹, -(CRₐRₐ¹)ᵣ₁C(O)NRₐRₐ¹, -(CRₐRₐ¹)ᵣ₁NRₐC(O)Rₐ¹, -(CRₐRₐ¹)ᵣ₁S(O)ₚRₐ³, -(CRₐRₐ¹)ᵣ₁SO₂NRₐRₐ¹, -(CRₐRₐ¹)ᵣ₁NRₐSO₂Rₐ³, -(CRₐRₐ¹)ᵣ₁-C₃-₁₀ carbocycle substituted with 0-2 R₁¹, and -(CRₐRₐ¹)ᵣ₁-₅-₁₄ membered heterocycle consisting of carbon atoms and 1-₄ heteroatoms selected from the group consisting of N, O, and S(O)ₚ, and substituted with 0-2 R₁¹;

alternatively, when two Rₖ groups are attached to the same carbon atom they form a spiro ring C that is a 3-₁₁ membered carbocycle substituted with 0-2 R₁¹ or a 3-₁₃ membered heterocycle consisting of: carbon atoms, 0-₃
carbonyl groups, 0-4 double bonds, and from 1-5 ring heteroatoms selected from O, N, and S(O)\(_p\), and substituted with 0-2 R\(^c_1\), provided that ring C contains other than a S-S, O-O, or S-O bond; and,

alternatively, when two R\(^c\) groups are attached to adjacent carbon atoms, together with the carbon atoms to which they are attached they form a 5-7 membered carbocyclic or heterocyclic ring consisting of: carbon atoms, 0-2 heteroatoms selected from the group consisting of N, O, and S(O)\(_p\), and 0-3 double bonds, and substituted with 0-2 R\(^c_1\).

In another preferred embodiment, the present invention provides a novel compound, wherein;

R\(^1\) is selected from: H and C\(_{1-6}\) alkyl;

R\(^2\) is selected from: Q, -C\(_{1-6}\) alkylene-Q, -C\(_{2-6}\) alkenylene-Q, -C\(_{2-6}\) alkynylene-Q,

\(- (C^\alpha R^1)_{1} O (C^\alpha R^1)_{1} r - Q, \)

\(- (C^\alpha R^1)_{1} NR^a (C^\alpha R^1)_{1} r - Q, \)

\(- (C^\alpha R^1)_{1} C (O) O (C^\alpha R^1)_{1} r - Q, \)

\(- (C^\alpha R^1)_{1} C (O) NR^a (C^\alpha R^1)_{1} r - Q, \)

\(- (C^\alpha R^1)_{1} S (O) p (C^\alpha R^1)_{1} r - Q, \)

\(- (C^\alpha R^1)_{1} SO_2 NR^a (C^\alpha R^1)_{1} r - Q, \)

\(- (C^\alpha R^1)_{1} NR^a SO_2 (C^\alpha R^1)_{1} r - Q; \)

Q, at each occurrence, is independently selected from: H, a C\(_{3-10}\) carbocycle substituted with 0-5 R\(^d\), and a 5-10
membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)ₚ, and substituted with 0-5 Rᵈ;

5 R³ is selected from: Q¹, -C₁₋₆ alkylene-Q¹,
-C₂₋₆ alkenylene-Q¹, -C₂₋₆ alkynylene-Q¹,
-(CRᵃRᵃˡ)ᵣ₁O(CH₂)ᵢ₋ᵢ₋₁Q¹, -(CRᵃRᵃˡ)ᵣ₁NRᵃ(CRᵃRᵃˡ)ᵢ₋ᵢ₋₁Q¹,
-(CRᵃRᵃˡ)ᵣ₁NRᵃC(O)(CRᵃRᵃˡ)ᵢ₋ᵢ₋₁Q¹,
-(CRᵃRᵃˡ)ᵣ₁C(O)NRᵃ(CRᵃRᵃˡ)ᵢ₋ᵢ₋₁Q¹,

10 -(CRᵃRᵃˡ)ᵣ₁C(O)(CRᵃRᵃˡ)ᵢ₋ᵢ₋₁Q¹,
-(CRᵃRᵃˡ)ᵣ₁C(O)O(CRᵃRᵃˡ)ᵢ₋ᵢ₋₁Q¹,
-(CRᵃRᵃˡ)ᵣ₁S(O)ₚ(CRᵃRᵃˡ)ᵢ₋ᵢ₋₁Q¹, and
-(CRᵃRᵃˡ)ᵣ₁SO₂NRᵃ(CRᵃRᵃˡ)ᵢ₋ᵢ₋₁Q¹;

15 Q¹, at each occurrence, is independently selected from: H, a C₃₋₁₀ carbocycle substituted with 0-5 Rᵈ, and a 5-10 membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)ₚ, and substituted with 0-5 Rᵈ;

20 R⁴ is selected from: H, C₁₋₆ alkyl substituted with 0-1 Rᵇ, C₂₋₆ alkenyl substituted with 0-1 Rᵇ, and C₂₋₆ alkynyl substituted with 0-1 Rᵇ;

25 alternatively, R³ and R⁴ together with the carbon atom to which they are attached combine to form a 3-8 membered carbocyclic or heterocyclic ring consisting of carbon atoms and 0-2 ring heteroatoms selected from O, N, NR¹⁰, and S(O)ₚ, and substituted with 0-3 Rᶜ;
R\(^{10}\), at each occurrence, is independently selected from: H, C\(_{1-6}\) alkyl substituted with 0-2 R\(^{c1}\), C\(_{2-6}\) alkenyl substituted with 0-2 R\(^{c1}\), C\(_{2-6}\) alkynyl substituted with 0-2 R\(^{c1}\), -(CR\(^{aRa1}\))\(_{6}\)NR\(^{aRa1}\), -(CR\(^{aRa1}\))\(_{1}\)C(O)Ra\(^{1}\),
-(CR\(^{aRa1}\))\(_{1}\)C(O)ORa\(^{1}\), -(CR\(^{aRa1}\))\(_{1}\)C(O)NR\(^{aRa1}\),
-(CR\(^{aRa1}\))\(_{1}\)NR\(^{aRa1}\)C(O)Ra\(^{1}\), -(CR\(^{aRa1}\))\(_{1}\)S(O)\(_{p}\)Ra\(^{3}\),
-(CR\(^{aRa1}\))\(_{1}\)SO\(_{2}\)NR\(^{aRa1}\), -(CR\(^{aRa1}\))\(_{6}\)NR\(^{aRa1}\)SO\(_{2}\)Ra\(^{3}\),
-(CR\(^{aRa1}\))\(_{1}\)C\(_{3-10}\) carbocycle substituted with 0-2 R\(^{c1}\), and -(CR\(^{aRa1}\))\(_{1}\)5-14 membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)\(_{p}\), and substituted with 0-2 R\(^{c1}\);

R\(^{c}\), at each occurrence, is independently selected from: H, C\(_{1-6}\) alkyl substituted with 0-2 R\(^{c1}\), C\(_{2-6}\) alkenyl substituted with 0-2 R\(^{c1}\), C\(_{2-6}\) alkynyl substituted with 0-2 R\(^{c1}\), OR\(^{a}\), Cl, F, Br, I, =O, -CN, NO\(_{2}\), CF\(_{3}\), -CF\(_{2}\)CF\(_{3}\), -(CR\(^{aRa1}\))\(_{1}\)NR\(^{aRa1}\), -(CR\(^{aRa1}\))\(_{1}\)C(O)Ra\(^{1}\),
-(CR\(^{aRa1}\))\(_{1}\)C(O)ORa\(^{1}\), -(CR\(^{aRa1}\))\(_{1}\)C(O)NR\(^{aRa1}\),
-(CR\(^{aRa1}\))\(_{1}\)NR\(^{aRa1}\)C(O)Ra\(^{1}\), -(CR\(^{aRa1}\))\(_{1}\)S(O)\(_{p}\)Ra\(^{3}\),
-(CR\(^{aRa1}\))\(_{1}\)SO\(_{2}\)NR\(^{aRa1}\), -(CR\(^{aRa1}\))\(_{1}\)NR\(^{aRa1}\)SO\(_{2}\)Ra\(^{3}\),
-(CR\(^{aRa1}\))\(_{1}\)C\(_{3-10}\) carbocycle substituted with 0-2 R\(^{c1}\), and -(CR\(^{aRa1}\))\(_{1}\)5-10 membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)\(_{p}\), and substituted with 0-2 R\(^{c1}\);

R\(^{c1}\), at each occurrence, is independently selected from: H, C\(_{1-4}\) alkyl, OR\(^{a}\), Cl, F, Br, I, =O, CF\(_{3}\), -CN, NO\(_{2}\),
-NR\textsuperscript{a}R\textsuperscript{a1}, -C(O)OR\textsuperscript{a}, and -C(O)NR\textsuperscript{a}R\textsuperscript{a1};

R\textsuperscript{d}, at each occurrence, is independently selected from:

C\textsubscript{1-6} alkyl, -OR\textsuperscript{a}, Cl, F, Br, I, =O, -CN, NO\textsubscript{2}, -NR\textsuperscript{a}R\textsuperscript{a1},

-C(O)R\textsuperscript{a}, -C(O)OR\textsuperscript{a}, -C(O)NR\textsuperscript{a}R\textsuperscript{a1}, -C(S)NR\textsuperscript{a}R\textsuperscript{a1},

-NR\textsuperscript{a}C(O)NR\textsuperscript{a}R\textsuperscript{a1}, -OC(O)NR\textsuperscript{a}R\textsuperscript{a1}, -NR\textsuperscript{a}C(O)OR\textsuperscript{a1},

-S(O)\textsubscript{2}NR\textsuperscript{a}R\textsuperscript{a1}, -NR\textsuperscript{a}S(O)\textsubscript{2}R\textsuperscript{a3}, -NR\textsuperscript{a}S(O)\textsubscript{2}NR\textsuperscript{a}R\textsuperscript{a1},

-O(S)\textsubscript{2}NR\textsuperscript{a}R\textsuperscript{a1}, -NR\textsuperscript{a}S(O)\textsubscript{2}R\textsuperscript{a3}, -S(O)\textsubscript{p}Ra\textsuperscript{a3}, CF\textsubscript{3}, -CF\textsubscript{2}CF\textsubscript{3}, C\textsubscript{3-6} carbocycle, and a 5-6 membered heterocycle

consisting of carbon atoms and 1-4 heteroatoms

selected from the group consisting of N, O, and S(O)\textsubscript{p}; and,

R\textsuperscript{e}, at each occurrence, is independently selected from: H,

C\textsubscript{1-4} alkyl, -OR\textsuperscript{a}, Cl, F, Br, I, =O, CF\textsubscript{3}, -CN, NO\textsubscript{2},

-NR\textsuperscript{a}R\textsuperscript{a}, -C(O)OR\textsuperscript{a}, and -C(O)NR\textsuperscript{a}R\textsuperscript{a}.

[4] In another preferred embodiment, the present invention provides a novel compound, wherein;

R\textsuperscript{2} is selected from: Q, -C\textsubscript{1-6} alkylene-Q,

-C\textsubscript{1-6} alkenylene-Q, -(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r}O(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r}-Q,

-(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r}NR\textsuperscript{a}(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r}-Q, -(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r}C(O) (CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r}-Q,

-(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r}C(O)O(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r}-Q, -(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r}C(O)NR\textsuperscript{a}R\textsuperscript{a1},

-(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r}C(O)NR\textsuperscript{a}(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r}-Q,

-(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r}S(O)\textsubscript{p}(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r}-Q, and

-(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r}SO\textsubscript{2}NR\textsuperscript{a}(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r}-Q;
Q, at each occurrence, is independently selected from: H, a C₃-6 carbocycle substituted with 0-3 Rᵈ, and a 5-10 membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)ₓ, and substituted with 0-3 Rᵈ;

R³ is selected from: Q¹, -C₁-₆ alkylene-Q¹,
-C₂₋₆ alkenylene-Q¹, -(CRᵃRᵃ�)ᵣ₁₀(CH₂)ᵣ-Q¹,
-(CRᵃRᵃ�)ᵣ₁NRᵃ(CRᵃRᵃ�)ᵣ-Q¹,
-(CRᵃRᵃ�)ᵣ₁C(O)NRᵃ(CRᵃRᵃ�)ᵣ-Q¹,
-(CRᵃRᵃ�)ᵣ₁C(O)(CRᵃRᵃ�)ᵣ-Q¹,
-(CRᵃRᵃ�)ᵣ₁C(O)O(CRᵃRᵃ�)ᵣ-Q¹,
-(CRᵃRᵃ�)ᵣ₁S(O)ₓ(CRᵃRᵃ�)ᵣ-Q¹, and
-(CRᵃRᵃ�)ᵣ₁SO₂NRᵃ(CRᵃRᵃ�)ᵣ-Q¹;

Q¹, at each occurrence, is independently selected from: H, a C₃-₆ carbocycle substituted with 0-3 Rᵈ, and a 5-10 membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)ₓ, and substituted with 0-3 Rᵈ;

R⁴ is selected from: H and C₁-₆ alkyl;

alternatively, R³ and R⁴ together with the carbon atom to which they are attached combine to form a 3-6 membered carbocyclic or heterocyclic ring consisting of carbon atoms and 0-2 ring heteroatoms selected from O, N, NR¹⁰, and S(O)ₓ, and substituted with 0-3 Rᶜ;
R^{10}, at each occurrence, is independently selected from: H, C_{1-6} alkyl substituted with 0-1 R^{11}, C_{2-6} alkenyl substituted with 0-1 R^{11}, C_{2-6} alkynyl substituted with 0-1 R^{11}, -(CR^{a}R^{a1})_{r1}C(O)R^{a1}, -(CR^{a}R^{a1})_{r1}C(O)OR^{a1}, -(CR^{a}R^{a1})_{r1}C(O)NR^{a}R^{a1}, -(CR^{a}R^{a1})_{r1}S(O)_{p}R^{a3}, -(CR^{a}R^{a1})_{r1}SO_{2}NR^{a}R^{a1}, -(CR^{a}R^{a1})_{r1}C_{3-6} carbocycle substituted with 0-2 R^{c1}, and -(CR^{a}R^{a1})_{r1}C_{3-6} heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)_{p}, and substituted with 0-2 R^{c1};

Z is selected from: phenyl substituted with 0-3 R^{b}, and a 5-6 membered heteroaryl consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)_{p}, and substituted with 0-3 R^{b};

provided that X, Y, and Z do not combine to form a N-O, O-O, or S(O)_{p}-O group;

Z^{a} is 4-quinolinyl substituted with 0-2 R^{c};

R^{a}, at each occurrence, is independently selected from: H and C_{1-4} alkyl;

R^{a1}, at each occurrence, is independently selected from: H, C_{1-4} alkyl, phenyl, and benzyl;

alternatively, R^{a} and R^{a1} when attached to a nitrogen are taken together with the nitrogen to which they are attached form a 5 or 6 membered heterocycle consisting
of carbon atoms and 0-1 additional heteroatoms
selected from N, NR^{a2}, O, and S(O)_{p};

R^{b}, at each occurrence, is independently selected from:
5  C_{1-6} alkyl, -OR^{a}, Cl, F, Br, =O, -CN, -NR^{a}R^{a1}, -C(O)R^{a},
   -C(O)OR^{a}, -C(O)NR^{a}R^{a1}, -S(O)_{2}NR^{a}R^{a1}, -S(O)_{p}R^{a3}, and CF_{3};

R^{c}, at each occurrence, is independently selected from: H, C_{1-6} alkyl substituted with 0-1 R^{c1}, C_{2-6} alkenyl
10 substituted with 0-1 R^{c1}, C_{2-6} alkynyl substituted with 0-1 R^{c1}, -OR^{a}, Cl, F, Br, =O, -CN, CF_{3}, -NR^{a}R^{a1},
   -(CR^{a}R^{a1})_{r}C(O)R^{a1}, -(CR^{a}R^{a1})_{r}C(O)OR^{a1},
   -(CR^{a}R^{a1})_{r}C(O)NR^{a}R^{a1}, -(CR^{a}R^{a1})_{r}S(O)_{p}R^{a3},
   -(CR^{a}R^{a1})_{r}SO_{2}NR^{a}R^{a1}, C_{3-6} carbocycle, and a 5-6
   membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)_{p}; and,

R^{d}, at each occurrence, is independently selected from:
20  C_{1-6} alkyl, -OR^{a}, Cl, F, Br, =O, -CN, -NR^{a}R^{a1}, -C(O)R^{a},
   -C(O)OR^{a}, -C(O)NR^{a}R^{a1}, -S(O)_{2}NR^{a}R^{a1}, -S(O)_{p}R^{a3}, CF_{3},
   C_{3-6} carbocycle, and a 5-6 membered heterocycle
   consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)_{p}.

[5] In another preferred embodiment, the present invention
provides a novel compound, wherein;

30  R^{1} is selected from: H and C_{1-4} alkyl;
R² is selected from: Q, -C₁₋₆ alkylene-Q,
       -(CRᵃRᵃ⁺)ᵣ₁C(O)(CRᵃR⁺)ᵣ⁻Q, -(CRᵃR⁺)ᵣ₁C(O)O(CRᵃR⁺)ᵣ⁻Q,
       -(CRᵃR⁺)ᵣ₁C(O)NRᵃR⁺, -(CRᵃR⁺)ᵣ₁C(O)NRᵃ(CRᵃR⁺)ᵣ⁻Q, and
       -(CRᵃR⁺)ᵣ₁S(O)ᵣ(CRᵃR⁺)ᵣ⁻Q;

Q, at each occurrence, is independently selected from: H, a
C₃₋₆ carbocycle substituted with 0-2 Rᵈ, and a 5-6
membered heterocycle consisting of carbon atoms and
1-4 heteroatoms selected from the group consisting of
N, O, and S(O)ᵣ, and substituted with 0-2 Rᵈ;

R³ is selected from: Q¹, -C₁₋₆ alkylene-Q¹,
       -(CRᵃR⁺)ᵣ₁O(CH₂)ᵣ⁻Q¹, -(CRᵃR⁺)ᵣ₁NRᵃ(CRᵃR⁺)ᵣ⁻Q¹,
       -(CRᵃR⁺)ᵣ₁C(O)NRᵃ(CRᵃR⁺)ᵣ⁻Q¹,
       -(CRᵃR⁺)ᵣ₁C(O)(CRᵃR⁺)ᵣ⁻Q¹,
       -(CRᵃR⁺)ᵣ₁C(O)O(CRᵃR⁺)ᵣ⁻Q¹,
       -(CRᵃR⁺)ᵣ₁S(O)ᵣ(CRᵃR⁺)ᵣ⁻Q¹, and
       -(CRᵃR⁺)ᵣ₁SO₂NRᵃ(CRᵃR⁺)ᵣ⁻Q¹;

Q¹, at each occurrence, is independently selected from: H, a
C₃₋₆ carbocycle substituted with 0-2 Rᵈ, and a 5-6
membered heterocycle consisting of carbon atoms and
1-4 heteroatoms selected from the group consisting of
N, O, and S(O)ᵣ, and substituted with 0-2 Rᵈ;

R⁴ is selected from: H and C₁₋₄ alkyl;

alternatively, R³ and R⁴ together with the carbon atom to
which they are attached combine to form a 3-6 membered
carbocyclic or heterocyclic ring consisting of carbon atoms and 0-2 ring heteroatoms selected from O, N, NR\(^{10}\), and S(O)\(_{p}\), and substituted with 0-2 R\(^{c}\);

5 \(R^{10}\), at each occurrence, is independently selected from: H, C\(_{1-6}\) alkyl substituted with 0-1 R\(^{c}\), C\(_{2-6}\) alkenyl substituted with 0-1 R\(^{c}\), C\(_{2-6}\) alkynyl substituted with 0-1 R\(^{c}\), -(CR\(^{a}\)R\(^{a1}\))\(_{1}\)C(O)Ra\(_{1}\), -(CR\(^{a}\)R\(^{a1}\))\(_{1}\)C(O)ORa\(_{1}\), -(CR\(^{a}\)R\(^{a1}\))\(_{1}\)C(O)NRaR\(^{a1}\), -(CR\(^{a}\)R\(^{a1}\))\(_{1}\)S(O)\(_{p}\)Ra\(_{3}\), -(CR\(^{a}\)R\(^{a1}\))\(_{1}\)SO\(_{2}\)NRaR\(^{a1}\), -(CH\(_{2}\))\(_{1}\)-C\(_{3-6}\) carbocycle substituted with 0-2 R\(^{c}\), and -(CH\(_{2}\))\(_{1}\)5-6 membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)\(_{p}\), and substituted with 0-2 R\(^{c}\);

10 X-Y is CH\(_{2}\) or OCH\(_{2}\);

Z is phenyl substituted with 0-3 R\(^{b}\);

20 R\(^{a}\), at each occurrence, is independently selected from: H and C\(_{1-4}\) alkyl;

R\(^{a1}\), at each occurrence, is independently selected from: H, C\(_{1-4}\) alkyl, phenyl, and benzyl;

25 R\(^{b}\), at each occurrence, is independently selected from:

C\(_{1-4}\) alkyl, -OR\(^{a}\), Cl, F, =O, -NRaR\(^{a1}\), -C(O)Ra, -C(O)OR\(^{a}\), -C(O)NRaR\(^{a1}\), -S(O)\(_{2}\)NRaR\(^{a1}\), -S(O)\(_{p}\)Ra\(_{3}\), and CF\(_{3}\);
R^c, at each occurrence, is independently selected from: H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -OR^a, Cl, F, Br, =O, -NR^aR^a, CF_3, -(CR^aR^a)_1C(O)R^a, 
-(CR^aR^a)_1C(O)OR^a, -(CR^aR^a)_1C(O)NR^aR^a, 
-(CR^aR^a)_1S(O)_pR^a, -(CR^aR^a)_1SO_2NR^aR^a, and phenyl; and,

R^d, at each occurrence, is independently selected from:
C_{1-6} alkyl, -OR^a, Cl, F, Br, =O, -NR^aR^a, -C(O)R^a, 
-C(O)NR^aR^a, -S(O)_2NR^aR^a, -S(O)_pR^a, CF_3, and phenyl.

[6] In another preferred embodiment, the present invention 
provides a novel compound, wherein;

R^1 is selected from: H, methyl, and ethyl;

R^2 is selected from: Q, -C_{1-6} alkyne-Q, -C(O)(CR^aR^a)_r-Q, 
-C(O)O(CR^aR^a)_r-Q, -C(O)NR^a(CR^aR^a)_r-Q, and 
-S(O)_p(CR^aR^a)_r-Q;

Q, at each occurrence, is independently selected from: H, 
cyclopropyl substituted with 0-1 R^d, cyclopentyl 
substituted with 0-1 R^d, cyclohexyl substituted with 
0-1 R^d, phenyl substituted with 0-2 R^d, and a 
heteroaryl substituted with 0-3 R^d, wherein the 
heteroaryl is selected from pyridyl, quinolinyl, 
thiazolyl, furanyl, imidazolyl, and isoxazolyl;

R^3 is selected from: Q^1, -C_{1-6} alkyne-Q^1,
-C(O)NR^a(CR^aR^al)_r-Q^1, -C(O)(CR^aR^al)_r-Q^1,
-C(O)O(CR^aR^al)_r-Q^1, and -(CR^aR^al)_r1S(O)_p(CR^aR^al)_r-Q^1;

Q^1, at each occurrence, is independently selected from: H, cyclopropyl substituted with 0-1 R^d, cyclopentyl substituted with 0-1 R^d, cyclohexyl substituted with 0-1 R^d, phenyl substituted with 0-2 R^d, and a heteroaryl substituted with 0-3 R^d, wherein the heteroaryl is selected from pyridyl, quinolinyl, thiazolyl, furanyl, imidazolyl, and isoxazolyl;

R^4 is selected from: H, methyl, and ethyl;

R^5 is H;

R^a, at each occurrence, is independently selected from: H, methyl, and ethyl;

R^a1, at each occurrence, is independently selected from: H, methyl, and ethyl;

R^a2, at each occurrence, is independently selected from: H, methyl, and ethyl;

R^c, at each occurrence, is independently selected from: H, C_1-6 alkyl, C_2-6 alkenyl, C_2-6 alkynyl, -OR^a, Cl, F, Br, =O, -NR^aR^al, CF_3, -(CR^aR^al)_r1C(O)R^al,
-(CR^aR^al)_r1C(O)OR^a, -(CR^aR^al)_r1C(O)NR^aR^al,
-(CR^aR^al)_r1S(O)_pR^al, and -(CR^aR^al)_r1SO_2NR^aR^al;

p, at each occurrence, is selected from 0, 1, and 2;
r, at each occurrence, is selected from 0, 1, 2, and 3; and,

r1, at each occurrence, is selected from 0, 1, 2, and 3.

[7] In another embodiment, the present invention provides a novel compound of formula I:

\[
\begin{align*}
\text{O} & \quad \text{N} \\
\text{R}^5 & \quad \text{R}^4 \\
\text{R}^3 & \quad \text{O} \\
\text{S} & \quad \text{Z} \\
\text{W} & \quad \text{X} \\
\text{Y} & \quad \text{Z}^\alpha \\
\text{OH} & \quad \text{R}^2 \\
\text{R}^1 & \quad \text{I}
\end{align*}
\]

or a stereoisomer or pharmaceutically acceptable salt form thereof, wherein;

R1 and R2 together with the carbon atom to which they are attached combine to form a 3-10 membered carbocyclic or heterocyclic ring consisting of carbon atoms and 0-2 ring heteroatoms selected from O, N, NR10, and S(O)p, and substituted with 0-4 Rc;

R3 is selected from: Q1, -C1-6 alkylene-Q1, -C2-6 alkenylene-Q1, -C2-6 alkynylene-Q1, -(CRaRa1)r1O(CH2)r-Q1, -(CRaRa1)r1NRa(CRaRa1)r-Q1, -(CRaRa1)r1NRaC(O)(CRaRa1)r-Q1, -(CRaRa1)r1C(O)NRa(CRaRa1)r-Q1, -(CRaRa1)r1C(O)(CRaRa1)r-Q1, -(CRaRa1)r1C(O)O(CRaRa1)r-Q1, -(CRaRa1)r1S(O)p(CRaRa1)r-Q1, and
-(CRaRa1)r1SO2NRaN(RaRa1)r1-Q1;

Q1, at each occurrence, is independently selected from: H, a C3-13 carbocycle substituted with 0-5 Rd, and a 5-14 membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)ₚ, and substituted with 0-5 Rd;

R₄ is selected from: H, C₁₋₆ alkyl substituted with 0-1 Rᵇ, C₂₋₆ alkenyl substituted with 0-1 Rᵇ, and C₂₋₆ alkynyl substituted with 0-1 Rᵇ;

R₅ is selected from: H, and C₁₋₄ alkyl;

R₁₀, at each occurrence, is independently selected from: H, C₁₋₆ alkyl substituted with 0-2 Rᶜ₁, C₂₋₆ alkenyl substituted with 0-2 Rᶜ₁, C₂₋₆ alkynyl substituted with 0-2 Rᶜ₁, -(CRaRa1)sNRaN(RaRa1), -(CRaRa1)r1C(O)NRaNOH,
- (CRaRa1)r1C(O)Ra₁, - (CRaRa1)r1C(O)ORa₁,
- (CRaRa1)r1C(S)ORa₁, - (CRaRa1)r1C(O)NRaN(RaRa1),
- (CRaRa1)sNRaₚC(O)Ra₁, - (CRaRa1)r1C(S)NRaN(RaRa1),
- (CRaRa1)sOC(O)NRaN(RaRa1), - (CRaRa1)sNRaNₚC(O)ORa₁,
- (CRaRa1)sNRaNₚC(O)NRaN(RaRa1), - (CRaRa1)r1S(O)ₚRaₚ,
- (CRaRa1)r1SO₂NRaN(RaRa1), - (CRaRa1)sNRaSO₂Raₚ,
- (CRaRa1)sNRaSO₂NRaN(RaRa1), -(CRaRa1)r₁-C₃₋₁₀ carbocycle substituted with 0-2 Rᶜ₁, and -(CRaRa1)r₁-5-14 membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)ₚ, and substituted with 0-2 Rᶜ₁;
X-Y is CH₂, CH₂O or OCH₂;

Z is selected from: a C₆-₁₀ aryl substituted with 0-5 R⁰, and a 5-14 membered heteroaryl consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)ₚ, and substituted with 0-5 R⁰;

provided that X, Y, and Z do not combine to form a N-O, O-O, or S(O)ₚ-O, group;

Z⁰ is substituted with 0-5 R⁰, and is a 8-14 membered heterocycle consisting of carbon atoms, 1-3 N atoms, and 0-1 heteroatom selected from the group consisting of O, and S(O)ₚ;

R⁰, at each occurrence, is independently selected from: H, C₁-₆ alkyl, phenyl, and benzyl;

R¹, at each occurrence, is independently selected from: H, C₁-₆ alkyl substituted with 0-1 R⁰, C₂-₆ alkenyl substituted with 0-1 R⁰, C₂-₆ alkynyl substituted with 0-1 R⁰, and -(CH₂)ₓ-3-8 membered carbocyclic or heterocyclic ring consisting of carbon atoms and 0-2 ring heteroatoms selected from N, NR², O, and S(O)ₚ, and substituted with 0-3 R⁰;

alternatively, R⁰ and R¹ when attached to a nitrogen are taken together with the nitrogen to which they are attached form a 5 or 6 membered heterocycle consisting
of carbon atoms and 0-1 additional heteroatoms
selected from N, NR\textsuperscript{a2}, O, and S(O)\textsubscript{p};

R\textsuperscript{a2}, at each occurrence, is independently selected from:

C\textsubscript{1-4} alkyl, phenyl, and benzyl;

R\textsuperscript{a3}, at each occurrence, is independently selected from:

H, C\textsubscript{1-6} alkyl substituted with 0-1 R\textsuperscript{ci}, C\textsubscript{2-6} alkenyl
substituted with 0-1 R\textsuperscript{ci}, C\textsubscript{2-6} alkynyl substituted with
0-1 R\textsuperscript{ci}, and -(CH\textsubscript{2})\textsubscript{r}-3-8 membered carbocyclic or
heterocyclic ring consisting of carbon atoms and 0-2
ring heteroatoms selected from N, NR\textsuperscript{a2}, O, and S(O)\textsubscript{p}
and substituted with 0-3 R\textsuperscript{ci};

R\textsuperscript{b}, at each occurrence, is independently selected from:

C\textsubscript{1-6} alkyl substituted with 0-1 R\textsuperscript{ci}, -OR\textsuperscript{a}, Cl, F, Br,
I, =O, -CN, NO\textsubscript{2}, -NR\textsuperscript{a}R\textsuperscript{a1}, -C(O)R\textsuperscript{a}, -C(O)OR\textsuperscript{a},
-C(O)NR\textsuperscript{a}R\textsuperscript{a1}, -C(S)NR\textsuperscript{a}R\textsuperscript{a1}, -NR\textsuperscript{a}C(O)NR\textsuperscript{a}R\textsuperscript{a1},
-OC(O)NR\textsuperscript{a}R\textsuperscript{a1}, -NR\textsuperscript{a}C(O)OR\textsuperscript{a}, -S(O)\textsubscript{2}NR\textsuperscript{a}R\textsuperscript{a1},
-NR\textsuperscript{a}S(O)\textsubscript{2}R\textsuperscript{a3}, -NR\textsuperscript{a}S(O)\textsubscript{2}NR\textsuperscript{a}R\textsuperscript{a1},
-OS(O)\textsubscript{2}NR\textsuperscript{a}R\textsuperscript{a1}, -NR\textsuperscript{a}S(O)\textsubscript{2}R\textsuperscript{a3}, -S(O)\textsubscript{p}R\textsuperscript{a3},
CF\textsubscript{3}, -CF\textsubscript{2}CF\textsubscript{3}, -CHF\textsubscript{2}, -CH\textsubscript{2}F, and phenyl;

R\textsuperscript{c}, at each occurrence, is independently selected from:

H, C\textsubscript{1-6} alkyl substituted with 0-2 R\textsuperscript{ci}, C\textsubscript{2-6} alkenyl
substituted with 0-2 R\textsuperscript{ci}, C\textsubscript{2-6} alkynyl substituted with
0-2 R\textsuperscript{ci}, -OR\textsuperscript{a}, Cl, F, Br, I, =O, -CN, NO\textsubscript{2}, CF\textsubscript{3}, -OCF\textsubscript{3},
-CF\textsubscript{2}CF\textsubscript{3}, -CH\textsubscript{2}F, -CHF\textsubscript{2}, -(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r}\textsubscript{1}NR\textsuperscript{a}R\textsuperscript{a1},
-(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r}\textsubscript{1}C(=NCN)NR\textsuperscript{a}R\textsuperscript{a1}, -(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r}\textsubscript{1}C(=NR\textsuperscript{a})NR\textsuperscript{a}R\textsuperscript{a1},
-(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r}\textsubscript{1}C(=NOR\textsuperscript{a})NR\textsuperscript{a}R\textsuperscript{a1}, -(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r}\textsubscript{1}C(O)NR\textsuperscript{a}OH,
-(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r}\textsubscript{1}C(O)R\textsuperscript{a1}, -(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r}\textsubscript{1}C(O)OR\textsuperscript{a1},
- (CRAra1) R1C(S)ORa1, - (CRAra1) R1C(O)NRaRar1,
- (CRAra1) R1NRaC(O)Ra1, - (CRAra1) R1C(S)NRaRar1,
- (CRAra1) R1OC(O)NRaRar1, - (CRAra1) R1NRaC(O)ORa1,
- (CRAra1) R1NRaC(O)NRaRar1, - (CRAra1) R1S(O)PrRa3,
- (CRAra1) R1SO2NRaRar1, - (CRAra1) R1NRaSO2Ra3,
- (CRAra1) R1NRaSO2NRaRar1, - (CRAra1) R1-C3-10 carbocycle
substituted with 0-2 RC1, and - (CRAra1) R1-5-14 membered
heterocycle consisting of carbon atoms and 1-4
heteroatoms selected from the group consisting of N, O, and S(O)Pr, and substituted with 0-2 RC1;

alternatively, when two RC groups are attached to the same
carbon atom they form a spiro ring C that is a 3-11
membered carbocycle substituted with 0-2 RC1 or a 3-13
membered heterocycle consisting of: carbon atoms, 0-3
carbonyl groups, 0-4 double bonds, and from 1-5 ring
heteroatoms selected from O, N, and S(O)Pr, and
substituted with 0-2 RC1, provided that ring C
contains other than a S-S, O-O, or S-O bond;

alternatively, when two RC groups are attached to adjacent
carbon atoms, together with the carbon atoms to which
they are attached they form a 5-7 membered carbocyclic
or heterocyclic ring consisting of: carbon atoms, 0-2
heteroatoms selected from the group consisting of N,
O, and S(O)Pr, and 0-3 double bonds, and substituted
with 0-2 RC1;
R<sup>c1</sup>, at each occurrence, is independently selected from: H, C<sub>1-6</sub> alkyl, -OR<sup>a</sup>, Cl, F, Br, I, =O, -CN, NO<sub>2</sub>, -NR<sub>a</sub>R<sup>al</sup>, -C(O)R<sup>a</sup>, -C(O)OR<sup>a</sup>, -C(O)NR<sup>ar</sup>R<sup>al</sup>, -NR<sub>a</sub>C(O)NR<sub>a</sub>R<sup>al</sup>, -OC(O)NR<sup>ar</sup>R<sup>al</sup>, -NR<sub>a</sub>C(O)OR<sup>al</sup>, -S(O)<sub>2</sub>NR<sup>ar</sup>R<sup>al</sup>, -NR<sub>as</sub>S(O)<sub>2</sub>R<sup>a2</sup>, -NR<sub>as</sub>S(O)<sub>2</sub>NR<sup>ar</sup>R<sup>al</sup>, -OS(O)<sub>2</sub>NR<sup>ar</sup>R<sup>al</sup>, -NR<sub>as</sub>S(O)<sub>2</sub>R<sup>a2</sup>, -S(O)<sub>r</sub>R<sup>ra2</sup>, CF<sub>3</sub>, -OCF<sub>3</sub>, -CF<sub>2</sub>CF<sub>3</sub>, -CH<sub>2</sub>F, and -CHF<sub>2</sub>;

R<sup>d</sup>, at each occurrence, is independently selected from:
C<sub>1-6</sub> alkyl, -OR<sup>a</sup>, Cl, F, Br, I, =O, -CN, NO<sub>2</sub>, -NR<sub>a</sub>R<sup>al</sup>, -C(O)R<sup>a</sup>, -C(O)OR<sup>a</sup>, -C(O)NR<sup>ar</sup>R<sup>al</sup>, -C(S)NR<sup>ar</sup>R<sup>al</sup>, -NR<sub>a</sub>C(O)NR<sup>ar</sup>R<sup>al</sup>, -OC(O)NR<sup>ar</sup>R<sup>al</sup>, -NR<sub>a</sub>C(O)OR<sup>al</sup>, -S(O)<sub>2</sub>NR<sup>ar</sup>R<sup>al</sup>, -NR<sub>as</sub>S(O)<sub>2</sub>R<sup>ar3</sup>, -NR<sub>as</sub>S(O)<sub>2</sub>NR<sup>ar</sup>R<sup>al</sup>, -OS(O)<sub>2</sub>NR<sup>ar</sup>R<sup>al</sup>, -NR<sub>as</sub>S(O)<sub>2</sub>R<sup>ar3</sup>, -S(O)<sub>r</sub>R<sup>ra3</sup>, CF<sub>3</sub>, -CF<sub>2</sub>CF<sub>3</sub>, C<sub>3-10</sub> carbocycle, and a 5-14 membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)<sub>r</sub>;

R<sup>e</sup>, at each occurrence, is independently selected from: H, C<sub>1-6</sub> alkyl, -OR<sup>a</sup>, Cl, F, Br, I, =O, -CN, NO<sub>2</sub>, -NR<sub>a</sub>R<sup>a</sup>, -C(O)R<sup>a</sup>, -C(O)OR<sup>a</sup>, -C(O)NR<sup>ar</sup>R<sup>a</sup>, -NR<sub>a</sub>C(O)NR<sup>ar</sup>R<sup>a</sup>, -OC(O)NR<sup>ar</sup>R<sup>a</sup>, -NR<sub>a</sub>C(O)OR<sup>a</sup>, -S(O)<sub>2</sub>NR<sup>ar</sup>R<sup>a</sup>, -NR<sub>as</sub>S(O)<sub>2</sub>R<sup>a2</sup>, -NR<sub>as</sub>S(O)<sub>2</sub>NR<sup>ar</sup>R<sup>a</sup>, -OS(O)<sub>2</sub>NR<sup>ar</sup>R<sup>a</sup>, -NR<sub>as</sub>S(O)<sub>2</sub>R<sup>a2</sup>, -S(O)<sub>r</sub>R<sup>ra2</sup>, CF<sub>3</sub>, -OCF<sub>3</sub>, -CF<sub>2</sub>CF<sub>3</sub>, -CH<sub>2</sub>F, and -CHF<sub>2</sub>;

p, at each occurrence, is selected from 0, 1, and 2;

r, at each occurrence, is selected from 0, 1, 2, 3, and 4;

r<sub>1</sub>, at each occurrence, is selected from 0, 1, 2, 3, and 4; and,
s, at each occurrence, is selected from 1, 2, 3, and 4.

[8] In another preferred embodiment, the present invention provides a novel compound, wherein:

Zₐ is substituted with 0-4 Rₐ and is selected from the group:

\[
\begin{align*}
  &\text{\includegraphics[width=0.2\textwidth]{chemical_structure.png}}
\end{align*}
\]

W is S, SO, SO₂, O, or NR¹⁺;

R¹⁺, at each occurrence, is independently selected from: H, C₁₋₄ alkyl, phenyl, and benzyl;

Rᵦ, at each occurrence, is independently selected from: H, C₁₋₆ alkyl substituted with 0-2 R¹, C₂₋₆ alkenyl substituted with 0-2 R¹, C₂₋₆ alkynyl substituted with 0-2 R¹, OR, Cl, F, Br, I, =O, -CN, NO₂, CF₃, -OCF₃, -CF₂CF₃, -CH₂F, -CHF₂, -(CRᵦR¹)ᵦ₁NRᵦR¹ᵦ, -(CRᵦR¹)ᵦ₁C(O)R¹ᵦ, -(CRᵦR¹)ᵦ₁C(O)OR¹ᵦ, -(CRᵦR¹)ᵦ₁C(O)NRᵦR¹ᵦ, -(CRᵦR¹)ᵦ₁NRᵦC(O)R¹ᵦ, -(CRᵦR¹)ᵦ₁S(O)ᵦ₁Rᵦ, -(CRᵦR¹)ᵦ₁SO₂NRᵦR¹ᵦ,
-(CR\textsuperscript{a}R\textsuperscript{b})\textsubscript{r1}NR\textsuperscript{a}SO\textsubscript{2}R\textsuperscript{a3}, -(CR\textsuperscript{a}R\textsuperscript{b})\textsubscript{r1}-C\textsubscript{3-10} carbocycle substituted with 0-2 R\textsuperscript{c1}, and -(CR\textsuperscript{a}R\textsuperscript{b})\textsubscript{r1}-5-14 membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)\textsubscript{p}, and substituted with 0-2 R\textsuperscript{c1};

alternatively, when two R\textsuperscript{c} groups are attached to the same carbon atom they form a spiro ring C that is a 3-11 membered carbocycle substituted with 0-2 R\textsuperscript{c1} or a 3-13 membered heterocycle consisting of: carbon atoms, 0-3 carbonyl groups, 0-4 double bonds, and from 1-5 ring heteroatoms selected from O, N, and S(O)\textsubscript{p}, and substituted with 0-2 R\textsuperscript{c1}, provided that ring C contains other than a S-S, O-O, or S-O bond; and,

alternatively, when two R\textsuperscript{c} groups are attached to adjacent carbon atoms, together with the carbon atoms to which they are attached they form a 5-7 membered carbocyclic or heterocyclic ring consisting of: carbon atoms, 0-2 heteroatoms selected from the group consisting of N, O, and S(O)\textsubscript{p}, and 0-3 double bonds, and substituted with 0-2 R\textsuperscript{c1}.

[9] In another preferred embodiment, the present invention provides a novel compound, wherein;

R\textsuperscript{1} and R\textsuperscript{2} together with the carbon atom to which they are attached combine to form a 3-8 membered carbocyclic or heterocyclic ring consisting of carbon atoms and 0-2
ring heteroatoms selected from O, N, NR\textsuperscript{10}, and S(O)\textsubscript{p}, and substituted with 0-4 Rc;

R\textsuperscript{3} is selected from: Q\textsuperscript{1}, -C\textsubscript{1-6} alkyne-Q\textsuperscript{1},
- C\textsubscript{2-6} alkenylene-Q\textsuperscript{1}, - C\textsubscript{2-6} alkynylene-Q\textsuperscript{1},
- (CR\textsuperscript{a}Ra\textsuperscript{1})\textsubscript{r1}O(CH\textsubscript{2})\textsubscript{r}Q\textsuperscript{1}, -(CR\textsuperscript{a}Ra\textsuperscript{1})\textsubscript{r1}NR\textsuperscript{a}(CR\textsuperscript{a}Ra\textsuperscript{1})\textsubscript{r}Q\textsuperscript{1},
- (CR\textsuperscript{a}Ra\textsuperscript{1})\textsubscript{r1}NR\textsuperscript{a}C(O)(CR\textsuperscript{a}Ra\textsuperscript{1})\textsubscript{r}Q\textsuperscript{1},
- (CR\textsuperscript{a}Ra\textsuperscript{1})\textsubscript{r1}C(O)NR\textsuperscript{a}(CR\textsuperscript{a}Ra\textsuperscript{1})\textsubscript{r}Q\textsuperscript{1},
- (CR\textsuperscript{a}Ra\textsuperscript{1})\textsubscript{r1}C(O)(CR\textsuperscript{a}Ra\textsuperscript{1})\textsubscript{r}Q\textsuperscript{1},
- (CR\textsuperscript{a}Ra\textsuperscript{1})\textsubscript{r1}C(O)O(CR\textsuperscript{a}Ra\textsuperscript{1})\textsubscript{r}Q\textsuperscript{1},
- (CR\textsuperscript{a}Ra\textsuperscript{1})\textsubscript{r1}S(O)\textsubscript{p}(CR\textsuperscript{a}Ra\textsuperscript{1})\textsubscript{r}Q\textsuperscript{1}, and
- (CR\textsuperscript{a}Ra\textsuperscript{1})\textsubscript{r1}SO\textsubscript{2}NR\textsuperscript{a}(CR\textsuperscript{a}Ra\textsuperscript{1})\textsubscript{r}Q\textsuperscript{1};

Q\textsuperscript{1}, at each occurrence, is independently selected from: H, a C\textsubscript{3-10} carbocycle substituted with 0-5 Rd, and a 5-10 membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)\textsubscript{p}, and substituted with 0-5 Rd;

R\textsuperscript{10}, at each occurrence, is independently selected from: H, C\textsubscript{1-6} alkyl substituted with 0-2 R\textsuperscript{c1}, C\textsubscript{2-6} alkenyl substituted with 0-2 R\textsuperscript{c1}, C\textsubscript{2-6} alkynyl substituted with 0-2 R\textsuperscript{c1}, -(CR\textsuperscript{a}Ra\textsuperscript{1})\textsubscript{s}NR\textsuperscript{a}Ra\textsuperscript{1}, -(CR\textsuperscript{a}Ra\textsuperscript{1})\textsubscript{r1}C(O)Ra\textsuperscript{1},
- (CR\textsuperscript{a}Ra\textsuperscript{1})\textsubscript{r1}C(O)OR\textsuperscript{a1}, -(CR\textsuperscript{a}Ra\textsuperscript{1})\textsubscript{r1}C(O)NR\textsuperscript{a}Ra\textsuperscript{1},
- (CR\textsuperscript{a}Ra\textsuperscript{1})\textsubscript{s}NR\textsuperscript{a}C(O)Ra\textsuperscript{1}, -(CR\textsuperscript{a}Ra\textsuperscript{1})\textsubscript{r1}S(O)\textsubscript{p}Ra\textsuperscript{3},
- (CR\textsuperscript{a}Ra\textsuperscript{1})\textsubscript{r1}SO\textsubscript{2}NR\textsuperscript{a}Ra\textsuperscript{1}, -(CR\textsuperscript{a}Ra\textsuperscript{1})\textsubscript{s}NR\textsuperscript{a}SO\textsubscript{2}Ra\textsuperscript{3},
- (CR\textsuperscript{a}Ra\textsuperscript{1})\textsubscript{r1}-C\textsubscript{3-10} carbocycle substituted with 0-2 R\textsuperscript{c1}, and -(CR\textsuperscript{a}Ra\textsuperscript{1})\textsubscript{r1}5-14 membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the
group consisting of N, O, and S(O)p, and substituted with 0-2 Rc1;

Rc, at each occurrence, is independently selected from: H, C1-6 alkyl substituted with 0-2 Rc1, C2-6 alkenyl substituted with 0-2 Rc1, C2-6 alkynyl substituted with 0-2 Rc1, -ORa, Cl, F, Br, I, =O, -CN, NO2, CF3, -CF2CF3, -(CRaRa1)R1NRaRa1, -(CRaRa1)R1C(O)Ra1, -(CRaRa1)R1C(O)ORa1, -(CRaRa1)R1C(O)NRaRa1, -(CRaRa1)R1NRaC(O)Ra1, -(CRaRa1)R1S(O)pRa3, -(CRaRa1)R1SO2NRaRa1, -(CRaRa1)R1NRA2SO2Ra3, -(CRaRa1)R1-C3-10 carbocycle substituted with 0-2 Rc1, and -(CRaRa1)R1-5-10 membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)p, and substituted with 0-2 Rc1;

Rc1, at each occurrence, is independently selected from: H, C1-4 alkyl, -ORa, Cl, F, Br, I, =O, CF3, -CN, NO2, -NRaRa1, -C(O)ORa, and -C(O)NRaRa1;

Rd, at each occurrence, is independently selected from:

C1-6 alkyl, -ORa, Cl, F, Br, I, =O, -CN, NO2, -NRaRa1, -C(O)Ra, -C(O)ORa, -C(O)NRaRa1, -C(S)NRaRa1, -NRaC(O)NRaRa1, -OC(O)NRaRa1, -NRaC(O)ORa1, -S(O)2NRaRa1, -NRaS(O)2Ra3, -NRaS(O)2NRaRa1, -OS(O)2NRaRa1, -NRaS(O)2Ra3, -S(O)pRa3, CF3, -CF2CF3, C3-6 carbocycle, and a 5-6 membered heterocycle consisting of carbon atoms and 1-4 heteroatoms.
selected from the group consisting of N, O, and S(O)\_p; and,

\[ \text{R}^a, \text{at each occurrence, is independently selected from: H, C}\_1-4 \text{ alkyl, -OR}^a, \text{Cl, F, Br, I, =O, CF}_3, \text{-CN, NO}_2, \]

\[ \text{-NR}^a\text{R}^a, \text{-C(O)OR}^a, \text{and -C(O)NR}^a\text{R}^a. \]

[10] In another preferred embodiment, the present invention provides a novel compound, wherein:

\[ \text{R}^1 \text{ and R}^2 \text{ together with the carbon atom to which they are attached combine to form a 3-6 membered carbocyclic or heterocyclic ring consisting of carbon atoms and 0-2 ring heteroatoms selected from O, N, NR}^{10}, \text{and S(O)}_p, \]

\[ \text{and substituted with 0-3 R}^c; \]

\[ \text{R}^3 \text{ is selected from: Q}^1, \text{-C}\_1-6 \text{ alkylene-Q}^1, \]

\[ \text{-C}\_2-6 \text{ alkenylene-Q}^1, \text{-}\{(\text{CR}^a\text{R}^{a1})\}_\text{r1O(CH}_2\}_\text{r-Q}^1, \]

\[ \text{-}(\text{CR}^a\text{R}^{a1})\text{r1NR}^a(\text{CR}^a\text{R}^{a1})\text{r-Q}^1, \]

\[ \text{-}(\text{CR}^a\text{R}^{a1})\text{r1C(O)NR}^a(\text{CR}^a\text{R}^{a1})\text{r-Q}^1, \]

\[ \text{-}(\text{CR}^a\text{R}^{a1})\text{r1C(O)(CR}^a\text{R}^{a1})\text{r-Q}^1, \]

\[ \text{-}(\text{CR}^a\text{R}^{a1})\text{r1C(O)O(CR}^a\text{R}^{a1})\text{r-Q}^1, \]

\[ \text{-}(\text{CR}^a\text{R}^{a1})\text{r1S(O)}_p(\text{CR}^a\text{R}^{a1})\text{r-Q}^1, \]

\[ \text{-}(\text{CR}^a\text{R}^{a1})\text{r1SO}^2\text{NR}^a(\text{CR}^a\text{R}^{a1})\text{r-Q}^1; \]

\[ \text{Q}^1, \text{at each occurrence, is independently selected from: H, a C}\_3-6 \text{ carbocycle substituted with 0-3 R}^d, \text{and a 5-10 membered heterocycle consisting of carbon atoms and} \]
1-4 heteroatoms selected from the group consisting of N, O, and S(O)\_p and substituted with 0-3 R^d;

R^d is selected from: H and C\_1-6 alkyl;

R^{10}, at each occurrence, is independently selected from: H, C\_1-6 alkyl substituted with 0-1 R^c, C\_2-6 alkenyl substituted with 0-1 R^c, C\_2-6 alkynyl substituted with 0-1 R^c, -(CR^aR^a\_1)\_r\_1C(O)R^a\_1, -(CR^aR^a\_1)\_r\_1C(O)OR^a\_1,
-\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\:\\n
Z is selected from: phenyl substituted with 0-3 R\^b, and a 5-6 membered heteroaryl consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)\_p, and substituted with 0-3 R\^b;

provided that X, Y, and Z do not combine to form a N-O, O-O, or S(O)\_p-O group;

Z\^a is 4-quinolinyl substituted with 0-2 R\^c;

R\^a, at each occurrence, is independently selected from: H and C\_1-4 alkyl;
R\textsuperscript{a1}, at each occurrence, is independently selected from: H, C\textsubscript{1-4} alkyl, phenyl, and benzyl;

alternatively, R\textsuperscript{a} and R\textsuperscript{a1} when attached to a nitrogen are taken together with the nitrogen to which they are attached form a 5 or 6 membered heterocycle consisting of carbon atoms and 0-1 additional heteroatoms selected from N, NR\textsuperscript{a}\textsuperscript{2}, O, and S(O)\textsubscript{p};

R\textsuperscript{b}, at each occurrence, is independently selected from:

C\textsubscript{1-6} alkyl, -OR\textsuperscript{a}, Cl, F, Br, =O, -CN, -NR\textsuperscript{a}R\textsuperscript{a1}, -C(O)R\textsuperscript{a}, -C(O)OR\textsuperscript{a}, -C(O)NR\textsuperscript{a}R\textsuperscript{a1}, -S(O)\textsubscript{2}NR\textsuperscript{a}R\textsuperscript{a1}, -S(O)\textsubscript{p}R\textsuperscript{a3}, and CF\textsubscript{3};

R\textsuperscript{c}, at each occurrence, is independently selected from: H, C\textsubscript{1-6} alkyl substituted with 0-1 R\textsuperscript{c1}, C\textsubscript{2-6} alkenyl substituted with 0-1 R\textsuperscript{c1}, C\textsubscript{2-6} alkynyl substituted with 0-1 R\textsuperscript{c1}, -OR\textsuperscript{a}, Cl, F, Br, =O, -CN, CF\textsubscript{3}, -NR\textsuperscript{a}R\textsuperscript{a1}, -(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r1}C(O)R\textsuperscript{a1}, -(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r1}C(O)OR\textsuperscript{a1}, -(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r1}C(O)NR\textsuperscript{a}R\textsuperscript{a1}, -(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r1}S(O)\textsubscript{p}R\textsuperscript{a3},

-C(O)\textsubscript{2}NR\textsuperscript{a}R\textsuperscript{a1}, C\textsubscript{3-6} carbocycle, and a 5-6 membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)\textsubscript{p}; and,

R\textsuperscript{d}, at each occurrence, is independently selected from:

C\textsubscript{1-6} alkyl, -OR\textsuperscript{a}, Cl, F, Br, =O, -CN, -NR\textsuperscript{a}R\textsuperscript{a1}, -C(O)R\textsuperscript{a}, -C(O)OR\textsuperscript{a}, -C(O)NR\textsuperscript{a}R\textsuperscript{a1}, -S(O)\textsubscript{2}NR\textsuperscript{a}R\textsuperscript{a1}, -S(O)\textsubscript{p}R\textsuperscript{a3}, CF\textsubscript{3}, C\textsubscript{3-6} carbocycle, and a 5-6 membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)\textsubscript{p}. 
[11] In another preferred embodiment, the present invention provides a novel compound, wherein:

$R^1$ and $R^2$ together with the carbon atom to which they are attached combine to form a 3-6 membered carbocyclic or heterocyclic ring consisting of carbon atoms and 0-2 ring heteroatoms selected from $O$, $N$, $NR^{10}$, and $S(O)_p$, and substituted with 0-2 $R^c$;

$R^3$ is selected from: $Q^1$, -C$_{1-6}$ alkylene-$Q^1$,

- $(CR^aR^{a1})_r(O(CH_2)_r-Q^1,$
- $(CR^aR^{a1})_rNR^a(CR^aR^{a1})_r-Q^1,$
- $(CR^aR^{a1})_rC(O)NR^a(CR^aR^{a1})_r-Q^1,$
- $(CR^aR^{a1})_rC(O)(CR^aR^{a1})_r-Q^1,$
- $(CR^aR^{a1})_rC(O)O(CR^aR^{a1})_r-Q^1,$
- $(CR^aR^{a1})_rS(O)_p(CR^aR^{a1})_r-Q^1,$ and
- $(CR^aR^{a1})_rSO_2NR^a(CR^aR^{a1})_r-Q^1$;

$Q^1$, at each occurrence, is independently selected from: H, a C$_{3-6}$ carbocycle substituted with 0-2 $R^d$, and a 5-6 membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of $N$, $O$, and $S(O)_p$, and substituted with 0-2 $R^d$;

$R^4$ is selected from: H and C$_{1-4}$ alkyl;

$R^{10}$, at each occurrence, is independently selected from: H, C$_{1-6}$ alkyl substituted with 0-1 $R^{c1}$, C$_{2-6}$ alkenyl
substituted with 0-1 R^1, C_{2-6} alkynyl substituted with 0-1 R^1, -(CR^aR^a)_{r_1}C(O)R^a, -(CR^aR^a)_{r_1}C(O)OR^a, 
-(CR^aR^a)_{r_1}C(O)NR^aR^a, -(CR^aR^a)_{r_1}S(O)_{p}Ra^3, 
-(CR^aR^a)_{r_1}SO_{2}NR^aR^a, -(CH_2)_{r_1}-C_{3-6} carbocycle

substituted with 0-2 R^1, and -(CH_2)_{r_1}-5-6 membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)_{p}, and substituted with 0-2 R^1;

X-Y is CH_2 or CH_2O;

Z is phenyl substituted with 0-3 R^b;

R^a, at each occurrence, is independently selected from: H and C_{1-4} alkyl;

R^a, at each occurrence, is independently selected from: H, C_{1-4} alkyl, phenyl, and benzyl;

R^b, at each occurrence, is independently selected from:
C_{1-4} alkyl, -OR^a, Cl, F, =O, -NR^aR^a, -C(O)R^a, 
-C(O)OR^a, -C(O)NR^aR^a, -S(O)_{2}NR^aR^a, -S(O)_{p}Ra^3, and CF_3;

R^c, at each occurrence, is independently selected from: H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -OR^a, Cl, F, 
Br, =O, -NR^aR^a, CF_3, -(CR^aR^a)_{r_1}C(O)R^a, 
-(CR^aR^a)_{r_1}C(O)OR^a, -(CR^aR^a)_{r_1}C(O)NR^aR^a, 
-(CR^aR^a)_{r_1}S(O)_{p}Ra^3, -(CR^aR^a)_{r_1}SO_{2}NR^aR^a, and phenyl;
R^d, at each occurrence, is independently selected from:
C\textsubscript{1-6} alkyl, -OR\textsuperscript{a}, Cl, F, Br, =O, -NR\textsuperscript{a}R\textsuperscript{a1}, -C(O)R\textsuperscript{a},
-C(O)NR\textsuperscript{a}R\textsuperscript{a1}, -S(O)\textsubscript{2}NR\textsuperscript{a}R\textsuperscript{a1}, -S(O)\textsubscript{2}R\textsuperscript{a}, CF\textsubscript{3}, and phenyl.

[12] In another preferred embodiment, the present invention
provides a novel compound selected from the group:

10 hydroxy([4-{{4-[(2-methyl-4-
quinoilihyl)methoxy]phenyl}sulfonyl]tetrahydro-2H-
pyran-4-yl}methyl)formamide;

hydroxy([4-{{4-[(2-methyl-1H-benzimidazol-1-
yl)methyl]phenyl}sulfonyl]tetrahydro-2H-pyran-4-
yl}methyl)formamide; and

hydroxy([4-{{4-[(2-methyl-4-
quinoilihyl)methyl]phenyl}sulfonyl]tetrahydro-2H-pyran-
4-yl}methyl)formamide;

or a pharmaceutically acceptable salt form thereof.

[13] In another embodiment, the present invention provides
a novel compound of formula I:

\[
\text{I}
\]
or a stereoisomer or pharmaceutically acceptable salt form thereof, wherein;

R¹ and R⁴ together with the carbon atoms to which they are attached combine to form a 3-10 membered carbocyclic or heterocyclic ring consisting of carbon atoms and 0-2 ring heteroatoms selected from O, N, NR₁⁰, and S(O)ₚ, and substituted with 0-4 Rᶜ;

10  R² is selected from: Q, -C₁₋₆ alkylene-Q,
- C₂₋₆ alkenylene-Q, -C₂₋₆ alkynylene-Q,
- (CRᵃRaˡ)ᵣ₁O(CRᵃRaˡ)ᵣ₋Q,
- (CRᵃRaˡ)ᵣ₁NRᵃ(CRᵃRaˡ)ᵣ₋Q, -(CRᵃRaˡ)ᵣ₁C(O)(CRᵃRaˡ)ᵣ₋Q,
- (CRᵃRaˡ)ᵣ₁C(O)O(CRᵃRaˡ)ᵣ₋Q, -(CRᵃRaˡ)ᵣ₁OC(O)(CRᵃRaˡ)ᵣ₋Q,
15  - (CRᵃRaˡ)ᵣ₁C(O)NRᵃ(CRᵃRaˡ)ᵣ₋Q, -(CRᵃRaˡ)ᵣ₁C(O)NRᵃ(CRᵃRaˡ)ᵣ₋Q,
- (CRᵃRaˡ)ᵣ₁NRᵃC(O)(CRᵃRaˡ)ᵣ₋Q,
- (CRᵃRaˡ)ᵣ₁OC(O)O(CRᵃRaˡ)ᵣ₋Q,
- (CRᵃRaˡ)ᵣ₁OC(O)NRᵃ(CRᵃRaˡ)ᵣ₋Q,
- (CRᵃRaˡ)ᵣ₁NRᵃC(O)O(CRᵃRaˡ)ᵣ₋Q,
20  - (CRᵃRaˡ)ᵣ₁NRᵃC(O)NRᵃ(CRᵃRaˡ)ᵣ₋Q,
- (CRᵃRaˡ)ᵣ₁S(O)ₚ(CRᵃRaˡ)ᵣ₋Q,
- (CRᵃRaˡ)ᵣ₁SO₂NRᵃ(CRᵃRaˡ)ᵣ₋Q,
- (CRᵃRaˡ)ᵣ₁NRᵃSO₂(CRᵃRaˡ)ᵣ₋Q, and
- (CRᵃRaˡ)ᵣ₁NRᵃSO₂NRᵃ(CRᵃRaˡ)ᵣ₋Q;

Q, at each occurrence, is independently selected from: H, a C₃₋₁₃ carbocycle substituted with 0-5 Rᵈ, and a 4-14 membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)ₚ, and substituted with 0-5 Rᵈ;
R³ is selected from: Q¹, -C₁₋₆ alkylene-Q¹,
- C₂₋₆ alkenylene-Q¹, -C₂₋₆ alkynylene-Q¹,
- (CRAr¹)₉₋₁₀(CH₂)ᵣ₋₅(Q¹), -(CRAr¹)₉₋₁₀NRA(CRAr¹)ᵣ₋₅Q¹,
- (CRAr¹)₉₋₁₀NRᵃC(O)(CRAr¹)ᵣ₋₅Q¹,
- (CRAr¹)₉₋₁₀C(O)NRᵃ(CRAr¹)ᵣ₋₅Q¹,
- (CRAr¹)₉₋₁₀C(O)(CRAr¹)ᵣ₋₅Q¹,
- (CRAr¹)₉₋₁₀C(O)O(CRAr¹)ᵣ₋₅Q¹,
- (CRAr¹)₉₋₁₀S(O)ₚ(CRAr¹)ᵣ₋₅Q¹, and
- (CRAr¹)₉₋₁₀SO₂NRᵃ(CRAr¹)ᵣ₋₅Q¹;

Q¹, at each occurrence, is independently selected from: H, a C₃₋₁₃ carbocycle substituted with 0-5 Rᵈ, and a 5-14 membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)ₚ, and substituted with 0-5 Rᵈ;

R⁵ is selected from: H, and C₁₋₄ alkyl;

R₁⁰, at each occurrence, is independently selected from: H, C₁₋₆ alkyl substituted with 0-2 Rᶜ¹, C₂₋₆ alkenyl substituted with 0-2 Rᶜ¹, C₂₋₆ alkynyl substituted with 0-2 Rᶜ¹, -(CRAr¹)ₛNRᵃRᵃ₁, -(CRAr¹)₉₋₁₀C(O)NRᵃOH,
- (CRAr¹)₉₋₁₀C(O)Rᵃ₁, -(CRAr¹)₉₋₁₀C(O)ORᵃ₁,
- (CRAr¹)₉₋₁₀C(S)ORᵃ₁, -(CRAr¹)₉₋₁₀C(O)NRᵃRᵃ₁,
- (CRAr¹)ₛNRᵃC(O)Rᵃ₁, -(CRAr¹)₉₋₁₀C(S)NRᵃRᵃ₁,
- (CRAr¹)ₛOC(O)NRᵃRᵃ₁, -(CRAr¹)ₛNRᵃC(O)ORᵃ₁,
- (CRAr¹)ₛNRᵃC(O)NRᵃRᵃ₁, -(CRAr¹)₉₋₁₀S(O)ᵩRᵃ³,
- (CRAr¹)₉₋₁₀SO₂NRᵃRᵃ₁, -(CRAr¹)ₛNRᵃSO₂Rᵃ³,
-\((\text{CR}^a\text{Ra}^1)_s\text{NR}^a\text{SO}_2\text{NR}^a\text{Ra}^1)_{r_1}\text{-C}_3\text{-C}_10\) carbocycle substituted with 0-2 \(\text{R}^c\), and \(-\text{(CR}^a\text{Ra}^1)_{r_1}\text{-}5\text{-}14\) membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)_p, and substituted with 0-2 \(\text{R}^c\);

\(\text{X-Y}\) is CH\(_2\), CH\(_2\)O or OCH\(_2\);

\(\text{Z}\) is selected from: a C\(_6\)-10 aryl substituted with 0-5 \(\text{R}^b\), and a 5-14 membered heteroaryl consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)_p, and substituted with 0-5 \(\text{R}^b\);

provided that \(\text{X, Y, and Z}\) do not combine to form a N-O, O-O, or S(O)_p-O, group;

\(\text{Z}^a\) is substituted with 0-5 \(\text{R}^c\) and is a 8-14 membered heterocycle consisting of carbon atoms, 1-3 N atoms, and 0-1 heteroatom selected from the group consisting of O, and S(O)_p;

\(\text{R}^a\), at each occurrence, is independently selected from: H, C\(_1\)-6 alkyl, phenyl, and benzyl;

\(\text{R}^a\), at each occurrence, is independently selected from: H, C\(_1\)-6 alkyl substituted with 0-1 \(\text{R}^e\), C\(_2\)-6 alkenyl substituted with 0-1 \(\text{R}^e\), C\(_2\)-6 alkynyl substituted with 0-1 \(\text{R}^e\), and \(-\text{(CH}_2\text{)}_{r-3}\text{-}8\) membered carbocyclical or heterocyclic ring consisting of carbon atoms and 0-2
ring heteroatoms selected from N, NR<sup>a2</sup>, O, and S(O)<sub>p</sub>, and substituted with 0-3 R;<sup>e</sup>

alternatively, R<sup>a</sup> and R<sup>a1</sup> when attached to a nitrogen are taken together with the nitrogen to which they are attached form a 5 or 6 membered heterocycle consisting of carbon atoms and 0-1 additional heteroatoms selected from N, NR<sup>a2</sup>, O, and S(O)<sub>p</sub>;

10 R<sup>a2</sup>, at each occurrence, is independently selected from:
C<sub>1-4</sub> alkyl, phenyl, and benzyl;

R<sup>a3</sup>, at each occurrence, is independently selected from: H, C<sub>1-6</sub> alkyl substituted with 0-1 R<sup>c1</sup>, C<sub>2-6</sub> alkenyl substituted with 0-1 R<sup>c1</sup>, C<sub>2-6</sub> alkynyl substituted with 0-1 R<sup>c1</sup>, and -(CH<sub>2</sub>)<sub>r</sub>-3-8 membered carbocyclic or heterocyclic ring consisting of carbon atoms and 0-2 ring heteroatoms selected from N, NR<sup>a2</sup>, O, and S(O)<sub>p</sub> and substituted with 0-3 R<sup>c1</sup>;

15 R<sup>b</sup>, at each occurrence, is independently selected from:
C<sub>1-6</sub> alkyl substituted with 0-1 R<sup>c1</sup>, -OR<sup>a</sup>, Cl, F, Br, I, =O, -CN, NO<sub>2</sub>, -NR<sup>a</sup>R<sup>a1</sup>, -C(O)R<sup>a</sup>, -C(O)OR<sup>a</sup>, -C(O)NR<sup>a</sup>R<sup>a1</sup>, -C(S)NR<sup>a</sup>R<sup>a1</sup>, -NR<sup>a</sup>C(O)NR<sup>a</sup>R<sup>a1</sup>, -OC(O)NR<sup>a</sup>R<sup>a1</sup>, -NR<sup>a</sup>R<sup>a</sup>NR<sup>a</sup>R<sup>a1</sup>, -S(O)NR<sup>a</sup>R<sup>a1</sup>, -NR<sup>a</sup>S(O)NR<sup>a</sup>R<sup>a1</sup>, -S(O)NR<sup>a</sup>R<sup>a1</sup>, -NR<sup>a</sup>S(O)<sub>2</sub>R<sup>a3</sup>, -S(O)<sub>2</sub>NR<sup>a</sup>R<sup>a1</sup>, -NR<sup>a</sup>S(O)<sub>2</sub>R<sup>a3</sup>, -S(O)<sub>p</sub>R<sup>a3</sup>, CF<sub>3</sub>, -CF<sub>2</sub>CF<sub>3</sub>, -CHF<sub>2</sub>, -CH<sub>2</sub>F, and phenyl;

20 R<sup>c</sup>, at each occurrence, is independently selected from: H, C<sub>1-6</sub> alkyl substituted with 0-2 R<sup>c1</sup>, C<sub>2-6</sub> alkenyl
substituted with 0-2 R<sup>c1</sup>, C<sub>2-6</sub> alkynyl substituted with 0-2 R<sup>c1</sup>, -OR<sup>a</sup>, Cl, F, Br, I, =O, =CN, NO<sub>2</sub>, CF<sub>3</sub>, -OCF<sub>3</sub>, -CF<sub>2</sub>CF<sub>3</sub>, -CH<sub>2</sub>F, -CHF<sub>2</sub>, -(CR<sup>a</sup>R<sup>a</sup>)<sub>1</sub>NR<sup>a</sup>R<sup>a</sup>, -(CR<sup>a</sup>R<sup>a</sup>)<sub>1</sub>C(=NCN)NR<sup>a</sup>R<sup>a</sup>, -(CR<sup>a</sup>R<sup>a</sup>)<sub>1</sub>C(=NOR<sup>a</sup>)NR<sup>a</sup>R<sup>a</sup>, -(CR<sup>a</sup>R<sup>a</sup>)<sub>1</sub>C(O)NR<sup>a</sup>R<sup>a</sup>, -(CR<sup>a</sup>R<sup>a</sup>)<sub>1</sub>C(O)NR<sup>a</sup>OH, -(CR<sup>a</sup>R<sup>a</sup>)<sub>1</sub>C(O)OR<sup>a</sup>, -(CR<sup>a</sup>R<sup>a</sup>)<sub>1</sub>C(S)OR<sup>a</sup>, -(CR<sup>a</sup>R<sup>a</sup>)<sub>1</sub>C(O)NR<sup>a</sup>R<sup>a</sup>, -(CR<sup>a</sup>R<sup>a</sup>)<sub>1</sub>NR<sup>a</sup>C(O)R<sup>a</sup>, -(CR<sup>a</sup>R<sup>a</sup>)<sub>1</sub>C(S)NR<sup>a</sup>R<sup>a</sup>, -(CR<sup>a</sup>R<sup>a</sup>)<sub>1</sub>NC(O)NR<sup>a</sup>R<sup>a</sup>, -(CR<sup>a</sup>R<sup>a</sup>)<sub>1</sub>NR<sup>a</sup>C(O)OR<sup>a</sup>, -(CR<sup>a</sup>R<sup>a</sup>)<sub>1</sub>NR<sup>a</sup>C(O)NR<sup>a</sup>Al, -(CR<sup>a</sup>R<sup>a</sup>)<sub>1</sub>S(O)R<sup>a</sup>Al, -(CR<sup>a</sup>R<sup>a</sup>)<sub>1</sub>SO<sub>2</sub>NR<sup>a</sup>Al, -(CR<sup>a</sup>R<sup>a</sup>)<sub>1</sub>NR<sup>a</sup>SO<sub>2</sub>R<sup>a</sup>Al, -(CR<sup>a</sup>R<sup>a</sup>)<sub>1</sub>NR<sup>a</sup>SO<sub>2</sub>NR<sup>a</sup>Al, -(CR<sup>a</sup>R<sup>a</sup>)<sub>1</sub>-C<sub>3-10</sub> carbocycle substituted with 0-2 R<sup>c1</sup>, and -(CR<sup>a</sup>R<sup>a</sup>)<sub>1</sub>-5-14 membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)P, and substituted with 0-2 R<sup>c1</sup>.

alternatively, when two R<sup>c</sup> groups are attached to the same carbon atom they form a spiro ring C that is a 3-11 membered carbocycle substituted with 0-2 R<sup>c1</sup> or a 3-13 membered heterocycle consisting of: carbon atoms, 0-3 carbonyl groups, 0-4 double bonds, and from 1-5 ring heteroatoms selected from O, N, and S(O)P, and substituted with 0-2 R<sup>c1</sup>, provided that ring C contains other than a S-S, O-O, or S-O bond;

alternatively, when two R<sup>c</sup> groups are attached to adjacent carbon atoms, together with the carbon atoms to which they are attached they form a 5-7 membered carbocyclic or heterocyclic ring consisting of: carbon atoms, 0-2
heteroatoms selected from the group consisting of N, O, and S(O)ₚ, and 0-3 double bonds, and substituted with 0-2 R¹;

5 R¹, at each occurrence, is independently selected from: H, C₁₋₆ alkyl, -ORₐ, Cl, F, Br, I, =O, -CN, NO₂, -NRₐRa₁, -C(O)Ra, -C(O)ORₐ, -C(O)NRₐRa₁, -NRₐC(O)NRₐRa₁, -OC(O)NRₐRa₁, -NRₐC(O)ORₐ₁, -S(O)₂NRₐRa₁, -NRₐS(O)₂Ra₂, -NRₐS(O)₂NRₐRa₁, -OS(O)₂NRₐRa₁, -NRₐS(O)₂Ra₂, -S(O)ₚRa₂, CF₃, -OCF₃, -CF₂CF₃, -CH₂F, and -CHF₂;

10 Rd, at each occurrence, is independently selected from: C₁₋₆ alkyl, -ORₐ, Cl, F, Br, I, =O, -CN, NO₂, -NRₐRa₁, -C(O)Ra, -C(O)ORₐ, -C(O)NRₐRa₁, -C(S)NRₐRa₁, -NRₐC(O)NRₐRa₁, -OC(O)NRₐRa₁, -NRₐC(O)ORₐ₁, -S(O)₂NRₐRa₁, -NRₐS(O)₂Ra₃, -NRₐS(O)₂NRₐRa₁, -OS(O)₂NRₐRa₁, -NRₐS(O)₂Ra₂, -S(O)ₚRa₂, CF₃, -CF₂CF₃, C₃₋₁₀ carbocycle, and a 5-14 membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)ₚ;

20 Re, at each occurrence, is independently selected from: H, C₁₋₆ alkyl, -ORₐ, Cl, F, Br, I, =O, -CN, NO₂, -NRₐRa, -C(O)Ra, -C(O)ORₐ, -C(O)NRₐRa, -NRₐC(O)NRₐRa, -OC(O)NRₐRa, -NRₐC(O)ORₐ, -S(O)₂NRₐRa, -NRₐS(O)₂Ra₂, -NRₐS(O)₂NRₐRa, -OS(O)₂NRₐRa, -NRₐS(O)₂Ra₂, -S(O)ₚRa₂, CF₃, -OCF₃, -CF₂CF₃, -CH₂F, and -CHF₂;

30 p, at each occurrence, is selected from 0, 1, and 2;
r, at each occurrence, is selected from 0, 1, 2, 3, and 4;

r1, at each occurrence, is selected from 0, 1, 2, 3, and 4; and,

s, at each occurrence, is selected from 1, 2, 3, and 4.

[14] In another preferred embodiment, the present invention provides a novel compound, wherein;

Z^a is substituted with 0-4 R^c and is selected from the group:

\[ \text{Diagram of structures} \]

W is S, SO, SO₂, O, or NR₁₁;

R₁₁, at each occurrence, is independently selected from: H, C₁₋₄ alkyl, phenyl, and benzyl;

R^c, at each occurrence, is independently selected from: H, C₁₋₆ alkyl substituted with 0-2 R^c₁, C₂₋₆ alkenyl substituted with 0-2 R^c₁, C₂₋₆ alkynyl substituted with 0-2 R^c₁, -OR^a, Cl, F, Br, I, =O, -CN, NO₂, CF₃, -OCF₃, -CF₂CF₃, -CH₂F, -CHF₂, -(CR^aR^a₁)ₓ₁NR^aR^a₁, -(CR^aR^a₁)ₓ₁C(O)R^a₁, -(CR^aR^a₁)ₓ₁C(O)OR^a₁,
-(CR^aR^a)^{r_1}C(O)NR^aR^a, -(CR^aR^a)^{r_1}NR^aC(O)R^a,
-(CR^aR^a)^{r_1}S(O)_{p}R^a, -(CR^aR^a)^{r_1}SO_{2}NR^aR^a,
-(CR^aR^a)^{r_1}NR^aSO_{2}R^a, -(CR^aR^a)^{r_1}C_{3-10} carbocycle
substituted with 0-2 R^{c_1}, and -(CR^aR^a)^{r_1} 5-14 membered
heterocycle consisting of carbon atoms and 1-4
heteroatoms selected from the group consisting of N,
O, and S(O)_{p}, and substituted with 0-2 R^{c_1};

alternatively, when two R^{c} groups are attached to the same
carbon atom they form a spiro ring C that is a 3-11
membered carbocycle substituted with 0-2 R^{c_1} or a 3-13
membered heterocycle consisting of: carbon atoms, 0-3
carbonyl groups, 0-4 double bonds, and from 1-5 ring
heteroatoms selected from O, N, and S(O)_{p}, and
substituted with 0-2 R^{c_1}, provided that ring C
contains other than a S-S, O-O, or S-O bond; and,

alternatively, when two R^{c} groups are attached to adjacent
carbon atoms, together with the carbon atoms to which
they are attached they form a 5-7 membered carbocyclic
or heterocyclic ring consisting of: carbon atoms, 0-2
heteroatoms selected from the group consisting of N,
O, and S(O)_{p}, and 0-3 double bonds, and substituted
with 0-2 R^{c_1}.

[15] In another preferred embodiment, the present invention
provides a novel compound, wherein;

R^{1} and R^{4} together with the carbon atoms to which they are
attached combine to form a 3-8 membered carbocyclic or
heterocyclic ring consisting of carbon atoms and 0-2 ring heteroatoms selected from O, N, NR<sup>10</sup>, and S(O)<sub>p</sub>, and substituted with 0-4 R<sup>c</sup>;

5 R<sup>2</sup> is selected from: Q, -C<sub>1-6</sub> alkyne-Q,
   -C<sub>2-6</sub> alkenylene-Q, -C<sub>2-6</sub> alkynylene-Q,
   -(CR<sup>a</sup>R<sup>al</sup>)<sub>r<sub>1</sub>O(CR<sup>a</sup>R<sup>al</sup>)<sub>r</sub>-Q,
   -(CR<sup>a</sup>R<sup>al</sup>)<sub>r<sub>1</sub>NR<sup>a</sup>(CR<sup>a</sup>R<sup>al</sup>)<sub>r</sub>-Q,
   -(CR<sup>a</sup>R<sup>al</sup>)<sub>r<sub>1</sub>C(O)(CR<sup>a</sup>R<sup>al</sup>)<sub>r</sub>-Q,
   -(CR<sup>a</sup>R<sup>al</sup>)<sub>r<sub>1</sub>C(O)O(CR<sup>a</sup>R<sup>al</sup>)<sub>r</sub>-Q,
   -(CR<sup>a</sup>R<sup>al</sup>)<sub>r<sub>1</sub>C(O)NR<sup>a</sup>R<sup>al</sup>;<nolabel>

10 -(CR<sup>a</sup>R<sup>al</sup>)<sub>r<sub>1</sub>C(O)NR<sup>a</sup>(CR<sup>a</sup>R<sup>al</sup>)<sub>r</sub>-Q,
   -(CR<sup>a</sup>R<sup>al</sup>)<sub>r<sub>1</sub>S(O)<sub>p</sub>(CR<sup>a</sup>R<sup>al</sup>)<sub>r</sub>-Q,
   -(CR<sup>a</sup>R<sup>al</sup>)<sub>r<sub>1</sub>SO<sub>2</sub>NR<sup>a</sup>(CR<sup>a</sup>R<sup>al</sup>)<sub>r</sub>-Q, and
   -(CR<sup>a</sup>R<sup>al</sup>)<sub>r<sub>1</sub>NR<sup>a</sup>SO<sub>2</sub>(CR<sup>a</sup>R<sup>al</sup>)<sub>r</sub>-Q;

15 Q, at each occurrence, is independently selected from: H, a C<sub>3-10</sub> carbocycle substituted with 0-5 R<sup>d</sup>, and a 5-10 membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)<sub>p</sub>, and substituted with 0-5 R<sup>d</sup>;

20 R<sup>3</sup> is selected from: Q<sup>1</sup>, -C<sub>1-6</sub> alkyne-Q<sup>1</sup>,
   -C<sub>2-6</sub> alkenylene-Q<sup>1</sup>, -C<sub>2-6</sub> alkynylene-Q<sup>1</sup>,
   -(CR<sup>a</sup>R<sup>al</sup>)<sub>r<sub>1</sub>O(CH<sub>2</sub>)<sub>r</sub>-Q<sup>1</sup>, -(CR<sup>a</sup>R<sup>al</sup>)<sub>r<sub>1</sub>NR<sup>a</sup>(CR<sup>a</sup>R<sup>al</sup>)<sub>r</sub>-Q<sup>1</sup>,
   -(CR<sup>a</sup>R<sup>al</sup>)<sub>r<sub>1</sub>NRC(O)(CR<sup>a</sup>R<sup>al</sup>)<sub>r</sub>-Q<sup>1</sup>,
   -(CR<sup>a</sup>R<sup>al</sup>)<sub>r<sub>1</sub>C(O)NR<sup>a</sup>(CR<sup>a</sup>R<sup>al</sup>)<sub>r</sub>-Q<sup>1</sup>,
   -(CR<sup>a</sup>R<sup>al</sup>)<sub>r<sub>1</sub>C(O)O(CR<sup>a</sup>R<sup>al</sup>)<sub>r</sub>-Q<sup>1</sup>,
   -(CR<sup>a</sup>R<sup>al</sup>)<sub>r<sub>1</sub>C(O)NR<sup>a</sup>R<sup>al</sup>;<nolabel>

25 -(CR<sup>a</sup>R<sup>al</sup>)<sub>r<sub>1</sub>C(O)NR<sup>a</sup>(CR<sup>a</sup>R<sup>al</sup>)<sub>r</sub>-Q<sup>1</sup>,
   -(CR<sup>a</sup>R<sup>al</sup>)<sub>r<sub>1</sub>S(O)<sub>p</sub>(CR<sup>a</sup>R<sup>al</sup>)<sub>r</sub>-Q<sup>1</sup>, and
   -(CR<sup>a</sup>R<sup>al</sup>)<sub>r<sub>1</sub>SO<sub>2</sub>NR<sup>a</sup>(CR<sup>a</sup>R<sup>al</sup>)<sub>r</sub>-Q<sup>1</sup>.
Q\(^1\), at each occurrence, is independently selected from: H, a C\(_{3-10}\) carbocycle substituted with 0-5 R\(^d\), and a 5-10 membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)\(_p\), and substituted with 0-5 R\(^d\);

R\(^{10}\), at each occurrence, is independently selected from: H, C\(_{1-6}\) alkyl substituted with 0-2 R\(^{c1}\), C\(_{2-6}\) alkenyl substituted with 0-2 R\(^{c1}\), C\(_{2-6}\) alkynyl substituted with 0-2 R\(^{c1}\), -(CR\(^a\)R\(^a\))\(_1\)NRA\(^a\)R\(^a\), -(CR\(^a\)R\(^a\))\(_1\)C(O)R\(^a\), -(CR\(^a\)R\(^a\))\(_1\)C(O)OR\(^a\), -(CR\(^a\)R\(^a\))\(_1\)C(O)NRA\(^a\)R\(^a\), -(CR\(^a\)R\(^a\))\(_1\)NRA\(^a\)C(O)R\(^a\), -(CR\(^a\)R\(^a\))\(_1\)S(O)\(_p\)R\(^a\)R\(^a\), -(CR\(^a\)R\(^a\))\(_1\)SO\(_2\)NRA\(^a\)R\(^a\), -(CR\(^a\)R\(^a\))\(_1\)NR\(^a\)SO\(_2\)R\(^a\), -(CR\(^a\)R\(^a\))\(_1\)C(O)OR\(^a\), -(CR\(^a\)R\(^a\))\(_1\)C(O)NR\(^a\)R\(^a\), -(CR\(^a\)R\(^a\))\(_1\)NRA\(^a\)C(O)R\(^a\), -(CR\(^a\)R\(^a\))\(_1\)S(O)\(_p\)R\(^a\)R\(^a\), -(CR\(^a\)R\(^a\))\(_1\)SO\(_2\)NRA\(^a\)R\(^a\), -(CR\(^a\)R\(^a\))\(_1\)SR\(^a\)SO\(_2\)R\(^a\),

R\(^c\), at each occurrence, is independently selected from: H, C\(_{1-6}\) alkyl substituted with 0-2 R\(^{c1}\), C\(_{2-6}\) alkenyl substituted with 0-2 R\(^{c1}\), C\(_{2-6}\) alkynyl substituted with 0-2 R\(^{c1}\), -OR\(^a\), Cl, F, Br, I, =O, -CN, NO\(_2\), CF\(_3\), CF\(_2\)CF\(_3\), -(CR\(^a\)R\(^a\))\(_1\)NRA\(^a\)R\(^a\), -(CR\(^a\)R\(^a\))\(_1\)C(O)R\(^a\), -(CR\(^a\)R\(^a\))\(_1\)C(O)OR\(^a\), -(CR\(^a\)R\(^a\))\(_1\)C(O)NR\(^a\)R\(^a\), -(CR\(^a\)R\(^a\))\(_1\)NRA\(^a\)C(O)R\(^a\), -(CR\(^a\)R\(^a\))\(_1\)S(O)\(_p\)R\(^a\)R\(^a\), -(CR\(^a\)R\(^a\))\(_1\)SO\(_2\)NRA\(^a\)R\(^a\), -(CR\(^a\)R\(^a\))\(_1\)SR\(^a\)SO\(_2\)R\(^a\),

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-(CR<sup>a</sup>R<sup>al</sup>)<sub>r</sub>-C<sub>3</sub>-10 carbocycle substituted with 0-2 R<sup>c1</sup>, and -(CR<sup>a</sup>R<sup>al</sup>)<sub>r</sub>-5-10 membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)O, and substituted with 0-2 R<sup>c1</sup>;

R<sup>c1</sup>, at each occurrence, is independently selected from: H, C<sub>1-4</sub> alkyl, -OR<sup>a</sup>, Cl, F, Br, I, =O, CF<sub>3</sub>, -CN, NO<sub>2</sub>, -NR<sup>a</sup>R<sup>al</sup>, -C(O)OR<sup>a</sup>, and -C(O)NR<sup>a</sup>R<sup>al</sup>;

R<sup>d</sup>, at each occurrence, is independently selected from: C<sub>1-6</sub> alkyl, -OR<sup>a</sup>, Cl, F, Br, I, =O, -CN, NO<sub>2</sub>, -NR<sup>a</sup>R<sup>al</sup>, -C(O)R<sup>a</sup>, -C(O)OR<sup>a</sup>, -C(O)NR<sup>a</sup>R<sup>al</sup>, -C(S)NR<sup>a</sup>R<sup>al</sup>, -NR<sup>a</sup>C(O)NR<sup>a</sup>R<sup>al</sup>, -OC(O)NR<sup>a</sup>R<sup>al</sup>, -NR<sup>a</sup>C(O)OR<sup>a</sup>, -NR<sup>a</sup>S(O)NR<sup>a</sup>R<sup>al</sup>, -NR<sup>a</sup>S(O)NR<sup>a</sup>R<sup>al</sup>, -NR<sup>a</sup>S(O)NR<sup>a</sup>R<sup>al</sup>, -OS(O)NR<sup>a</sup>R<sup>al</sup>, -NR<sup>a</sup>S(O)NR<sup>a</sup>R<sup>al</sup>, -S(O)NR<sup>a</sup>R<sup>al</sup>, CF<sub>3</sub>, -CF<sub>2</sub>CF<sub>3</sub>, C<sub>3</sub>-6 carbocycle, and a 5-6 membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)O; and,

R<sup>e</sup>, at each occurrence, is independently selected from: H, C<sub>1-4</sub> alkyl, -OR<sup>a</sup>, Cl, F, Br, I, =O, CF<sub>3</sub>, -CN, NO<sub>2</sub>, -NR<sup>a</sup>R<sup>a</sup>, -C(O)OR<sup>a</sup>, and -C(O)NR<sup>a</sup>R<sup>a</sup>.

[16] In another preferred embodiment, the present invention provides a novel compound, wherein;
R^1 and R^4 together with the carbon atoms to which they are attached combine to form a 3-6 membered carbocyclic or heterocyclic ring consisting of carbon atoms and 0-2 ring heteroatoms selected from O, N, NR^10, and S(O)_p, and substituted with 0-3 R^c;

R^2 is selected from: Q, -C_{1-6} alkylene-Q,
- C_{1-6} alkenylene-Q, -(CR^aR^{a1})_r1O(CR^aR^{a1})_r-Q,
- (CR^aR^{a1})_r1NR^a(CR^aR^{a1})_r-Q, -(CR^aR^{a1})_r1C(O)(CR^aR^{a1})_r-Q,
- (CR^aR^{a1})_r1C(O)O(CR^aR^{a1})_r-Q, -(CR^aR^{a1})_r1C(O)NR^aR^{a1},
- (CR^aR^{a1})_r1C(O)NR^a(CR^aR^{a1})_r-Q,
- (CR^aR^{a1})_r1S(O)_p(CR^aR^{a1})_r-Q, and
- (CR^aR^{a1})_r1SO_2NR^a(CR^aR^{a1})_r-Q;

Q, at each occurrence, is independently selected from: H, a C_{3-6} carbocycle substituted with 0-3 R^d, and a 5-10 membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)_p, and substituted with 0-3 R^d;

R^3 is selected from: Q^1, -C_{1-6} alkylene-Q^1,
- C_{2-6} alkenylene-Q^1, -(CR^aR^{a1})_r1O(CH_2)_r-Q^1,
- (CR^aR^{a1})_r1NR^a(CR^aR^{a1})_r-Q^1,
- (CR^aR^{a1})_r1C(O)NR^a(CR^aR^{a1})_r-Q^1,
- (CR^aR^{a1})_r1C(O)(CR^aR^{a1})_r-Q^1,
- (CR^aR^{a1})_r1C(O)O(CR^aR^{a1})_r-Q^1,
- (CR^aR^{a1})_r1S(O)_p(CR^aR^{a1})_r-Q^1, and
- (CR^aR^{a1})_r1SO_2NR^a(CR^aR^{a1})_r-Q^1;
Q, at each occurrence, is independently selected from: H, a C₃₋₆ carbocycle substituted with 0-3 Rd, and a 5-10 membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)p, and substituted with 0-3 Rd;

R¹₀, at each occurrence, is independently selected from: H, C₁₋₆ alkyl substituted with 0-1 Rc¹, C₂₋₆ alkenyl substituted with 0-1 Rc¹, C₂₋₆ alkynyl substituted with 0-1 Rc¹, -(CRᵃRa¹)₁R₁C(O)Ra¹, -(CRᵃRa¹)₁C(O)ORᵃ¹,
-(CRᵃRa¹)₁C(O)NRᵃRa¹, -(CRᵃRa¹)₁S(O)pRa³,
-(CRᵃRa¹)₁SO₂NRᵃRa¹, -(CRᵃRa¹)₁-C₃₋₆ carbocycle substituted with 0-2 Rc¹, and -(CRᵃRa¹)₁-5-10 membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)p, and substituted with 0-2 Rc¹;

Z is selected from: phenyl substituted with 0-3 Rb, and a 5-6 membered heteroaryl consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)p, and substituted with 0-3 Rb;

provided that X, Y, and Z do not combine to form a N-O, O-O, or S(O)p-O group;

Zᵃ is 4-quinolinylnyl substituted with 0-2 Rc;

Rᵃ, at each occurrence, is independently selected from: H and C₁₋₄ alkyl;
Ra¹, at each occurrence, is independently selected from: H, C₁-₄ alkyl, phenyl, and benzyl;

alternatively, Ra and Ra¹ when attached to a nitrogen are taken together with the nitrogen to which they are attached form a 5 or 6 membered heterocycle consisting of carbon atoms and 0-1 additional heteroatoms selected from N, NR², O, and S(O)₃;

Rb, at each occurrence, is independently selected from:
C₁-₆ alkyl, -ORᵃ, Cl, F, Br, =O, -CN, -NRᵃRa¹, -C(O)Ra, -C(O)ORᵃ, -C(O)NRᵃRa¹, -S(O)₂NRᵃRa¹, -S(O)₃Ra³, and CF₃;

RC, at each occurrence, is independently selected from: H, C₁-₆ alkyl substituted with 0-1 Rc¹, C₂-₆ alkenyl substituted with 0-1 Rc¹, C₂-₆ alkynyl substituted with 0-1 Rc¹, -ORᵃ, Cl, F, Br, =O, -CN, CF₃, -NRᵃRa¹,
-(CRᵃRa¹)ᵣ₁C(O)Ra¹, -(CRᵃRa¹)ᵣ₁C(O)ORᵃ,
-(CRᵃRa¹)ᵣ₁C(O)NRᵃRa¹, -(CRᵃRa¹)ᵣ₁S(O)₃Ra³,
-(CRᵃRa¹)ᵣ₁SO₂NRᵃRa¹, C₃-₆ carbocycle, and a 5-6 membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)₃; and,

Rd, at each occurrence, is independently selected from:
C₁-₆ alkyl, -ORᵃ, Cl, F, Br, =O, -CN, -NRᵃRa¹, -C(O)Ra, -C(O)ORᵃ, -C(O)NRᵃRa¹, -S(O)₂NRᵃRa¹, -S(O)₃Ra³, CF₃, C₃-₆ carbocycle, and a 5-6 membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)₃.
[17] In another preferred embodiment, the present invention provides a novel compound, wherein:

R¹ and R⁴ together with the carbon atoms to which they are attached combine to form a 3-6 membered carbocyclic or heterocyclic ring consisting of carbon atoms and 0-2 ring heteroatoms selected from O, N, NR², and S(O)ₚ, and substituted with 0-2 R²c;

R² is selected from: Q, -C₁₋₆ alkylene-Q,
- (CR²Ra₁)ᵣ₁C(O)(CR²Ra₁)ᵣ-Q, - (CR²Ra₁)ᵣ₁C(O)O(CR²Ra₁)ᵣ-Q,
- (CR²Ra₁)ᵣ₁C(O)NR²Ra₁, - (CR²Ra₁)ᵣ₁C(O)NR²(CR²Ra₁)ᵣ-Q, and
- (CR²Ra₁)ᵣ₁S(O)ₚ(CR²Ra₁)ᵣ-Q;

Q, at each occurrence, is independently selected from: H, a C₁₋₆ carbocycle substituted with 0-2 Rᵈ, and a 5-6 membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)ₚ, and substituted with 0-2 Rᵈ;

R³ is selected from: Q¹, -C₁₋₆ alkylene-Q¹,
- (CR³Ra₁)ᵣ₁O(CH₂)ᵣ-Q¹, - (CR³Ra₁)ᵣ₁NR²(CR³Ra₁)ᵣ-Q¹,
- (CR³Ra₁)ᵣ₁C(O)NR²(CR³Ra₁)ᵣ-Q¹,
- (CR³Ra₁)ᵣ₁C(O)(CR³Ra₁)ᵣ-Q¹,
- (CR³Ra₁)ᵣ₁C(O)O(CR³Ra₁)ᵣ-Q¹,
- (CR³Ra₁)ᵣ₁S(O)ₚ(CR³Ra₁)ᵣ-Q¹, and
- (CR³Ra₁)ᵣ₁SO₂NR²(CR³Ra₁)ᵣ-Q¹;
Q\(^1\), at each occurrence, is independently selected from: H, a C\(_{3-6}\) carbocycle substituted with 0-2 Rd, and a 5-6 membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)\(_p\), and substituted with 0-2 Rd;

R\(^{10}\), at each occurrence, is independently selected from: H, C\(_{1-6}\) alkyl substituted with 0-1 Rc\(_1\), C\(_{2-6}\) alkenyl substituted with 0-1 Rc\(_1\), C\(_{2-6}\) alkynyl substituted with 0-1 Rc\(_1\), -(CR\(^{a\text{Ra1}}\)\(_1\))C(O)Ra\(_1\), -(CR\(^{a\text{Ra1}}\)\(_1\))C(O)ORa\(_1\), -(CR\(^{a\text{Ra1}}\)\(_1\))C(O)NRa\(_1\), -(CR\(^{a\text{Ra1}}\)\(_1\))S(O)\(_p\)Ra\(_3\), -(CR\(^{a\text{Ra1}}\)\(_1\))SO\(_2\)NRa\(_1\), -(CH\(_2\)\(_{r1}\))C\(_{3-6}\) carbocycle substituted with 0-2 Rc\(_1\), and -(CH\(_2\)\(_{r1}\))5-6 membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)\(_p\), and substituted with 0-2 Rc\(_1\);

X-Y is CH\(_2\) or CH\(_2\)O;

Z is phenyl substituted with 0-3 R\(^b\);

R\(^a\), at each occurrence, is independently selected from: H and C\(_{1-4}\) alkyl;

R\(^{a1}\), at each occurrence, is independently selected from: H, C\(_{1-4}\) alkyl, phenyl, and benzyl;

R\(^b\), at each occurrence, is independently selected from:

C\(_{1-4}\) alkyl, -OR\(^a\), Cl, F, =O, -NR\(^{a\text{Ra1}}\), -C(O)Ra,
-C(O)OR\(^a\), -C(O)NR\(^{a\text{Ra1}}\), -S(O)\(_2\)NR\(^{a\text{Ra1}}\), -S(O)\(_p\)Ra\(_3\), and CF\(_3\);
RC, at each occurrence, is independently selected from: H, C₁-₆ alkyl, C₂-₆ alkenyl, C₂-₆ alkynyl, -ORᵃ, Cl, F, Br, =O, -NRᵃRa¹, CF₃, -(CrᵃRa¹)₂C(Ο)ORᵃ, -(CrᵃRa¹)₂C(Ο)NRᵃRa¹, -(CrᵃRa¹)₂S(Ο)₃Ra³, -(CrᵃRa¹)₂SO₂NRᵃRa¹, and phenyl;

and,

RD, at each occurrence, is independently selected from:

C₁-₆ alkyl, -ORᵃ, Cl, F, Br, =O, -NRᵃRa¹, -(C(Ο)Ra), -C(Ο)NRᵃRa¹, -(C(Ο)NRᵃRa¹), -S(Ο)₂NRᵃRa¹, -(C(Ο)₃Ra³, CF₃, and phenyl.

[18] In another preferred embodiment, the present invention provides a novel compound selected from the group:

hydroxy[4-((4-[(2-methyl-4-
quinoliny1)methoxy]phenyl)sulfonyl)tetrahydro-3-furanyl]formamide;

hydroxy[4-((4-[(2-methyl-1H-benzimidazol-1-
yl)methyl]phenyl)sulfonyl)tetrahydro-3-furanyl]formamide; and

hydroxy[4-((4-[(2-methyl-4-
quinoliny1)methyl]phenyl)sulfonyl)tetrahydro-3-furanyl]formamide;

or a pharmaceutically acceptable salt form thereof.
In another embodiment, the present invention provides a novel pharmaceutical composition, comprising: a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of the present invention or a pharmaceutically acceptable salt form thereof.

In another embodiment, the present invention provides a novel method for treating an inflammatory disorder, comprising: administering to a patient in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutically acceptable salt form thereof.

In another embodiment, the present invention provides a novel method of treating a condition or disease mediated by MMPs, TACE, aggrecanase, or a combination thereof in a mammal, comprising: administering to the mammal in need of such treatment a therapeutically effective amount of a compound of the present invention or a pharmaceutically acceptable salt form thereof.

In another embodiment, the present invention provides a novel method comprising: administering a compound of the present invention or a pharmaceutically acceptable salt form thereof in an amount effective to treat a condition or disease mediated by MMPs, TACE, aggrecanase, or a combination thereof.
In another embodiment, the present invention provides a novel method of treating a disease or condition selected from acute infection, acute phase response, age related macular degeneration, alcoholic liver disease, allergy, allergic asthma, anorexia, aneurism, aortic aneurism, asthma, atherosclerosis, atopic dermatitis, autoimmune disease, autoimmune hepatitis, Bechet's disease, cachexia, calcium pyrophosphate dihydrate deposition disease, cardiovascular effects, chronic fatigue syndrome, chronic obstruction pulmonary disease, coagulation, congestive heart failure, corneal ulceration, Crohn's disease, enteropathic arthropathy, Felty's syndrome, fever, fibromyalgia syndrome, fibrotic disease, gingivitis, glucocorticoid withdrawal syndrome, gout, graft versus host disease, hemorrhage, HIV infection, hyperoxic alveolar injury, infectious arthritis, inflammation, intermittent hydrarthrosis, Lyme disease, meningitis, multiple sclerosis, myasthenia gravis, mycobacterial infection, neovascular glaucoma, osteoarthritis, pelvic inflammatory disease, periodontitis, polymyositis/dermatomyositis, post-ischaemic reperfusion injury, post-radiation asthenia, psoriasis, psoriatic arthritis, pulmonary emphysema, pydoderma gangrenosum, relapsing polychondritis, Reiter's syndrome, rheumatic fever, rheumatoid arthritis, sarcoidosis, scleroderma, sepsis syndrome, Still's disease, shock, Sjogren's syndrome, skin inflammatory diseases, solid tumor growth and tumor invasion by secondary metastases, spondylitis, stroke, systemic lupus erythematosus, ulcerative colitis, uveitis, vasculitis, and Wegener's granulomatosis.
In another embodiment, the present invention provides novel compounds of the present invention for use in therapy.

In another embodiment, the present invention provides the use of novel compounds of the present invention for the manufacture of a medicament for the treatment of a condition or disease mediated by MMPs, TACE, aggrecanase, or a combination thereof.

In another embodiment, the present invention provides a method for treating inflammatory disorders, comprising: administering, to a host in need of such treatment, a therapeutically effective amount of one of the compounds of the present invention, in combination with one or more additional anti-inflammatory agents selected from selective COX-2 inhibitors, interleukin-1 antagonists, dihydroorotate synthase inhibitors, p38 MAP kinase inhibitors, TNF-α inhibitors, TNF-α sequestration agents, and methotrexate.

In another embodiment, the present invention provides a novel article of manufacture, comprising:

(a) a first container;

(b) a pharmaceutical composition located within the first container, wherein the composition, comprises: a first therapeutic agent, comprising: a compound of the present invention or a pharmaceutically acceptable salt form thereof; and,
(c) a package insert stating that the pharmaceutical composition can be used for the treatment of an inflammatory disorder.

In another embodiment, the present invention provides a novel article of manufacture, comprising:
(a) a first container;
(b) a pharmaceutical composition located within the first container, wherein the composition, comprises: a first therapeutic agent, comprising: a compound of the present invention or a pharmaceutically acceptable salt form thereof; and,
(c) a package insert stating that the pharmaceutical composition can be used in combination with a second therapeutic agent to treat an inflammatory disorder.

In another preferred embodiment, the present invention provides a novel article of manufacture, further comprising:
(d) a second container;
wherein components (a) and (b) are located within the second container and component (c) is located within or outside of the second container.

In another preferred embodiment, the present invention provides a novel compound, wherein;

\[ R^1 \text{ is selected from: H and C}_{1-6} \text{ alkyl.} \]
In another preferred embodiment, the present invention provides a novel compound, wherein;

R^1 is selected from: H and C_{1-4} alkyl.

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In another preferred embodiment, the present invention provides a novel compound, wherein;

R^1 is selected from: H, methyl, and ethyl.

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In another embodiment, the present invention provides a novel compound, wherein;

15 R^2 is selected from: Q, -C_{1-6} alkyne-Q, -C_{2-6} alkenylene-Q, -C_{2-6} alkynylene-Q,
- (CRA^1Ra^1)_r1O(CRA^1Ra^1)_r-Q,
- (CRA^1Ra^1)_r1NRa^1(CRA^1Ra^1)_r-Q, - (CRA^1Ra^1)_r1C(O)(CRA^1Ra^1)_r-Q,
- (CRA^1Ra^1)_r1C(O)O(CRA^1Ra^1)_r-Q, - (CRA^1Ra^1)_r1C(O)NRa^1,
- (CRA^1Ra^1)_r1C(O)NRa^1(CRA^1Ra^1)_r-Q,
- (CRA^1Ra^1)_r1S(O)P(CRA^1Ra^1)_r-Q,
- (CRA^1Ra^1)_r1SO_{2}NRa^1(CRA^1Ra^1)_r-Q, and
- (CRA^1Ra^1)_r1NRa^1SO_{2}(CRA^1Ra^1)_r-Q.

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In another embodiment, the present invention provides a novel compound, wherein;

25 R^2 is selected from: Q, -C_{1-6} alkyne-Q, -C_{1-6} alkenylene-Q, -(CRA^1Ra^1)_r1O(CRA^1Ra^1)_r-Q,
- (CRA^1Ra^1)_r1NRa^1(CRA^1Ra^1)_r-Q, - (CRA^1Ra^1)_r1C(O)(CRA^1Ra^1)_r-Q,

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In another embodiment, the present invention provides a novel compound, wherein:

R\textsuperscript{2} is selected from: Q, -C\textsubscript{1-6} alkylene-Q,

- (CR\textsuperscript{a}Ra\textsuperscript{1})\textsubscript{r}C(O)(CR\textsuperscript{a}Ra\textsuperscript{1})\textsubscript{r}-Q, - (CR\textsuperscript{a}Ra\textsuperscript{1})\textsubscript{r}C(O)NR\textsuperscript{a}Ra\textsuperscript{1},

- (CR\textsuperscript{a}Ra\textsuperscript{1})\textsubscript{r}C(O)NR\textsuperscript{a}Ra\textsuperscript{1} - Q, and

- (CR\textsuperscript{a}Ra\textsuperscript{1})\textsubscript{r}SO\textsubscript{2}NR\textsuperscript{a}Ra\textsuperscript{1} - Q.

In another embodiment, the present invention provides a novel compound, wherein:

R\textsuperscript{2} is selected from: Q, -C\textsubscript{1-6} alkylene-Q, -C(O)(CR\textsuperscript{a}Ra\textsuperscript{1})\textsubscript{r}-Q,

- C(O)O(CR\textsuperscript{a}Ra\textsuperscript{1})\textsubscript{r}-Q, -C(O)NR\textsuperscript{a}Ra\textsuperscript{1} - Q, and

- S(O)\textsubscript{p}(CR\textsuperscript{a}Ra\textsuperscript{1})\textsubscript{r}-Q.

In another embodiment, the present invention provides a novel compound, wherein:

Q is selected from: H, a C\textsubscript{3-10} carbocycle substituted with 0-5 R\textsuperscript{d}, and a 5-10 membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)\textsubscript{p}, and substituted with 0-5 R\textsuperscript{d}.
In another embodiment, the present invention provides a novel compound, wherein;

Q is selected from: H, a C₃₋₆ carbocycle substituted with 0-3 Rᵈ, and a 5-10 membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)ₓ, and substituted with 0-3 Rᵈ.

In another embodiment, the present invention provides a novel compound, wherein;

Q is selected from: H, a C₃₋₆ carbocycle substituted with 0-2 Rᵈ, and a 5-6 membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)ₓ, and substituted with 0-2 Rᵈ.

In another embodiment, the present invention provides a novel compound, wherein;

Q is selected from: H, cyclopropyl substituted with 0-1 Rᵈ, cyclopentyl substituted with 0-1 Rᵈ, cyclohexyl substituted with 0-1 Rᵈ, phenyl substituted with 0-2 Rᵈ, and a heteroaryl substituted with 0-3 Rᵈ, wherein the heteroaryl is selected from pyridyl, quinolinyl, thiazolyl, furanyl, imidazolyl, and isoxazolyl.
In another embodiment, the present invention provides a novel compound, wherein;

R³ is selected from: Q¹, -C₁₋₆ alkylene-Q¹,
-C₂₋₆ alkenylene-Q¹, -(CRᵃRa¹)ᵣ₁O(CH₂)ᵣ-Q¹,
-(CRᵃRa¹)ᵣ₁NRᵃ(CRᵃRa¹)ᵣ-Q¹,
-(CRᵃRa¹)ᵣ₁C(O)NRᵃ(CRᵃRa¹)ᵣ-Q¹,
-(CRᵃRa¹)ᵣ₁C(O)(CRᵃRa¹)ᵣ-Q¹,
-(CRᵃRa¹)ᵣ₁C(O)O(CRᵃRa¹)ᵣ-Q¹,
-(CRᵃRa¹)ᵣ₁S(O)ₚ(CRᵃRa¹)ᵣ-Q¹, and
-(CRᵃRa¹)ᵣ₁SO₂NRᵃ(CRᵃRa¹)ᵣ-Q¹.

In another embodiment, the present invention provides a novel compound, wherein;

R³ is selected from: Q¹, -C₁₋₆ alkylene-Q¹,
-(CRᵃRa¹)ᵣ₁O(CH₂)ᵣ-Q¹, -(CRᵃRa¹)ᵣ₁NRᵃ(CRᵃRa¹)ᵣ-Q¹,
-(CRᵃRa¹)ᵣ₁C(O)NRᵃ(CRᵃRa¹)ᵣ-Q¹,
-(CRᵃRa¹)ᵣ₁C(O)(CRᵃRa¹)ᵣ-Q¹,
-(CRᵃRa¹)ᵣ₁C(O)O(CRᵃRa¹)ᵣ-Q¹,
-(CRᵃRa¹)ᵣ₁S(O)ₚ(CRᵃRa¹)ᵣ-Q¹, and
-(CRᵃRa¹)ᵣ₁SO₂NRᵃ(CRᵃRa¹)ᵣ-Q¹.

In another embodiment, the present invention provides a novel compound, wherein;

R³ is selected from: Q¹, -C₁₋₆ alkylene-Q¹,
-(C(O)NRᵃ(CRᵃRa¹)ᵣ-Q¹, -(C(O)(CRᵃRa¹)ᵣ-Q¹,
-(C(O)O(CRᵃRa¹)ᵣ-Q¹, and -(CRᵃRa¹)ᵣ₁S(O)ₚ(CRᵃRa¹)ᵣ-Q¹.
In another embodiment, the present invention provides a novel compound, wherein;

5 $Q^1$ is selected from: $H$, a $C_{3-10}$ carbocycle substituted with 0-5 $R^d$, and a 5-10 membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of $N$, $O$, and $S(O)_p$, and substituted with 0-5 $R^d$.

10 In another embodiment, the present invention provides a novel compound, wherein;

$Q^1$ is selected from: $H$, a $C_{3-6}$ carbocycle substituted with 0-3 $R^d$, and a 5-10 membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of $N$, $O$, and $S(O)_p$, and substituted with 0-3 $R^d$.

15 In another embodiment, the present invention provides a novel compound, wherein;

$Q^1$ is selected from: $H$, a $C_{3-6}$ carbocycle substituted with 0-2 $R^d$, and a 5-6 membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of $N$, $O$, and $S(O)_p$, and substituted with 0-2 $R^d$.

20 In another embodiment, the present invention provides a novel compound, wherein;

$Q^1$ is selected from: $H$, a $C_{3-6}$ carbocycle substituted with 0-2 $R^d$, and a 5-6 membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of $N$, $O$, and $S(O)_p$, and substituted with 0-2 $R^d$.

25 In another embodiment, the present invention provides a novel compound, wherein;
Q^1 is selected from: H, cyclopropyl substituted with 0-1 R^d, cyclopentyl substituted with 0-1 R^d, cyclohexyl substituted with 0-1 R^d, phenyl substituted with 0-2 R^d, and a heteroaryl substituted with 0-3 R^d, wherein the heteroaryl is selected from pyridyl, quinolinyl, thiazolyl, furanyl, imidazolyl, and isoxazolyl.

In another embodiment, the present invention provides a novel compound, wherein:

R^4 is selected from: H and C\textsubscript{1-6} alkyl.

In another embodiment, the present invention provides a novel compound, wherein:

R^4 is selected from: H and C\textsubscript{1-4} alkyl.

In another embodiment, the present invention provides a novel compound, wherein:

R^4 is selected from: H, methyl, and ethyl.

In another embodiment, the present invention provides a novel compound, wherein:

R^3 and R^d together with the carbon atom to which they are attached combine to form a 3-8 membered carbocyclic or heterocyclic ring consisting of carbon atoms and 0-2
ring heteroatoms selected from O, N, NR\textsubscript{10}, and S(O)\textsubscript{p}, and substituted with 0-3 R\textsubscript{c}.

In another embodiment, the present invention provides a novel compound, wherein;

R\textsuperscript{3} and R\textsuperscript{4} together with the carbon atom to which they are attached combine to form a 3-6 membered carbocyclic or heterocyclic ring consisting of carbon atoms and 0-2 ring heteroatoms selected from O, N, NR\textsubscript{10}, and S(O)\textsubscript{p}, and substituted with 0-3 R\textsubscript{c}.

In another embodiment, the present invention provides a novel compound, wherein;

R\textsuperscript{3} and R\textsuperscript{4} together with the carbon atom to which they are attached combine to form a 3-6 membered carbocyclic or heterocyclic ring consisting of carbon atoms and 0-2 ring heteroatoms selected from O, N, NR\textsubscript{10}, and S(O)\textsubscript{p}, and substituted with 0-2 R\textsubscript{c}.

In another embodiment, the present invention provides a novel compound, wherein;

R\textsuperscript{5} is selected from: H, methyl, and ethyl.

In another embodiment, the present invention provides a novel compound, wherein;

R\textsuperscript{5} is H.
In another embodiment, the present invention provides a novel compound, wherein;

R\textsuperscript{10}, at each occurrence, is independently selected from: H, C\textsubscript{1-6} alkyl substituted with 0-2 R\textsuperscript{c1}, C\textsubscript{2-6} alkenyl substituted with 0-2 R\textsuperscript{c1}, C\textsubscript{2-6} alkynyl substituted with 0-2 R\textsuperscript{c1}, -(CR\textsuperscript{a}Ra\textsuperscript{a})\textsubscript{2}NR\textsuperscript{a}Ra\textsuperscript{a}, -(CR\textsuperscript{a}Ra\textsuperscript{a})\textsubscript{r1}C(O)Ra\textsuperscript{a}, -(CR\textsuperscript{a}Ra\textsuperscript{a})\textsubscript{r1}C(O)OR\textsuperscript{a}, -(CR\textsuperscript{a}Ra\textsuperscript{a})\textsubscript{r1}C(O)NR\textsuperscript{a}Ra\textsuperscript{a}, -(CR\textsuperscript{a}Ra\textsuperscript{a})\textsubscript{r1}SO\textsubscript{2}NR\textsuperscript{a}Ra\textsuperscript{a}, -(CR\textsuperscript{a}Ra\textsuperscript{a})\textsubscript{r1-C3-10} carbocycle substituted with 0-2 R\textsuperscript{c1}, and -(CR\textsuperscript{a}Ra\textsuperscript{a})\textsubscript{r1-5-14} membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)\textsubscript{p}, and substituted with 0-2 R\textsuperscript{c1}.

In another embodiment, the present invention provides a novel compound, wherein;

R\textsuperscript{10}, at each occurrence, is independently selected from: H, C\textsubscript{1-6} alkyl substituted with 0-1 R\textsuperscript{c1}, C\textsubscript{2-6} alkenyl substituted with 0-1 R\textsuperscript{c1}, C\textsubscript{2-6} alkynyl substituted with 0-1 R\textsuperscript{c1}, -(CR\textsuperscript{a}Ra\textsuperscript{a})\textsubscript{r1}C(O)Ra\textsuperscript{a}, -(CR\textsuperscript{a}Ra\textsuperscript{a})\textsubscript{r1}C(O)OR\textsuperscript{a}, -(CR\textsuperscript{a}Ra\textsuperscript{a})\textsubscript{r1}C(O)NR\textsuperscript{a}Ra\textsuperscript{a}, -(CR\textsuperscript{a}Ra\textsuperscript{a})\textsubscript{r1}SO\textsubscript{2}NR\textsuperscript{a}Ra\textsuperscript{a}, -(CR\textsuperscript{a}Ra\textsuperscript{a})\textsubscript{r1-C3-6} carbocycle substituted with 0-2 R\textsuperscript{c1}, and -(CR\textsuperscript{a}Ra\textsuperscript{a})\textsubscript{r1-5-10} membered heterocycle consisting of carbon atoms and 1-4
heteroatoms selected from the group consisting of N, O, and S(O)ₚ, and substituted with 0-2 Rᶜ¹.

In another embodiment, the present invention provides a novel compound, wherein;

R¹₀, at each occurrence, is independently selected from: H, C₁₋₆ alkyl substituted with 0-1 Rᶜ¹, C₂₋₆ alkenyl substituted with 0-1 Rᶜ¹, C₂₋₆ alkynyl substituted with 0-1 Rᶜ¹, -(CRᵃRᵃ¹)ʳ₁C(O)Rᵃ¹, -(CRᵃRᵃ¹)ʳ₁C(O)ORᵃ¹, -(CRᵃRᵃ¹)ʳ₁C(O)NRᵃRᵃ¹, -(CRᵃRᵃ¹)ʳ₁S(O)ₚRᵃ³,
-(CRᵃRᵃ¹)ʳ₁SO₂NRᵃRᵃ¹, -(CH₂)ʳ₁-C₃₋₆ carbocycle substituted with 0-2 Rᶜ¹, and -(CH₂)ʳ₁-5-6 membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)ₚ, and substituted with 0-2 Rᶜ¹.

In another embodiment, the present invention provides a novel compound, wherein;

X-Y is CH₂ or OCH₂.

In another embodiment, the present invention provides a novel compound, wherein;

X-Y is CH₂.

In another embodiment, the present invention provides a novel compound, wherein;
X-Y is OCH₂.

In another embodiment, the present invention provides a novel compound, wherein:

Z is selected from: phenyl substituted with 0-3 R⁵, and a 5-6 membered heteroaryl consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)₃, and substituted with 0-3 R⁵.

In another embodiment, the present invention provides a novel compound, wherein:

Z is phenyl substituted with 0-3 R⁵.

In another embodiment, the present invention provides a novel compound, wherein:

Z² is substituted with 0-4 R⁶ and is selected from the group:

W is S, SO, SO₂, O, or NR¹¹; and
R^{11}, at each occurrence, is independently selected from: H, C_{1-4} alkyl, phenyl, and benzyl.

In another embodiment, the present invention provides a novel compound, wherein:

Z^a is 4-quinolinyl substituted with 0-2 R^c.

In another embodiment, the present invention provides a novel compound, wherein:

R^a, at each occurrence, is independently selected from: H and C_{1-4} alkyl;

R^{a1}, at each occurrence, is independently selected from: H, C_{1-4} alkyl, phenyl, and benzyl; and

alternatively, R^a and R^{a1} when attached to a nitrogen are taken together with the nitrogen to which they are attached form a 5 or 6 membered heterocycle consisting of carbon atoms and 0-1 additional heteroatoms selected from N, NR^{a2}, O, and S(O)_{p}.

In another embodiment, the present invention provides a novel compound, wherein:

R^a, at each occurrence, is independently selected from: H and C_{1-4} alkyl; and
R\textsuperscript{a1}, at each occurrence, is independently selected from: H, C\textsubscript{1-4} alkyl, phenyl, and benzyl.

In another embodiment, the present invention provides a novel compound, wherein;

R\textsuperscript{a}, at each occurrence, is independently selected from: H, methyl, and ethyl; and

R\textsuperscript{a1}, at each occurrence, is independently selected from: H, methyl, and ethyl.

In another embodiment, the present invention provides a novel compound, wherein;

R\textsuperscript{a2}, at each occurrence, is independently selected from: H, methyl, and ethyl.

In another embodiment, the present invention provides a novel compound, wherein;

R\textsuperscript{c}, at each occurrence, is independently selected from: H, C\textsubscript{1-6} alkyl substituted with 0-2 R\textsuperscript{c1}, C\textsubscript{2-6} alkenyl substituted with 0-2 R\textsuperscript{c1}, C\textsubscript{2-6} alkynyl substituted with 0-2 R\textsuperscript{c1}, -OR\textsuperscript{a}, Cl, F, Br, I, =O, -CN, NO\textsubscript{2}, CF\textsubscript{3}, -OCF\textsubscript{3}, -CF\textsubscript{2}CF\textsubscript{3}, -CH\textsubscript{2}F, -CHF\textsubscript{2}, -\text{(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r1}NR\textsuperscript{a}R\textsuperscript{a1}}, -\text{(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r1}C(0)R\textsuperscript{a1}}, -\text{(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r1}C(0)OR\textsuperscript{a1}}, -\text{(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r1}C(0)NR\textsuperscript{a}R\textsuperscript{a1}}, -\text{(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r1}NR\textsuperscript{a}C(0)R\textsuperscript{a1}},
-(CR^R_1^1)_{r_1} S(O)^P R^a_3, -(CR^R_1^1)_{r_1} SO_2 NR^a R^a_1,
-(CR^R_1^1)_{r_1} NR^a SO_2 R^a_3, -(CR^R_1^1)_{r_1} -C_3-10 carbocycle
substituted with 0-2 R^c_1, and -(CR^R_1^1)_{r_1} -5-14 membered
heterocycle consisting of carbon atoms and 1-4
heteroatoms selected from the group consisting of N,
O, and S(O)^P, and substituted with 0-2 R^c_1;

alternatively, when two R^c groups are attached to the same
carbon atom they form a spiro ring C that is a 3-11
membered carbocycle substituted with 0-2 R^c_1 or a 3-13
membered heterocycle consisting of: carbon atoms, 0-3
carbonyl groups, 0-4 double bonds, and from 1-5 ring
heteroatoms selected from O, N, and S(O)^P, and
substituted with 0-2 R^c_1, provided that ring C
contains other than a S-S, O-O, or S-O bond; and,

alternatively, when two R^c groups are attached to adjacent
carbon atoms, together with the carbon atoms to which
they are attached they form a 5-7 membered carbocyclic
or heterocyclic ring consisting of: carbon atoms, 0-2
heteroatoms selected from the group consisting of N,
O, and S(O)^P, and 0-3 double bonds, and substituted
with 0-2 R^c_1.

In another embodiment, the present invention provides
a novel compound, wherein;

R^c, at each occurrence, is independently selected from: H,
C_{1-6} alkyl substituted with 0-2 R^c_1, C_{2-6} alkenyl
substituted with 0-2 R^c_1, C_{2-6} alkynyl substituted with
0-2 R^c_1, -OR^a, C1, F, Br, I, =O, -CN, NO_2, CF_3,
-CF₂CF₃, -(CRAra)R₁NRaR₁, -(CRAra)R₁C(O)Ra₁,
-(CRAra)R₁C(O)ORa₁, -(CRAra)R₁C(O)NRaR₁,
-(CRAra)R₁NRaC(O)Ra₁, -(CRAra)R₁S(O)pRa₃,
-(CRAra)R₁SO₂NRaR₁, -(CRAra)R₁NRaSO₂Ra₃,
- (CRAra)R₁-C₃-10 carbocycle substituted with 0-2 Rć₁,
and -(CRAra)R₁-5-10 membered heterocycle consisting of
carbon atoms and 1-4 heteroatoms selected from the
group consisting of N, O, and S(O)p, and substituted
with 0-2 Rć₁;

In another embodiment, the present invention provides
a novel compound, wherein:

Rć, at each occurrence, is independently selected from: H,
C₁-6 alkyl substituted with 0-1 Rć₁, C₂-6 alkenyl
substituted with 0-1 Rć₁, C₂-6 alkynyl substituted with
0-1 Rć₁, -ORa, Cl, F, Br, =O, -CN, CF₃, -NRaRaR₁,
-(CRAra)R₁C(O)Ra₁, -(CRAra)R₁C(O)ORa₁,
-(CRAra)R₁C(O)NRaR₁, -(CRAra)R₁S(O)pRa₃,
-(CRAra)R₁SO₂NRaR₁, C₃-6 carbocycle, and a 5-6
membered heterocycle consisting of carbon atoms and
1-4 heteroatoms selected from the group consisting of
N, O, and S(O)p.

In another embodiment, the present invention provides
a novel compound, wherein:

Rć, at each occurrence, is independently selected from: H,
C₁-6 alkyl, C₂-6 alkenyl, C₂-6 alkynyl, -ORa, Cl, F,
Br, =O, -NRaRaR₁, CF₃, -(CRAra)R₁C(O)Ra₁,
(-CR^aR^b)_1C(0)OR^a, (-CR^aR^b)_1C(0)NR^aR^b, 
(-CR^aR^b)_1S(0)OR^b, (-CR^aR^b)_1SO_2NR^aR^b, and phenyl.

In another embodiment, the present invention provides a novel compound, wherein:

R^C, at each occurrence, is independently selected from: H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -OR^a, Cl, F, Br, =O, -NR^aR^b, CF_3, (-CR^aR^b)_1C(0)R^a,
(-CR^aR^b)_1C(0)OR^a, (-CR^aR^b)_1C(0)NR^aR^b,
(-CR^aR^b)_1S(0)OR^b, and (-CR^aR^b)_1SO_2NR^aR^b.

In another embodiment, the present invention provides a novel compound, wherein:

R^Cl, at each occurrence, is independently selected from: H, C_{1-4} alkyl, -OR^a, Cl, F, Br, I, =O, CF_3, -CN, NO_2,
-NR^aR^b, -C(0)OR^a, and -C(0)NR^aR^b;

In another embodiment, the present invention provides a novel compound, wherein:

R^d, at each occurrence, is independently selected from:
C_{1-6} alkyl, -OR^a, Cl, F, Br, I, =O, -CN, NO_2, -NR^aR^b,
-C(0)R^a, -C(0)OR^a, -C(0)NR^aR^b, -C(S)NR^aR^b,
-NR^aC(0)NR^aR^b, -OC(0)NR^aR^b, -NR^aC(0)OR^a,
-S(O)_2NR^aR^b, -NR^aS(O)_2R^a, -NR^aS(O)_2NR^aR^b,
-OS(O)NRaR^a, -NRaS(O)2Ra^a, -S(O)2Ra^a, CF3, -CF2CF3,
C3-6 carbocycle, and a 5-6 membered heterocycle
consisting of carbon atoms and 1-4 heteroatoms
selected from the group consisting of N, O, and S(O)p.

In another embodiment, the present invention provides
a novel compound, wherein;

R^d, at each occurrence, is independently selected from:
C1-6 alkyl, -OR^a, Cl, F, Br, =O, -CN, -NRaR^a, -C(O)Ra,
-C(O)OR^a, -C(O)NRaR^a, -S(O)NRaR^a, -S(O)2R^a,
C3-6 carbocycle, and a 5-6 membered heterocycle
consisting of carbon atoms and 1-4 heteroatoms
selected from the group consisting of N, O, and S(O)p.

In another embodiment, the present invention provides
a novel compound, wherein;

R^d, at each occurrence, is independently selected from:
C1-6 alkyl, -OR^a, Cl, F, Br, =O, -NRaR^a, -C(O)Ra,
-C(O)NRaR^a, -S(O)2NRaR^a, -S(O)2Ra^a, CF3, and phenyl.

In another embodiment, the present invention provides
a novel compound, wherein;

R^e, at each occurrence, is independently selected from: H,
C1-4 alkyl, -OR^a, Cl, F, Br, I, =O, CF3, -CN, NO2,
-NRaR^a, -C(O)OR^a, and -C(O)NRaR^a.

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This invention also encompasses all combinations of preferred aspects of the invention noted herein. It is understood that any and all embodiments of the present invention may be taken in conjunction with any other embodiment to describe additional even more preferred embodiments of the present invention. It is also understood that each and every element of any embodiment is intended to be a separate specific embodiment. Furthermore, any elements of an embodiment are meant to be combined with any and all other elements from any of the embodiments to describe additional embodiments.

DEFINITIONS

The compounds herein described may have asymmetric centers. Compounds of the present invention containing an asymmetrically substituted atom may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis from optically active starting materials. Geometric isomers of double bonds such as olefins and C=N double bonds can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. Cis and trans geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms. All chiral, diastereomeric, racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomeric form is specifically indicated. All processes used to prepare compounds of the
present invention and intermediates made therein are considered to be part of the present invention.

Preferably, the molecular weight of compounds of the present invention is less than about 500, 550, 600, 650, 700, 750, 800, 850, or 900 grams per mole. More preferably, the molecular weight is less than about 850 grams per mole. Even more preferably, the molecular weight is less than about 750 grams per mole. Still more preferably, the molecular weight is less than about 700 grams per mole.

The term "substituted," as used herein, means that any one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substituent is keto (i.e., =O), then 2 hydrogens on the atom are replaced. Keto substituents are not present on aromatic moieties. When a ring system (e.g., carbocyclic or heterocyclic) is said to be substituted with a carbonyl group or a double bond, it is intended that the carbonyl group or double bond be part (i.e., within) of the ring.

The term "acylation" as used herein describes the functionalization of a primary or secondary amine by reacting it with an "acylator" to form a stable compound. Examples of acylators include (but are not limited to) an acid chloride, a carboxylic acid anhydride, a sulfonyl chloride, a chloroformate, an isocyanate, an isothiocyanate, etc. the product of which is an amide, a sulfonamide, a carbamate, a urea, and a thiourea respectively.

The present invention is intended to include all isotopes of atoms occurring in the present compounds.
Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include tritium and deuterium. Isotopes of carbon include C-13 and C-14.

The term "independently selected from", "independently, at each occurrence" or similar language, means that the labeled R substitution group may appear more than once and that each appearance may be a different atom or molecule found in the definition of that labeled R substitution group. Thus if the labeled R^a substitution group appear four times in a given permutation of Formula I, then each of those labeled R^a substitution groups may be a different group falling in the definition of R^a. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

When any variable (e.g., R^6) occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-2 R^6, then said group may optionally be substituted with up to two R^6 groups and R^6 at each occurrence is selected independently from the definition of R^6. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom on the ring. When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound of a given formula, then such substituent may be bonded via any
atom in such substituent. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

In cases wherein there are amines on the compounds of this invention, these can be converted to amine N-oxides by treatment with MCPBA and or hydrogen peroxides to afford other compounds of this invention. Thus, all shown amines are considered to cover both the shown amine and its N-oxide (N\(\rightarrow\)O) derivative.

As used herein, "alkyl" or "alkylene" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. \(C_{1-10}\) alkyl (or alkylene), is intended to include \(C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9,\) and \(C_{10}\) alkyl groups. Examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, and s-pentyl. "Haloalkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with 1 or more halogen (for example \(-C_yF_w\) where \(v = 1\) to \(3\) and \(w = 1\) to \((2v+1)\)). Examples of haloalkyl include, but are not limited to, trifluoromethyl, trichloromethyl, pentafluoroethyl, and pentachloroethyl. "Alkoxy" represents an alkyl group as defined above with the indicated number of carbon atoms attached through an oxygen bridge. \(C_{1-10}\) alkoxy, is intended to include \(C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9,\) and \(C_{10}\) alkoxy groups. Examples of alkoxy include, but are not limited to, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy, t-butoxy, n-pentoxy, and s-pentoxy. "Cycloalkyl" is intended to include saturated ring groups, such as cyclopropyl, cyclobutyl, or cyclopentyl. \(C_{3-7}\)
cycloalkyl, is intended to include C₃, C₄, C₅, C₆, and C₇
cycloalkyl groups. "Alkenyl" or "alkenylenne" is intended
to include hydrocarbon chains of either a straight or
branched configuration and one or more unsaturated
5 carbon-carbon bonds which may occur in any stable point
along the chain, such as ethenyl and propenyl. C₂₋₁₀
alkenyl (or alkenylene), is intended to include C₂, C₃, C₄,
C₅, C₆, C₇, C₈, C₉, and C₁₀ alkenyl groups. "Alkynyl" or
"alkynylene" is intended to include hydrocarbon chains of
either a straight or branched configuration and one or more
triple carbon-carbon bonds which may occur in any stable
point along the chain, such as ethynyl and propynyl. C₂₋₁₀
alkynyl (or alkynylene), is intended to include C₂, C₃, C₄,
C₅, C₆, C₇, C₈, C₉, and C₁₀ alkynyl groups.
15 "Halo" or "halogen" as used herein refers to fluoro,
chloro, bromo, and iodo; and "counterion" is used to
represent a small, negatively charged species such as
chloride, bromide, hydroxide, acetate, and sulfate.

As used herein, "carbocycle" or "carbocyclic residue"
is intended to mean any stable 3, 4, 5, 6, or 7-membered
monocyclic or bicyclic or 7, 8, 9, 10, 11, 12, or
13-membered bicyclic or tricyclic, any of which may be
saturated, partially unsaturated, or aromatic. Examples of
such carbocycles include, but are not limited to,
25 cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl,
cycloheptyl, adamantyl, cyclooctyl, [3.3.0]bicyclooctane,
[4.3.0]bicyclononane, [4.4.0]bicyclodecane,
[2.2.2]bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl,
adamantyl, and tetrahydronaphthyl.

As used herein, the term "heterocycle" or
"heterocyclic group" is intended to mean a stable 5, 6, or
7-membered monocyclic or bicyclic or 7, 8, 9, or 10-
membered bicyclic heterocyclic ring which is saturated, partially unsaturated or unsaturated (aromatic), and which consists of carbon atoms and 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of N, O and S and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The nitrogen and sulfur heteroatoms may optionally be oxidized. The nitrogen atom may be substituted or unsubstituted (i.e., N or NR wherein R is H or another substituent, if defined). The heterocyclic ring may be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure. The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. A nitrogen in the heterocycle may optionally be quaternized. It is preferred that when the total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another. It is preferred that the total number of S and O atoms in the heterocycle is not more than 1. As used herein, the term "aromatic heterocyclic group" or "heteroaryl" is intended to mean a stable 5, 6, or 7-membered monocyclic or bicyclic or 7, 8, 9, or 10-membered bicyclic heterocyclic aromatic ring which consists of carbon atoms and 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of N, O and S. It is to be noted that total number of S and O atoms in the aromatic heterocycle is not more than 1.

Examples of heterocycles include, but are not limited to, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiophenyl, benzoazolyl, benzthiazolyl, benztiazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazoliny1, carbazolyl, 4H-carbazolyl, carboliny1,
chromanyl, chromenyl, cinnolinyl, decahydroquinolinylnyl, 2H, 6H-1,5,2-dithiazinyl, dihydrofuro[2,3-b]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinylnyl, imidazolyl, 1H-indazolylnyl, indolenyl, indolinylnyl, indolizinylnyl, indolyl, 3H-indolinylnyl, isobenzofuranylnyl, isochromanyl, isochromenyl, isochromonylnyl, isoindolinylnyl, isoindolyl, isoquinolinylnyl, isothiazolylnyl, isoxazolyl, methylenedioxyphenyl, morpholinylnyl, naphthyridinylnyl, octahydroisoquinolinylnyl, oxadiazolyl, 1,2,3-oxadiazolynyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinylnyl, pyrimidinyl, phenanthridinylnyl, phenanthrolinyl, phenazinylnyl, phenothiazinylnyl, phenoxathiinylnyl, phenoxazinylnyl, phthalazinylnyl, piperazinylnyl, piperidinylnyl, piperidonylnyl, 4-piperidonylnyl, piperonylnyl, pteridinylnyl, purinylnyl, pyranylnyl, pyrazinyl, pyrazolidinyl, pyrazolinylnyl, pyrazolyl, pyridazinylnyl, pyridoxazolyl, pyridoimidazolyl, pyridothiazolyl, pyridinylnyl, pyrydinylnyl, pyrrolidinyl, pyrrolinylnyl, 2H-pyrrolylnyl, pyrrolylnyl, quinoxalinyl, quinolinyl, 4H-quinolizinylnyl, quinolinylnyl, quinuclidinyl, tetrahydrofuranylnyl, tetrahydroisoquinolinylnyl, tetrahydroquinolinylnyl, tetrazolyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazylnyl, thienyl, thienothiazolyl, thienoxazolyl, thienimidazolyl, thienyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, xanthenyl, 1,1-dioxido-2,3-dihydro-4H-1,4-benzothiazin-4-yl, 1,1-dioxido-3,4-dihydro-2H-1-benzothiopyran-4-yl, 3,4-dihydro-2H-chromen-4-yl, imidazo[1,2-a]pyridinylnyl, imidazo[1,5-a]pyridinylnyl, and pyrazolo[1,5-a]pyridinylnyl. Also included are fused ring and spiro compounds containing, for example, the above heterocycles.
The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; and alkali or organic salts of acidic residues such as carboxylic acids. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, and nitric; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, and isethionic.

The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound that contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting
the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, PA, 1985, p. 1418, the disclosure of which is hereby incorporated by reference.

Since prodrugs are known to enhance numerous desirable qualities of pharmaceuticals (e.g., solubility, bioavailability, manufacturing, etc.) the compounds of the present invention may be delivered in prodrug form. Thus, the present invention is intended to cover prodrugs of the presently claimed compounds, methods of delivering the same and compositions containing the same. "Prodrugs" are intended to include any covalently bonded carriers which release an active parent drug of the present invention in vivo when such prodrug is administered to a mammalian subject. Prodrugs the present invention are prepared by modifying functional groups present in the compound in such a way that the modifications are cleaved, either in routine manipulation or in vivo, to the parent compound. Prodrugs include compounds of the present invention wherein a hydroxy, amino, or sulfhydryl group is bonded to any group that, when the prodrug of the present invention is administered to a mammalian subject, it cleaves to form a free hydroxyl, free amino, or free sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups in the compounds of the present invention.
"Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

As used herein, "treating" or "treatment" cover the treatment of a disease-state in a mammal, particularly in a human, and include: (a) preventing the disease-state from occurring in a mammal, in particular, when such mammal is predisposed to the disease-state but has not yet been diagnosed as having it; (b) inhibiting the disease-state, i.e., arresting it development; and/or (c) relieving the disease-state, i.e., causing regression of the disease state.

"Therapeutically effective amount" is intended to include an amount of a compound of the present invention or an amount of the combination of compounds claimed effective to inhibit a desired metalloprotease in a host. The combination of compounds is preferably a synergistic combination. Synergy, as described for example by Chou and Talalay, Adv. Enzyme Regul. 22:27-55 (1984), occurs when the effect (in this case, inhibition of the desired target) of the compounds when administered in combination is greater than the additive effect of the compounds when administered alone as a single agent. In general, a synergistic effect is most clearly demonstrated at suboptimal concentrations of the compounds. Synergy can be in terms of lower cytotoxicity, increased anti-inflammatory effect, or some other beneficial effect of the combination compared with the individual components.
SYNTHESIS

The compounds of the present invention can be prepared in a number of ways well known to one skilled in the art of organic synthesis. The compounds of the present invention can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or variations thereon as appreciated by those skilled in the art. Preferred methods include, but are not limited to, those described below.

All references cited herein are hereby incorporated in their entirety herein by reference.

The novel compounds of this invention may be prepared using the reactions and techniques described in this section. The reactions are performed in solvents appropriate to the reagents and materials employed and are suitable for the transformations being effected. Also, in the description of the synthetic methods described below, it is to be understood that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of the experiment and work up procedures, are chosen to be the conditions standard for that reaction, which should be readily recognized by one skilled in the art. It is understood by one skilled in the art of organic synthesis that the functionality present on various portions of the molecule must be compatible with the reagents and reactions proposed. Such restrictions to the substituents that are compatible with the reaction conditions will be readily apparent to one skilled in the art and alternate methods must then be used.

Compounds of formula I which are N-formyl hydroxylamines \( R^5 = H \) can be prepared from (but not
limited to) a t-butyl protected hydroxyl amine by the sequence depicted in Scheme I. The amine 1 can be formylated using standard conditions (AcOCHO, pyridine, for a synthesis of AcOCHO see: Edwards and Reeves; J. Amer. Chem. Soc. 1942, 64, 1583) to give 2. Further manipulation to the desired Z-X-Y-heteroaromatic substituents would yield 3 and then the hydroxyl unmasked by acid hydrolysis with TFA to give 4.

Scheme 1

Compounds of formula I wherein R³ and R⁴ combine to form a carbocyclic or heterocyclic ring can be synthesized according to Scheme 2. Sulfone 5 can be derived from commercially available 4-(methylsulfonyl)phenol by benzyl protection (benzylbromide, TEA) followed by deprotonation (BuLi, THF) and trapping with trimethylsilyl chloride. Olefination of ketone 6 with the sulfone 5 would yield the unsaturated sulfone 7. Michael addition of t-butylhydroxylamine would deliver the β,β-disustituted-
hydroxyamino sulfone 8. Formylation followed by
debenzylation of the phenol would yield 9. Alkylation
using electrophile 10 and unmasking of the hydroxyl would
give 12.

Scheme 2

Compounds of formula I wherein R¹ and R² combine to
form a carbocyclic or heterocyclic ring can be synthesized
according to Scheme 3. α-sulfonyl ester 13 (derived from
4-benzylloxymethyl sulfone using conditions similar to those
reported by Lee and Oh, Bull Korean Chem Soc. 1991, 12(3),
347) can be bis-alkylated using Mitsunobu conditions with
an appropriate diol 14 (for related examples using
Mitsunobu conditions, see: Yu, J. et al. Synlett, 1995, 11,
1127). The ester can then be reduced to aldehyde 16
followed by reductive amination with t-butylhydroxylamine
to afford 17. Formylation and further functionalization
to the appropriate substituents would follow as described previously to give 21.

Scheme 3

\[
\begin{align*}
\text{BnO} & \text{S} & \text{CO}_2\text{Me} \quad \xrightarrow{\text{PPh}_3, \text{DEAD}} \quad \text{BnO} & \text{S} & \text{CO}_2\text{Me} \\
13 & \quad & 14 & \quad & 15 \\
\text{BnO} & \text{S} & \text{ CHO} \quad \xrightarrow{\text{tBuONH}_2, \text{NaBH}_3\text{CN}} \quad \text{BnO} & \text{S} & \text{NHBu} \quad \xrightarrow{\text{AcOCHO, pyr}} \\
16 & \quad & 17 & \quad & 10 \\
\text{BnO} & \text{S} & \text{CHO} \quad \xrightarrow{\text{H}_2, \text{Pd/C}} \quad \text{BnO} & \text{S} & \text{CHO} \quad \xrightarrow{\text{Cl}, \text{CsCO}_3} \\
18 & \quad & 19 & \quad & 20 \\
\text{N} & \text{O} \quad \xrightarrow{\text{TFA}} \quad \text{N} & \text{O} \\
21 & \quad & 22 \\
\text{X} = \text{CH}_2, \text{O}, \text{NBOC}, \text{NH}, \text{N-Alkyl}
\end{align*}
\]

Compounds of formula I wherein R³ and R⁴ are alkyl or hydrogen can be prepared as described in Scheme 4. The β-sulfonyl ester 13 can be mono-alkylated with 22 to give 23 and then converted as previously described to the desired N-formyl-hydroxylamine 24. In addition, the di-alkylated species can be arrived at by further alkylation of 23 with an appropriate alcohol 25 and transformed as previously described to 27.
Compounds of formula I wherein $R^1$ and $R^2$ are alkyl and proton or di-alkyl can be prepared as described in Scheme 5. The sulfone 5 can be condensed with an aldehyde or a ketone 28. Michael addition of t-butyl hydroxylamine and following a similar sequence as described in Scheme 2 the N-formyl-hydroxylamine 31 can be prepared.
Compounds such as 35 (Scheme 6), derived from 32 by Boc protection of the free amine 30, can be alkylated with appropriate electrophiles to give multiply substituted sulfones. The protected amine can be converted to the desired N-formyl hydroxylamine 35 as described previously.

Compounds of formula I wherein \( R^1 \) and \( R^4 \) combine to form a ring can be prepared according to Scheme 7. The \( \beta \)-bromo sulfone 36 can be displaced with 4-hydroxy-
phenylsulfide 37 to give 38. (For syntheses of similar examples, see: Trost, B.M. et al. J. Am. Chem. Soc. 1976, 98, 4887.) Alkylation with 10 and oxidation gives 39. Reductive amination and conversion to the N-hydroxyformamide as described previously gives 42.

**Scheme 7**

![Scheme Diagram]

Compounds of formula I wherein R¹ and R² combine to form a ring (Scheme 8) and Z¹ is benzimidazole and X-Y is CH₂ can be prepared from intermediate 15. Removal of the benzyl group, triflate formation and palladium-catalyzed carbonylation would yield the acid 44. Reduction yields alcohol 45. Bromination and alkylation with an appropriate benzimidazole, in this case 2-methyl-1H-benzimidazole) would yield the methylene linked species 47. This would then be taken on using analogous procedures to Scheme 3.
Alternatively (Scheme 9) the bromide 49 could be alkylated with an appropriate indole (50) to give the N- or the 3-linked variant 51/52 or alkylated with a dihydrobenzothiazine 53 to give 56. These could then be converted to the desired N-hydroxyformamide derivatives 54, 55, 57 as described in Scheme 3.
For systems with \( R^1 \) and \( R^4 \) linked in a ring, \( X-Y \) being \(-\text{CH}_2-\), and \( Z^a \) being a substituted benzimidazole, 1- or 3-linked 2-substituted indole, or \( N \)-linked 4-benzothiazine, the synthesis would use starting material 38 (Scheme 10). Benzyl protection of the phenol followed by oxidation yields the sulfone 58 that is reductively aminated with a O-t-butyldioxymethylamine to give 59. Boc protection followed by hydrogenation yields the phenol 60. Manipulation to the hydroxynmethyl group proceeds as described in Scheme 8.
This can be taken on as described in Scheme 8 to methylene-linked aromatics, in this case the 2-substituted benzimidazole.

Scheme 10

To obtain molecules of formula I in which X-Y is CH₂ and Z₁ is a substituted quinoline (Scheme 11), 45 can be converted via oxidation to aldehyde 63 followed by addition of the lithium anion of 64 to give 65. Mesylation and reduction would give the methylene-linked quinoline 66. Following similar sequences outlined in Scheme 3 the desired N-hydroxyformamide compounds would be achieved. Similarly the compounds like 61 can be converted to the desired methylene linked quinolines 68.
One diastereomer of a compound of formula I may display superior activity compared with the others. Thus, the following stereochemistries are considered to be a part of the present invention.
When required, separation of the racemic material can be achieved by HPLC using a chiral column or by a resolution using a resolving agent such as camphoric chloride as in Wilen, S. H. *Tables of Resolving Agents and Optical Resolutions* 1972, 308 pp or using enantiomerically pure acids and bases. A chiral compound of Formula I may also be directly synthesized using a chiral catalyst or a chiral ligand, e.g., Jacobsen, E. *Acc. Chem. Res.* 2000, 33, 421-431 or using other enantio- and diastereo-selective reactions and reagents known to one skilled in the art of asymmetric synthesis.

Other features of the invention will become apparent in the course of the following descriptions of exemplary embodiments that are given for illustration of the invention and are not intended to be limiting thereof.

EXAMPLES

Abbreviations used in the Examples are defined as follows: "1 x" for once, "2 x" for twice, "3 x" for thrice, "°C" for degrees Celsius, "eq" for equivalent or equivalents, "g" for gram or grams, "mg" for milligram or
milligrams, "mL" for milliliter or milliliters, "µL" for microliter or microliters, "¹H" for proton, "h" for hour or hours, "M" for molar, "min" for minute or minutes, "MHz" for megahertz, "MS" for mass spectroscopy, "NMR" for nuclear magnetic resonance spectroscopy, "rt" for room temperature, "tlc" for thin layer chromatography, "v/v" for volume to volume ratio. "α", "β", "R" and "S" are stereochemical designations familiar to those skilled in the art.

Example 1

\text{Hydroxy}\left[4-\left(4-[(2-methyl-4-quinoliny1)methoxy]phenyl\right)\text{sulfonyl}\right]\text{tetrahydro-2H-pyran-4-yl]methyl\text{formamide}}

(1a) A solution of 4-methylsulfonylphenol (1 eq) in dichloromethane and triethylamine (2 eq) is treated with benzyl bromide (1.1 eq) and stirred at room temperature. The mixture is partitioned between water and dichloromethane. The organic layer is washed with brine, dried (MgSO\textsubscript{4}), filtered and concentrated. Purification on silica gel using standard conditions (Still, W.C. et al. \textit{J. Org. Chem.} 1978, 43, 2923) yields the desired protected phenol.

(1b) A solution of the sulfone (1 eq) from reaction (1a) in tetrahydrofuran is cooled to -30 °C and treated with Lithium diisopropylamide (LDA) (2 eq). The mixture is stirred for 30 min and treated with methyl chloroformate (1.5 eq). The reaction is quenched with saturated aqueous ammonium chloride and extracted with ethyl acetate. The organic layers are washed with brine, dried (MgSO\textsubscript{4}).
filtered and concentrated. Purification on silica gel using standard conditions yields the desired β-sulfonyl ester.

(1c) A solution of triphenylphosphine (4 eq) and diethylene glycol (4 eq) in THF is treated with diethyl azodicarboxylate (4 eq) and stirred at rt. The β-sulfonyl ester (1 eq) from reaction (1b) is added to the reaction and the mixture stirred at rt. The reaction is partitioned between water and ethyl acetate and the aqueous layer extracted with ethyl acetate 2x. The organic layers washed with brine, dried (MgSO₄), filtered, and concentrated. Purification on silica gel using standard conditions yields the substituted ester.

(1d) The ester (1 eq) from reaction (1c) in dichloromethane at -78 °C is treated with diisobutylaluminumhydride (1 eq) and stirred at -78 °C and then quenched by addition of methanol (1 eq) and saturated aqueous Rochelle's salt. After warming to rt and vigorous stirring until the mixture becomes biphasic, the layers are separated and the aqueous layer extracted 2x with dichloromethane. The organic layers are washed with brine, dried (MgSO₄), filtered and concentrated. Purification on silica gel using standard conditions yields the desired aldehyde.

(1e) The aldehyde (1 eq) from reaction (1d), t-butylhydroxylamine (2 eq) and diisopropylethylamine (4 eq) in dichloromethane is treated with sodium cyanoborohydride (2 eq) and stirred at rt. The mixture is partitioned between water and dichloromethane. The organic layer
washed with brine, dried (MgSO$_4$), filtered and concentrated. Purification on silica gel using standard conditions gives the desired amine.

(1f) The amine (1 eq) from reaction (1e) in dichloromethane at 0°C is treated with pyridine (1.5 eq) and formic acetyl anhydride (4 eq). The mixture is quenched with water and extracted with dichloromethane. The organic layers are washed with brine, dried (MgSO$_4$), filtered, and concentrated. Purification on silica gel using standard conditions yields the desired formylamide.

(1g) The amide from reaction (1f) in methanol is treated with 20% palladium hydroxide on carbon (0.1 eq) and shaken under hydrogen atmosphere (50 psi) on a Parr shaking apparatus. The reaction is filtered to remove catalyst and concentrated to give the desired phenol.

(1h) The phenol (1 eq) from reaction (1g) in dimethylsulfoxide is treated with CsCO$_3$ (3g) and 4-chloromethyl-2-methylquinoline (1 eq). Following completion, the reaction is partitioned between water and ethyl acetate. The organic layers are washed with brine, dried (MgSO$_4$), filtered and concentrated. Purification on silica gel using standard conditions yields the desired quinoline.

(1i) The quinoline (1 eq) from reaction (1h) is treated with a solution of dichloromethane/TFA (1/1) and stirred until complete. Concentration, dilution with water, and freeze-drying under high-vacuum gives the desired N-hydroxyformamide.
Example 2

Hydroxy[4-{(4-[(2-methyl-4-quinoliny1)methoxy]phenyl)sulfonyl]tetrahydro-3-furanyl]formamide

(2a) A solution of 4-bromodihydro-3(2H)-furanone (1 eq) (for a synthesis see: Baker, T. J. and Wiemer, D. F. J. Org. Chem. 1998, 63, 2613-2618) in ethanol is treated with 4-hydroxythiophenol (1 eq) and sodium hydroxide (1 eq). After completion, the reaction is neutralized with 1N HCl to pH 7. Following extraction with ethyl acetate and drying with MgSO₄, the reaction is concentrated. Purification on silica gel using standard conditions yields the desired phenol.

(2b) Following conditions similar to reaction (1g), the phenol from reaction (2a) is converted to the desired quinoline sulfide.

(2c) A solution of the sulfide (1 eq) from reaction (2b) in dichloromethane/water (4:1) is treated with Oxone® (3 eq) and stirred at rt. Following partitioning between water and dichloromethane, the organic layers are washed with brine, dried (MgSO₄), filtered and concentrated. Purification on silica gel using standard conditions yields the desired keto-sulfone.

(2d) Following conditions similar to those described in reaction (1e), (1h) and (1f), the keto-sulfone is converted to the desired N-hydroxyformamide.
Example 3

Hydroxy[(4-{(4-{(2-methyl-1H-benzimidazol-1-yl)methyl}phenyl)sulfonyl)tetrahydro-2H-pyran-4-yl}methyl]formamide

5

(3a) The ester from reaction (1c) in methanol is treated with 10% palladium on carbon (0.1 eq) and shaken on a Parr® apparatus under 50 psi of hydrogen for 1 h. The mixture is filtered to remove the catalyst and concentrated to give the desired phenol.

(3b) The phenol from reaction (3a) in dichloromethane is treated with diisopropylethylamine (1.25 eq) and N-phenyltriflamide (1.25 eq) and stirred overnight at rt. The mixture is partitioned between water and dichloromethane, then washed with brine, dried (MgSO₄), filtered and concentrated. Purification on silica gel using standard conditions yields the desired triflate.

20 (3c) The triflate from reaction (3b), palladium (II) acetate (0.1 eq), potassium acetate (5 eq), 1,1'-bis(diphenylphosphino)ferrocene (dppf) (1.2 eq) are combined in DMF and heated to 60 °C under a balloon of carbon monoxide. After several hours the mixture is cooled to rt, diluted with water and extracted with ethyl acetate. The organic layers are washed with water then brine dried (MgSO₄), filtered and concentrated. Purification on silica gel using standard conditions yields the desired acid.

30 (3d) The acid from reaction (3d) in tetrahydrofuran is treated with borane-THF complex (1 M in THF, 5 eq) at 0 °C. The mixture after several hours is quenched with saturated
aqueous NH₄Cl solution then extracted with ethyl acetate. The organic layers are washed with water then brine dried (MgSO₄), filtered and concentrated. Purification on silica gel using standard conditions yields the desired alcohol.

(3e) The alcohol from reaction (3d) in dichloromethane is treated with carbon tetrabromide (1.25 eq) and triphenylphosphine (1.5 eq) and stirred at rt then diluted with water, washed with brine, dried (MgSO₄), filtered and concentrated. Purification on silica gel using standard conditions yields the desired bromide.

(3f) The bromide from reaction (3e) in dimethylsulfoxide is treated with 2-methylbenzimidazole (1.25 eq) and CsCO₃ (3 eq) and heated to 40 ºC. The mixture after several hours is partitioned between ethyl acetate and water, washed with brine, dried (MgSO₄), filtered and concentrated. Purification on silica gel using standard conditions yields the desired product.

(3h) Using procedures analogous to reactions (1d-1f) and (1i), the ester from reaction (3f) is converted to the desired N-hydroxyformamide.

Example 4

Hydroxy[4-((4-{(2-methyl-1H-benzimidazol-1-yl)methyl}phenyl)sulfonyl)tetrahydro-3-furanyl]formamide

(4a) The phenol from reaction (2a) is treated with benzyl bromide (1 eq) in dimethylsulfoxide and CsCO₃ (3 eq). The mixture is stirred at rt for several hours then partitioned
between ethyl acetate and water, washed with brine, dried (MgSO₄), filtered and concentrated. Purification on silica gel using standard conditions yields the desired protected phenol.

(4b) Using procedures analogous to (1e), the ketone from reaction (4a) is converted to the desired amine.

(4c) The amine from reaction (4b) in DMF is treated with di-t-butyldicarbonate (1 eq) and triethylamine (2 eq) and stirred at rt. The mixture partitioned between ethyl acetate and water, washed with brine, dried (MgSO₄), filtered and concentrated. Purification on silica gel using standard conditions yields the desired BOC protected amine.

(4d) Using procedures analogous to reaction (1g), the product from (4c) is converted to the desired phenol.

(4e) Using procedures analogous to those in (3b)-(3d), the phenol from (4d) is converted to the desired alcohol derivative.

(4f) Using procedures analogous to those in (3e)-(3f), the phenol from (4d) is converted to the desired benzimidazole derivative.

(4g) Using analogous procedures to (1h) and (1f), the product from (4f) is converted to the desire N-hydroxyformamide.
Example 5

**Hydroxy\{4-((4-[[2-methyl-4-quinolinyl]methyl]phenyl)sulfonyl)tetrahydro-2H-pyran-4-yl\}methyl\}formamide**

(5a) The alcohol from (3d) in dichloromethane is treated with Dess-Martin reagent and stirred at rt for several hours. The mixture is partitioned between ethyl acetate and water, washed with brine, dried (MgSO₄), filtered and concentrated. Purification on silica gel using standard conditions yields the desired aldehyde.

(5b) A solution of 4-bromo-2-methyl quinoline in THF at -78 °C is treated with t-butyl lithium (2.5 eq) and stirred for 30 min. To this mixture is added the aldehyde from (5a) (1 eq) and the mixture is slowly warmed to 0 °C and quenched with saturated aqueous NH₄Cl solution. The mixture is partitioned between ethyl acetate and water, washed with brine, dried (MgSO₄), filtered and concentrated. Purification on silica gel using standard conditions yields the desired alcohol.

(5c) The alcohol from (5b) in dichloromethane 0 °C is treated with triethyl amine (2 eq) and methanesulfonyl chloride (1.1 eq) and warmed to rt. The mixture is partitioned between ethyl acetate and water, washed with brine, dried (MgSO₄), filtered and concentrated. Purification on silica gel using standard conditions yields the desired mesylate.
(5d) Using procedures analogous to (1d)-(1f) and (1i), the aldehyde from reaction (5c) is converted to the desired N-hydroxyformamide.

Example 6

Hydroxy[4-(((4-[(2-methyl-4-quinolinyl)methyl]phenyl)sulfonyl)tetrahydro-3-furanyl]formamide

(6a) Using analogous procedures to (5a)-(5b) and (1g), the alcohol from (4f) is converted to the desired quinoline.

(6b) Using procedures analogous to (1i) and (1h), the product from (6a) is converted to the desired N-hydroxyformamide.

The following tables contain representative examples of the present invention. Each entry in each table is intended to be paired with each formula at the start of the table. For example, Example 1 is intended to be paired with each of formulae A-AI.

Table 1

![Chemical structures for Table 1]
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Table 2

A

B

C

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**UTILITY**

The compounds of formula I are expected to possess matrix metalloprotease and/or aggrecanase and/or TNF-α inhibitory activity. The MMP inhibitory activity of the compounds of the present invention is demonstrated using assays of MMP activity, for example, using the assay described below for assaying inhibitors of MMP activity. The compounds of the present invention are expected to be bioavailable in vivo as demonstrated, for example, using
the ex vivo assay described below. The compounds of formula I are expected to have the ability to suppress/inhibit cartilage degradation in vivo, for example, as demonstrated using the animal model of acute cartilage degradation described below.

The compounds provided by this invention should also be useful as standards and reagents in determining the ability of a potential pharmaceutical to inhibit MPs. These would be provided in commercial kits comprising a compound of this invention.

Metalloproteinases have also been implicated in the degradation of basement membranes to allow infiltration of cancer cells into the circulation and subsequent penetration into other tissues leading to tumor metastasis (Stetler-Stevenson, Cancer and Metastasis Reviews, 1990, 9, 289-303). The compounds of the present invention should be useful for the prevention and treatment of invasive tumors by inhibition of this aspect of metastasis.

The compounds of the present invention should also have utility for the prevention and treatment of osteopenia associated with matrix metalloprotease-mediated breakdown of cartilage and bone that occurs in osteoporosis patients.

Compounds that inhibit the production or action of TACE, aggrecanase and/or MMP's are potentially useful for the treatment or prophylaxis of various inflammatory, infectious, immunological or malignant diseases or conditions. Thus, the present invention relates to a method of treating various inflammatory, infectious, immunological or malignant diseases. These include acute infection, acute phase response, age related macular degeneration, alcoholic liver disease, allergy, allergic asthma, anorexia, aneurism, aortic aneurism, asthma,
atherosclerosis, atopic dermatitis, autoimmune disease, autoimmune hepatitis, Bechet's disease, cachexia (including cachexia resulting from cancer or HIV), calcium pyrophosphate dihydrate deposition disease, cardiovascular effects, chronic fatigue syndrome, chronic obstruction pulmonary disease, coagulation, congestive heart failure, corneal ulceration, Crohn's disease, enteropathic arthropathy (including inflammatory bowel disease), Felty's syndrome, fever, fibromyalgia syndrome, fibrotic disease, gingivitis, glucocorticoid withdrawal syndrome, gout, graft versus host disease, hemorrhage, HIV infection, hyperoxic alveolar injury, infectious arthritis, inflammation, intermittent hydrarthrosis, Lyme disease, meningitis, multiple sclerosis, myasthenia gravis, mycobacterial infection, neovascular glaucoma, osteoarthritis, pelvic inflammatory disease, periodontitis, polymyositis/dermatomyositis, post-ischaemic reperfusion injury, post-radiation asthenia, psoriasis, psoriatic arthritis, pulmonary emphysema, pyoderma gangrenosum, relapsing polychondritis, Reiter's syndrome, rheumatic fever, rheumatoid arthritis (including juvenile rheumatoid arthritis and adult rheumatoid arthritis), sarcoidosis, scleroderma, sepsis syndrome, Still's disease, shock, Sjogren's syndrome, skin inflammatory diseases, solid tumor growth and tumor invasion by secondary metastases, spondylitis, stroke, systemic lupus erythematosus, ulcerative colitis, uveitis, vasculitis, and Wegener's granulomatosis.

Some compounds of the present invention have been shown to inhibit TNF production in lipopolysacharride stimulated mice, for example, using the assay for TNF
induction in mice and in human whole blood as described below.

Some compounds of the present invention have been shown to inhibit aggrecanase, a key enzyme in cartilage breakdown, as determined by the aggrecanase assay described below.

The compounds of the present invention can be administered alone or in combination with one or more additional anti-inflammatory agents. These agents include, but are not limited to, selective COX-2 inhibitors, interleukin-1 antagonists, dihydroorotate synthase inhibitors, p38 MAP kinase inhibitors, TNF-α inhibitors, and TNF-α sequestration agents.

By "administered in combination" or "combination therapy" it is meant that a compound of the present invention and one or more additional therapeutic agents are administered concurrently to the mammal being treated. When administered in combination each component may be administered at the same time or sequentially in any order at different points in time. Thus, each component may be administered separately but sufficiently closely in time so as to provide the desired therapeutic effect.

The term selective COX-2 inhibitors, as used herein, denotes agents that selectively inhibit COX-2 function. Such agents include, but are not limited to, celecoxib (Celebrex®), rofecoxib (Vioxx®), meloxicam (Movicox®), etoricoxib, and valdecoxib.

TNF-α sequestration agents that may be used in combination with the compounds of this invention, are TNF-α binding proteins or anti-TNF-α antibodies. These agents include, but are not limited to, etanercept (Enbrel®),
infliximab (Remicade®), adalimumab (D2E7), CDP-571 (Humicec®), and CDP-870.

Other anti-inflammatory agents that may be used in combination with the compounds of this invention, include, but are not limited to, methotrexate, interleukin-1 antagonists (e.g., anakinra (Kineret®)), dihydroorotate synthase inhibitors (e.g., leflunomide (Arava®)), and p38 MAP kinase inhibitors.

Administration of the compounds of the present invention (i.e., a first therapeutic agent) in combination with at least one additional therapeutic agent (i.e., a second therapeutic agent), preferably affords an efficacy advantage over the compounds and agents alone, preferably while permitting the use of lower doses of each (i.e., a synergistic combination). A lower dosage minimizes the potential of side effects, thereby providing an increased margin of safety. It is preferred that at least one of the therapeutic agents is administered in a sub-therapeutic dose. It is even more preferred that all of the therapeutic agents be administered in sub-therapeutic doses. Sub-therapeutic is intended to mean an amount of a therapeutic agent that by itself does not give the desired therapeutic effect for the condition or disease being treated. Synergistic combination is intended to mean that the observed effect of the combination is greater than the sum of the individual agents administered alone.

As used herein "μg" denotes microgram, "mg" denotes milligram, "g" denotes gram, "μL" denotes microliter, "mL" denotes milliliter, "L" denotes liter, "nM" denotes nanomolar, "μM" denotes micromolar, "mM" denotes
millimolar, "M" denotes molar and "nm" denotes nanometer. "Sigma stands for the Sigma-Aldrich Corp. of St. Louis, MO.

A compound is considered to be active if it has an IC₅₀ or Kᵢ value of less than about 10 μM for the inhibition of a desired MP. Preferred compounds of the present invention have Kᵢ's or IC₅₀'s of ≤ 1 μM. More preferred compounds of the present invention have Kᵢ's or IC₅₀'s of ≤ 0.1 μM. Even more preferred compounds of the present invention have Kᵢ's or IC₅₀'s of ≤ 0.01 μM. Still more preferred compounds of the present invention have Kᵢ's or IC₅₀'s of ≤ 0.001 μM.

Aggrecanase Enzymatic Assay

A novel enzymatic assay was developed to detect potential inhibitors of aggrecanase. The assay uses active aggrecanase accumulated in media from stimulated bovine nasal cartilage (BNC) or related cartilage sources and purified cartilage aggrecan monomer or a fragment thereof as a substrate.

The substrate concentration, amount of aggrecanases time of incubation and amount of product loaded for Western analysis were optimized for use of this assay in screening putative aggrecanase inhibitors. Aggrecanase is generated by stimulation of cartilage slices with interleukin-1 (IL-1), tumor necrosis factor alpha (TNF-α) or other stimuli. Matrix metalloproteinases (MMPs) are secreted from cartilage in an inactive, zymogen form following stimulation, although active enzymes are present within the matrix. We have shown that following depletion of the extracellular aggrecan matrix, active MMPs are released into the culture media (Tortorella, M.D. et al. Trans.
Ortho. Res. Soc. 1995, 20, 341). Therefore, in order to accumulate BNC aggrecanase in culture media, cartilage is first depleted of endogenous aggrecan by stimulation with 500 mg/ml human recombinant IL-8 for 6 days with media changes every 2 days. Cartilage is then stimulated for an additional 8 days without media change to allow accumulation of soluble, active aggrecanase in the culture media. In order to decrease the amount of other matrix metalloproteinases released into the media during aggrecanase accumulation, agents which inhibit MMP-1, -2, -3, and -9 biosynthesis are included during stimulation. This BNC conditioned media, containing aggrecanase activity is then used as the source of aggrecanase for the assay. Aggrecanase enzymatic activity is detected by monitoring production of aggrecan fragments produced exclusively by cleavage at the Glu373-Ala374 bond within the aggrecan core protein by Western analysis using the monoclonal antibody, BC-3 (Hughes, CE, et al., Biochem J 306:799-804, 1995). This antibody recognizes aggrecan fragments with the N-terminus, 374ARGSVIL, generated upon cleavage by aggrecanase. The BC-3 antibody recognizes this neoepitope only when it is at the N-terminus and not when it is present internally within aggrecan fragments or within the aggrecan protein core. Other proteases produced by cartilage in response to IL-1 do not cleave aggrecan at the Glu373-Ala374 aggrecanase site; therefore, only products produced upon cleavage by aggrecanase are detected. Kinetic studies using this assay yield a Km of 1.5 +/- 0.35 μM for aggrecanase.

To evaluate inhibition of aggrecanase, compounds are prepared as 10 mM stocks in DMSO, water or other solvents and diluted to appropriate concentrations in water. Drug
(50 µL) is added to 50 µL of aggrecanase-containing media and 50 µL of 2 mg/mL aggrecan substrate and brought to a final volume of 200 µL in 0.2 M Tris, pH 7.6, containing 0.4 M NaCl and 40 mM CaCl₂. The assay is run for 4 h at 37 °C, quenched with 20 mM EDTA and analyzed for aggrecanase-generated products. A sample containing enzyme and substrate without drug is included as a positive control and enzyme incubated in the absence of substrate serves as a measure of background.

Removal of the glycosaminoglycan side chains from aggrecan is necessary for the BC-3 antibody to recognize the ARGSVIL epitope on the core protein. Therefore, for analysis of aggrecan fragments generated by cleavage at the Glu373-Ala374 site, proteoglycans and proteoglycan fragments are enzymatically deglycosylated with chondroitinase ABC (0.1 units/10 µg GAG) for 2 h at 37 °C and then with keratanase (0.1 units/10 µg GAG) and keratanase II (0.002 units/10 µg GAG) for 2 h at 37 °C in buffer containing 50 mM sodium acetate, 0.1 M Tris/HCl, pH 6.5. After digestion, aggrecan in the samples is precipitated with 5 volumes of acetone and resuspended in 30 µL of Tris glycine SDS sample buffer (Novex®) containing 2.5% beta mercaptoethanol. Samples are loaded and then separated by SDS-PAGE under reducing conditions with 4-12% gradient gels, transferred to nitrocellulose and immunolocated with 1:500 dilution of antibody BC3. Subsequently, membranes are incubated with a 1:5000 dilution of goat anti-mouse IgG alkaline phosphatase second antibody and aggrecan catabolites visualized by incubation with appropriate substrate for 10-30 minutes to achieve optimal color development. Blots are quantitated by
scanning densitometry and inhibition of aggrecanase determined by comparing the amount of product produced in the presence versus absence of compound.

5 TNF PBMC ASSAY

Human peripheral blood mononuclear cells (PBMC) were obtained from normal donor blood by leukophoresis and isolated by Ficoll-Paque density separation. PBMCs were suspended in .5 mL RPMI 1640 with no serum at 2 x 10^6 cells/mL in 96 well polystyrene plates. Cells were preincubated 10 minutes with compound, then stimulated with 1 µg/mL LPS (Lipopolysaccharide, Salmonella typhimurium) to induce TNF production. After an incubation of 5 h at 37 °C in 95% air, 5% CO₂ environment, culture supernatants were removed and tested by standard sandwich ELISA for TNF production.

TNF Human Whole Blood Assay

Blood is drawn from normal donors into tubes containing 143 USP units of heparin/10 mL. 225 µL of blood is plated directly into sterile polypropylene tubes. Compounds are diluted in DMSO/serum free media and added to the blood samples so the final concentration of compounds are 50, 10, 5, 1, .5, .1, and .01 µM. The final concentration of DMSO does not exceed 0.5%. Compounds are preincubated for 15 min before the addition of 100 mg/mL LPS. Plates are incubated for 5 hours in an atmosphere of 5% CO₂ in air. At the end of 5 h, 750 µL of serum free media is added to each tube and the samples are spun at 1200 RPM for 10 min. The supernatant is collected off the top and assayed for TNF-α production by a standard sandwich
ELISA. The ability of compounds to inhibit TNF-α production by 50% compared to DMSO treated cultures is given by the IC₅₀ value.

5 TNF Induction In Mice

Test compounds are administered to mice either I.P. or P.O. at time zero. Immediately following compound administration, mice receive an I.P. injection of 20 mg of D-galactosamine plus 10 μg of lipopolysaccharide. One hour later, animals are anesthetized and bled by cardiac puncture. Blood plasma is evaluated for TNF levels by an ELISA specific for mouse TNF. Administration of representative compounds of the present invention to mice results in a dose-dependent suppression of plasma TNF levels at one hour in the above assay.

MMP ASSAYS

The enzymatic activities of recombinant MMP-1, 2, 3, 7, 8, 9, 10, 12, 13, 14, 15, and 16 were measured at 25°C with a fluorometric assay (Copeland, R.A. et al. Bioorganic Med. Chem. Lett. 1995, 5, 1947-1952). Final enzyme concentrations in the assay were between 0.05 and 10 nM depending on the enzyme and the potency of the inhibitor tested. The permissive peptide substrate, MCA-Pro-Leu-Gly-Leu-DPA-Ala-Arg-NH₂, was present at a final concentration of 10 μM in all assays. Initial velocities, in the presence or absence of inhibitor, were measured as slopes of the linear portion of the product progress curves. IC₅₀ values were determined by plotting the inhibitor concentration dependence of the fractional velocity for each enzyme, and fitting the data by non-linear least squares methods to the standard isotherm equation.
(Copeland, R.A. Enzymes: A practical Introduction to Structure, Mechanism and Data Analysis, Wiley-VHC, New York, 1996, pp 187-223). All of the compounds studied here were assumed to act as competitive inhibitors of the enzyme, binding to the active site Zn atom as previously demonstrated by crystallographic studies of MMP-3 complexed with related hydroxamic acids (Rockwell, A. et al. J. Am. Chem. Soc. 1996, 118, 10337-10338). Based on the assumption of competitive inhibition, the IC50 values were converted to Ki values as previously described.

Compounds tested in the above assay are considered to be active if they exhibit a Ki of ≤ 10 μM. Preferred compounds of the present invention have Ki’s of ≤ 1 μM. More preferred compounds of the present invention have Ki’s of ≤ 0.1 μM. Even more preferred compounds of the present invention have Ki’s of ≤ 0.01 μM. Still more preferred compounds of the present invention have Ki’s of ≤ 0.001 μM.

Using the methodology described above, a number of compounds of the present invention were found to exhibit Ki’s of ≤ 10 μM, thereby confirming the utility of the compounds of the present invention.

The present invention also encompasses an article of manufacture. As used herein, article of manufacture is intended to include, but not be limited to, kits and packages. The article of manufacture of the present invention, comprises: (a) a first container; (b) a pharmaceutical composition located within the first container, wherein the composition, comprises: a first therapeutic agent, comprising: a compound of the present invention or a pharmaceutically acceptable salt form thereof; and, (c) a package insert stating that the
pharmaceutical composition can be used for the treatment of an inflammatory disorder (as defined previously). In another embodiment, the package insert states that the pharmaceutical composition can be used in combination (as defined previously) with a second therapeutic agent to treat an inflammatory disorder. The article of manufacture can further comprise: (d) a second container, wherein components (a) and (b) are located within the second container and component (c) is located within or outside of the second container. Located within the first and second containers means that the respective container holds the item within its boundaries.

The first container is a receptacle used to hold a pharmaceutical composition. This container can be for manufacturing, storing, shipping, and/or individual/bulk selling. First container is intended to cover a bottle, jar, vial, flask, syringe, tube (e.g., for a cream preparation), or any other container used to manufacture, hold, store, or distribute a pharmaceutical product.

The second container is one used to hold the first container and, optionally, the package insert. Examples of the second container include, but are not limited to, boxes (e.g., cardboard or plastic), crates, cartons, bags (e.g., paper or plastic bags), pouches, and sacks. The package insert can be physically attached to the outside of the first container via tape, glue, staple, or another method of attachment, or it can rest inside the second container without any physical means of attachment to the first container. Alternatively, the package insert is located on the outside of the second container. When located on the outside of the second container, it is preferable that the package insert is physically attached via tape, glue,
staple, or another method of attachment. Alternatively, it can be adjacent to or touching the outside of the second container without being physically attached.

The package insert is a label, tag, marker, etc. that recites information relating to the pharmaceutical composition located within the first container. The information recited will usually be determined by the regulatory agency governing the area in which the article of manufacture is to be sold (e.g., the United States Food and Drug Administration). Preferably, the package insert specifically recites the indications for which the pharmaceutical composition has been approved. The package insert may be made of any material on which a person can read information contained therein or thereon. Preferably, the package insert is a printable material (e.g., paper, plastic, cardboard, foil, adhesive-backed paper or plastic, etc.) on which the desired information has been formed (e.g., printed or applied).

Dosage and Formulation

The compounds of the present invention can be administered orally using any pharmaceutically acceptable dosage form known in the art for such administration. The active ingredient can be supplied in solid dosage forms such as dry powders, granules, tablets or capsules, or in liquid dosage forms, such as syrups or aqueous suspensions. The active ingredient can be administered alone, but is generally administered with a pharmaceutical carrier. A valuable treatise with respect to pharmaceutical dosage forms is Remington's Pharmaceutical Sciences, Mack Publishing.
The compounds of the present invention can be administered in such oral dosage forms as tablets, capsules (each of which includes sustained release or timed release formulations), pills, powders, granules, elixirs, tinctures, suspensions, syrups, and emulsions. Likewise, they may also be administered in intravenous (bolus or infusion), intraperitoneal, subcutaneous, or intramuscular form, all using dosage forms well known to those of ordinary skill in the pharmaceutical arts. An effective but non-toxic amount of the compound desired can be employed as an antiinflammatory and antiarthritic agent.

The compounds of this invention can be administered by any means that produces contact of the active agent with the agent's site of action in the body of a mammal. They can be administered by any conventional means available for use in conjunction with pharmaceuticals, either as individual therapeutic agents or in a combination of therapeutic agents. They can be administered alone, but generally administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

The dosage regimen for the compounds of the present invention will, of course, vary depending upon known factors, such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration; the species, age, sex, health, medical condition, and weight of the recipient; the nature and extent of the symptoms; the kind of concurrent treatment; the frequency of treatment; the route of administration, the renal and hepatic function of the patient, and the effect desired. An ordinarily skilled physician or veterinarian can readily determine and prescribe the effective amount of the drug
required to prevent, counter, or arrest the progress of the condition.

By way of general guidance, the daily oral dosage of each active ingredient, when used for the indicated effects, will range between about 0.001 to 1000 mg/kg of body weight, preferably between about 0.01 to 100 mg/kg of body weight per day, and most preferably between about 1.0 to 20 mg/kg/day. For a normal male adult human of approximately 70 kg of body weight, this translates into a dosage of 70 to 1400 mg/day. Intravenously, the most preferred doses will range from about 1 to about 10 mg/kg/min during a constant rate infusion. Advantageously, compounds of the present invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three, or four times daily.

The compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

In the methods of the present invention, the compounds herein described in detail can form the active ingredient, and are typically administered in admixture with suitable pharmaceutical diluents, excipients, or carriers (collectively referred to herein as carrier materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs,
syrups and the like, and consistent with conventional pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch, sucrose, glucose, methyl cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like; for oral administration in liquid form, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents, and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth, or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum, and the like.

The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine, or phosphatidylcholines.

Compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such
polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues.

Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoclylates, and crosslinked or amphipathic block copolymers of hydrogels.

Dosage forms (pharmaceutical compositions) suitable for administration may contain from about 1 mg to about 100 mg of active ingredient per dosage unit. In these pharmaceutical compositions the active ingredient will ordinarily be present in an amount of about 0.5-95% by weight based on the total weight of the composition.

The active ingredient can be administered orally in solid dosage forms, such as capsules, tablets, and powders, or in liquid dosage forms, such as elixirs, syrups, and suspensions. It can also be administered parenterally, in sterile liquid dosage forms.

Gelatin capsules may contain the active ingredient and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the
atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance. In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, are suitable stabilizing agents. Also used are citric acid and its salts and sodium EDTA. In addition, parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl- or propyl-paraben, and chlorobutanol.

Suitable pharmaceutical carriers are described in Remington's Pharmaceutical Sciences, Mack Publishing Company, a standard reference text in this field.

The compounds of the present invention may be administered in combination with a second therapeutic agent, especially non-steroidal anti-inflammatory drugs (NSAID's). The compound of Formula I and such second therapeutic agent can be administered separately or as a physical combination in a single dosage unit, in any dosage form and by various routes of administration, as described above.

The compound of Formula I may be formulated together with the second therapeutic agent in a single dosage unit (that is, combined together in one capsule, tablet, powder, or liquid, etc.). When the compound of Formula I and the
second therapeutic agent are not formulated together in a single dosage unit, the compound of Formula I and the second therapeutic agent may be administered essentially at the same time, or in any order; for example the compound of Formula I may be administered first, followed by administration of the second agent. When not administered at the same time, preferably the administration of the compound of Formula I and the second therapeutic agent occurs less than about one hour apart, more preferably less than about 5 to 30 minutes apart.

Preferably the route of administration of the compound of Formula I is oral. Although it is preferable that the compound of Formula I and the second therapeutic agent are both administered by the same route (that is, for example, both orally), if desired, they may each be administered by different routes and in different dosage forms (that is, for example, one component of the combination product may be administered orally, and another component may be administered intravenously).

The dosage of the compound of Formula I when administered alone or in combination with a second therapeutic agent may vary depending upon various factors such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration, the age, health and weight of the recipient, the nature and extent of the symptoms, the kind of concurrent treatment, the frequency of treatment, and the effect desired, as described above.

Particularly when provided as a single dosage unit, the potential exists for a chemical interaction between the combined active ingredients. For this reason, when the compound of Formula I and a second therapeutic agent are
combined in a single dosage unit they are formulated such that although the active ingredients are combined in a single dosage unit, the physical contact between the active ingredients is minimized (that is, reduced). For example, one active ingredient may be enteric coated. By enteric coating one of the active ingredients, it is possible not only to minimize the contact between the combined active ingredients, but also, it is possible to control the release of one of these components in the gastrointestinal tract such that one of these components is not released in the stomach but rather is released in the intestines. One of the active ingredients may also be coated with a sustained-release material which effects a sustained-release throughout the gastrointestinal tract and also serves to minimize physical contact between the combined active ingredients. Furthermore, the sustained-released component can be additionally enteric coated such that the release of this component occurs only in the intestine. Still another approach would involve the formulation of a combination product in which the one component is coated with a sustained and/or enteric release polymer, and the other component is also coated with a polymer such as a low viscosity grade of hydroxypropyl methylcellulose (HPMC) or other appropriate materials as known in the art, in order to further separate the active components. The polymer coating serves to form an additional barrier to interaction with the other component.

These as well as other ways of minimizing contact between the components of combination products of the present invention, whether administered in a single dosage form or administered in separate forms but at the same time
by the same manner, will be readily apparent to those skilled in the art, once armed with the present disclosure.

The present invention also includes pharmaceutical kits useful, for example, in the treatment or prevention of osteoarthritis or rheumatoid arthritis, which comprise one or more containers containing a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I. Such kits may further include, if desired, one or more of various conventional pharmaceutical kit components, such as, for example, containers with one or more pharmaceutically acceptable carriers, additional containers, etc., as will be readily apparent to those skilled in the art. Instructions, either as inserts or as labels, indicating quantities of the components to be administered, guidelines for administration, and/or guidelines for mixing the components, may also be included in the kit.

In the present disclosure it should be understood that the specified materials and conditions are important in practicing the invention but that unspecified materials and conditions are not excluded so long as they do not prevent the benefits of the invention from being realized.

Although this invention has been described with respect to specific embodiments, the details of these embodiments are not to be construed as limitations. Various equivalents, changes and modifications may be made without departing from the spirit and scope of this invention, and it is understood that such equivalent embodiments are part of this invention.
WHAT IS CLAIMED IS:

1. A compound of formula I:

\[
\begin{align*}
&\text{R}^1 \text{ is selected from: } H, \text{ C}_{1-6} \text{ alkyl substituted with } 0-1 \text{ R}^b, \\
&\text{C}_{2-6} \text{ alkenyl substituted with } 0-1 \text{ R}^b, \text{ and } \text{C}_{2-6} \text{ alkynyl substituted with } 0-1 \text{ R}^b; \\
&\text{R}^2 \text{ is selected from: } Q, \text{ C}_{1-6} \text{ alkyne-Q,} \\
&\text{C}_{2-6} \text{ alkenylene-Q, } \text{C}_{2-6} \text{ alkylnylene-Q,} \\
&-(\text{CR}^{\text{aral}})_{r1}\text{O}(\text{CR}^{\text{aral}})_{r-Q}, \\
&-(\text{CR}^{\text{aral}})_{r1}\text{NR}^{\text{aral}}(\text{CR}^{\text{aral}})_{r-Q}, -(\text{CR}^{\text{aral}})_{r1}\text{C(O)(CR}^{\text{aral}})_{r-Q}, \\
&-(\text{CR}^{\text{aral}})_{r1}\text{C(O)}\text{O(CR}^{\text{aral}})_{r-Q}, -(\text{CR}^{\text{aral}})_{r1}\text{OC(O)(CR}^{\text{aral}})_{r-Q}, \\
&-(\text{CR}^{\text{aral}})_{r1}\text{C(O)NR}^{\text{aral}}, -(\text{CR}^{\text{aral}})_{r1}\text{C(O)NR}^{\text{aral}}(\text{CR}^{\text{aral}})_{r-Q}, \\
&-(\text{CR}^{\text{aral}})_{r1}\text{NR}^{\text{aral}}\text{C(O)(CR}^{\text{aral}})_{r-Q}, \\
&-(\text{CR}^{\text{aral}})_{r1}\text{OC(O)}\text{O(CR}^{\text{aral}})_{r-Q}, \\
&-(\text{CR}^{\text{aral}})_{r1}\text{OC(O)NR}^{\text{aral}}(\text{CR}^{\text{aral}})_{r-Q}, \\
&-(\text{CR}^{\text{aral}})_{r1}\text{NR}^{\text{aral}}\text{C(O)O(CR}^{\text{aral}})_{r-Q}, \\
&-(\text{CR}^{\text{aral}})_{r1}\text{NR}^{\text{aral}}\text{C(O)NR}^{\text{aral}}(\text{CR}^{\text{aral}})_{r-Q}, \\
&-(\text{CR}^{\text{aral}})_{r1}\text{S(O)P(CR}^{\text{aral}})_{r-Q}, \\
&-(\text{CR}^{\text{aral}})_{r1}\text{SO}_{2}\text{NR}^{\text{aral}}(\text{CR}^{\text{aral}})_{r-Q}, \\
&-(\text{CR}^{\text{aral}})_{r1}\text{NR}^{\text{aral}}\text{SO}_{2}(\text{CR}^{\text{aral}})_{r-Q}, \text{ and} \\
&-(\text{CR}^{\text{aral}})_{r1}\text{NR}^{\text{aral}}\text{SO}_{2}\text{NR}^{\text{aral}}(\text{CR}^{\text{aral}})_{r-Q};
\end{align*}
\]
Q, at each occurrence, is independently selected from: H, a
C_{3-13} carbocycle substituted with 0-5 R^d, and a 4-14
membered heterocycle consisting of carbon atoms and
1-4 heteroatoms selected from the group consisting of
N, O, and S(O)_{P}, and substituted with 0-5 R^d;

R^3 is selected from: Q^1, -C_{1-6} alkyne-Q^1,
-C_{2-6} alkenylene-Q^1, -C_{2-6} alkynylene-Q^1,
-(CR^aR^a)_{\gamma}O(CH_2)_\gamma-Q^1, -(CR^aR^a)_{\gamma}NR^a(CR^aR^a)_{\gamma}-Q^1,
-(CR^aR^a)_{\gamma}NR^aC(O)(CR^aR^a)_{\gamma}-Q^1,
-(CR^aR^a)_{\gamma}C(O)NR^a(CR^aR^a)_{\gamma}-Q^1,
-(CR^aR^a)_{\gamma}C(O)(CR^aR^a)_{\gamma}-Q^1,
-(CR^aR^a)_{\gamma}C(O)O(CR^aR^a)_{\gamma}-Q^1,
-(CR^aR^a)_{\gamma}SO_{2}NR^a(CR^aR^a)_{\gamma}-Q^1;

Q^1, at each occurrence, is independently selected from: H, a
C_{3-13} carbocycle substituted with 0-5 R^d, and a 5-14
membered heterocycle consisting of carbon atoms and
1-4 heteroatoms selected from the group consisting of
N, O, and S(O)_{P}, and substituted with 0-5 R^d;

R^4 is selected from: H, C_{1-6} alkyl substituted with 0-1 R^b,
C_{2-6} alkenyl substituted with 0-1 R^b, and C_{2-6} alkynyl
substituted with 0-1 R^b;

alternatively, R^3 and R^4 together with the carbon atom to
which they are attached combine to form a 3-10
membered carbocyclic or heterocyclic ring consisting
of carbon atoms and 0-2 ring heteroatoms selected from 0, N, NR$^{10}$, and S(O)$_p$, and substituted with 0-3 R$^c$;

R$^5$ is selected from: H, and C$_{1-4}$ alkyl;

R$^{10}$, at each occurrence, is independently selected from: H, C$_{1-6}$ alkyl substituted with 0-2 R$^c$, C$_{2-6}$ alkenyl substituted with 0-2 R$^c$, C$_{2-6}$ alkynyl substituted with 0-2 R$^c$, -(CR$^{aRa1}$)$_s$NR$^{aRa1}$, -(CR$^{aRa1}$)$_r$C(O)NR$^a$OH,

- (CR$^{aRa1}$)$_r$C(O)Ra$^1$, - (CR$^{aRa1}$)$_r$C(O)OR$^a$,

- (CR$^{aRa1}$)$_r$C(S)OR$^a$, - (CR$^{aRa1}$)$_r$C(O)NR$^{aRa1}$,

- (CR$^{aRa1}$)$_s$NR$^{aC}(O)Ra$, - (CR$^{aRa1}$)$_r$C(S)NR$^{aRa1}$,

- (CR$^{aRa1}$)$_s$OC(O)NR$^{aRa1}$, - (CR$^{aRa1}$)$_s$NR$^{aC}(O)OR$^a$,

- (CR$^{aRa1}$)$_s$NR$^{aC}(O)NR$^{aRa1}$, - (CR$^{aRa1}$)$_r$S(O)$_p$Ra$^3$,

- (CR$^{aRa1}$)$_r$SO$_2$NR$^{aRa1}$, - (CR$^{aRa1}$)$_s$NR$^{aSO}_2$Ra$^3$,

- (CR$^{aRa1}$)$_s$NR$^{aSO}_2$NR$^{aRa1}$, - (CR$^{aRa1}$)$_r$-C$_{3-10}$ carbocycle substituted with 0-2 R$^c$, and -(CR$^{aRa1}$)$_r$-5-14 membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)$_p$, and substituted with 0-2 R$^c$;

X-Y is CH$_2$, CH$_2$O or OCH$_2$;

Z is selected from: a C$_{6-10}$ aryl substituted with 0-5 R$^b$, and a 5-14 membered heteroaryl consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)$_p$, and substituted with 0-5 R$^b$;

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provided that X, Y, and Z do not combine to form a N-O,
0-O, or S(O)\textsubscript{p}-O, group;

Z\textsuperscript{a} is substituted with 0-5 R\textsuperscript{c} and is a 8-14 membered
5 heterocycle consisting of carbon atoms, 1-3 N atoms,
and 0-1 heteroatom selected from the group consisting
of O, and S(O)\textsubscript{p};

R\textsuperscript{a}, at each occurrence, is independently selected from: H,
10 C\textsubscript{1-6} alkyl, phenyl, and benzyl;

R\textsuperscript{a1}, at each occurrence, is independently selected from: H,
C\textsubscript{1-6} alkyl substituted with 0-1 R\textsuperscript{e}, C\textsubscript{2-6} alkenyl
substituted with 0-1 R\textsuperscript{e}, C\textsubscript{2-6} alkynyl substituted with
15 0-1 R\textsuperscript{e}, and -(CH\textsubscript{2})\textsubscript{1-3} membered carbocyclic or
heterocyclic ring consisting of carbon atoms and 0-2
ring heteroatoms selected from N, NR\textsuperscript{a2}, O, and S(O)\textsubscript{p},
and substituted with 0-3 R\textsuperscript{e};

20 alternatively, R\textsuperscript{a} and R\textsuperscript{a1} when attached to a nitrogen are
taken together with the nitrogen to which they are
attached form a 5 or 6 membered heterocycle consisting
of carbon atoms and 0-1 additional heteroatoms
selected from N, NR\textsuperscript{a2}, O, and S(O)\textsubscript{p};

25 R\textsuperscript{a2}, at each occurrence, is independently selected from:
C\textsubscript{1-4} alkyl, phenyl, and benzyl;

R\textsuperscript{a3}, at each occurrence, is independently selected from: H,
30 C\textsubscript{1-6} alkyl substituted with 0-1 R\textsuperscript{c1}, C\textsubscript{2-6} alkenyl
substituted with 0-1 R\textsuperscript{c1}, C\textsubscript{2-6} alkynyl substituted with
0-1 R^c_1, and -(CH_2)_r-3-8 membered carbocyclic or heterocyclic ring consisting of carbon atoms and 0-2 ring heteroatoms selected from N, NR^2a, O, and S(O)p, and substituted with 0-3 R^c_1;

R^b, at each occurrence, is independently selected from:
C_1-6 alkyl substituted with 0-1 R^c_1, -OR^a, Cl, F, Br, I, =O, -CN, NO_2, -NR^aR^a_1, -C(O)R^a, -C(O)OR^a,
-C(O)NR^aR^a_1, -C(S)NR^aR^a_1, -NR^aC(O)NR^aR^a_1, -OC(O)NR^aR^a_1,
-NR^aC(O)OR^a, -S(O)_2NR^aR^a_1, -NR^aS(O)_2R^a_3,
-NR^aS(O)_2NR^aR^a_1, -OS(O)_2NR^aR^a_1, -NR^aS(O)_2R^a_3, -S(O)pR^a_3,
CF_3, -CF_2CF_3, -CHF_2, -CH_2F, and phenyl;

R^c, at each occurrence, is independently selected from: H, C_1-6 alkyl substituted with 0-2 R^c_1, C_2-6 alkenyl substituted with 0-2 R^c_1, C_2-6 alkynyl substituted with 0-2 R^c_1, -OR^a, Cl, F, Br, I, =O, -CN, NO_2, CF_3, -OCF_3,
-CF_2CF_3, -CH_2F, -CHF_2, -(CR^aR^a_1)_r_1NR^aR^a_1,
-(CR^aR^a_1)_r_1C(=NCN)NR^aR^a_1, -(CR^aR^a_1)_r_1C(=NR^a)NR^aR^a_1,
-(CR^aR^a_1)_r_1C(=NOR^a)NR^aR^a_1, -(CR^aR^a_1)_r_1C(O)NR^aOH,
-(CR^aR^a_1)_r_1C(O)R^a_1, -(CR^aR^a_1)_r_1C(O)OR^a_1,
-(CR^aR^a_1)_r_1C(S)OR^a_1, -(CR^aR^a_1)_r_1C(O)NR^aR^a_1,
-(CR^aR^a_1)_r_1NRC(O)R^a_1, -(CR^aR^a_1)_r_1C(S)NR^aR^a_1,
-(CR^aR^a_1)_r_1OC(O)NR^aR^a_1, -(CR^aR^a_1)_r_1NRC(O)OR^a_1,
-(CR^aR^a_1)_r_1NRC(O)NR^aR^a_1, -(CR^aR^a_1)_r_1S(O)pR^a_3,
-(CR^aR^a_1)_r_1SO_2NR^aR^a_1, -(CR^aR^a_1)_r_1NRSO_2R^a_3,
-(CR^aR^a_1)_r_1NRSO_2NR^aR^a_1, -(CR^aR^a_1)_r_1-C_3-10 carbocycle substituted with 0-2 R^c_1, and -(CR^aR^a_1)_r_1-5-14 membered heterocycle consisting of carbon atoms and 1-4
heteroatoms selected from the group consisting of N, O, and S(O)₂, and substituted with 0-2 \( R^{c1} \);

alternatively, when two \( R^{c} \) groups are attached to the same carbon atom they form a spiro ring C that is a 3-11 membered carbocycle substituted with 0-2 \( R^{c1} \) or a 3-13 membered heterocycle consisting of: carbon atoms, 0-3 carbonyl groups, 0-4 double bonds, and from 1-5 ring heteroatoms selected from O, N, and S(O)₂, and substituted with 0-2 \( R^{c1} \), provided that ring C contains other than a S-S, O-O, or S-O bond;

alternatively, when two \( R^{c} \) groups are attached to adjacent carbon atoms, together with the carbon atoms to which they are attached they form a 5-7 membered carbocyclic or heterocyclic ring consisting of: carbon atoms, 0-2 heteroatoms selected from the group consisting of N, O, and S(O)₂, and 0-3 double bonds, and substituted with 0-2 \( R^{c1} \);

\( R^{c1} \), at each occurrence, is independently selected from: H, C₁₋₆ alkyl, -OR⁺, Cl, F, Br, I, =O, =CN, NO₂, -NR⁺⁺R⁺⁺⁺, -C(O)R⁺, -C(O)OR⁺, -C(O)NR⁺⁺R⁺⁺⁺, -NR⁺⁺⁺C(O)NR⁺⁺⁺R⁺⁺⁺, -OC(O)NR⁺⁺⁺R⁺⁺⁺, -NR⁺⁺⁺⁺C(O)OR⁺⁺⁺⁺, -S(O)₂NR⁺⁺⁺⁺R⁺⁺⁺⁺, -NR⁺⁺⁺⁺⁺S(O)₂R⁺⁺⁺⁺++, -NR⁺⁺⁺⁺⁺⁺S(O)₂R⁺⁺⁺⁺⁺⁺, -OS(O)₂NR⁺⁺⁺⁺R⁺⁺⁺⁺++, -NR⁺⁺⁺⁺⁺⁺⁺S(O)₂R⁺⁺⁺⁺⁺⁺⁺, -S(O)₂R⁺⁺⁺⁺++, CF₃, -CCF₃, -CF₂CF₃, -CH₂F, and -CHF₂;

\( R^{d} \), at each occurrence, is independently selected from: C₁₋₆ alkyl, -OR⁺, Cl, F, Br, I, =O, =CN, NO₂, -NR⁺⁺R⁺⁺⁺, -C(O)R⁺, -C(O)OR⁺, -C(O)NR⁺⁺R⁺⁺⁺, -C(S)NR⁺⁺⁺R⁺⁺⁺, -NR⁺⁺⁺⁺C(O)NR⁺⁺⁺⁺R⁺⁺⁺⁺, -OC(O)NR⁺⁺⁺⁺R⁺⁺⁺⁺, -NR⁺⁺⁺⁺⁺⁺C(O)OR⁺⁺⁺⁺⁺⁺;
-S(O)\_2NR^aR^a, -NR^aS(O)\_2R^a, -NR^aS(O)\_2NR^aR^a,
-OS(O)\_2NR^aR^a, -NR^aS(O)\_2R^a, -S(O)\_pR^a, CF\_3, -CF\_2CF\_3,
C\_3-10 carbocycle, and a 5-14 membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)\_p;

R^e, at each occurrence, is independently selected from: H, C\_1-6 alkyl, -OR^a, Cl, F, Br, I, =O, -CN, NO\_2, -NR^aR^a,
-C(O)R^a, -C(O)OR^a, -C(O)NR^aR^a, -NR^aC(O)NR^aR^a,
-OC(O)NR^aR^a, -NR^aC(O)OR^a, -S(O)\_2NR^aR^a, -NR^aS(O)\_2R^a,
-NR^aS(O)\_2NR^aR^a, -OS(O)\_2NR^aR^a, -NR^aS(O)\_2R^a, -S(O)\_pR^a,
CF\_3, -OCF\_3, -CF\_2CF\_3, -CH\_2F, and -CHF\_2;

p, at each occurrence, is selected from 0, 1, and 2;

r, at each occurrence, is selected from 0, 1, 2, 3, and 4;

r1, at each occurrence, is selected from 0, 1, 2, 3, and 4; and,

s, at each occurrence, is selected from 1, 2, 3, and 4.

2. A compound according to Claim 1, wherein;

Z^a is substituted with 0-4 R^c and is selected from the group:
W is S, SO, SO₂, O, or NR¹¹;

R¹¹, at each occurrence, is independently selected from: H, C₁₋₄ alkyl, phenyl, and benzyl;

R², at each occurrence, is independently selected from: H, C₁₋₆ alkyl substituted with 0-2 R¹₁, C₂₋₆ alkenyl substituted with 0-2 R¹₂, -OR¹, Cl, F, Br, I, =O, -CN, NO₂, CF₃, -OCF₃, -CF₂CF₃, -CH₂F, -CHF₂, -(CR₃R₄R₅)¹₁NR₆R₇, -(CR₃R₄R₅)¹₁C(O)R₆, -(CR₃R₄R₅)¹₁C(O)OR₆, -(CR₃R₄R₅)¹₁C(O)NR₆R₇, -(CR₃R₄R₅)¹₁NR₆C(O)R₇, -(CR₃R₄R₅)¹₁S(O)₃R₆, -(CR₃R₄R₅)¹₁SO₂NR₆R₇, -(CR₃R₄R₅)¹₁NR₆SO₃R₆, -(CR₃R₄R₅)¹₁-C₃₋₁₀ carbocycle substituted with 0-2 R¹₂, and -(CR₃R₄R₅)¹₁-5-14 membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)₃, and substituted with 0-2 R¹₂;

alternatively, when two R² groups are attached to the same carbon atom they form a spiro ring C that is a 3-11 membered carbocycle substituted with 0-2 R¹₂ or a 3-13 membered heterocycle consisting of: carbon atoms, 0-3
carbonyl groups, 0-4 double bonds, and from 1-5 ring heteroatoms selected from O, N, and S(O)p, and substituted with 0-2 Rc1, provided that ring C contains other than a S-S, O-O, or S-O bond; and,

alternatively, when two Rc groups are attached to adjacent carbon atoms, together with the carbon atoms to which they are attached they form a 5-7 membered carbocyclic or heterocyclic ring consisting of: carbon atoms, 0-2 heteroatoms selected from the group consisting of N, O, and S(O)p, and 0-3 double bonds, and substituted with 0-2 Rc1.

3. A compound according to Claim 2, wherein;

R1 is selected from: H and C1-6 alkyl;

R2 is selected from: Q, -C1-6 alkylene-Q,
-C2-6 alkenylene-Q, -C2-6 alkylnylene-Q,
-(CRaRb)1O(CRaRb)x-Q,
-(CRaRb)x1NRa(CRaRb)x-Q, -(CRaRb)x1C(O)(CRaRb)x-Q,
-(CRaRb)x1C(O)O(CRaRb)x-Q, -(CRaRb)x1C(O)NRaRb,
-(CRaRb)x1C(O)NRa(CRaRb)x-Q,
-(CRaRb)x1S(O)p(CRaRb)x-Q,
-(CRaRb)x1SO2NRa(CRaRb)x-Q, and
-(CRaRb)x1NRaSO2(CRaRb)x-Q;

Q, at each occurrence, is independently selected from: H, a C3-10 carbocycle substituted with 0-5 Rd, and a 5-10 membered heterocycle consisting of carbon atoms and
1-4 heteroatoms selected from the group consisting of 
N, O, and S(O)\textsubscript{p}, and substituted with 0-5 R\textsuperscript{d};

R\textsuperscript{3} is selected from: Q\textsuperscript{1}, -C\textsubscript{1-6} alkylenec-\textsuperscript{Q},
-C\textsubscript{2-6} alkenylene-\textsuperscript{Q}, -C\textsubscript{2-6} alkynylene-\textsuperscript{Q},
-(CR\textsuperscript{a}R\textsuperscript{al})\textsubscript{r1}O(CH\textsubscript{2})\textsubscript{r}-Q\textsuperscript{1}, -(CR\textsuperscript{a}R\textsuperscript{al})\textsubscript{r1}NR\textsuperscript{a}(CR\textsuperscript{a}R\textsuperscript{al})\textsubscript{r}-Q\textsuperscript{1},
-(CR\textsuperscript{a}R\textsuperscript{al})\textsubscript{r1}NR\textsuperscript{a}C(O) (CR\textsuperscript{a}R\textsuperscript{al})\textsubscript{r}-Q\textsuperscript{1},
-(CR\textsuperscript{a}R\textsuperscript{al})\textsubscript{r1}C(O) NR\textsuperscript{a}(CR\textsuperscript{a}R\textsuperscript{al})\textsubscript{r}-Q\textsuperscript{1},
-(CR\textsuperscript{a}R\textsuperscript{al})\textsubscript{r1}C(O) (CR\textsuperscript{a}R\textsuperscript{al})\textsubscript{r}-Q\textsuperscript{1},
-(CR\textsuperscript{a}R\textsuperscript{al})\textsubscript{r1}C(O) O (CR\textsuperscript{a}R\textsuperscript{al})\textsubscript{r}-Q\textsuperscript{1},
-(CR\textsuperscript{a}R\textsuperscript{al})\textsubscript{r1}S(O)\textsubscript{p} (CR\textsuperscript{a}R\textsuperscript{al})\textsubscript{r}-Q\textsuperscript{1}, and
-(CR\textsuperscript{a}R\textsuperscript{al})\textsubscript{r1}SO\textsubscript{2}NR\textsuperscript{a}(CR\textsuperscript{a}R\textsuperscript{al})\textsubscript{r}-Q\textsuperscript{1};

Q\textsuperscript{1}, at each occurrence, is independently selected from: H,
a C\textsubscript{3-10} carbocycle substituted with 0-5 R\textsuperscript{d}, and a 5-10
membered heterocycle consisting of carbon atoms and
1-4 heteroatoms selected from the group consisting of
N, O, and S(O)\textsubscript{p}, and substituted with 0-5 R\textsuperscript{d};

R\textsuperscript{4} is selected from: H, C\textsubscript{1-6} alkyl substituted with 0-1 R\textsuperscript{b},
C\textsubscript{2-6} alkenyl substituted with 0-1 R\textsuperscript{b}, and C\textsubscript{2-6} alkynyl
substituted with 0-1 R\textsuperscript{b};

alternatively, R\textsuperscript{3} and R\textsuperscript{4} together with the carbon atom to
which they are attached combine to form a 3-8 membered
carbocyclic or heterocyclic ring consisting of carbon
atoms and 0-2 ring heteroatoms selected from O, N,
NR\textsuperscript{10}, and S(O)\textsubscript{p}, and substituted with 0-3 R\textsuperscript{c};
R\textsuperscript{10}, at each occurrence, is independently selected from: H, C\textsubscript{1-6} alkyl substituted with 0-2 R\textsuperscript{C1}, C\textsubscript{2-6} alkenyl substituted with 0-2 R\textsuperscript{C1}, C\textsubscript{2-6} alkynyl substituted with 0-2 R\textsuperscript{C1}, -\text{(CR\textsuperscript{a}Ra\textsuperscript{1})\textsubscript{1}C(O)Ra\textsuperscript{1}}, -(CR\textsuperscript{a}Ra\textsuperscript{1})\textsubscript{1}C(O)ORa\textsuperscript{1}, -(CR\textsuperscript{a}Ra\textsuperscript{1})\textsubscript{1}C(O)NRa\textsuperscript{a}Ra\textsuperscript{1}, -(CR\textsuperscript{a}Ra\textsuperscript{1})\textsubscript{1}C(O)NRa\textsuperscript{a}Ra\textsuperscript{1}, -(CR\textsuperscript{a}Ra\textsuperscript{1})\textsubscript{1}S(O)\textsubscript{p}Ra\textsuperscript{3}, -(CR\textsuperscript{a}Ra\textsuperscript{1})\textsubscript{1}SO\textsubscript{2}NRa\textsuperscript{a}Ra\textsuperscript{1}, -(CR\textsuperscript{a}Ra\textsuperscript{1})\textsubscript{1}SO\textsubscript{2}NRa\textsuperscript{a}Ra\textsuperscript{1}, -(CR\textsuperscript{a}Ra\textsuperscript{1})\textsubscript{1}NR\textsubscript{a}Ra\textsuperscript{1}, -(CR\textsuperscript{a}Ra\textsuperscript{1})\textsubscript{1}NR\textsubscript{a}Ra\textsuperscript{1}, -(CR\textsuperscript{a}Ra\textsuperscript{1})\textsubscript{1}NR\textsubscript{a}Ra\textsuperscript{1}, -(CR\textsuperscript{a}Ra\textsuperscript{1})\textsubscript{1}NR\textsubscript{a}Ra\textsuperscript{1}, -(CR\textsuperscript{a}Ra\textsuperscript{1})\textsubscript{1}NR\textsubscript{a}Ra\textsuperscript{1}, -(CR\textsuperscript{a}Ra\textsuperscript{1})\textsubscript{1}NR\textsubscript{a}Ra\textsuperscript{1}, -(CR\textsuperscript{a}Ra\textsuperscript{1})_\text{C}\textsubscript{3-10} carbocycle substituted with 0-2 R\textsuperscript{C1}, and -(CR\textsuperscript{a}Ra\textsuperscript{1})_\text{C}\textsubscript{1-5-14} membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)\textsubscript{p}, and substituted with 0-2 R\textsuperscript{C1};

R\textsuperscript{C}, at each occurrence, is independently selected from: H, C\textsubscript{1-6} alkyl substituted with 0-2 R\textsuperscript{C1}, C\textsubscript{2-6} alkenyl substituted with 0-2 R\textsuperscript{C1}, C\textsubscript{2-6} alkynyl substituted with 0-2 R\textsuperscript{C1}, -OR\textsuperscript{a}, Cl, F, Br, I, =O, -CN, NO\textsubscript{2}, CF\textsubscript{3}, -CF\textsubscript{2}CF\textsubscript{3}, -(CR\textsuperscript{a}Ra\textsuperscript{1})_\text{C}\textsubscript{3-10} carbocycle substituted with 0-2 R\textsuperscript{C1}, and -(CR\textsuperscript{a}Ra\textsuperscript{1})_\text{C}\textsubscript{1-5-10} membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)\textsubscript{p}, and substituted with 0-2 R\textsuperscript{C1};

R\textsuperscript{C1}, at each occurrence, is independently selected from: H, C\textsubscript{1-4} alkyl, -OR\textsuperscript{a}, Cl, F, Br, I, =O, CF\textsubscript{3}, -CN, NO\textsubscript{2},
-NRₐRₐ₁, -C(O)ORₐ, and -C(O)NRₐRₐ₁;

Rᵈ, at each occurrence, is independently selected from:
- C₁₋₆ alkyl, -ORₐ, Cl, F, Br, I, =O, -CN, NO₂, -NRₐRₐ₁,
- C(O)Rₐ, -C(O)ORₐ, -C(O)NRₐRₐ₁, -C(S)NRₐRₐ₁,
- NRₐC(O)NRₐRₐ₁, -OC(O)NRₐRₐ₁, -NRₐC(O)ORₐ₁,
- S(O)₂NRₐRₐ₁, -NRₐS(O)₂Rₐ₃, -NRₐS(O)₂NRₐRₐ₁,
- OS(O)₂NRₐRₐ₁, -NRₐS(O)₂Rₐ₃, -S(O)ₚRₐ₃, CF₃, -CF₂CF₃,
- C₃₋₆ carbocycle, and a 5-6 membered heterocycle
consisting of carbon atoms and 1-4 heteroatoms
selected from the group consisting of N, O, and S(O)ₚ;
and,

Rₑ, at each occurrence, is independently selected from: H,
- C₁₋₄ alkyl, -ORₐ, Cl, F, Br, I, =O, CF₃, -CN, NO₂,
- NRₐRₐ₁, -C(O)ORₐ, and -C(O)NRₐRₐ₁.

4. A compound according to Claim 3, wherein;

R² is selected from: Q, -C₁₋₆ alkylene-Q,
- C₁₋₆ alkenylene-Q, -(CRₐRₐ₁)ᵣ₁O(CRₐRₐ₁)ᵣ₋Q,
- (CRₐRₐ₁)ᵣ₁NRₐ(CRₐRₐ₁)ᵣ₋Q, -(CRₐRₐ₁)ᵣ₁C(O) (CRₐRₐ₁)ᵣ₋Q,
- (CRₐRₐ₁)ᵣ₁C(O)O(CRₐRₐ₁)ᵣ₋Q, -(CRₐRₐ₁)ᵣ₁C(O)NRₐRₐ₁,
- (CRₐRₐ₁)ᵣ₁C(O)NRₐ(CRₐRₐ₁)ᵣ₋Q,
- (CRₐRₐ₁)ᵣ₁S(O)ₚ(CRₐRₐ₁)ᵣ₋Q, and
- (CRₐRₐ₁)ᵣ₁SO₂NRₐ(CRₐRₐ₁)ᵣ₋Q;

Q, at each occurrence, is independently selected from: H, a
- C₃₋₆ carbocycle substituted with 0-3 Rᵈ, and a 5-10
membered heterocycle consisting of carbon atoms and
1-4 heteroatoms selected from the group consisting of
N, O, and S(O)\_p, and substituted with 0-3 R^d;

5 R^3 is selected from: Q^1, -C\_1-6 alkylene-Q^1,
-C\_2-6 alkenylene-Q^1, -(CR^aRa^1)\_r1O(CH\_2)\_r-Q^1,
-(CR^aRa^1)\_r1NR^a(CR^aRa^1)\_r-Q^1,
-(CR^aRa^1)\_r1C(O)NR^a(CR^aRa^1)\_r-Q^1,
-(CR^aRa^1)\_r1C(O)(CR^aRa^1)\_r-Q^1,
10 -(CR^aRa^1)\_r1C(O)O(CR^aRa^1)\_r-Q^1,
-(CR^aRa^1)\_r1S(O)\_p(CR^aRa^1)\_r-Q^1, and
-(CR^aRa^1)\_r1SO\_2NR^a(CR^aRa^1)\_r-Q^1;

Q^1, at each occurrence, is independently selected from: H,
a C\_3-6 carbocycle substituted with 0-3 R^d, and a 5-10
membered heterocycle consisting of carbon atoms and
1-4 heteroatoms selected from the group consisting of
N, O, and S(O)\_p, and substituted with 0-3 R^d;

15 R^4 is selected from: H and C\_1-6 alkyl;

alternatively, R^3 and R^4 together with the carbon atom to
which they are attached combine to form a 3-6 membered
carbocyclic or heterocyclic ring consisting of carbon
atoms and 0-2 ring heteroatoms selected from O, N,
NR\^10, and S(O)\_p, and substituted with 0-3 R^c;

25 R\^10, at each occurrence, is independently selected from: H,
C\_1-6 alkyl substituted with 0-1 R\^c1, C\_2-6 alkenyl
substituted with 0-1 R1, C2-6 alkynyl substituted with 0-1 R1, -(CRaRb)1C(O)R1, -(CRaRb)1C(O)OR1a, 
-(CRaRb)1C(O)NRaRb1, -(CRaRb)1S(O)2R1, 
-(CRaRb)1SO2NRaRb1, -(CRaRb)1-C1-C6 carbocycle
5 substituted with 0-2 R1, and -(CRaRb)1-5-10 membered
heterocycle consisting of carbon atoms and 1-4
heteroatoms selected from the group consisting of N,
O, and S(O)2, and substituted with 0-2 R1;

10 Z is selected from: phenyl substituted with 0-3 Rb, and a
5-6 membered heteroarylyl consisting of carbon atoms and
1-4 heteroatoms selected from the group consisting of
N, O, and S(O)2, and substituted with 0-3 Rb;

15 provided that X, Y, and Z do not combine to form a N-O,
O-O, or S(O)2-O group;

Za is 4-quinolinyl substituted with 0-2 Rc;

20 Ra, at each occurrence, is independently selected from: H
and C1-4 alkyl;

Rb, at each occurrence, is independently selected from: H,
C1-4 alkyl, phenyl, and benzyl;

25 alternatively, Ra and Rb when attached to a nitrogen are
taken together with the nitrogen to which they are
attached form a 5 or 6 membered heterocycle consisting
of carbon atoms and 0-1 additional heteroatoms
selected from N, NRa2, O, and S(O)2;
R^b, at each occurrence, is independently selected from:
C_{1-6} alkyl, -OR^a, Cl, F, Br, =O, -CN, -NR^aR^a_1, -C(O)R^a,
-C(O)OR^a, -C(O)NR^aR^a_1, -S(O)_2NR^aR^a_1, -S(O)_pR^a_3, and CF_3;

5 R^c, at each occurrence, is independently selected from: H,
C_{1-6} alkyl substituted with 0-1 R^c_1, C_{2-6} alkenyl
substituted with 0-1 R^c_1, C_{2-6} alkynyl substituted with
0-1 R^c_1, -OR^a, Cl, F, Br, =O, -CN, CF_3, -NR^aR^a_1,
-(CR^aR^a_1)_r_1C(O)R^a_1, -(CR^aR^a_1)_r_1C(O)OR^a_1,
-(CR^aR^a_1)_r_1C(O)NR^aR^a_1, -(CR^aR^a_1)_r_1S(O)_pR^a_3,
-(CR^aR^a_1)_r_1SO_2NR^aR^a_1, C_{3-6} carbocycle, and a 5-6
membered heterocycle consisting of carbon atoms and
1-4 heteroatoms selected from the group consisting of
N, O, and S(O)_p; and,

10 R^d, at each occurrence, is independently selected from:
C_{1-6} alkyl, -OR^a, Cl, F, Br, =O, -CN, -NR^aR^a_1, -C(O)R^a,
-C(O)OR^a, -C(O)NR^aR^a_1, -S(O)_2NR^aR^a_1, -S(O)_pR^a_3, CF_3,
C_{3-6} carbocycle, and a 5-6 membered heterocycle
consisting of carbon atoms and 1-4 heteroatoms
selected from the group consisting of N, O, and S(O)_p.

15 5. A compound according to Claim 4, wherein;

20 R^1 is selected from: H and C_{1-4} alkyl;

R^2 is selected from: Q, -C_{1-6} alkylene-Q,
- (CR\textsuperscript{a}R\textsuperscript{al})\textsubscript{r1}C(O)(CR\textsuperscript{a}R\textsuperscript{al})\textsubscript{r}-Q, 
- (CR\textsuperscript{a}R\textsuperscript{al})\textsubscript{r1}C(O)O(CR\textsuperscript{a}R\textsuperscript{al})\textsubscript{r}-Q, 
- (CR\textsuperscript{a}R\textsuperscript{al})\textsubscript{r1}C(O)NR\textsuperscript{a}R\textsuperscript{al}, 
- (CR\textsuperscript{a}R\textsuperscript{al})\textsubscript{r1}C(O)NR\textsuperscript{a}(CR\textsuperscript{a}R\textsuperscript{al})\textsubscript{r}-Q, and 
- (CR\textsuperscript{a}R\textsuperscript{al})\textsubscript{r1}S(O)\textsubscript{p}(CR\textsuperscript{a}R\textsuperscript{al})\textsubscript{r}-Q;

Q, at each occurrence, is independently selected from: H, a C\textsubscript{3-6} carbocycle substituted with 0-2 R\textsuperscript{d}, and a 5-6 membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)\textsubscript{p}, and substituted with 0-2 R\textsuperscript{d};

R\textsuperscript{3} is selected from: Q\textsuperscript{1}, -C\textsubscript{1-6} alkylene-Q\textsuperscript{1},
- (CR\textsuperscript{a}R\textsuperscript{al})\textsubscript{r1}O(CH\textsubscript{2})\textsubscript{r}-Q\textsuperscript{1}, 
- (CR\textsuperscript{a}R\textsuperscript{al})\textsubscript{r1}NR\textsuperscript{a}(CR\textsuperscript{a}R\textsuperscript{al})\textsubscript{r}-Q\textsuperscript{1}, 
- (CR\textsuperscript{a}R\textsuperscript{al})\textsubscript{r1}C(O)NR\textsuperscript{a}(CR\textsuperscript{a}R\textsuperscript{al})\textsubscript{r}-Q\textsuperscript{1}, 
- (CR\textsuperscript{a}R\textsuperscript{al})\textsubscript{r1}C(O)(CR\textsuperscript{a}R\textsuperscript{al})\textsubscript{r}-Q\textsuperscript{1}, 
- (CR\textsuperscript{a}R\textsuperscript{al})\textsubscript{r1}C(O)O(CR\textsuperscript{a}R\textsuperscript{al})\textsubscript{r}-Q\textsuperscript{1}, 
- (CR\textsuperscript{a}R\textsuperscript{al})\textsubscript{r1}S(O)\textsubscript{p}(CR\textsuperscript{a}R\textsuperscript{al})\textsubscript{r}-Q\textsuperscript{1}, and 
- (CR\textsuperscript{a}R\textsuperscript{al})\textsubscript{r1}SO\textsubscript{2}NR\textsuperscript{a}(CR\textsuperscript{a}R\textsuperscript{al})\textsubscript{r}-Q\textsuperscript{1};

Q\textsuperscript{1}, at each occurrence, is independently selected from: H, a C\textsubscript{3-6} carbocycle substituted with 0-2 R\textsuperscript{d}, and a 5-6 membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)\textsubscript{p}, and substituted with 0-2 R\textsuperscript{d};

R\textsuperscript{4} is selected from: H and C\textsubscript{1-4} alkyl;

alternatively, R\textsuperscript{3} and R\textsuperscript{4} together with the carbon atom to which they are attached combine to form a 3-6 membered carbocyclic or heterocyclic ring consisting of carbon
atoms and 0-2 ring heteroatoms selected from O, N, NR\(^{10}\), and S(O)\(_p\), and substituted with 0-2 R\(^c\);

R\(^{10}\), at each occurrence, is independently selected from: H, C\(_{1-6}\) alkyl substituted with 0-1 R\(^{c1}\), C\(_{2-6}\) alkenyl substituted with 0-1 R\(^{c1}\), C\(_{2-6}\) alkynyl substituted with 0-1 R\(^{c1}\), -(CR\(^{a}R\(^{a1}\))\(_{1}\)C(O)R\(^{a1}\), -(CR\(^{a}R\(^{a1}\))\(_{1}\)C(O)OR\(^{a1}\), -(CR\(^{a}R\(^{a1}\))\(_{1}\)C(O)NR\(^{a}R\(^{a1}\)), -(CR\(^{a}R\(^{a1}\))\(_{1}\)S(O)\(_p\)Ra\(^3\), -(CR\(^{a}R\(^{a1}\))\(_{1}\)SO\(_2\)NR\(^{a}R\(^{a1}\)), -(CH\(_2\))\(_{1}\)-C\(_{3-6}\) carbocycle substituted with 0-2 R\(^{c1}\), and -(CH\(_2\))\(_{1}\)-5-6 membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)\(_p\), and substituted with 0-2 R\(^{c1}\);

X-Y is CH\(_2\) or OCH\(_2\);

Z is phenyl substituted with 0-3 R\(^b\);

R\(^a\), at each occurrence, is independently selected from: H and C\(_{1-4}\) alkyl;

R\(^{a1}\), at each occurrence, is independently selected from: H, C\(_{1-4}\) alkyl, phenyl, and benzyl;

R\(^b\), at each occurrence, is independently selected from: C\(_{1-4}\) alkyl, -OR\(^a\), Cl, F, =O, -NR\(^{a}R\(^{a1}\), -C(O)Ra, -C(O)OR\(^a\), -C(O)NR\(^{a}R\(^{a1}\), -S(O)\(_2\)NR\(^{a}R\(^{a1}\), -S(O)\(_p\)Ra\(^3\), and CF\(_3\);
RC, at each occurrence, is independently selected from: H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, –OR¹, Cl, F, Br, =O, –NR²R³, CF₃, –(CR²R³)₁C(O)R¹, –(CR²R³)₁C(O)OR¹, –(CR²R³)₁C(O)NR²R³, –(CR²R³)₁S(O)₂R³, and phenyl;
5 and,
Rᵈ, at each occurrence, is independently selected from: C₁₋₆ alkyl, –OR¹, Cl, F, Br, =O, –NR²R³, –C(O)R¹, –C(O)NR²R³, –S(O)₂NR²R³, –S(O)₂R³, CF₃, and phenyl.
10

6. A compound according to Claim 5, wherein;
15 R¹ is selected from: H, methyl, and ethyl;

R² is selected from: Q, –C₁₋₆ alkylene-Q, –C(O)(CR²R³)₁-Q, –C(O)O(CR²R³)₁-Q, –C(O)NR²(CR²R³)₁-Q, and –S(O)₂(CR²R³)₁-Q;
20 Q, at each occurrence, is independently selected from: H, cyclopropyl substituted with 0-1 Rᵈ, cyclopentyl substituted with 0-1 Rᵈ, cyclohexyl substituted with 0-1 Rᵈ, phenyl substituted with 0-2 Rᵈ, and a heteroaryl substituted with 0-3 Rᵈ, wherein the heteroaryl is selected from pyridyl, quinolinyl, thiazolyl, furanyl, imidazolyl, and isoxazolyl;
25 R³ is selected from: Q¹, –C₁₋₆ alkylene-Q¹, –C(O)(CR²R³)₁-Q¹, and –C(O)(CR²R³)₁-Q¹,
30
-C(O)O(CR^aR^al)_r-Q^1, and -(CR^aR^al)_rS(O)_p(CR^aR^al)_r-Q^1;

Q^1, at each occurrence, is independently selected from: H, cyclopropyl substituted with 0-1 R^d, cyclopentyl substituted with 0-1 R^d, cyclohexyl substituted with 0-1 R^d, phenyl substituted with 0-2 R^d, and a heteroaryl substituted with 0-3 R^d, wherein the heteroaryl is selected from pyridyl, quinolinyl, thiazolyl, furanyl, imidazolyl, and isoxazolyl;

R^4 is selected from: H, methyl, and ethyl;

R^5 is H;

R^a, at each occurrence, is independently selected from: H, methyl, and ethyl;

R^al, at each occurrence, is independently selected from: H, methyl, and ethyl;

R^a2, at each occurrence, is independently selected from: H, methyl, and ethyl;

R^c, at each occurrence, is independently selected from: H, C_1-6 alkyl, C_2-6 alkenyl, C_2-6 alkynyl, -OR^a, Cl, F, Br, =O, -NR^aR^al, CF_3, -(CR^aR^al)_rC(O)R^al,
-(CR^aR^al)_rC(O)OR^a, -(CR^aR^al)_rC(O)NR^aR^al,
-(CR^aR^al)_rS(O)_pR^a3, and -(CR^aR^al)_rSO_2NR^aR^al;

p, at each occurrence, is selected from 0, 1, and 2;
r, at each occurrence, is selected from 0, 1, 2, and 3; and,

r1, at each occurrence, is selected from 0, 1, 2, and 3.

7. A compound of formula I:

\[
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{O} \\
\text{OH} \\
\text{R}^1 \\
\text{R}^2 \\
\text{R}^3 \\
\text{R}^4 \\
\text{R}^5 \\
\text{S} \\
\text{X} \\
\text{Y} \\
\text{Z}^a
\end{array}
\]

or a stereoisomer or pharmaceutically acceptable salt form thereof, wherein;

R¹ and R² together with the carbon atom to which they are attached combine to form a 3-10 membered carbocyclic or heterocyclic ring consisting of carbon atoms and 0-2 ring heteroatoms selected from O, N, NR¹⁰, and S(O)ₚ, and substituted with 0-4 R⁰;

R³ is selected from: Q¹, -C₁-₆ alkylene-Q¹, -C₂-₆ alkenylene-Q¹, -C₂-₆ alkylnylene-Q¹, -(CRᵃRᵃ¹)ₓ₁O(CH₂)ₓ₋Q¹, -(CRᵃRᵃ¹)ₓ₁NRᵃ(CRᵃRᵃ¹)ₓ₋Q¹, -(CRᵃRᵃ¹)ₓ₁NRᵃC(O)(CRᵃRᵃ¹)ₓ₋Q¹, -(CRᵃRᵃ¹)ₓ₁C(O)NRᵃ(CRᵃRᵃ¹)ₓ₋Q¹, -(CRᵃRᵃ¹)ₓ₁C(O)(CRᵃRᵃ¹)ₓ₋Q¹, -(CRᵃRᵃ¹)ₓ₁C(O)O(CRᵃRᵃ¹)ₓ₋Q¹, -(CRᵃRᵃ¹)ₓ₁S(O)ₚ(CRᵃRᵃ¹)ₓ₋Q¹, and -(CRᵃRᵃ¹)ₓ₁SO₂NRᵃ(CRᵃRᵃ¹)ₓ₋Q¹;
Q^1, at each occurrence, is independently selected from: H, a C_{3-13} carbocycle substituted with 0-5 R^d, and a 5-14 membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)_{p}, and substituted with 0-5 R^d;

R^4 is selected from: H, C_{1-6} alkyl substituted with 0-1 R^b, C_{2-6} alkenyl substituted with 0-1 R^b, and C_{2-6} alkynyl substituted with 0-1 R^b;

R^5 is selected from: H, and C_{1-4} alkyl;

R^{10}, at each occurrence, is independently selected from: H, C_{1-6} alkyl substituted with 0-2 R^{c1}, C_{2-6} alkenyl substituted with 0-2 R^{c1}, C_{2-6} alkynyl substituted with 0-2 R^{c1}, -(CR^aR^{al})_sNR^aR^{al}, -(CR^aR^{al})_r1C(O)NR^aOH, -(CR^aR^{al})_r1C(O)R^{al}, -(CR^aR^{al})_r1C(O)OR^{al}, -(CR^aR^{al})_r1C(S)OR^{al}, -(CR^aR^{al})_r1C(O)NR^aR^{al}, -(CR^aR^{al})_sNR^aC(O)R^{al}, -(CR^aR^{al})_r1C(S)NR^aR^{al}, -(CR^aR^{al})_sOC(O)NR^aR^{al}, -(CR^aR^{al})_sNR^aC(O)OR^{al}, -(CR^aR^{al})_sNR^aC(O)NR^aR^{al}, -(CR^aR^{al})_r1S(O)_{p}R^{a3}, -(CR^aR^{al})_r1SO_{2}NR^aR^{al}, -(CR^aR^{al})_sNR^aSO_{2}R^{a3}, -(CR^aR^{al})_sNR^aSO_{2}NR^aR^{al}, -(CR^aR^{al})_r1-C_{3-10} carbocycle substituted with 0-2 R^{c1}, and -(CR^aR^{al})_r1-5-14 membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)_{p}, and substituted with 0-2 R^{c1};

X-Y is CH_{2}, CH_{2}O or OCH_{2};
Z is selected from: a C_{6-10} aryl substituted with 0-5 R^b, and a 5-14 membered heteroaryl consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)\_p, and substituted with 0-5 R^b; 

provided that X, Y, and Z do not combine to form a N-O, O-O, or S(O)\_p-O, group; 

Z^a is substituted with 0-5 R^c, and is a 8-14 membered heterocycle consisting of carbon atoms, 1-3 N atoms, and 0-1 heteroatom selected from the group consisting of O, and S(O)\_p; 

R^a, at each occurrence, is independently selected from: H, C_{1-6} alkyl, phenyl, and benzyl; 

R^{a1}, at each occurrence, is independently selected from: H, C_{1-6} alkyl substituted with 0-1 R^e, C_{2-6} alkenyl substituted with 0-1 R^e, C_{2-6} alkynyl substituted with 0-1 R^e, and -(CH_2)_r-3-8 membered carbocyclic or heterocyclic ring consisting of carbon atoms and 0-2 ring heteroatoms selected from N, NR^{a2}, O, and S(O)\_p, and substituted with 0-3 R^e; 

alternatively, R^a and R^{a1} when attached to a nitrogen are taken together with the nitrogen to which they are attached form a 5 or 6 membered heterocycle consisting of carbon atoms and 0-1 additional heteroatoms selected from N, NR^{a2}, O, and S(O)\_p;
R^a2, at each occurrence, is independently selected from:
C\textsubscript{1-4} alkyl, phenyl, and benzyl;

5 R^a3, at each occurrence, is independently selected from: H, C\textsubscript{1-6} alkyl substituted with 0-1 R^c1, C\textsubscript{2-6} alkenyl substituted with 0-1 R^c1, C\textsubscript{2-6} alkynyl substituted with 0-1 R^c1, and -(CH\textsubscript{2})\textsubscript{r}-3-8 membered carbocyclic or heterocyclic ring consisting of carbon atoms and 0-2 ring heteroatoms selected from N, NR\textsuperscript{2a}, O, and S(O)\textsubscript{p} and substituted with 0-3 R^c1;

R\textsuperscript{b}, at each occurrence, is independently selected from:
C\textsubscript{1-6} alkyl substituted with 0-1 R^c1, -OR\textsuperscript{a}, Cl, F, Br,
I, =O, -CN, NO\textsubscript{2}, -NR\textsuperscript{a}R\textsuperscript{al}, -C(O)R\textsuperscript{a}, -C(O)OR\textsuperscript{a},
-C(O)NR\textsuperscript{a}R\textsuperscript{al}, -(S)NR\textsuperscript{a}R\textsuperscript{al}, -NR\textsuperscript{a}C(O)NR\textsuperscript{a}R\textsuperscript{al}, -OC(O)NR\textsuperscript{a}R\textsuperscript{al},
-NR\textsuperscript{a}C(O)OR\textsuperscript{a}, -S(O)\textsubscript{2}NR\textsuperscript{a}R\textsuperscript{al}, -NR\textsuperscript{a}S(O)\textsubscript{2}R\textsuperscript{a3},
-NR\textsuperscript{a}S(O)\textsubscript{2}NR\textsuperscript{a}R\textsuperscript{al}, -OS(O)\textsubscript{2}NR\textsuperscript{a}R\textsuperscript{al}, -NR\textsuperscript{a}S(O)\textsubscript{2}R\textsuperscript{a3}, -S(O)\textsubscript{p}R\textsuperscript{a3},
CF\textsubscript{3}, -CF\textsubscript{2}CF\textsubscript{3}, -CHF\textsubscript{2}, -CH\textsubscript{2}F, and phenyl;

20 R\textsuperscript{c}, at each occurrence, is independently selected from: H, C\textsubscript{1-6} alkyl substituted with 0-2 R^c1, C\textsubscript{2-6} alkenyl substituted with 0-2 R^c1, C\textsubscript{2-6} alkynyl substituted with 0-2 R^c1, -OR\textsuperscript{a}, Cl, F, Br, I, =O, -CN, NO\textsubscript{2}, CF\textsubscript{3}, -OCF\textsubscript{3},
-CF\textsubscript{2}CF\textsubscript{3}, -CH\textsubscript{2}F, -CHF\textsubscript{2}, -(CR\textsuperscript{a}R\textsuperscript{al})\textsubscript{r1}NR\textsuperscript{a}R\textsuperscript{al},
-(CR\textsuperscript{a}R\textsuperscript{al})\textsubscript{r1}C(=NCN)NR\textsuperscript{a}R\textsuperscript{al}, -(CR\textsuperscript{a}R\textsuperscript{al})\textsubscript{r1}C(=NRA)NR\textsuperscript{a}R\textsuperscript{al},
-(CR\textsuperscript{a}R\textsuperscript{al})\textsubscript{r1}C(=NORA)NR\textsuperscript{a}R\textsuperscript{al}, -(CR\textsuperscript{a}R\textsuperscript{al})\textsubscript{r1}C(O)NR\textsuperscript{a}OH,
-(CR\textsuperscript{a}R\textsuperscript{al})\textsubscript{r1}C(O)Ra1, -(CR\textsuperscript{a}R\textsuperscript{al})\textsubscript{r1}C(O)OR\textsuperscript{a1},
-(CR\textsuperscript{a}R\textsuperscript{al})\textsubscript{r1}C(S)OR\textsuperscript{a1}, -(CR\textsuperscript{a}R\textsuperscript{al})\textsubscript{r1}C(O)NR\textsuperscript{a}R\textsuperscript{al},
-(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r1}NR\textsuperscript{a}C(O)R\textsuperscript{a1}, -(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r1}C(S)NR\textsuperscript{a}R\textsuperscript{a1},
-(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r1}OC(O)NR\textsuperscript{a}R\textsuperscript{a1}, -(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r1}NR\textsuperscript{a}C(O)OR\textsuperscript{a1},
-(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r1}NR\textsuperscript{a}C(O)NR\textsuperscript{a}R\textsuperscript{a1}, -(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r1}S(O)\textsubscript{p}R\textsuperscript{a3},
-(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r1}SO\textsubscript{2}NR\textsuperscript{a}R\textsuperscript{a1}, -(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r1}NR\textsuperscript{a}SO\textsubscript{2}R\textsuperscript{a3},
-(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r1}NR\textsuperscript{a}SO\textsubscript{2}NR\textsuperscript{a}R\textsuperscript{a1}, -(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r1}-C\textsubscript{3-10} carbocycle substituted with 0-2 R\textsuperscript{c1}, and -(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r1}-5-14 membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)\textsubscript{p}, and substituted with 0-2 R\textsuperscript{c1};

alternatively, when two R\textsuperscript{c} groups are attached to the same carbon atom they form a spiro ring C that is a 3-11 membered carbocycle substituted with 0-2 R\textsuperscript{c1} or a 3-13 membered heterocycle consisting of: carbon atoms, 0-3 carbonyl groups, 0-4 double bonds, and from 1-5 ring heteroatoms selected from O, N, and S(O)\textsubscript{p}, and substituted with 0-2 R\textsuperscript{c1}, provided that ring C contains other than a S-S, O-O, or S-O bond;

alternatively, when two R\textsuperscript{c} groups are attached to adjacent carbon atoms, together with the carbon atoms to which they are attached they form a 5-7 membered carbocyclic or heterocyclic ring consisting of: carbon atoms, 0-2 heteroatoms selected from the group consisting of N, O, and S(O)\textsubscript{p}, and 0-3 double bonds, and substituted with 0-2 R\textsuperscript{c1};

R\textsuperscript{c1}, at each occurrence, is independently selected from: H, C\textsubscript{1-6} alkyl, -OR\textsuperscript{a}, Cl, F, Br, I, =O, -CN, NO\textsubscript{2}, -NR\textsuperscript{a}R\textsuperscript{a1}, -C(O)R\textsuperscript{a}, -C(O)OR\textsuperscript{a}, -C(O)NR\textsuperscript{a}R\textsuperscript{a1}, -NR\textsuperscript{a}C(O)NR\textsuperscript{a}R\textsuperscript{a1},
-OC(O)NR\textsubscript{a}Ra\textsubscript{1}, -NR\textsubscript{a}C(O)OR\textsubscript{a}1, -S(O)\textsubscript{2}NR\textsubscript{a}Ra\textsubscript{1}, -NR\textsubscript{a}S(O)\textsubscript{2}Ra\textsubscript{2},
-NR\textsubscript{a}S(O)\textsubscript{2}NR\textsubscript{a}Ra\textsubscript{1}, -OS(O)\textsubscript{2}NR\textsubscript{a}Ra\textsubscript{1}, -NR\textsubscript{a}S(O)\textsubscript{2}Ra\textsubscript{2}, -S(O)\textsubscript{p}Ra\textsubscript{2},
CF\textsubscript{3}, -OCF\textsubscript{3}, -CF\textsubscript{2}CF\textsubscript{3}, -CH\textsubscript{2}F, and -CHF\textsubscript{2};

5 Rd, at each occurrence, is independently selected from:
C\textsubscript{1-6} alkyl, -OR\textsubscript{a}, Cl, F, Br, I, =O, -CN, NO\textsubscript{2}, -NR\textsubscript{a}Ra\textsubscript{1},
-C(O)Ra\textsubscript{a}, -C(O)OR\textsubscript{a}, -C(O)NR\textsubscript{a}Ra\textsubscript{1}, -C(S)NR\textsubscript{a}Ra\textsubscript{1},
-NR\textsubscript{a}C(O)NR\textsubscript{a}Ra\textsubscript{1}, -OC(O)NR\textsubscript{a}Ra\textsubscript{1}, -NR\textsubscript{a}C(O)OR\textsubscript{a}1,
-S(O)\textsubscript{2}NR\textsubscript{a}Ra\textsubscript{1}, -NR\textsubscript{a}S(O)\textsubscript{2}Ra\textsubscript{3}, -NR\textsubscript{a}S(O)\textsubscript{2}NR\textsubscript{a}Ra\textsubscript{1},

-OS(O)\textsubscript{2}NR\textsubscript{a}Ra\textsubscript{1}, -NR\textsubscript{a}S(O)\textsubscript{2}Ra\textsubscript{3}, -S(O)\textsubscript{p}Ra\textsubscript{3}, CF\textsubscript{3}, -CF\textsubscript{2}CF\textsubscript{3},
C\textsubscript{3-10} carbocycle, and a 5-14 membered heterocycle
consisting of carbon atoms and 1-4 heteroatoms
selected from the group consisting of N, O, and S(O)\textsubscript{p};

15 Re, at each occurrence, is independently selected from: H,
C\textsubscript{1-6} alkyl, -OR\textsubscript{a}, Cl, F, Br, I, =O, -CN, NO\textsubscript{2}, -NR\textsubscript{a}Ra\textsubscript{a},
-C(O)Ra\textsubscript{a}, -C(O)OR\textsubscript{a}, -C(O)NR\textsubscript{a}Ra\textsubscript{a}, -NR\textsubscript{a}C(O)NR\textsubscript{a}Ra\textsubscript{a},
-OC(O)NR\textsubscript{a}Ra\textsubscript{a}, -NR\textsubscript{a}C(O)OR\textsubscript{a}, -S(O)\textsubscript{2}NR\textsubscript{a}Ra\textsubscript{a}, -NR\textsubscript{a}S(O)\textsubscript{2}Ra\textsubscript{2},
-NR\textsubscript{a}S(O)\textsubscript{2}NR\textsubscript{a}Ra\textsubscript{a}, -OS(O)\textsubscript{2}NR\textsubscript{a}Ra\textsubscript{a}, -NR\textsubscript{a}S(O)\textsubscript{2}Ra\textsubscript{2}, -S(O)\textsubscript{p}Ra\textsubscript{2},
CF\textsubscript{3}, -OCF\textsubscript{3}, -CF\textsubscript{2}CF\textsubscript{3}, -CH\textsubscript{2}F, and -CHF\textsubscript{2};

p, at each occurrence, is selected from 0, 1, and 2;

r, at each occurrence, is selected from 0, 1, 2, 3, and 4;

25 rl, at each occurrence, is selected from 0, 1, 2, 3, and 4;
and,

s, at each occurrence, is selected from 1, 2, 3, and 4.
8. A compound according to Claim 7, wherein;

\[ Z^a \] is substituted with 0-4 \( R^c \) and is selected from the group:

\[ \begin{align*}
\text{[Chemical Structures]} \end{align*} \]

\[ W \] is S, SO, SO₂, O, or NR\(^{11} \);

\[ \text{R}^{11}, \text{at each occurrence, is independently selected from: H, C}_1-4 \text{ alkyl, phenyl, and benzyl;} \]

\[ \text{R}^c, \text{at each occurrence, is independently selected from: H, C}_1-6 \text{ alkyl substituted with 0-2 R}^{c1}, \text{C}_2-6 \text{ alkenyl substituted with 0-2 R}^{c1}, -OR^a, \text{Cl, F, Br, I, =O, =CN, NO}_2, \text{CF}_3, -O\text{CF}_3, -\text{CF}_2\text{CF}_3, -\text{CH}_2\text{F, CHF}_2, -(\text{CR}^{aR^1})_1\text{NR}^{aR^1}, -(\text{CR}^{aR^1})_1\text{C(O)R}^1, -(\text{CR}^{aR^1})_1\text{C(O)OR}^1, -(\text{CR}^{aR^1})_1\text{NR}^{aR^1}, -(\text{CR}^{aR^1})_1\text{NR}^{aC(O)R}^1, -(\text{CR}^{aR^1})_1\text{S(O)R}^3, -(\text{CR}^{aR^1})_1\text{SO}_2\text{NR}^{aR^1}, -(\text{CR}^{aR^1})_1\text{NR}^{aSO}_2\text{R}^3, -(\text{CR}^{aR^1})_1\text{C}_3-10 \text{ carbocycle substituted with 0-2 R}^{c1}, \text{and } -(\text{CR}^{aR^1})_1\text{-5-14 membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)\_p, and substituted with 0-2 R}^{c1}; \]

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alternatively, when two $R^c$ groups are attached to the same carbon atom they form a spiro ring C that is a 3-11 membered carbocycle substituted with 0-2 $R^{c1}$ or a 3-13 membered heterocycle consisting of: carbon atoms, 0-3 carbonyl groups, 0-4 double bonds, and from 1-5 ring heteroatoms selected from O, N, and S(O)$_p$, and substituted with 0-2 $R^{c1}$, provided that ring C contains other than a S-S, O-O, or S-O bond; and,

alternatively, when two $R^c$ groups are attached to adjacent carbon atoms, together with the carbon atoms to which they are attached they form a 5-7 membered carbocyclic or heterocyclic ring consisting of: carbon atoms, 0-2 heteroatoms selected from the group consisting of N, O, and S(O)$_p$, and 0-3 double bonds, and substituted with 0-2 $R^{c1}$.

9. A compound according to Claim 8, wherein;

$R^1$ and $R^2$ together with the carbon atom to which they are attached combine to form a 3-8 membered carbocyclic or heterocyclic ring consisting of carbon atoms and 0-2 ring heteroatoms selected from O, N, NR$_{10}$, and S(O)$_p$, and substituted with 0-4 $R^c$;

$R^3$ is selected from: $Q^1$, \(-C_{1-6} \text{ alkyene-} Q^1\), \(-C_{2-6} \text{ alkenylene-} Q^1\), \(-C_{2-6} \text{ alkynylene-} Q^1\), \(-(CR^aR^{a1})_rO(CH_2)_r-Q^1\), \(-(CR^aR^{a1})_rNRA(CR^aR^{a1})_r-Q^1\), \(-(CR^aR^{a1})_rNRA(O)(CR^aR^{a1})_r-Q^1\),
\(-\text{CR}_{\text{Raal}}^1)_{\text{r}}\text{C}(\text{O})\text{NR}_{\text{Ra}}^\text{a}(\text{CR}_{\text{Raal}}^\text{a})_{\text{r}}-Q^1,\)
\(-\text{CR}_{\text{Raal}}^1)_{\text{r}}\text{C}(\text{O})(\text{CR}_{\text{Raal}}^\text{a})_{\text{r}}-Q^1,\)
\(-\text{CR}_{\text{Raal}}^1)_{\text{r}}\text{C}(\text{O})\text{O}((\text{CR}_{\text{Raal}}^\text{a})_{\text{r}}-Q^1,\)
\(-\text{CR}_{\text{Raal}}^1)_{\text{r}}\text{S}(\text{O})_{\text{p}}(\text{CR}_{\text{Raal}}^\text{a})_{\text{r}}-Q^1,\text{ and}\)
\(-\text{CR}_{\text{Raal}}^1)_{\text{r}}\text{SO}_{2}\text{NR}_{\text{Ra}}^\text{a}(\text{CR}_{\text{Raal}}^\text{a})_{\text{r}}-Q^1;\)

\(Q^1,\text{ at each occurrence, is independently selected from: }\text{H,}\)
a \(C_{3-10}\text{ carbocycle substituted with 0-5 }R^d,\text{ and a }5-10\)
membered heterocycle consisting of carbon atoms and
1-4 heteroatoms selected from the group consisting of
\(N, O,\text{ and }S(O)_{\text{p}},\text{ and substituted with 0-5 }R^d;\)

\(R^{10},\text{ at each occurrence, is independently selected from: }\text{H,}\)
\(C_{1-6}\text{ alkyl substituted with 0-2 }R^{c1},\text{ C}_{2-6}\text{ alkenyl}\)
substituted with 0-2 \(R^{c1},\text{ C}_{2-6}\text{ alkynyl substituted with}\)
0-2 \(R^{c1},\text{ }-(\text{CR}_{\text{Raal}}^\text{a})_{\text{r}}\text{NR}_{\text{Ra}}^\text{a},\text{ }-(\text{CR}_{\text{Raal}}^\text{a})_{\text{r}}\text{C}(\text{O})\text{R}^\text{a},\)
\(-\text{CR}_{\text{Raal}}^1)_{\text{r}}\text{C}(\text{O})\text{OR}^\text{a},\text{ }-(\text{CR}_{\text{Raal}}^\text{a})_{\text{r}}\text{C}(\text{O})\text{NR}_{\text{Ra}}^\text{a},\)
\(-\text{CR}_{\text{Raal}}^1)_{\text{r}}\text{NR}_{\text{Ra}}^\text{a}C(\text{O})\text{R}^\text{a},\text{ }-(\text{CR}_{\text{Raal}}^\text{a})_{\text{r}}\text{S}(\text{O})_{\text{p}}R^\text{a3},\)
\(-\text{CR}_{\text{Raal}}^1)_{\text{r}}\text{SO}_{2}\text{NR}_{\text{Ra}}^\text{a},\text{ }-(\text{CR}_{\text{Raal}}^\text{a})_{\text{r}}\text{SO}_{2}R^\text{a3},\)
\(-\text{CR}_{\text{Raal}}^1)_{\text{r}}\text{C}_{3-10}\text{ carbocycle substituted with 0-2 }R^{c1},\)
and \(-\text{CR}_{\text{Raal}}^1)_{\text{r}}\text{-C}_{3-10}\text{ membered heterocycle consisting of}\)
carbon atoms and 1-4 heteroatoms selected from the
the group consisting of \(N, O,\text{ and }S(O)_{\text{p}},\text{ and substituted}\)
with 0-2 \(R^{c1};\)

\(R^c,\text{ at each occurrence, is independently selected from: }\text{H,}\)
\(C_{1-6}\text{ alkyl substituted with 0-2 }R^{c1},\text{ C}_{2-6}\text{ alkenyl}\)
substituted with 0-2 \(R^{c1},\text{ C}_{2-6}\text{ alkynyl substituted with}\)
0-2 \(R^{c1},\text{ }-\text{OR}^\text{a},\text{ Cl, F, Br, I, }=\text{O, }-\text{CN, NO}_{2},\text{ CF}_3,\)
-CF₂CF₃, -(CRₐRₐ¹)ₗ₁NRₐNRₐ¹, -(CRₐRₐ¹)ₗ₁C(O)Rₐ¹,
\( (\text{CRₐRₐ¹})ₗ₁C(O)ORₐ¹, \) \( (\text{CRₐRₐ¹})ₗ₁C(O)NRₐNRₐ¹, \)
\( (\text{CRₐRₐ¹})ₗ₁NRₐC(O)Rₐ¹, \) \( (\text{CRₐRₐ¹})ₗ₁C(\text{S(O})ₚRₐ³, \)
\( (\text{CRₐRₐ¹})ₗ₁SO₂NRₐNRₐ¹, \) \( (\text{CRₐRₐ¹})ₗ₁NRₐSO₂Rₐ³, \)
\( (\text{CRₐRₐ¹})ₗ₁-C₃₋₁₀ \text{ carbocycle substituted with 0-2 R}^{c¹}, \)
and \( (\text{CRₐRₐ¹})ₗ₁-5-10 \text{ membered heterocycle consisting of} \)
carbon atoms and 1-4 heteroatoms selected from the
\( \text{group consisting of N, O, and S(O)}ₚ, \text{ and substituted} \)
\( \text{with 0-2 R}^{c¹}; \)

\( \text{R}^{c¹}, \text{ at each occurrence, is independently selected from: H,} \)
\( \text{C}_₁₋₄ \text{ alkyl, -OR}ₐ, \text{ Cl, F, Br, I, =O, CF₃, -CN, NO₂,} \)
\( -\text{NRₐRₐ¹}, -\text{C(O)OR}ₐ, \text{ and -C(O)NRₐRₐ¹;} \)

\( \text{R}^{d}, \text{ at each occurrence, is independently selected from:} \)
\( \text{C}_₁₋₆ \text{ alkyl, -OR}ₐ, \text{ Cl, F, Br, I, =O, -CN, NO₂, -NRₐRₐ¹,} \)
\( \text{-C(O)R}ₐ, \text{-C(O)OR}ₐ, \text{-C(O)NRₐRₐ¹, -C(S)NRₐRₐ¹,} \)
\( \text{-NRₐC(O)NRₐRₐ¹, -OC(O)NRₐRₐ¹, -NRₐC(O)ORₐ¹,} \)
\( \text{-S(O)₂NRₐRₐ¹, -NRₐRₐS(O)₂Rₐ³, -NRₐRₐS(O)₂NRₐRₐ¹,} \)
\( \text{-OS(O)₂NRₐRₐ¹, -NRₐRₐS(O)₂Rₐ³, -S(O)ₚRₐ³, CF₃, -CF₂CF₃,} \)
\( \text{C}_₁₋₆ \text{ carbocycle, and a 5-6 membered heterocycle} \)
\( \text{consisting of carbon atoms and 1-4 heteroatoms} \)
\( \text{selected from the group consisting of N, O, and S(O)}ₚ; \text{ and}, \)

\( \text{R}^{e}, \text{ at each occurrence, is independently selected from: H,} \)
\( \text{C}_₁₋₄ \text{ alkyl, -OR}ₐ, \text{ Cl, F, Br, I, =O, CF₃, -CN, NO₂,} \)
\( -\text{NRₐRₐ¹, -C(O)OR}ₐ, \text{ and -C(O)NRₐRₐ¹.} \)

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10. A compound according to Claim 9, wherein;

R\(^1\) and R\(^2\) together with the carbon atom to which they are attached combine to form a 3-6 membered carbcyclic or heterocyclic ring consisting of carbon atoms and 0-2 ring heteroatoms selected from O, N, NR\(^{10}\), and S(O)\(_p\), and substituted with 0-3 R\(^c\);

R\(^3\) is selected from: Q\(^1\), -C\(_{1-6}\) alkenylene-Q\(^1\),

- C\(_{2-6}\) alkenylene-Q\(^1\), -(CR\(^{ra1}\))\(_r\)O(CH\(_2\))\(_r\)-Q\(^1\),
- (CR\(^{ra1}\))\(_r\)N\(^a\)(CR\(^{ra1}\))\(_r\)-Q\(^1\),
- (CR\(^{ra1}\))\(_r\)C(O)N\(^a\)(CR\(^{ra1}\))\(_r\)-Q\(^1\),
- (CR\(^{ra1}\))\(_r\)C(O)(CR\(^{ra1}\))\(_r\)-Q\(^1\),
- (CR\(^{ra1}\))\(_r\)C(O)O(CR\(^{ra1}\))\(_r\)-Q\(^1\),
- (CR\(^{ra1}\))\(_r\)SO\(_2\)N\(^a\)(CR\(^{ra1}\))\(_r\)-Q\(^1\),

Q\(^1\), at each occurrence, is independently selected from: H, a C\(_{3-6}\) carbcyclic substituted with 0-3 R\(^d\), and a 5-10 membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)\(_p\) and substituted with 0-3 R\(^d\);

R\(^4\) is selected from: H and C\(_{1-6}\) alkyl;

R\(^{10}\), at each occurrence, is independently selected from: H, C\(_{1-6}\) alkyl substituted with 0-1 R\(^c1\), C\(_{2-6}\) alkenyl substituted with 0-1 R\(^c1\), C\(_{2-6}\) alkynyl substituted with 0-1 R\(^c1\), -(CR\(^{ra1}\))\(_r\)C(O)R\(^a1\), -(CR\(^{ra1}\))\(_r\)C(O)OR\(^a1\),
- (CR\(^{ra1}\))\(_r\)C(O)NR\(^a\)R\(^a1\), -(CR\(^{ra1}\))\(_r\)S(O)\(_p\)R\(^a3\),
-(CRaR^al)_{r1}SO_{2}NRaRa1, -(CRaR^al)_{r1-C3-6} carbocycle
substituted with 0-2 R^c_{1}, and -(CRaR^al)_{r1-5-10} membered
heterocycle consisting of carbon atoms and 1-4
heteroatoms selected from the group consisting of N,
O, and S(O)_{p}, and substituted with 0-2 R^c_{1};

Z is selected from: phenyl substituted with 0-3 R^b, and a
5-6 membered heteroaryl consisting of carbon atoms and
1-4 heteroatoms selected from the group consisting of
N, O, and S(O)_{p}, and substituted with 0-3 R^b;

provided that X, Y, and Z do not combine to form a N-O,
O-O, or S(O)_{p}-O group;

Z^a is 4-quinolinyl substituted with 0-2 R^c;

R^a, at each occurrence, is independently selected from: H
and C_{1-4} alkyl;

R^al, at each occurrence, is independently selected from: H,
C_{1-4} alkyl, phenyl, and benzyl;

alternatively, R^a and R^al when attached to a nitrogen are
taken together with the nitrogen to which they are
attached form a 5 or 6 membered heterocycle consisting
of carbon atoms and 0-1 additional heteroatoms
selected from N, NR^a2, O, and S(O)_{p};

R^b, at each occurrence, is independently selected from:
C_{1-6} alkyl, -OR^a, C1, F, Br, =O, -CN, -NRaRa1, -C(O)Ra,
-C(O)OR^a, -C(O)NRaRa1, -S(O)_{2}NRaRa1, -S(O)_{p}Ra3, and CF_{3};
R^c, at each occurrence, is independently selected from: H, C_{1-6} alkyl substituted with 0-1 R^c, C_{2-6} alkenyl substituted with 0-1 R^c, C_{2-6} alkynyl substituted with 0-1 R^c, -OR^a, Cl, F, Br, =O, -CN, CF_3, -NR^aR^{a1}, -(CR^aR^{a1})_1C(O)R^{a1}, -(CR^aR^{a1})_1C(O)OR^{a1}, -(CR^aR^{a1})_1C(O)NR^aR^{a1}, -(CR^aR^{a1})_1S(O)R^{a3}, -(CR^aR^{a1})_1SO_2NR^aR^{a1}, C_{3-6} carbocycle, and a 5-6 membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)_p; and,

R^d, at each occurrence, is independently selected from: C_{1-6} alkyl, -OR^a, Cl, F, Br, =O, -CN, -NR^aR^{a1}, -C(O)R^a, -C(O)OR^a, -C(O)NR^aR^{a1}, -S(O)_2NR^aR^{a1}, -S(O)_pR^{a3}, CF_3, C_{3-6} carbocycle, and a 5-6 membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)_p.

11. A compound according to Claim 10, wherein;

R^1 and R^2 together with the carbon atom to which they are attached combine to form a 3-6 membered carbocyclic or heterocyclic ring consisting of carbon atoms and 0-2 ring heteroatoms selected from O, N, NR^{10}, and S(O)_p, and substituted with 0-2 R^c;

R^3 is selected from: Q^1, -C_{1-6} alkylene-Q^1, -(CR^aR^{a1})_1O(CH_2)_r-Q^1, -(CR^aR^{a1})_1NR^a(CR^aR^{a1})_r-Q^1,
\[-(\text{CR}^\text{R}^\text{a}^\text{R}^\text{a})_1 \text{C}(\text{O})\text{NR}^\text{a}(\text{CR}^\text{a}^\text{R}^\text{a}^\text{R}^\text{a})_r - \text{Q}^1,\]
\[-(\text{CR}^\text{R}^\text{a}^\text{R}^\text{a})_1 \text{C}(\text{O})(\text{CR}^\text{a}^\text{R}^\text{a}^\text{R}^\text{a})_r - \text{Q}^1,\]
\[-(\text{CR}^\text{R}^\text{a}^\text{R}^\text{a})_1 \text{C}(\text{O})\text{O}(\text{CR}^\text{a}^\text{R}^\text{a}^\text{R}^\text{a})_r - \text{Q}^1,\]
\[-(\text{CR}^\text{R}^\text{a}^\text{R}^\text{a})_1 \text{S}(\text{O})_p (\text{CR}^\text{a}^\text{R}^\text{a}^\text{R}^\text{a})_r - \text{Q}^1,\]
\[-(\text{CR}^\text{R}^\text{a}^\text{R}^\text{a})_1 \text{SO}_2\text{NR}^\text{a}(\text{CR}^\text{a}^\text{R}^\text{a}^\text{R}^\text{a})_r - \text{Q}^1;\]

\(\text{Q}^1\), at each occurrence, is independently selected from: \(\text{H}\), a C\(_3\)-C\(_6\) carbocycle substituted with 0-2 R\(_d\), and a 5-6 membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)\(_p\), and substituted with 0-2 R\(_d\);

R\(_d\) is selected from: \(\text{H}\) and C\(_1\)-C\(_4\) alkyl;

R\(_{10}\), at each occurrence, is independently selected from: \(\text{H}\), C\(_1\)-C\(_6\) alkyl substituted with 0-1 R\(_{c1}\), C\(_2\)-C\(_6\) alkenyl substituted with 0-1 R\(_{c1}\), C\(_2\)-C\(_6\) alkynyl substituted with 0-1 R\(_{c1}\), -(CR\(_{a}^\text{R}^\text{a}^\text{R}^\text{a})_1 \text{C}(\text{O})\text{R}^\text{a}, -(\text{CR}^\text{a}^\text{R}^\text{a}^\text{R}^\text{a})_1 \text{C}(\text{O})\text{OR}^\text{a},\)
\[-(\text{CR}^\text{a}^\text{R}^\text{a}^\text{R}^\text{a})_1 \text{C}(\text{O})\text{NR}^\text{a}\text{R}^\text{a}, -(\text{CR}^\text{a}^\text{R}^\text{a}^\text{R}^\text{a})_1 \text{S}(\text{O})_p \text{R}^\text{a};\]
\[-(\text{CR}^\text{a}^\text{R}^\text{a}^\text{R}^\text{a})_1 \text{SO}_2\text{NR}^\text{a}\text{R}^\text{a}, -(\text{CH}_2)_1 \text{C}_3\text{C}_6\text{ carbocycle substituted with 0-2 R}_c^1, \text{ and } -(\text{CH}_2)_1 \text{C}_5\text{C}_6\text{ membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)_p, and substituted with 0-2 R}_c^1;\]

X-Y is CH\(_2\) or CH\(_2\)O;

Z is phenyl substituted with 0-3 R\(_b\);
R\textsuperscript{a}, at each occurrence, is independently selected from: H and C\textsubscript{1-4} alkyl;

R\textsuperscript{a1}, at each occurrence, is independently selected from: H, C\textsubscript{1-4} alkyl, phenyl, and benzyl;

R\textsuperscript{b}, at each occurrence, is independently selected from: C\textsubscript{1-4} alkyl, -OR\textsuperscript{a}, Cl, F, =O, -NR\textsuperscript{a}R\textsuperscript{a1}, -C(O)R\textsuperscript{a}, -C(O)OR\textsuperscript{a}, -C(O)NR\textsuperscript{a}R\textsuperscript{a1}, -S(O)\textsubscript{2}NR\textsuperscript{a}R\textsuperscript{a1}, -S(O)\textsubscript{p}Ra\textsuperscript{3}, and CF\textsubscript{3};

R\textsuperscript{c}, at each occurrence, is independently selected from: H, C\textsubscript{1-6} alkyl, C\textsubscript{2-6} alkenyl, C\textsubscript{2-6} alkynyl, -OR\textsuperscript{a}, Cl, F, Br, =O, -NR\textsuperscript{a}R\textsuperscript{a1}, CF\textsubscript{3}, -(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r1}C(O)R\textsuperscript{a1}, -(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r1}C(O)OR\textsuperscript{a}, -(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r1}C(O)NR\textsuperscript{a}R\textsuperscript{a1}, -(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r1}S(O)\textsubscript{p}Ra\textsuperscript{3}, -(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r1}SO\textsubscript{2}NR\textsuperscript{a}R\textsuperscript{a1}, and phenyl;

and,

R\textsuperscript{d}, at each occurrence, is independently selected from: C\textsubscript{1-6} alkyl, -OR\textsuperscript{a}, Cl, F, Br, =O, -NR\textsuperscript{a}R\textsuperscript{a1}, -C(O)R\textsuperscript{a}, -C(O)NR\textsuperscript{a}R\textsuperscript{a1}, -S(O)\textsubscript{2}NR\textsuperscript{a}R\textsuperscript{a1}, -S(O)\textsubscript{p}Ra\textsuperscript{3}, CF\textsubscript{3}, and phenyl.

12. A compound according to Claim 7, wherein the compound is selected from the group:

hydroxy[{4-[(2-methyl-1H-benzimidazol-1-yl)methyl]phenyl}sulfonyl]tetrahydro-2H-pyran-4-yl]methyl]formamide; and

5 hydroxy[{4-[(2-methyl-4-quinoliny1)methyl]phenyl}sulfonyl]tetrahydro-2H-pyran-4-yl]methyl]formamide;

or a pharmaceutically acceptable salt form thereof.

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13. A compound of formula I:

\[ \text{I} \]

or a stereoisomer or pharmaceutically acceptable salt form thereof, wherein;

\[ R^1 \text{ and } R^4 \text{ together with the carbon atoms to which they are attached combine to form a 3-10 membered carbocyclic or heterocyclic ring consisting of carbon atoms and 0-2 ring heteroatoms selected from } O, N, NR^{10}, \text{ and } S(O)_p, \text{ and substituted with } 0-4 \text{ R}^c; \]

\[ R^2 \text{ is selected from: } Q, -C_{1-6} \text{ alkylene-Q,} \]

\[ -C_{2-6} \text{ alkenylene-Q, } -C_{2-6} \text{ alkyylene-Q,} \]

\[ -(CR^aR^{a1})_rO(CR^aR^{a1})_r-Q, \]

\[ -(CR^aR^{a1})_r1NR^a(CR^aR^{a1})_r-Q, -(CR^aR^{a1})_r1C(O)(CR^aR^{a1})_r-Q, \]
-(CR^aR^{al})_{r}C(O)O(CR^aR^{al})_{r} - Q,  -(CR^aR^{al})_{r}OC(O) (CR^aR^{al})_{r} - Q,
-(CR^aR^{al})_{r}C(O)NR^aR^{al},  -(CR^aR^{al})_{r}C(O)NR^a(R^aR^{al})_{r} - Q,
-(CR^aR^{al})_{r}NR^aC(O)(CR^aR^{al})_{r} - Q,
-(CR^aR^{al})_{r}OC(O)O (CR^aR^{al})_{r} - Q,
5  -(CR^aR^{al})_{r}OC(O)NR^a(CR^aR^{al})_{r} - Q,
-(CR^aR^{al})_{r}NR^aC(O)O(CR^aR^{al})_{r} - Q,
-(CR^aR^{al})_{r}NR^aC(O)NR^a(CR^aR^{al})_{r} - Q,
-(CR^aR^{al})_{r}S(O)_{p}(CR^aR^{al})_{r} - Q,
-(CR^aR^{al})_{r}SO_{2}NR^a(CR^aR^{al})_{r} - Q,
10  -(CR^aR^{al})_{r}NR^aSO_{2}(CR^aR^{al})_{r} - Q, and
-(CR^aR^{al})_{r}NR^aSO_{2}NR^a(CR^aR^{al})_{r} - Q;

Q, at each occurrence, is independently selected from: H, a
C_{3-13} carbocycle substituted with 0-5 R^d, and a 4-14
membered heterocycle consisting of carbon atoms and
1-4 heteroatoms selected from the group consisting of
N, O, and S(O)_{p}, and substituted with 0-5 R^d;

R^3 is selected from: Q^1, -C_{1-6} alkyene-Q^1,
20  -C_{2-6} alkenylene-Q^1,  -C_{2-6} alkynylene-Q^1,
-(CR^aR^{al})_{r}O(CH_2)_{r} - Q^1,  -(CR^aR^{al})_{r}NR^a(CR^aR^{al})_{r} - Q^1,
-(CR^aR^{al})_{r}NR^aC(O)(CR^aR^{al})_{r} - Q^1,
-(CR^aR^{al})_{r}C(O)NR^a(CR^aR^{al})_{r} - Q^1,
-(CR^aR^{al})_{r}C(O)(CR^aR^{al})_{r} - Q^1,
25  -(CR^aR^{al})_{r}C(O)O(CR^aR^{al})_{r} - Q^1,
-(CR^aR^{al})_{r}S(O)_{p}(CR^aR^{al})_{r} - Q^1, and
-(CR^aR^{al})_{r}SO_{2}NR^a(CR^aR^{al})_{r} - Q^1;
Q\(^1\), at each occurrence, is independently selected from: H, a C\(_{3-13}\) carbocycle substituted with 0-5 R\(^d\), and a 5-14 membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)\(_p\), and substituted with 0-5 R\(^d\);

R\(^5\) is selected from: H, and C\(_{1-4}\) alkyl;

R\(^{10}\), at each occurrence, is independently selected from: H, C\(_{1-6}\) alkyl substituted with 0-2 R\(^c\), C\(_{2-6}\) alkenyl substituted with 0-2 R\(^c\), C\(_{2-6}\) alkynyl substituted with 0-2 R\(^c\), -(CR\(_a\)R\(_a\))\(_s\)NR\(_a\)R\(_a\), -(CR\(_a\)R\(_a\))\(_r\)1C(O)NR\(_a\)OH,
-(CR\(_a\)R\(_a\))\(_r\)1C(O)Ra\(_1\), -(CR\(_a\)R\(_a\))\(_r\)1C(O)OR\(_a\),
-(CR\(_a\)R\(_a\))\(_r\)1C(S)OR\(_a\), -(CR\(_a\)R\(_a\))\(_r\)1C(O)NR\(_a\)Ra\(_1\),
-(CR\(_a\)R\(_a\))\(_s\)NR\(_a\)C(O)Ra\(_1\), -(CR\(_a\)R\(_a\))\(_r\)1C(S)NR\(_a\)Ra\(_1\),
-(CR\(_a\)R\(_a\))\(_s\)OC(O)NR\(_a\)Ra\(_1\), -(CR\(_a\)R\(_a\))\(_s\)NR\(_a\)C(O)OR\(_a\),
-(CR\(_a\)R\(_a\))\(_s\)NR\(_a\)C(O)NR\(_a\)Ra\(_1\), -(CR\(_a\)R\(_a\))\(_r\)1S(O)\(_p\)Ra\(_3\),
-(CR\(_a\)R\(_a\))\(_r\)1SO\(_2\)NR\(_a\)Ra\(_1\), -(CR\(_a\)R\(_a\))\(_s\)NR\(_a\)SO\(_2\)Ra\(_3\),
-(CR\(_a\)R\(_a\))\(_s\)NR\(_a\)SO\(_2\)NR\(_a\)Ra\(_1\), -(CR\(_a\)R\(_a\))\(_r\)1-C\(_{3-10}\) carbocycle substituted with 0-2 R\(^c\), and -(CR\(_a\)R\(_a\))\(_r\)1-5-14 membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)\(_p\), and substituted with 0-2 R\(^c\);

X-Y is CH\(_2\), CH\(_2\)O or OCH\(_2\);

Z is selected from: a C\(_{6-10}\) aryl substituted with 0-5 R\(^b\), and a 5-14 membered heteroaryl consisting of carbon atoms and 1-4 heteroatoms selected from the group
consisting of N, O, and S(O)ₚ, and substituted with
0-5 Rᵇ;

provided that X, Y, and Z do not combine to form a N-O,
0-0, or S(O)ₚ-O, group;

Zᵃ is substituted with 0-5 Rᶜ and is a 8-14 membered
heterocycle consisting of carbon atoms, 1-3 N atoms,
and 0-1 heteroatom selected from the group consisting
of O, and S(O)ₚ;

Rᵃ, at each occurrence, is independently selected from: H,
C₁-₆ alkyl, phenyl, and benzyl;

Rᵃˡ, at each occurrence, is independently selected from: H,
C₁-₆ alkyl substituted with 0-1 Rᵉ, C₂-₆ alkenyl
substituted with 0-1 Rᵉ, C₂-₆ alkynyl substituted with
0-1 Rᵉ, and -(CH₂)ₓ-3-8 membered carbocyclic or
heterocyclic ring consisting of carbon atoms and 0-2
ring heteroatoms selected from N, NRᵃ², O, and S(O)ₚ,
and substituted with 0-3 Rᵉ;

alternatively, Rᵃ and Rᵃˡ when attached to a nitrogen are
taken together with the nitrogen to which they are
attached form a 5 or 6 membered heterocycle consisting
of carbon atoms and 0-1 additional heteroatoms
selected from N, NRᵃ², O, and S(O)ₚ;

Rᵃ², at each occurrence, is independently selected from:
C₁-₄ alkyl, phenyl, and benzyl;
R\textsuperscript{a3}, at each occurrence, is independently selected from: H, C\textsubscript{1-6} alkyl substituted with 0-1 R\textsuperscript{c1}, C\textsubscript{2-6} alkenyl substituted with 0-1 R\textsuperscript{c1}, C\textsubscript{2-6} alkynyl substituted with 0-1 R\textsuperscript{c1}, and -(CH\textsubscript{2})\textsubscript{r}-3-8 membered carbocyclic or heterocyclic ring consisting of carbon atoms and 0-2 ring heteroatoms selected from N, NR\textsuperscript{2a}, O, and S(O)\textsubscript{p} and substituted with 0-3 R\textsuperscript{c1};

R\textsuperscript{b}, at each occurrence, is independently selected from:

C\textsubscript{1-6} alkyl substituted with 0-1 R\textsuperscript{c1}, -OR\textsuperscript{a}, Cl, F, Br, I, =O, -CN, NO\textsubscript{2}, -NR\textsuperscript{a}R\textsuperscript{a1}, -C(O)R\textsuperscript{a}, -C(O)OR\textsuperscript{a}, 
-C(O)NR\textsuperscript{a}R\textsuperscript{a1}, -C(S)NR\textsuperscript{a}R\textsuperscript{a1}, -NR\textsuperscript{a}C(O)NR\textsuperscript{a}R\textsuperscript{a1}, -OC(O)NR\textsuperscript{a}R\textsuperscript{a1}, 
-NR\textsuperscript{a}C(O)OR\textsuperscript{a}, -S(O)\textsubscript{2}NR\textsuperscript{a}R\textsuperscript{a1}, -NR\textsuperscript{a}S(O)\textsubscript{2}R\textsuperscript{a3}, 
-NR\textsuperscript{a}S(O)\textsubscript{2}NR\textsuperscript{a}R\textsuperscript{a1}, -OS(O)\textsubscript{2}NR\textsuperscript{a}R\textsuperscript{a1}, -NR\textsuperscript{a}S(O)\textsubscript{2}R\textsuperscript{a3}, -S(O)\textsubscript{p}R\textsuperscript{a3}, 
CF\textsubscript{3}, -CF\textsubscript{2}CF\textsubscript{3}, -CHF\textsubscript{2}, -CH\textsubscript{2}F, and phenyl;

R\textsuperscript{c}, at each occurrence, is independently selected from: H, C\textsubscript{1-6} alkyl substituted with 0-2 R\textsuperscript{c1}, C\textsubscript{2-6} alkenyl substituted with 0-2 R\textsuperscript{c1}, C\textsubscript{2-6} alkynyl substituted with 
0-2 R\textsuperscript{c1}, -OR\textsuperscript{a}, Cl, F, Br, I, =O, -CN, NO\textsubscript{2}, CF\textsubscript{3}, -OCF\textsubscript{3}, 
-CF\textsubscript{2}CF\textsubscript{3}, -CH\textsubscript{2}F, -CHF\textsubscript{2}, -(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r}NR\textsuperscript{a}R\textsuperscript{a1}, 
-(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r}C(=NCN)NR\textsuperscript{a}R\textsuperscript{a1}, -(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r}C(=NR\textsuperscript{a})NR\textsuperscript{a}R\textsuperscript{a1}, 
-(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r}C(=NOR\textsuperscript{a})NR\textsuperscript{a}R\textsuperscript{a1}, -(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r}C(O)NR\textsuperscript{a}OH, 
-(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r}C(O)R\textsuperscript{a1}, -(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r}C(O)OR\textsuperscript{a1}, 
-(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r}C(S)OR\textsuperscript{a1}, -(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r}C(O)NR\textsuperscript{a}R\textsuperscript{a1}, 
-(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r}NRC(O)R\textsuperscript{a1}, -(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r}C(S)NR\textsuperscript{a}R\textsuperscript{a1}, 
-(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r}OC(O)NR\textsuperscript{a}R\textsuperscript{a1}, -(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r}NRC(O)OR\textsuperscript{a1}, 
-(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r}NRC(O)NR\textsuperscript{a}R\textsuperscript{a1}, -(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r}S(O)\textsubscript{p}R\textsuperscript{a3}, 
-(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r}SO\textsubscript{2}NR\textsuperscript{a}R\textsuperscript{a1}, -(CR\textsuperscript{a}R\textsuperscript{a1})\textsubscript{r}NR\textsuperscript{a}SO\textsubscript{2}R\textsuperscript{a3}, 

-(CR^aR^al)_r_1NR^aSO_2NR^aR^al, -(CR^aR^al)_r_1-C_3-10 carbocycle substituted with 0-2 R^c_1, and -(CR^aR^al)_r_1-5-14 membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)_p, and substituted with 0-2 R^c_1;

alternatively, when two R^c groups are attached to the same carbon atom they form a spiro ring C that is a 3-11 membered carbocycle substituted with 0-2 R^c_1 or a 3-13 membered heterocycle consisting of: carbon atoms, 0-3 carbonyl groups, 0-4 double bonds, and from 1-5 ring heteroatoms selected from O, N, and S(O)_p, and substituted with 0-2 R^c_1, provided that ring C contains other than a S-S, O-O, or S-O bond;

alternatively, when two R^c groups are attached to adjacent carbon atoms, together with the carbon atoms to which they are attached they form a 5-7 membered carbocyclic or heterocyclic ring consisting of: carbon atoms, 0-2 heteroatoms selected from the group consisting of N, O, and S(O)_p, and 0-3 double bonds, and substituted with 0-2 R^c_1;

R^c_1, at each occurrence, is independently selected from: H, C_1-6 alkyl, -OR^a, Cl, F, Br, I, =O, -CN, NO_2, -NR^aR^a_1, -C(O)R^a, -C(O)OR^a, -C(O)NR^aR^a_1, -NR^aC(O)NR^aR^a_1, -OC(O)NR^aR^a_1, -NR^aC(O)OR^a_1, -S(O)_2NR^aR^a_1, -NR^aS(O)_2R^a_2, -NR^aS(O)_2NR^aR^a_1, -OS(O)_2NR^aR^a_1, -NR^aS(O)_2R^a_2, -S(O)_pR^a_2, CF_3, -OCF_3, -CF_2CF_3, -CH_2F, and -CHF_2;
R⁹, at each occurrence, is independently selected from:

C₁-₆ alkyl, -OR⁹, Cl, F, Br, I, =O, -CN, NO₂, -NR³R⁹¹,
-C(O)R⁹, -C(O)OR⁹, -C(O)NR³R⁹¹, -C(S)NR³R⁹¹,
-NR³C(O)NR³R⁹¹, -OC(O)NR³R⁹¹, -NR³C(O)OR⁹¹,
-S(O)₂NR³R⁹¹, -NR³S(O)₂R³, -NR³S(O)₂NR³R⁹¹,
-OS(O)₂NR³R⁹¹, -NR³S(O)₂R³, -S(O)₂R³, CF₃, -CF₂CF₃,
C₃-10 carbocycle, and a 5-14 membered heterocycle
consisting of carbon atoms and 1-4 heteroatoms
selected from the group consisting of N, O, and S(O)ₚ;

R⁸, at each occurrence, is independently selected from: H,
C₁-₆ alkyl, -OR⁸, Cl, F, Br, I, =O, -CN, NO₂, -NR³R⁸,
-C(O)R⁸, -C(O)OR⁸, -C(O)NR³R⁸, -NR³C(O)NR³R⁸,
-OC(O)NR³R⁸, -NR³C(O)OR⁸, -S(O)₂NR³R⁸, -NR³S(O)₂R³,
-NR³S(O)₂NR³R⁸, -OS(O)₂NR³R⁸, -NR³S(O)₂R³, -S(O)₂R³, CF₃, -OCF₃, -CF₂CF₃, -CH₂F, and -CHF₂;

p, at each occurrence, is selected from 0, 1, and 2;

r, at each occurrence, is selected from 0, 1, 2, 3, and 4;

rl, at each occurrence, is selected from 0, 1, 2, 3, and 4;
and,

s, at each occurrence, is selected from 1, 2, 3, and 4.

14. A compound according to Claim 13, wherein;

Z⁸ is substituted with 0-4 R⁹ and is selected from the
group:
$W$ is $S$, $SO$, $SO_2$, $O$, or $NR^{11}$;

$R^{11}$, at each occurrence, is independently selected from: $H$, $C_1-4$ alkyl, phenyl, and benzyl;

$R^C$, at each occurrence, is independently selected from: $H$, $C_1-6$ alkyl substituted with 0-2 $R^C_1$, $C_2-6$ alkenyl substituted with 0-2 $R^C_1$, $C_2-6$ alkynyl substituted with 0-2 $R^C_1$, $-OR^a$, $Cl$, $F$, $Br$, $I$, $=O$, $-CN$, $NO_2$, $CF_3$, $-OCF_3$, $-CF_2CF_3$, $-CH_2F$, $-CHF_2$, $-(CR^aRa^1)_1NR^aRa^1$, $-(CR^aRa^1)_1C(O)Ra^1$, $-(CR^aRa^1)_1C(O)OR^aRa^1$, $-(CR^aRa^1)_1C(O)NR^aRa^1$, $-(CR^aRa^1)_1NR^aC(O)Ra^1$, $-(CR^aRa^1)_1SO_2NR^aRa^1$, $-(CR^aRa^1)_1NR^aSO_2Ra^3$, $-(CR^aRa^1)_1-C_3-10$ carbocycle substituted with 0-2 $R^C_1$, and $-(CR^aRa^1)_1-5-14$ membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of $N$, $O$, and $S(O)_p$, and substituted with 0-2 $R^C_1$;

Alternatively, when two $R^C$ groups are attached to the same carbon atom they form a spiro ring $C$ that is a 3-11 membered carbocycle substituted with 0-2 $R^C_1$ or a 3-13 membered heterocycle consisting of: carbon atoms, 0-3
carbonyl groups, 0-4 double bonds, and from 1-5 ring heteroatoms selected from O, N, and S(O)_p, and substituted with 0-2 R^c, provided that ring C contains other than a S-S, O-O, or S-O bond; and, 5

alternatively, when two R^c groups are attached to adjacent carbon atoms, together with the carbon atoms to which they are attached they form a 5-7 membered carbocyclic or heterocyclic ring consisting of: carbon atoms, 0-2 heteroatoms selected from the group consisting of N, O, and S(O)_p, and 0-3 double bonds, and substituted with 0-2 R^c.

15 15. A compound according to Claim 14, wherein;

R^1 and R^4 together with the carbon atoms to which they are attached combine to form a 3-8 membered carbocyclic or heterocyclic ring consisting of carbon atoms and 0-2 ring heteroatoms selected from O, N, NR^10, and S(O)_p, and substituted with 0-4 R^c;

R^2 is selected from: Q, -C_1-6 alkyne-Q, -C_2-6 alkenyne-Q, -C_2-6 alkynylene-Q, -C_1-6 alkenylene-Q, 

- (CR^aRa^1)_r1O(CR^aRa^1)_r-Q,
- (CR^aRa^1)_r1NR^a(CR^aRa^1)_r-Q, - (CR^aRa^1)_r1C(O)(CR^aRa^1)_r-Q,
- (CR^aRa^1)_r1C(O)O(CR^aRa^1)_r-Q, - (CR^aRa^1)_r1C(O)NR^aRa^1,
- (CR^aRa^1)_r1C(O)NR^a(CR^aRa^1)_r-Q,
- (CR^aRa^1)_r1S(O)_p(CR^aRa^1)_r-Q,
- (CR^aRa^1)_r1SO_2NR^a(CR^aRa^1)_r-Q, and
- (CR^aRa^1)_r1NR^aSO_2(CR^aRa^1)_r-Q;

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Q, at each occurrence, is independently selected from: H, a C_{3-10} carbocycle substituted with 0-5 R^d, and a 5-10 membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)_p, and substituted with 0-5 R^d;

R^3 is selected from: Q^1, -C_{1-6} alkyne-Q^1, -C_{2-6} alkenylene-Q^1, -C_{2-6} alkynylene-Q^1, -\((\text{CR}^a\text{Ra}^a)_1\text{O}(\text{CH}_2)_\text{r}-\text{Q}^1\), -\((\text{CR}^a\text{Ra}^a)_1\text{NR}^a(\text{CR}^a\text{Ra}^a)_1\text{r}-\text{Q}^1\), -\((\text{CR}^a\text{Ra}^a)_1\text{NR}^a\text{C}(\text{O})(\text{CR}^a\text{Ra}^a)_1\text{r}-\text{Q}^1\), -\((\text{CR}^a\text{Ra}^a)_1\text{C}(\text{O})\text{NR}^a(\text{CR}^a\text{Ra}^a)_1\text{r}-\text{Q}^1\), -\((\text{CR}^a\text{Ra}^a)_1\text{C}(\text{O})(\text{CR}^a\text{Ra}^a)_1\text{r}-\text{Q}^1\), -\((\text{CR}^a\text{Ra}^a)_1\text{C}(\text{O})\text{O}(\text{CR}^a\text{Ra}^a)_1\text{r}-\text{Q}^1\), -\((\text{CR}^a\text{Ra}^a)_1\text{S}(\text{O})_p(\text{CR}^a\text{Ra}^a)_1\text{r}-\text{Q}^1\), and -\((\text{CR}^a\text{Ra}^a)_1\text{SO}_2\text{NR}^a(\text{CR}^a\text{Ra}^a)_1\text{r}-\text{Q}^1\);

Q^1, at each occurrence, is independently selected from: H, a C_{3-10} carbocycle substituted with 0-5 R^d, and a 5-10 membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)_p, and substituted with 0-5 R^d;

R^{10}, at each occurrence, is independently selected from: H, C_{1-6} alkyl substituted with 0-2 R^c, C_{2-6} alkenyl substituted with 0-2 R^c, C_{2-6} alkynyl substituted with 0-2 R^c, -\((\text{CR}^a\text{Ra}^a)_1\text{sNR}^a\text{Ra}^a_1\), -\((\text{CR}^a\text{Ra}^a)_1\text{C}(\text{O})\text{Ra}^a_1\), -\((\text{CR}^a\text{Ra}^a)_1\text{C}(\text{O})\text{OR}^a_1\), -\((\text{CR}^a\text{Ra}^a)_1\text{C}(\text{O})\text{NR}^a\text{Ra}^a_1\), -\((\text{CR}^a\text{Ra}^a)_1\text{sNR}^a\text{C}(\text{O})\text{Ra}^a_1\), -\((\text{CR}^a\text{Ra}^a)_1\text{S}(\text{O})_p\text{Ra}^a_3\), -\((\text{CR}^a\text{Ra}^a)_1\text{SO}_2\text{NR}^a\text{Ra}^a_1\), -\((\text{CR}^a\text{Ra}^a)_1\text{sNR}^a\text{SO}_2\text{Ra}^a_3\),
-(CR^aR^a)^r_1-C_3-10 carbocycle substituted with 0-2 R^c, and -(CR^aR^a)^r_1-5-14 membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)_p, and substituted with 0-2 R^c;

R^c, at each occurrence, is independently selected from: H, C_1-6 alkyl substituted with 0-2 R^c, C_2-6 alkenyl substituted with 0-2 R^c, C_2-6 alkynyl substituted with 0-2 R^c, -OR^a, Cl, F, Br, I, =O, -CN, NO_2, CF_3, 
-CF_2CF_3, -(CR^aR^a)^r_1NR^aR^a, -(CR^aR^a)^r_1C(O)R^a, -(CR^aR^a)^r_1C(O)OR^a, -(CR^aR^a)^r_1C(O)NR^aR^a, -(CR^aR^a)^r_1C(O)NR^aR^a, -(CR^aR^a)^r_1C(O)NR^aR^a, -(CR^aR^a)^r_1C(O)NR^aR^a, -(CR^aR^a)^r_1SO_2NR^aR^a, -(CR^aR^a)^r_1SO_2NR^aR^a; 

-(CR^aR^a)^r_1-C_3-10 carbocycle substituted with 0-2 R^c, and -(CR^aR^a)^r_1-5-10 membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)_p, and substituted with 0-2 R^c;

R^c, at each occurrence, is independently selected from: H, C_1-4 alkyl, -OR^a, Cl, F, Br, I, =O, CF_3, -CN, NO_2, 
-NR^aR^a, -C(O)OR^a, and -C(O)NR^aR^a;

R^d, at each occurrence, is independently selected from: C_1-6 alkyl, -OR^a, Cl, F, Br, I, =O, -CN, NO_2, -NR^aR^a, 
-C(O)R^a, -C(O)OR^a, -C(O)NR^aR^a, -C(S)NR^aR^a, 
-NR^aC(O)NR^aR^a, -OC(O)NR^aR^a, -NR^aC(O)OR^a, 
-S(O)_2NR^aR^a, -NR^aS(O)_2R^a, -NR^aS(O)_2NR^aR^a,
-OS(O)₂NRₙRa₁, -NRₙS(O)₂Ra₃, -S(O)ₚRa₃, CF₃, -CF₂CF₃, C₃₋₆ carbocycle, and a 5-6 membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)ₚ; and,

Rₙ, at each occurrence, is independently selected from: H, C₁₋₄ alkyl, -ORₙ, Cl, F, Br, I, =O, CF₃, -CN, NO₂, -NRₙRa, -C(O)ORₙ, and -C(O)NRₙRa.

16. A compound according to Claim 15, wherein:

R¹ and R⁴ together with the carbon atoms to which they are attached combine to form a 3-6 membered carbocyclic or heterocyclic ring consisting of carbon atoms and 0-2 ring heteroatoms selected from O, N, NR¹⁰, and S(O)ₚ, and substituted with 0-3 Rᶜ;

R² is selected from: Q, -C₁₋₆ alkylene-Q,
-C₁₋₆ alkenylene-Q, -(CRₙRa₁)ᵣ₁O(CRₙRa₁)ᵣ₋Q,
-(CRₙRa₁)ᵣ₁NRₙ(CRₙRa₁)ᵣ₋Q, -(CRₙRa₁)ᵣ₁C(O)(CRₙRa₁)ᵣ₋Q,
-(CRₙRa₁)ᵣ₁C(O)O(CRₙRa₁)ᵣ₋Q, -(CRₙRa₁)ᵣ₁C(O)NRₙRa₁,
-(CRₙRa₁)ᵣ₁C(O)NRₙ(CRₙRa₁)ᵣ₋Q,
-(CRₙRa₁)ᵣ₁S(O)ₚ(CRₙRa₁)ᵣ₋Q, and
-(CRₙRa₁)ᵣ₁SO₂NRₙ(CRₙRa₁)ᵣ₋Q;

Q, at each occurrence, is independently selected from: H, a C₃₋₆ carbocycle substituted with 0-3 Rd, and a 5-10 membered heterocycle consisting of carbon atoms and
1-4 heteroatoms selected from the group consisting of N, O, and S(O)ₚ, and substituted with 0-3 Rᵈ;

R³ is selected from: Q¹, -C₁₋₆ alkyne-Q¹,
-C₂₋₆ alkenylene-Q¹, -(CRᵃRᵃ₁)ᵣ₁O(CH₂)ᵣ-Q¹,
-(CRᵃRᵃ₁)ᵣ₁NRᵃ(CRᵃRᵃ₁)ᵣ-Q¹,
-(CRᵃRᵃ₁)ᵣ₁C(O)NRᵃ(CRᵃRᵃ₁)ᵣ-Q¹,
-(CRᵃRᵃ₁)ᵣ₁C(O)(CRᵃRᵃ₁)ᵣ-Q¹,
-(CRᵃRᵃ₁)ᵣ₁C(O)O(CRᵃRᵃ₁)ᵣ-Q¹,
-(CRᵃRᵃ₁)ᵣ₁S(O)ₚ(CRᵃRᵃ₁)ᵣ-Q¹, and
-(CRᵃRᵃ₁)ᵣ₁SO₂NRᵃ(CRᵃRᵃ₁)ᵣ-Q¹;

Q¹, at each occurrence, is independently selected from: H, a C₃₋₆ carbocycle substituted with 0-3 Rᵈ, and a 5-10 membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)ₚ, and substituted with 0-3 Rᵈ;

R¹ₒ, at each occurrence, is independently selected from: H, C₁₋₆ alkyl substituted with 0-1 Rᶜ¹, C₂₋₆ alkenyl substituted with 0-1 Rᶜ¹, C₂₋₆ alkynyl substituted with 0-1 Rᶜ¹, -(CRᵃRᵃ₁)ᵣ₁C(O)Rᵃ¹, -(CRᵃRᵃ₁)ᵣ₁C(O)Oᵣᵃ¹,
-(CRᵃRᵃ₁)ᵣ₁C(O)NRᵃᵣᵃ¹, -(CRᵃRᵃ₁)ᵣ₁S(O)ₚᵣᵃ³,
-(CRᵃRᵃ₁)ᵣ₁SO₂NRᵃᵣᵃ¹, -(CRᵃRᵃ₁)ᵣ₁-C₃₋₆ carbocycle substituted with 0-2 Rᶜ¹, and -(CRᵃRᵃ₁)ᵣ₁-5-10 membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)ₚ, and substituted with 0-2 Rᶜ¹;
Z is selected from: phenyl substituted with 0-3 R\text{b}, and a 5-6 membered heteroaryl consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)\text{p}, and substituted with 0-3 R\text{b};

provided that X, Y, and Z do not combine to form a N-O, O-O, or S(O)\text{p}-O group;

Z\text{a} is 4-quinoliny1 substituted with 0-2 R\text{c};

R\text{a}, at each occurrence, is independently selected from: H and C\text{1-4} alkyl;

R\text{a1}, at each occurrence, is independently selected from: H, C\text{1-4} alkyl, phenyl, and benzyl;

alternatively, R\text{a} and R\text{a1} when attached to a nitrogen are taken together with the nitrogen to which they are attached form a 5 or 6 membered heterocycle consisting of carbon atoms and 0-1 additional heteroatoms selected from N, NR\text{a2}, O, and S(O)\text{p};

R\text{b}, at each occurrence, is independently selected from: C\text{1-6} alkyl, -OR\text{a}, Cl, F, Br, =O, -CN, -NR\text{a}R\text{a1}, -C(O)R\text{a}, -C(O)OR\text{a}, -C(O)NR\text{a}R\text{a1}, -S(O)\text{2}NR\text{a}R\text{a1}, -S(O)\text{p}R\text{a3}, and CF\text{3};

R\text{c}, at each occurrence, is independently selected from: H, C\text{1-6} alkyl substituted with 0-1 R\text{c1}, C\text{2-6} alkenyl substituted with 0-1 R\text{c1}, C\text{2-6} alkynyl substituted with 0-1 R\text{c1}, -OR\text{a}, Cl, F, Br, =O, -CN, CF\text{3}, -NR\text{a}R\text{a1}, -(CR\text{a}R\text{a1})\text{r1}C(O)R\text{a1}, -(CR\text{a}R\text{a1})\text{r1}C(O)OR\text{a1},
\[-(\text{CR}^\text{Ra})_r^1\text{C}(\text{O})\text{NR}^\text{Ra}^1, -(\text{CR}^\text{Ra})_r^1\text{S}(\text{O})_p\text{Ra}^3,\]
\[-(\text{CR}^\text{Ra})_r^1\text{SO}_2\text{NR}^\text{Ra}^1, \text{C}_3-6 \text{ carbocycle}, \text{ and a 5-6 membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(\text{O})_p; and,}\]

\text{R}^d, \text{ at each occurrence, is independently selected from:} \]
\[\text{C}_1-6 \text{ alkyl, } -\text{OR}^\text{a}, \text{Cl, F, Br, } =\text{O}, -\text{CN}, -\text{NR}^\text{Ra}^1, -\text{C}(\text{O})\text{Ra}, -\text{C}(\text{O})\text{OR}^\text{a}, -\text{C}(\text{O})\text{NR}^\text{Ra}^1, -\text{S}(\text{O})_2\text{NR}^\text{Ra}^1, -\text{S}(\text{O})_p\text{Ra}^3, \text{CF}_3, \text{C}_3-6 \text{ carbocycle, and a 5-6 membered heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(\text{O})_p}.\]

17. A compound according to Claim 16, wherein;

\text{R}^1 \text{ and R}^d \text{ together with the carbon atoms to which they are attached combine to form a 3-6 membered carbocyclic or heterocyclic ring consisting of carbon atoms and 0-2 ring heteroatoms selected from O, N, NR}^{10}, \text{ and S(\text{O})}_\text{p}, \text{ and substituted with 0-2 } \text{R}^c;\]

\text{R}^2 \text{ is selected from: Q, } -\text{C}_1-6 \text{ alkylene-Q,} \]
\[-(\text{CR}^\text{Ra})_r^1\text{C}(\text{O})(\text{CR}^\text{Ra})^1_r^-\text{Q}, -(\text{CR}^\text{Ra})_r^1\text{C}(\text{O})\text{O}(\text{CR}^\text{Ra})_r^-\text{Q},\]
\[-(\text{CR}^\text{Ra})_r^1\text{C}(\text{O})\text{NR}^\text{Ra}^1, -(\text{CR}^\text{Ra})_r^1\text{C}(\text{O})\text{NR}^\text{Ra}^1(\text{CR}^\text{Ra})_r^-\text{Q}, \text{ and}\]
\[-(\text{CR}^\text{Ra})_r^1\text{S}(\text{O})_p(\text{CR}^\text{Ra})_r^-\text{Q};\]

\text{Q, at each occurrence, is independently selected from: H, a } \text{C}_3-6 \text{ carbocycle substituted with 0-2 R}^d, \text{ and a 5-6 membered heterocycle consisting of carbon atoms and} \]

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1-4 heteroatoms selected from the group consisting of N, O, and S(O)\textsubscript{p}, and substituted with 0-2 R\textsuperscript{d};

R\textsuperscript{3} is selected from: Q\textsuperscript{1}, -C\textsubscript{1-6} alkylene-Q\textsuperscript{1},
- (CR\textsuperscript{a}Ra\textsuperscript{a})\textsubscript{r1}O(CH\textsubscript{2})\textsubscript{x}-Q\textsuperscript{1}, -(CR\textsuperscript{a}Ra\textsuperscript{a})\textsubscript{r1}NR\textsuperscript{a}a(CR\textsuperscript{a}Ra\textsuperscript{a})\textsubscript{r}-Q\textsuperscript{1},
4 - (CR\textsuperscript{a}Ra\textsuperscript{a})\textsubscript{r1}C(O)NR\textsuperscript{a}a(CR\textsuperscript{a}Ra\textsuperscript{a})\textsubscript{r}-Q\textsuperscript{1},
- (CR\textsuperscript{a}Ra\textsuperscript{a})\textsubscript{r1}C(O)(CR\textsuperscript{a}Ra\textsuperscript{a})\textsubscript{r}-Q\textsuperscript{1},
- (CR\textsuperscript{a}Ra\textsuperscript{a})\textsubscript{r1}C(O)O(CR\textsuperscript{a}Ra\textsuperscript{a})\textsubscript{r}-Q\textsuperscript{1},
- (CR\textsuperscript{a}Ra\textsuperscript{a})\textsubscript{r1}S(O)\textsubscript{p}(CR\textsuperscript{a}Ra\textsuperscript{a})\textsubscript{r}-Q\textsuperscript{1}, and
10 - (CR\textsuperscript{a}Ra\textsuperscript{a})\textsubscript{r1}SO\textsubscript{2}NR\textsuperscript{a}a(CR\textsuperscript{a}Ra\textsuperscript{a})\textsubscript{r}-Q\textsuperscript{1};

Q\textsuperscript{1}, at each occurrence, is independently selected from: H, a C\textsubscript{3-6} carbocycle substituted with 0-2 R\textsuperscript{d}, and a 5-6 membered heterocycle consisting of carbon atoms and
1-4 heteroatoms selected from the group consisting of N, O, and S(O)\textsubscript{p}, and substituted with 0-2 R\textsuperscript{d};

R\textsuperscript{10}, at each occurrence, is independently selected from: H, C\textsubscript{1-6} alkyl substituted with 0-1 R\textsuperscript{c1}, C\textsubscript{2-6} alkenyl
20 substituted with 0-1 R\textsuperscript{c1}, C\textsubscript{2-6} alkynyl substituted with
0-1 R\textsuperscript{c1}, -(CR\textsuperscript{a}Ra\textsuperscript{a})\textsubscript{r1}C(O)Ra\textsuperscript{a}, -(CR\textsuperscript{a}Ra\textsuperscript{a})\textsubscript{r1}C(O)ORa\textsuperscript{a},
- (CR\textsuperscript{a}Ra\textsuperscript{a})\textsubscript{r1}C(O)NRa\textsuperscript{a}, -(CR\textsuperscript{a}Ra\textsuperscript{a})\textsubscript{r1}S(O)\textsubscript{p}Ra\textsuperscript{3},
- (CR\textsuperscript{a}Ra\textsuperscript{a})\textsubscript{r1}SO\textsubscript{2}NRa\textsuperscript{a}, -(CH\textsubscript{2})\textsubscript{r1}-C\textsubscript{3-6} carbocycle
substituted with 0-2 R\textsuperscript{c1}, and -(CH\textsubscript{2})\textsubscript{r1}-5-6 membered
25 heterocycle consisting of carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)\textsubscript{p}, and substituted with 0-2 R\textsuperscript{c1};

X-Y is CH\textsubscript{2} or CH\textsubscript{2}O;
Z is phenyl substituted with 0-3 R²;

R¹, at each occurrence, is independently selected from: H and C₁-₄ alkyl;

R¹₁, at each occurrence, is independently selected from: H, C₁-₄ alkyl, phenyl, and benzyl;

R², at each occurrence, is independently selected from:

C₁-₄ alkyl, -OR¹, Cl, F, =O, -NR²R¹₁, -C(O)R¹,
-C(O)OR¹, -C(O)NR²R¹₁, -S(O)₂NR²R¹₁, -S(O)₃R³, and CF₃;

R³, at each occurrence, is independently selected from: H, C₁-₆ alkyl, C₂-₆ alkenyl, C₂-₆ alkynyl, -OR¹, Cl, F, Br, =O, -NR²R¹₁, CF₃, -(CR²R¹₁)ₗ₁C(O)R¹₁,
-(CR²R¹₁)ₗ₁C(O)OR¹, -(CR²R¹₁)ₗ₁C(O)NR²R¹₁,
-(CR²R¹₁)ₗ₁S(O)₃R³, -(CR²R¹₁)ₗ₁SO₂NR²R¹₁, and phenyl;

and,

R⁴, at each occurrence, is independently selected from:

C₁-₆ alkyl, -OR¹, Cl, F, Br, =O, -NR²R¹₁, -C(O)R¹,
-C(O)NR²R¹₁, -S(O)₂NR²R¹₁, -S(O)₃R³, CF₃, and phenyl.

18. A compound according to Claim 13, wherein the compound is selected from the group:

hydroxy[4-{4-[(2-methyl-4-
quinoilinyl)methoxy]phenyl}sulfonyl]tetrahydro-3-
furanyl]formamide;
hydroxy[4-((2-methyl-1H-benzimidazol-1-yl)methyl)phenyl]sulfonyl]tetrahydro-3-furanyl]formamide; and

5 hydroxy[4-((2-methyl-4-quinoliny1)methyl)phenyl]sulfonyl]tetrahydro-3-furanyl]formamide;

or a pharmaceutically acceptable salt form thereof.

10

19. A pharmaceutical composition, comprising: a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of any one of Claims 1-18 or a pharmaceutically acceptable salt form thereof.

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20. Use of a compound of any one of Claims 1-18 or a pharmaceutically acceptable salt form thereof in the manufacture of a medicament for treating treating an inflammatory disorder.

20

21. Use of a compound of any one of Claims 1-18 or a pharmaceutically acceptable salt form thereof in the manufacture of a medicament for treating a condition or disease mediated by MMPs, TACE, aggrecanase, or a combination thereof.

25

22. Use of a compound according to Claim 21, wherein the disease or condition is selected from acute infection,
acute phase response, age related macular degeneration, alcoholic liver disease, allergy, allergic asthma, aneurism, anorexia, aortic aneurism, asthma, athersclerosis, atopic dermatitis, autoimmune disease, autoimmune hepatitis, Bechet's disease, cachexia, calcium pyrophosphate dihydrate deposition disease, cardiovascular effects, chronic fatigue syndrome, chronic obstruction pulmonary disease, coagulation, congestive heart failure, corneal ulceration, Crohn's disease, enteropathic arthropathy, Felty's syndrome, fever, fibromyalgia syndrome, fibrotic disease, gingivitis, glucocorticoid withdrawal syndrome, gout, graft versus host disease, hemorrhage, HIV infection, hyperoxic alveolar injury, infectious arthritis, inflammation, intermittent hydrarthrosis, Lyme disease, meningitis, multiple sclerosis, myasthenia gravis, mycobacterial infection, neovascular glaucoma, osteoarthritis, pelvic inflammatory disease, periodontitis, polymyositis/dermatomyositis, post-ischaemic reperfusion injury, post-radiation asthenia, psoriasis, psoriatic arthritis, pulmonary emphysema, pydoderma gangrenosum, relapsing polychondritis, Reiter's syndrome, rheumatic fever, rheumatoid arthritis, sarcoidosis, scleroderma, sepsis syndrome, Still's disease, shock, Sjogren's syndrome, skin inflammatory diseases, solid tumor growth and tumor invasion by secondary metastases, spondylitis, stroke, systemic lupus erythematosus, ulcerative colitis, uveitis, vasculitis, and Wegener's granulomatosis.
23. A compound of any one of Claims 1-18 or a pharmaceutically acceptable salt form thereof for use in therapy.

24. Use of a compound of any one of Claims 1-18 in combination with one or more additional anti-inflammatory agents selected from selective COX-2 inhibitors, interleukin-1 antagonists, dihydroorotate synthase inhibitors, p38 MAP kinase inhibitors, TNF-α inhibitors, TNF-α sequestration agents, and methotrexate, for treating treating inflammatory disorders.
A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : Please See Extra Sheet.
US CL : Please See Extra Sheet.
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)
U.S. : 546/172, 199, 306.1; 548/652; 544/51
514/314, 892, 897, 419, 224.2

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)
CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y</td>
<td>WO 00/012478 A (ZENECA LIMITED) 09 March 2000, pages 4-6.</td>
<td>1-24</td>
</tr>
</tbody>
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☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

Date of the actual completion of the international search 20 FEBRUARY 2003

27 MAR 2003

Date of mailing of the international search report

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Form PCT/ISA/910 (second sheet) (July 1998)
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER:

IPC (7):

C07D 215/36, 401/00, 403/02, 209/02, 279/16
A61K 31/47, 31/445, 31/415, 31/40, 31/54

A. CLASSIFICATION OF SUBJECT MATTER:

US CL:

544/172, 199, 306:1; 546/452; 544/51
514/314, 322, 397, 412, 224:2