(57) Abrégé/Abstract:
The present invention relates to certain substituted heterocycles of Formula (I) which may be useful in the treatment of diseases related to uncontrolled proliferation, such as lymphoma, Hodgkin's Disease, leukemia, breast cancer, prostate cancer or cancers in general; and inflammation, such as osteoarthritis, rheumatoid arthritis, Crohn's Disease or Inflammatory Bowel Disease.
CROHN'S DISEASE OR INFLAMMATORY BOWEL DISEASE.

WO 01/16123 A1

(54) Title: BENZYLIDENE-THIAZOLIDINEDIONES AND ANALOGUES AND THEIR USE IN THE TREATMENT OF INFLAMMATION

(57) Abstract: The present invention relates to certain substituted heterocycles of Formula (I) which may be useful in the treatment of diseases related to uncontrolled proliferation, such as lymphoma, Hodgkin's Disease, leukemia, breast cancer, prostate cancer or cancers in general; and inflammation, such as osteoarthritis, rheumatoid arthritis,
This application claims priority to the U.S. provisional application Serial Number 60/151,670, filed August 31, 1999, the disclosure of which application is hereby incorporated in its entirety by this reference.

Background of the Invention

Tumor necrosis factor-alpha (TNF-α) is a pleiotropic cytokine that has been implicated as a significant mediator in a variety of inflammatory and immunological responses, as well as in the pathogenesis of endotoxic and septic shock. Nitric oxide synthases (e.g., NOS), are hemoproteins with a cytochrome "P450-like" active site, that catalyze the oxidation of arginine to nitric oxide (NO) and citrulline. The various isoforms of NOS reflect the diverse range of activities attributed to NO, such as, regulation of blood pressure, gastric motility, anti-bacterial activity, and neurotransmission. However, the cytotoxic nature of NO is involved in several neurodegenerative disorders, inflammatory and other diseases. Based on the connection between chronic inflammation and carcinogenic transformation, compounds that are effective anti-inflammatory agents are can be effective against cancer.

The present invention relates to certain substituted heterocycles, which are useful in the inhibition of certain inflammatory mediators such as, for example, TNF-α and/or nitric oxide synthase (NOS), including the isoforms thereof. These heterocycles can be useful in the treatment of diseases, such as cancer or uncontrolled proliferation, inflammation, and the like.

Summary of the Invention

The present invention relates to certain substituted heterocycles, which are useful in the inhibition of certain inflammatory mediators such as, for example, tumor necrosis factor-alpha (TNFα) and/or nitric oxide synthase including the isoforms thereof. These heterocycles can be useful in the treatment of diseases related to inflammation, cancer or uncontrolled proliferation, and autoimmune diseases.
Some disclosed embodiments of the invention relate to compounds of the
Formula (I):

wherein:

\[ R_1 \text{ and } R_2 \text{ are 1) independently or together hydrogen, alkyl, substituted alkyl, haloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substituted alkoxy, hydroxy, acyl, amino, mono-substituted amino, di-substituted amino, carboxyl, carboalkoxy, alkylcarboxamide, substituted alkylcarboxamide, dialkylcarboxamide, substituted dialkylcarboxamide or haloalkoxy; or 2) } R_1 \text{ and } R_2 \text{ together with the aromatic ring bonded thereto form a cycloalkyl, substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl residue that may optionally comprise 1 or 2 heteroatoms selected from O, S, NH or N-alkyl;}

\[ R_3 \text{ and } R_4 \text{ are independently or together hydrogen, alkyl, substituted alkyl, haloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, halogen, cyano, nitro, hydroxy, acyloxy, amino, mono-substituted amino, di-substituted amino, alkylsulfonamide, arylsulfonamide, alkylurea, arylurea, alkylcarbamate, arylcarbamate, heteroaryl, alkoxy, substituted alkoxy, haloalkoxy, thioalkyl, thiohaloalkyl, carboxyl, carboalkoxy, alkylcarboxamide, substituted alkylcarboxamide, dialkylcarboxamide or substituted dialkylcarboxamide;}

\[ A \text{ is } -CR_6R_7- \text{ where } R_6 \text{ and } R_7 \text{ are independently or together hydrogen, alkyl, substituted alkyl, alkoxy, substituted alkoxy or haloalkoxy; or } R_6 \text{ and } R_7;\]
together form a cycloalkyl residue that may optionally comprise 1 or 2 heteroatoms selected from O, S, NH and N-alkyl;

\[ \text{Ar is Formula (II), (III), (IV), (V) or (VI):} \]

\[
\begin{align*}
\text{(II)} & \quad \text{(III)} & \quad \text{(IV)} \\
\text{(V)} & \quad \text{(VI)}
\end{align*}
\]

where \( R_8, R_9 \) and \( R_{10} \) are independently or together hydrogen, alkyl, substituted alkyl, haloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, halogen, cyano, nitro, hydroxyl, acyloxy, amino, mono-substituted amino, di-substituted amino, alkylamide, alkylsulfonamide, arylsulfonamide, alkylurea, arylurea, alkylcarbamate, arylcarbamate, alkoxy, substituted alkoxy, haloalkoxy, thioalkyl, thiohaloalkyl, carboxy, carboalkoxy, alkylcarboxamide, substituted alkylcarboxamide, dialkylcarboxamide or substituted dialkylcarboxamide;

\[ R_8 \text{ is hydrogen, halogen, hydroxy, alkyl or substituted alkyl;} \]

- - - - - - represents a bond present or absent; and
W, X, Y and Z are independently or together –C(O)–, –C(S)–, –S–, –O– or
-NH-residues that together form a 2,4-thiazolidinedione, 2-thioxo-4-
thiazolidinedione, isoxazolidinedione, 2,4-imidazolidinedione or 2-thioxo-4-
imidazolidinedione residue; or a pharmaceutically acceptable salt thereof.

Other embodiments of the invention provide methods of synthesizing the
compounds of the invention.

In another aspect, this invention relates to the use of the compounds disclosed
herein for treating diseases of uncontrolled cellular proliferation; and for the treatment
inflammatory diseases.

The invention also provides for a method of treatment of a disease of uncontrolled
cellular proliferation comprising administering to a mammal diagnosed as having a
disease of uncontrolled cellular proliferation; and a method of treating an inflammatory
disease comprising administering to a mammal diagnosed as having an inflammatory
disease.

In another aspect, this invention relates to a pharmaceutical composition
comprising a compound disclosed herein in admixture with one or more pharmaceutically
acceptable excipients.

**Brief Description of the Drawings**

Figure 1 shows examples of the inhibition of TNFα activity.

Figure 2 shows examples of the inhibition of NOS activity.

Figure 3 shows examples of methods for the compounds disclosed herein wherein
n is 0 and m is 1.

Figure 4 shows examples of methods for synthesizing the compounds disclosed
herein wherein n and m are 1.

Figure 5 shows examples of methods for synthesizing the compounds disclosed
herein wherein n is 0 or 1 and m is 0.

**Detailed Description**

**Definitions**
In the specification and Formulae described herein the following terms are hereby defined.

The term "alkyl" denotes a radical containing 1 to 12 carbons, such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, t-butyl, amyl, t-amyl, n-pentyl and the like.

The term "alkenyl" denotes a radical containing 1 to 12 carbons such as vinyl, allyl, 2-butene, 3-butene, 2-pentene, 3-pentene, 4-pentenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 5-heptenyl, 6-heptenyl and the like. The term "alkenyl" includes dienes and trienes of straight and branch chains.

The term "alkynyl" denotes a radical containing 1 to 12 carbons, such as ethynyl, 1-propynyl, 2-propynyl, 1-butyne, 2-butyne, 3-butyne, 1-pentyne, 2-pentyne, 3-pentyne, 4-pentyne, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl and the like. The term "alkynyl" includes di- and tri-ynes.

The term "substituted alkyl" denotes a radical containing 1 to 12 carbons of the above definitions that are substituted with one or more groups, but preferably one, two or three groups, selected from hydroxyl, cycloalkyl, amino, mono-substituted amino, disubstituted amino, acyloxy, nitro, cyano, carboxy, carboalkoxy, alkylcarboxamide, substituted alkylcarboxamide, dialkylcarboxamide, substituted dialkylcarboxamide, substituted alkylsulfonamide, alkylsulfanyl, thioalkyl, thiohaloalkyl, alkoxy, substituted alkoxy or haloalkoxy. When more than one group is present then they may be the same or different.

The term "substituted alkenyl" denotes a radical containing 1 to 12 carbons of the above definitions that are substituted with one or more groups, but preferably one, two or three groups, selected from halogen, hydroxyl, cycloalkyl, amino, mono-substituted amino, disubstituted amino, acyloxy, nitro, cyano, carboxy, carboalkoxy, alkylcarboxamide, substituted alkylcarboxamide, dialkylcarboxamide, substituted dialkylcarboxamide, substituted alkylsulfonamide, alkylsulfanyl, thioalkyl, thiohaloalkyl, alkoxy, substituted alkoxy or haloalkoxy. When more than one group is present then they may be the same or different.

The term "substituted alkynyl" denotes a radical containing 1 to 8 carbons of the above definitions that are substituted with one or more groups, but preferably one or two groups, selected from halogen, hydroxyl, cycloalkyl, amino, mono-substituted amino, di-
substituted amino, acyloxy, nitro, cyano, carboxy, carboalkoxy, alkylicarboxamide, substituted alkylcarboxamide, dialkylcarboxamide, substituted dialkylcarboxamide, alkylsulfonyl, alkylsulfinyl, thioalkyl, thiohaloalkyl, alkoxy, substituted alkoxy or haloalkoxy.

The term “cycloalkyl” denotes a radical containing 3 to 8 carbons, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclopenyl, cyclohexyl, cycloheptyl and the like. The term “substituted cycloalkyl” denotes a cycloalkyl as defined above that is further substituted with one or more groups selected from halogen, alkyl, hydroxyl, alkoxy, substituted alkoxy, carboxy, carboalkoxy, alkylicarboxamide, substituted alkylcarboxamide, dialkylcarboxamide, substituted dialkylcarboxamide, amino, mono-substituted amino or di-substituted amino. When the cycloalkyl is substituted with more than one group, they may be the same or different.

The term “cycloalkenyl” denotes a radical containing 3 to 8 carbons, such as cyclopropenyl, 1-cyclobutenyl, 2-cyclobutenyl, 1-cyclopentenyl, 2-cyclopentenyl, 3-cyclopentenyl, 1-cyclohexyl, 2-cyclohexyl, 3-cyclohexyl and the like. The term “substituted cycloalkenyl” denotes a cycloalkyl as defined above further substituted with one or more groups selected from halogen, alkyl, hydroxyl, alkoxy, substituted alkoxy, haloalkoxy, carboxy, carboalkoxy, alkylicarboxamide, substituted alkylcarboxamide, dialkylcarboxamide, substituted dialkylcarboxamide, amino, mono-substituted amino or di-substituted amino. When the cycloalkenyl is substituted with more than one group, they may be the same or different.

The term “alkoxy” as used herein denotes a radical alkyl, defined above, attached directly to an oxygen such as methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, t-butoxy, iso-butoxy and the like.

The term “substituted alkoxy” denotes a radical alkoxy of the above definition that is substituted with one or more groups, but preferably one or two groups, selected from hydroxyl, cycloalkyl, amino, mono-substituted amino, di-substituted amino, acyloxy, nitro, cyano, carboxy, carboalkoxy, alkylicarboxamide, substituted alkylcarboxamide, dialkylcarboxamide, substituted dialkylcarboxamide, alkylicarboxamide, substituted dialkylcarboxamide, alkylsulfonyl, alkylsulfinyl, thioalkyl, thiohaloalkyl, alkoxy, substituted alkoxy or haloalkoxy. When more than one group is present then they may be the same or different.
The term “mono-substituted amino” denotes an amino substituted with one group selected from alkyl, substituted alkyl or arylalkyl wherein the terms have the same definitions found throughout.

The term “di-substituted amino” denotes an amino substituted with two radicals that may be same or different selected from aryl, substituted aryl, alkyl, substituted alkyl or arylalkyl wherein the terms have the same definitions found throughout. Some examples include dimethylamino, methylethylamino, diethylamino and the like.

The term “haloalkyl” denotes a radical alkyl, defined above, substituted with one or more halogens, preferably fluorine, such as a trifluoromethyl, pentafluoroethyl and the like.

The term “haloalkoxy” denotes a haloalkyl, as defined above, that is directly attached to an oxygen to form trifluoromethoxy, pentafluoroethoxy and the like.

The term “acyl” denotes a radical containing 1 to 8 carbons such as formyl, acetyl, propionyl, butanoyl, iso-butanoyl, pentanoyl, hexanoyl, heptanoyl, benzoyl and the like.

The term “acyloxy” denotes a radical containing 1 to 8 carbons of an acyl group defined above directly attached to an oxygen such as acetyloxy, propionyloxy, butanoyloxy, iso-butanoxyloxy, benzoyloxy and the like.

The term “aryl” denotes an aromatic ring radical containing 6 to 10 carbons that includes phenyl and naphthyl. The term “substituted aryl” denotes an aromatic radical as defined above that is substituted with one or more selected from hydroxyl, cycloalkyl, aryl, substituted aryl, heteroaryl, heterocyclic ring, substituted heterocyclic ring, amino, mono-substituted amino, di-substituted amino, acyloxy, nitro, cyano, carboxy, carboalkoxy, alkylcarboxamide, substituted alkylcarboxamide, dialkylcarboxamide, substituted dialkylcarboxamide, alkylsulfonyl, alkylsulfinyl, alkylthio, alkoxy, substituted alkoxy or haloalkoxy, wherein the terms are defined herein.

The term “halo” or “halogen” refers to a fluoro, chloro, bromo or iodo group.

The term “thioalkyl” denotes a sulfide radical containing 1 to 8 carbons, linear or branched. Examples include methylsulfide, ethyl sulfide, isopropylsulfide and the like.
The term "thiohaloalkyl" denotes a thioalkyl radical substituted with one or more halogens. Examples include trifluoromethylthio, 1,1-difluoroethylthio, 2,2,2-trifluoroethylthio and the like.

The term "carboalkoxy" refers to an alkyl ester of a carboxylic acid, wherein alkyl has the same definition as found above. Examples include carbomethoxy, carboxethoxy, carboisopropoxy and the like.

The term "alkylcarboxamide" denotes a single alkyl group attached to the amine of an amide, wherein alkyl has the same definition as found above. Examples include N-methylcarboxamide, N-ethylcarboxamide, N-(iso-propyl)carboxamide and the like.

The term "substituted alkylcarboxamide" denotes a single "substituted alkyl" group, as defined above, attached to the amine of an amide.

The term "dialkylcarboxamide" denotes two alkyl or arylalkyl groups that are the same or different attached to the amine of an amide, wherein alkyl has the same definition as found above. Examples of a dialkylcarboxamide include N,N-dimethylcarboxamide, N-methyl-N-ethylcarboxamide and the like. The term "substituted dialkylcarboxamide" denotes two alkyl groups attached to the amine of an amide, where one or both groups is a "substituted alkyl", as defined above. It is understood that these groups may be the same or different. Examples include N,N-dibenzylcarboxamide, N-benzyl-N-methylcarboxamide and the like.

The term "alkylamide" denotes an acyl radical attached to an amine or monoalkylamine, wherein the term acyl has the same definition as found above. Examples of "alkylamide" include acetamido, propionamido and the like.

The term "arylalkyl" defines an alkylene, such as –CH2– for example, which is substituted with an aryl group that may be substituted or unsubstituted as defined above. Examples of an "arylalkyl" include benzyl, phenylene and the like.

The term "heterocyclic ring" denotes five-membered or six-membered rings that are completely or partially saturated and substituted with at least one heteroatom but no more than three heteroatoms, selected from nitrogen, oxygen and sulfur. Examples include morpholino, piperidinyl, piperazinyl, tetrahydrofuranyl and the like. The term "substituted heterocyclic ring" refers to a heterocyclic ring that is substituted with one or
more groups from hydroxyl, alkyl, substituted alkyl, haloalkyl, phenyl, substituted
phenyl, heteroaryl, amino, mono-substituted amino, di-substituted amino, acyloxy, nitro,
cyano, carboxy, carboalkoxy, alkylcarboxamide, substituted alkylcarboxamide,
dialkylcarboxamide, substituted dialkylcarboxamide, alkylsulfonyl, alkylsulfinyl,
alylthio, alkoxy, substituted alkoxy or haloalkoxy. When more than one group is
present then the groups may be the same or different.

The term “heteroaryl” refers to a five-membered or six-membered heterocyclic
aromatic ring system containing 1 to 4 heteroatoms selected from nitrogen, oxygen
and/or sulfur. Examples include pyridinyl, pyrimidinyl, pyrrolyl, furanyl, tetrazolyl,
isoxazolyl and the like. The term “substituted heteroaryl” refers to heteroaryl that is
substituted with one or more groups from hydroxyl, alkyl, substituted alkyl, haloalkyl,
aryl, substituted aryl, heteroaryl, amino, mono-substituted amino, di-substituted amino,
acyloxy, nitro, cyano, carboxy, carboalkoxy, alkylcarboxamide, substituted
alkylcarboxamide, dialkylcarboxamide, substituted dialkylcarboxamide, alkylsulfonyl,
alylsulfinyl, alylthio, alkoxy, substituted alkoxy or haloalkoxy. When more than one
group is present then the groups may be the same or different.

A residue of a chemical species, as used in the specification and concluding
claims, refers to the moiety that is the resulting product of the chemical species in a
particular reaction scheme or subsequent formulation or chemical product, regardless of
whether the moiety is actually obtained from the chemical species. Thus, an ethylene
glycol residue in a polyester refers to one or more \(-\text{OCH}_2\text{CH}_2\text{O}\)- repeat units in the
polyester, regardless of whether ethylene glycol is used to prepare the polyester.
Similarly, a 2,4-thiazolidinedione residue in a chemical compound refers to one or more -
2,4-thiazolidinedione moieties of the compound, regardless of whether the residue was
obtained by reacting 2,4-thiazolidinedione to obtain the compound.

It must be noted that, as used in the specification and the appended claims, the
singular forms "a," "an" and "the" can include plural referents unless the context clearly
dictates otherwise. Thus, for example, reference to "an aromatic compound" includes
mixtures of aromatic compounds.
Compositions

Some disclosed embodiments of the invention relate to the Formula (I):

wherein:

5 n and m are independently 0 or 1;

R₁ and R₂ are independently or together hydrogen, alkyl, substituted alkyl, haloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substituted alkoxy, hydroxyl, acyl, amino, mono-substituted amino, di-substituted amino, carboxy, carboalkoxy, alkylcarboxamide, substituted alkylcarboxamide, dialkylcarboxamide, substituted dialkylcarboxamide or haloalkoxy; or R₁ and R₂ together with the aromatic ring form a cycloalkyl, substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl optionally comprising 1 or 2 heteroatoms selected from O, S, NH and N-alkyl;

10 R₃ and R₄ are independently or together hydrogen, alkyl, substituted alkyl, haloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, halogen, cyano, nitro, hydroxyl, acyloxy, amino, mono-substituted amino, di-substituted amino, alkylsulfonamide, arylsulfonamide, alkylurea, arylurea, alkylcarbamate, arylearbamate, heteroaryl, alkoxy, substituted alkoxy, haloalkoxy, thioalkyl, thiohaloalkyl, carboxy, carboalkoxy, alkylcarboxamide, substituted alkylcarboxamide, dialkylcarboxamide or substituted dialkylcarboxamide;

A is \(-CR₆R₇⁻\) where R₆ and R₇ are independently or together hydrogen, alkyl, substituted alkyl, alkoxy, substituted alkoxy or haloalkoxy; or R₆ and R₇ together form a cycloalkyl comprising 1 or 2 heteroatoms selected from O, S, NH and
N-alkyl;

Ar is Formula (II), (III), (IV), (V) or (VI):

\[ \text{Formulae:} \]

where \( R_8, R_9 \) and \( R_{10} \) are independently or together hydrogen, alkyl, substituted alkyl, haloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, halogen, cyano, nitro, hydroxyl, acyloxy, amino, mono-substituted amino, disubstituted amino, alkylamide, alkylsulfonamide, arylsulfonamide, alkylurea, arylurea, alkylcarbamate, arylcarbamate, alkoxy, substituted alkoxy, haloalkoxy, thioalkyl, thiohaloalkyl, carboxy, carboalkoxy, alkylcarboxamide, substituted alkylcarboxamide, dialkylcarboxamide or substituted dialkylcarboxamide;

\( R_5 \) is hydrogen, halogen, hydroxy, alkyl or substituted alkyl;

and

\( W, X, Y \) and \( Z \) are independently or together \(-\text{C(O)}-, -\text{C(S)}-, -\text{S}-, -\text{O}- \) or \(-\text{NH}-\), preferably such that they form a 2,4-thiazolidinedione, 2-thioxo-4-thiazolidinedione, isoxazolidinedione, 2,4-imidazolidinedione or 2-thioxo-4-imidazolidinedione residue. These residues can be illustrated by the following Formulae:
Any compound disclosed herein may be formulated as a pharmaceutically acceptable salt.

In some embodiments W, X, Y and Z are independently or together –C(O)–, –C(S)–, –S–, –O–, or –NH– to form a 2,4-thiazolidinedione, 2-thioxo-4-thiazolidinedione, 2,4-imidazolidinedione or 2-thioxo-4-imidazolidinedione residue.

In some embodiments n is 0; R₁ and R₂ are independently or together alkyl, substituted alkyl or hydroxyl; or R₁ and R₂ together with the aromatic ring bonded thereto form a substituted cycloalkyl optionally comprising 1 or 2 heteroatoms selected from O, NH or N-alkyl;

In another embodiment R₃ and R₄ are independently or together halogen, alkyl, substituted alkyl, haloalkyl, alkoxy, substituted alkoxy, amino, mono-substituted amino, di-substituted amino or haloalkoxy.

In one embodiment R₅ is hydrogen, alkyl or substituted alkyl.

In some embodiments of the compound of Formula (I), Ar comprises a substituted or unsubstituted C₆-C₁₈ aromatic ring residue wherein all ring atoms are carbon, which may be optionally be substituted with zero to three R₈, R₉ or R₁₀ substituent groups, with the proviso that the C₆-C₁₈ aromatic radical does not comprise compounds of the formula
wherein $R_8$, $R_9$ and $R_{10}$ are independently or together hydrogen, alkyl, substituted alkyl, haloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, halogen, cyano, nitro, hydroxyl, acyloxy, amino, mono-substituted amino, di-substituted amino, alkylamide, alkylsulfonamide, arylsulfonamide, alkylurea, arylurea, alkylcarbamate, arylcarbamate, alkoxy, substituted alkoxy, haloalkoxy, thioalkyl, thiohaloalkyl, carboxy, carboalkoxy, alkylcarboxamide, substituted alkylcarboxamide, dialkylcarboxamide or substituted dialkylcarboxamide.

It is to be understood that in no embodiment within the scope of the present invention does the Ar residue of the compound of Formula (I) comprise the formula:

wherein $R_8$, $R_9$ and $R_{10}$ are independently or together hydrogen, alkyl, substituted alkyl, haloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, halogen, cyano, nitro, hydroxyl, acyloxy, amino, mono-substituted amino, di-substituted amino, alkylamide, alkylsulfonamide, arylsulfonamide, alkylurea, arylurea, alkylcarbamate, arylcarbamate, alkoxy, substituted alkoxy, haloalkoxy, thioalkyl, thiohaloalkyl, carboxy, carboalkoxy, alkylcarboxamide, substituted alkylcarboxamide, dialkylcarboxamide or substituted dialkylcarboxamide.
In certain embodiments, the substituted or unsubstituted C₆-C₁₈ aromatic ring residue comprises a napthyl residue of the formula;

\[
\begin{align*}
\text{or} & \quad \text{or}
\end{align*}
\]

wherein the napthyl residue may be optionally substituted with zero to three R₈, R₉ or R₁₀ substituent groups.

In other embodiments, Ar comprises a substituted or unsubstituted C₂-C₁₈ heteroaromatic ring residue having from one to three ring atoms selected from O, S, N, NH and N-R₁₁ atoms or residues, and optionally substituted with zero to three R₈, R₉ or R₁₀ substituent groups, with the proviso that the C₂-C₁₈ heteroaromatic ring residue does not comprise compounds of the formula

\[
\begin{align*}
\text{or} & \quad \text{or}
\end{align*}
\]

wherein R₈ and R₉ are independently or together hydrogen, alkyl, substituted alkyl, haloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, halogen, cyano, nitro, hydroxy, acyloxy, amino, mono-substituted amino, di-substituted amino, alkylamide, alkylsulfonamide, arylsulfonamide, alkylurea, arylurea, alkylcarbamate, arylcarbamate, alkoxy, substituted alkoxy, haloalkoxy, thioalkyl, thiohaloalkyl, carboxy, carboalkoxy, alkylcarboxamide, substituted alkylcarboxamide, dialkylcarboxamide or substituted dialkylcarboxamide.
It is to be understood that in no embodiment within the scope of the present invention does the Ar residue of the compound of Formula (I) comprise the formula:

\[
\begin{align*}
\text{R}_8 & \quad \text{R}_9 \\
\text{N} & \quad \text{N}
\end{align*}
\]

, 

\[
\begin{align*}
\text{R}_8 & \quad \text{R}_9 \\
\text{N} & \quad \text{N}
\end{align*}
\]

, or 

\[
\begin{align*}
\text{R}_8 & \quad \text{R}_9 \\
\text{N} & \quad \text{N}
\end{align*}
\]

wherein \(\text{R}_8\) and \(\text{R}_9\) are independently or together hydrogen, alkyl, substituted alkyl, haloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, halogen, cyano, nitro, hydroxyl, acyloxy, amino, mono-substituted amino, di-substituted amino, alkyamide, alkylsulfonamide, arylsulfonamide, alkylurea, arylurea, alkylcarbamate, arylcarbamate, alkoxy, substituted alkoxy, haloalkoxy, thioalkyl, thiohaloalkyl, carboxy, carboalkoxy, alkylcarboxamide, substituted alkylcarboxamide, dialkylcarboxamide or substituted dialkylcarboxamide.

In certain preferred embodiments, the substituted or unsubstituted \(C_{2-18}\) heteroaromatic ring residue comprises one of the following heteroaromatic residues:
wherein the heteroaromatic residue may be optionally substituted with zero to three $R_8, R_9, R_{10},$ or $R_{11}$ substituent groups, wherein $R_{11}$ substituent groups comprise
alkyl, substituted alkyl, aryl, substituted aryl, acyl, heteroaryl, or substituted heteroaryl groups.

In certain embodiments, the substituted or unsubstituted heteroaromatic ring residue comprises a naphtyl residue of the formula;

wherein at least one carbon of the naphtyl residue is substituted with a nitrogen atom, and the naphtyl residue may be optionally substituted with zero to three $R_8, R_9$ or $R_{10}$ substituent groups.

In another embodiment $Ar$ is Formula (II), (III) or (VI):

wherein:

$R_8$ is alkyl, substituted alkyl, alkenyl, haloalkyl, hydroxy, acyloxy, halogen, alkoxy, substituted alkoxy, amino, mono-substituted amino, di-substituted amino, alkylamide or haloalkoxy; and

$R_9$ and $R_{10}$ are independent or together hydrogen, halogen, alkyl, substituted alkyl, haloalkyl, alkenyl, substituted alkenyl, alkoxy, hydroxyl, amino, mono-substituted amino, di-substituted amino, alkylamide or haloalkoxy.

In one embodiment - - - - represents a bond present and the compound has the structural Formula:
In one embodiment - - - - represents a bond absent and the compound has
the structural Formula:

In another embodiment of the invention R₁ and R₂ together with the aromatic ring
bonded thereto form a substituted cycloalkyl.

In still another embodiment R₃ is methyl, ethyl, trifluoromethyl, methoxy or
dimethylamino; and R₄ is hydrogen.

In another embodiment a R₁ and R₂ together with the aromatic ring bonded
thereto form a substituted cycloalkyl; R₃ is methyl, ethyl, trifluoromethyl, methoxy or
dimethylamino; and R₄ is hydrogen form a polycyclic residue. Preferably the polycyclic
residue is selected from:

1) 3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl,

2) 3-ethyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl,
3) 3-trifluoromethyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl,

4) 3-methoxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl, or

5) 3-dimethylamino-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl.

In one preferred embodiment, R₁ and R₂ together form a substituted cycloalkyl
with the aromatic ring of Formula I to give the 5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-
naphthyl radical:

in another preferred embodiment, R₁ and R₂ together form a substituted cycloalkyl with
the aromatic ring of Formula I optionally comprising 1 or 2 nitrogen heteroatoms to give
1-isopropyl-7-methyl-1,2,3,4-tetrahydro-6-quinolinyl radical;
or the 1,4-diisopropyl-6-methyl-1,2,3,4-tetrahydro-7-quinoxaliny radical:

In still another embodiment of the invention wherein the A group is present (i.e. n is 1) $R_1$ and $R_2$ together with the aromatic ring form a cycloalkyl or substituted cycloalkyl optionally comprising 1 or 2 nitrogen heteroatoms; $R_3$ is halogen, alkyl, substituted alkyl, haloalkyl, alkoxy, substituted alkoxy, haloalkoxy, amino, mono-substituted amino or di-substituted amino; and $R_6$ and $R_7$ together form a cycloalkyl comprising 1 or 2 oxygen heteroatoms and a compound of claim W, X, Y and Z are independently or together - C(O)-, -C(S)-, -S- or -NH- form a 2,4-thiazolidinedione, 2-thioxo-4-thiazolidinedione, 2-thioxo-4-imidazolidinedione or 2,4-imidazolidinedione residue.

This invention also relates to a pharmaceutical formulation comprising one or more compounds disclosed herein in an admixture with a pharmaceutically acceptable excipient.
Compounds disclosed herein may exist in various tautomeric forms. For example, 2,4-thiazolidinedione-containing compounds disclosed herein may exist in the form of tautomers (Xa), (Xb) and (Xc).

It is understood that tautomers may also exist with 2-thioxo-4-thiazolidinedione, 2,4-imidazolidinedione, 2-thioxo-4-imidazolidinedione and isoxazolidinedione containing compounds disclosed herein and these tautomeric forms are also within the scope of the invention.

For convenience, all of the tautomers are presented herein by a single formula, but it is understood that all the tautomers are within the scope of the invention.

When is present both $E$ and $Z$ configurations are within the scope of the invention. For example, 2,4-thiazolidinedione and 2-thioxo-4-thiazolidinedione of Formula (I) may have the following structures respectively:
The compounds disclosed herein may also include salts of the compounds, such as salts with cations. Cations with which the compounds of the invention may form pharmaceutically acceptable salts include alkali metals, such as sodium or potassium; alkaline earth metals, such as calcium; and trivalent metals, such as aluminum. The only constraint with respect to the selection of the cation is that it should not unacceptably increase the toxicity. Due to the tautomerism described above for the compounds, mono-, di- or tri-salts may be possible depending on the corresponding alkali metal. Also, one or more compounds disclosed herein may include salts formed by reaction of a nitrogen contained within the compound, such as an amine, aniline, substituted aniline, pyridyl and the like, with an acid, such as HCl, carboxylic acid and the like. Therefore, all possible salt forms in relationship to the tautomers and a salt formed from the reaction between a nitrogen and acid are within the scope of the invention.

The present invention provides, but is not limited to, the specific compounds set forth in the Examples as well as those set forth below, and a pharmaceutically acceptable salt thereof:

where \( n \) is 0, and \( \cdot \cdot \cdot \) is absent or present:

\[
2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-methoxybenzylidene-2,4-thiazolidinedione,
\]

\[
2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-trifluoromethoxybenzylidene-2,4-thiazolidinedione,
\]

\[
2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-dimethylaminobenzylidene-2,4-thiazolidinedione,
\]

\[
2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-chlorobenzylidene-2,4-thiazolidinedione,
\]

\[
2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-methylbenzylidene-2,4-thiazolidinedione,
\]

\[
2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-ethylbenzylidene-2,4-thiazolidinedione,
\]

\[
2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-trifluoromethylbenzylidene-2,4-thiazolidinedione,
\]

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2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-ethoxybenzylidene-2,4-thiazolidinedione,
2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-methoxy-4-fluorobenzylidene-2,4-thiazolidinedione,
2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-methoxy-6-fluorobenzylidene-2,4-thiazolidinedione,
2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-isopropoxybenzylidene-2,4-thiazolidinedione,
2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-aminobenzylidene-2,4-thiazolidinedione,
2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-acetamidobenzylidene-2,4-thiazolidinedione,
2-(3-Methoxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-trifluoromethoxybenzylidene-2,4-thiazolidinedione,
2-(3-Dimethylamino-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-trifluoromethoxybenzylidene-2,4-thiazolidinedione,
2-(3-Trifluoromethyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-methoxybenzylidene-2,4-thiazolidinedione,
2-(3-Trifluoromethyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-methylbenzylidene-2,4-thiazolidinedione,
2-(3-Trifluoromethyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-ethylbenzylidene-2,4-thiazolidinedione,
2-(3-Trifluoromethyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-trifluoromethoxybenzylidene-2,4-thiazolidinedione,
2-(3-Dimethylamino-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-dimethylaminobenzylidene-2,4-thiazolidinedione,
2-(3-Trifluoromethyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-chlorobenzylidene-2,4-thiazolidinedione,
2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-acetoxybenzylidene-2,4-thiazolidinedione,
2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-
hydroxybenzylidene-2,4-thiazolidinedione,
2-(3-Trifluoromethyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-
3-dimethylaminobenzylidene-2,4-thiazolidinedione,
4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-
methoxybenzylidene-2,4-thiazolidinedione,
4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-
trifluoromethoxybenzylidene-2,4-thiazolidinedione,
4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-
dimethylaminobenzylidene-2,4-thiazolidinedione,
4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-
chlorobenzylidene-2,4-thiazolidinedione,
4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-
methylbenzylidene-2,4-thiazolidinedione,
4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-
ethylbenzylidene-2,4-thiazolidinedione,
4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-
trifluoromethylbenzylidene-2,4-thiazolidinedione,
4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-4-
ethoxybenzylidene-2,4-thiazolidinedione,
4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-methoxy-5-
fluorobenzylidene-2,4-thiazolidinedione,
4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-2-fluoro-3-
methoxy-benzylidene-2,4-thiazolidinedione,
4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-
isopropoxybenzylidene-2,4-thiazolidinedione,
4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-
aminobenzylidene-2,4-thiazolidinedione,
4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-
acetamidobenzylidene-2,4-thiazolidinedione,
4-(3-Methoxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-
trifluoromethoxybenzylidene-2,4-thiazolidinedione,
4-(3-Dimethylamino-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-
trifluoromethoxybenzylidene-2,4-thiazolidinedione,
4-(3-Trifluoromethyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-
3-methoxybenzylidene-2,4-thiazolidinedione,
4-(3-Trifluoromethyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-
3-methylbenzylidene-2,4-thiazolidinedione,
4-(3-Trifluoromethyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-
3-ethylbenzylidene-2,4-thiazolidinedione,
4-(3-Trifluoromethyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-
3-trifluoromethoxybenzylidene-2,4-thiazolidinedione,
4-(3-Dimethylamino-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-
dimethylaminobenzylidene-2,4-thiazolidinedione,
4-(3-Trifluoromethyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-
3-chlorobenzylidene-2,4-thiazolidinedione,
4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-
acetoxybenzylidene-2,4-thiazolidinedione,
4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-
hydroxybenzylidene-2,4-thiazolidinedione,
4-(3-Trifluoromethyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-
3-dimethylaminobenzylidene-2,4-thiazolidinedione,
2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-
methoxybenzyl-2,4-thiazolidinedione,
2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-
trifluoromethoxybenzyl-2,4-thiazolidinedione,
2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-
dimethylaminobenzyl-2,4-thiazolidinedione,
2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-methylbenzyl-2,4-thiazolidinedione,
2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-ethylbenzyl-2,4-thiazolidinedione,
2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-trifluoromethylbenzyl-2,4-thiazolidinedione,
2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-ethoxybenzyl-2,4-thiazolidinedione,
2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-methoxy-4-fluorobenzyl-2,4-thiazolidinedione,
2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-methoxy-6-fluorobenzyl-2,4-thiazolidinedione,
2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-isopropoxybenzyl-2,4-thiazolidinedione,
2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-aminobenzyl-2,4-thiazolidinedione,
2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-acetamidobenzyl-2,4-thiazolidinedione,
2-(3-Methoxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-trifluoromethoxybenzyl-2,4-thiazolidinedione,
2-(3-Dimethylamino-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-trifluoromethoxybenzyl-2,4-thiazolidinedione,
2-(3-Trifluoromethyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-methoxybenzyl-2,4-thiazolidinedione,
2-(3-Trifluoromethyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-methylbenzyl-2,4-thiazolidinedione,
2-(3-Trifluoromethyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-ethylbenzyl-2,4-thiazolidinedione,
2-(3-Trifluoromethyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-trifluoromethoxybenzyl-2,4-thiazolidinedione,
2-(3-Dimethylamino-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-dimethylaminobenzyl-2,4-thiazolidinedione,
2-(3-Trifluoromethyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-chlorobenzyl-2,4-thiazolidinedione,
2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-acetoxybenzyl-2,4-thiazolidinedione,
2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-hydroxybenzyl-2,4-thiazolidinedione,
2-(3-Trifluoromethyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-dimethylaminobenzyl-2,4-thiazolidinedione,
4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-methoxybenzyl-2,4-thiazolidinedione,
4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-trifluoromethoxybenzyl-2,4-thiazolidinedione,
4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-dimethylaminobenzyl-2,4-thiazolidinedione,
4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-chlorobenzyl-2,4-thiazolidinedione,
4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-methylbenzyl-2,4-thiazolidinedione,
4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-ethylbenzyl-2,4-thiazolidinedione,
4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-trifluoromethylbenzyl-2,4-thiazolidinedione,
4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-4-ethoxybenzyl-2,4-thiazolidinedione,
4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-methoxy-5-fluorobenzyl-2,4-thiazolidinedione,
4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-2-fluoro-3-methoxy-benzyl-2,4-thiazolidinedione,
4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-isoproxybenzyl-2,4-thiazolidinedione,
4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-aminobenzyl-2,4-thiazolidinedione,
4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-acetamidobenzyl-2,4-thiazolidinedione,
4-(3-Methoxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-trifluoromethoxybenzyl-2,4-thiazolidinedione,
4-(3-Dimethylamino-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-trifluoromethoxybenzyl-2,4-thiazolidinedione,
4-(3-Trifluoromethyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-methoxybenzyl-2,4-thiazolidinedione,
4-(3-Trifluoromethyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-methylbenzyl-2,4-thiazolidinedione,
4-(3-Trifluoromethyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-ethylbenzyl-2,4-thiazolidinedione,
4-(3-Trifluoromethyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-trifluoromethoxybenzyl-2,4-thiazolidinedione,
4-(3-Dimethylamino-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-dimethylaminobenzyl-2,4-thiazolidinedione,
4-(3-Trifluoromethyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-chlorobenzyl-2,4-thiazolidinedione,
4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-acetoxybenzyl-2,4-thiazolidinedione,
4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-hydroxybenzyl-2,4-thiazolidinedione,
4-(3-Trifluoromethyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-dimethylaminobenzyl-2,4-thiazolidinedione,
2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-5-pyridylidene-2,4-thiazolidinedione,
2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-methoxy-5-pyridylidene-2,4-thiazolidinedione,

2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-5-pyridyl-2,4-thiazolidinedione, and

2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-methoxy-5-pyridyl-2,4-thiazolidinedione.

The structures for these compounds are shown below:
2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-methoxybenzylidene-2,4-thiazolidinedione

2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-trifluoromethoxybenzylidene-2,4-thiazolidinedione

2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-dimethylaminobenzylidene-2,4-thiazolidinedione

2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-chlorobenzylidene-2,4-thiazolidinedione

2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-methylbenzylidene-2,4-thiazolidinedione

2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-ethylbenzylidene-2,4-thiazolidinedione
2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-trifluoromethylbenzylidene-2,4-thiazolidinedione

2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-ethoxybenzylidene-2,4-thiazolidinedione

2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-methoxy-4-fluorobenzylidene-2,4-thiazolidinedione

2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-methoxy-6-fluorobenzylidene-2,4-thiazolidinedione

2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-isopropanoxybenzylidene-2,4-thiazolidinedione

2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-aminobenzylidene-2,4-thiazolidinedione
2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-acetamidobenzylidene-2,4-thiazolidinedione

2-(3-Methoxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-trifluoromethoxybenzylidene-2,4-thiazolidinedione

2-(3-Dimethylamino-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-trifluoromethoxybenzylidene-2,4-thiazolidinedione

2-(3-Trifluoromethyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-methoxybenzylidene-2,4-thiazolidinedione

2-(3-Trifluoromethyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-methylbenzylidene-2,4-thiazolidinedione

2-(3-Trifluoromethyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-ethylbenzylidene-2,4-thiazolidinedione

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2-(3-Trifluoromethyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-trifluoromethoxybenzylidene-2,4-thiazolidinedione

2-(3-Dimethylamino-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-dimethylamino benzylidene-2,4-thiazolidinedione

2-(3-Trifluoromethyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-chlorobenzylidene-2,4-thiazolidinedione

2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-acetoxybenzylidene-2,4-thiazolidinedione

2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-hydroxybenzylidene-2,4-thiazolidinedione

2-(3-Trifluoromethyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-dimethylamino benzylidene-2,4-thiazolidinedione
4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-methoxybenzylidene-2,4-thiazolidinedione

4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-trifluoromethoxybenzylidene-2,4-thiazolidinedione

4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-dimethylbenzylidene-2,4-thiazolidinedione

4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-chlorobenzylidene-2,4-thiazolidinedione

4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-methylbenzylidene-2,4-thiazolidinedione

4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-ethylbenzylidene-2,4-thiazolidinedione
4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-trifluoromethylbenzylidene-2,4-thiazolidinedione

4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-ethoxybenzylidene-2,4-thiazolidinedione

4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-methoxy-5-fluorobenzylidene-2,4-thiazolidinedione

4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-2-fluoro-3-methoxy-benzylidene-2,4-thiazolidinedione

4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-isopropoxybenzylidene-2,4-thiazolidinedione

4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-aminobenzylidene-2,4-thiazolidinedione
4-(3,5,5,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-acetamidobenzylidine-2,4-thiazolidinedione

4-(3-Methoxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-trifluoromethoxybenzylidine-2,4-thiazolidinedione

4-(3-Dimethylamino-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-trifluoromethoxybenzylidine-2,4-thiazolidinedione

4-(3-Trifluoromethyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-methoxybenzylidine-2,4-thiazolidinedione

4-(3-Trifluoromethyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-methylbenzylidine-2,4-thiazolidinedione

4-(3-Trifluoromethyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-ethylbenzylidine-2,4-thiazolidinedione
4-(3-Trifluoromethyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-trifluoromethoxybenzylidene-2,4-thiazolidinedione

4-(3-Dimethylamino-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-dimethylamino benzylidene-2,4-thiazolidinedione

4-(3-Trifluoromethyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-chlorobenzylidene-2,4-thiazolidinedione

4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-acetoxybenzylidene-2,4-thiazolidinedione

4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-hydroxybenzylidene-2,4-thiazolidinedione

4-(3-Trifluoromethyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-dimethylamino benzylidene-2,4-thiazolidinedione
2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-methoxybenzyl-2,4-thiazolidinedione

2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-trifluoromethoxybenzyl-2,4-thiazolidinedione

2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-dimethylaminobenzyl-2,4-thiazolidinedione

2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-chlorobenzyl-2,4-thiazolidinedione

2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-methylbenzyl-2,4-thiazolidinedione

2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-ethylbenzyl-2,4-thiazolidinedione
2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-trifluoromethylbenzyl-2,4-thiazolidinedione

2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-ethoxybenzyl-2,4-thiazolidinedione

2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-methoxy-4-fluorobenzyl-2,4-thiazolidinedione

2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-methoxy-6-fluorobenzyl-2,4-thiazolidinedione

2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-isopropoxybenzyl-2,4-thiazolidinedione

2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-aminobenzyl-2,4-thiazolidinedione
2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-acetamidobenzyl-2,4-
thiazolidinedione

2-(3-Methoxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-trifluoromethoxy-
benzyl-2,4-thiazolidinedione

2-(3-Dimethylamino-5,5,8,8-tetramethyl-5,6,7,8-
tetrahydro-2-naphthyl)-3-trifluoromethoxy-
benzyl-2,4-thiazolidinedione

2-(3-Trifluoromethyl-5,5,8,8-tetramethyl-5,6,7,8-
tetrahydro-2-naphthyl)-3-methoxybenzyl-2,4-thiazolidinedione

2-(3-Trifluoromethyl-5,5,8,8-tetramethyl-5,6,7,8-
tetrahydro-2-naphthyl)-3-methylbenzyl-2,4-thiazolidinedione

2-(3-Trifluoromethyl-5,5,8,8-tetramethyl-5,6,7,8-
tetrahydro-2-naphthyl)-3-ethylbenzyl-2,4-thiazolidinedione
2-(3-Trifluoromethyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-trifluoromethoxybenzyl-2,4-thiazolidinedione

2-(3-Dimethylamino-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-dimethylaminobenzyl-2,4-thiazolidinedione

2-(3-Trifluoromethyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-chlorobenzyl-2,4-thiazolidinedione

2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-acetoxybenzyl-2,4-thiazolidinedione

2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-hydroxybenzyl-2,4-thiazolidinedione

2-(3-Trifluoromethyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-dimethylaminobenzyl-2,4-thiazolidinedione
4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-methoxybenzyl-2,4-thiazolidinedione

4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-trifluoromethoxybenzyl-2,4-thiazolidinedione

4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-dimethylbenzyl-2,4-thiazolidinedione

4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-chlorobenzyl-2,4-thiazolidinedione

4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-methylbenzyl-2,4-thiazolidinedione

4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-ethylbenzyl-2,4-thiazolidinedione
4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-trifluoromethylbenzyl-2,4-thiazolidinedione

4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-ethoxybenzyl-2,4-thiazolidinedione

4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-methoxy-5-fluorobenzyl-2,4-thiazolidinedione

4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-2-fluoro-3-methoxy-benzyl-2,4-thiazolidinedione

4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-isopropoxybenzyl-2,4-thiazolidinedione

4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-aminobenzyl-2,4-thiazolidinedione
4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-acetamidobenzyl-2,4-thiazolidinedione

4-(3-Methoxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-trifluoromethoxybenzyl-2,4-thiazolidinedione

4-(3-Dimethylamino-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-trifluoromethoxybenzyl-2,4-thiazolidinedione

4-(3-Trifluoromethyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-methoxybenzyl-2,4-thiazolidinedione

4-(3-Trifluoromethyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-methylbenzyl-2,4-thiazolidinedione

4-(3-Trifluoromethyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-ethylbenzyl-2,4-thiazolidinedione
4-(3-Trifluoromethyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-trifluoromethoxybenzyl-2,4-thiazolidinedione

4-(3-Dimethylamino-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-dimethylamino-benzyl-2,4-thiazolidinedione

4-(3-Trifluoromethyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-chlorobenzyl-2,4-thiazolidinedione

4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-acetoxybenzyl-2,4-thiazolidinedione

4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-hydroxybenzyl-2,4-thiazolidinedione

4-(3-Trifluoromethyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-dimethylamino-benzyl-2,4-thiazolidinedione
In some embodiments of the compounds of Formula (I), when n is 1, R₁ and R₂ together with the aromatic ring form a substituted cycloalkyl optionally comprising 1 or 2 nitrogen heteroatoms; and R₃ is alkyl or substituted alkyl. In another preferred embodiment (i.e., wherein A is -CR₆R₇-) R₆ and R₇ are independently or together alkyl; or R₆ and R₇ together form a cycloalkyl comprising 1 or 2 oxygen heteroatoms. More preferably the cycloalkyl is a 1,3-dioxolane ring. Still with respect to when n is 1, preferably W, X, Y and Z are independently or together -C(O)-, -C(S)-, -S- or -NH- form a 2,4-thiazolidinedione, 2-thioxo-4-thiazolidinedione, 2-thioxo-4-imidazolidinedione or 2,4-imidazolidinedione.

In one embodiment - - - - - represents the bond is present.
In another embodiment - - - - represents the bond is absent.

Making the Compositions

Various synthetic methods may be employed in the production of the compounds disclosed herein. A representative set of synthetic pathways are shown in Figure 3 for n = 0. One method, for example, includes coupling a boronic acid of Formula (XX), $R_{14} = H$, with a carbonyl-containing aryl bromide of Formula (XXI), $R_{15} = Br$, to give biaryl (XXIV) that is substituted with a carbonyl group, preferably a formyl group (i.e., $R_5 = H$). Alternatively, boronic acid (XX) may be coupled with aryl bromide (XXV), $R_{15} = Br$, to give biaryl (XXVI) that is subsequently formylated using techniques known in the art, such as the Vilsmeier or the Vilsmeier-Haack reaction, the Gatterman reaction, the Duff reaction, the Reimer-Tiemann reaction or a like reaction. Coupling reactions such as that described for the formation of Biaryl (XXIV) and (XXVI) may also be conducted using boronic esters, such as where $R_{14}$ together with the boron from a pinacol borate ester (formation of pinacol esters: Ishiyama, T., et al., *J. Org. Chem.* 1995, 60, 7508-7510, Ishiyama, T., et al., *Tetrahedron Letters* 1997, 38, 3447-3450; coupling pinacol esters: Firooznia, F. et al., *Tetrahedron Letters* 1999, 40, 213-216, Manickam, G. et al., *Synthesis* 2000, 442-446; all four citations incorporated herein by reference). In addition, $R_{15}$ may also be $I$, $Cl$ or triflate (derived from a phenol).

Biaryl (XXVI) may also be acylated, for example by the Friedel-Crafts Acylation reaction or the like. Preferably, biaryl (XXVI) is formylated. Alternatively, in a two step manner, biaryl (XXVI) is formylated by first performing a halogenation step to give biaryl (XXVII), such as a bromination, followed by a halogen-metal exchange reaction using an alkyl lithium and reaction with DMF or equivalent known in the art to give biaryl (XXIV) where $R_3$ is $H$. The carbonyl group of biaryl (XXIV) may subsequently be condensed with a heterocycle possessing an active methylene moiety, such as 2,4-thiazolidinedione, 2-thioxo-4-thiazolidinedione, isoxazolidinedione, 2,4-imidazolidinedione or 2-thioxo-4-imidazolidinedione to give benzylidene (XXVIII). The carbonyl group of biaryl (XXIV) may also be reduced, such as with sodium borohydride, to benzyl alcohol (XXIX, $R_{20} = OH$) and converted to benzyl bromide (XXIX, $R_{20} = Br$) with HBr or some other method known in the art, such as PPh$_3$/CB$_3$. Benzyl bromide
(XXIX, R_{20} = Br) is allowed to react with the anion(s) of 2,4-thiazolidinedione to give biaryl [(XXX), where: W = -C(O)-, X = -NH-, Y = -C(O)- and Z = -S-]. Similarly, anions of other heterocycles disclosed herein may be used. Alternative, biaryl [(XXX), where: W = -C(O)-, X = -NH-, Y = -C(O)- and Z = -S-] may be prepared by a reduction of benzylidene [(XXVIII), such as hydrogenation in the presence of Pd/C, Mg/MgOH and the like.

In an alternative manner, the coupling may take place between aryl (XXII), such as where R_{15} = Br, and boronic acid (XXIII, R_{14} = H) to give the above mention biaryl (XXIV). Also aryl (XXII) may be coupled with boronic acid (XXXI) to give biaryl (XXVI). Employing the same strategy as described above biaryl (XXVI) may be either formylated or acetylated to achieve biaryl (XXIV).

In some embodiments of the invention provide a process for the preparation of a compound of the Formula (XV):

![Chemical structure](image)

(XV)

wherein:

R_1 and R_2 are independently or together hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substituted alkoxy, hydroxyl, acyl, amino, mono-substituted amino, di-substituted amino, carboxy, carboalkoxy, alkylcarboxamide, substituted alkylcarboxamide, dialkylcarboxamide, substituted dialkylcarboxamide or haloalkoxy; or R_1 and R_2 together with the aromatic ring form a cycloalkyl, substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl optionally comprising 1 or 2 heteroatoms selected from O, S, NH and N-alkyl;
R₃ and R₄ are independently or together hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, halogen, cyano, nitro, hydroxyl, acyloxy, amino, mono-substituted amino, di-substituted amino, alkylsulfonamide, arylsulfonamide, alkylurea, arylurea, arylcarbamate, arylcarbamate, heteroaryl, alkoxy, substituted alkoxy, haloalkoxy, thioalkyl, thiohaloalkyl, carboxy, carboalkoxy, alkylcarboxamide, substituted alkylcarboxamide, dialkylcarboxamide or substituted dialkylcarboxamide;

Ar is Formula (II), (III), (IV), (V) or (VI):

10

where R₈, R₉ and R₁₀ are independently or together hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, halogen, cyano, nitro, hydroxyl, acyloxy, amino, mono-substituted amino, di-substituted amino, alkylamidine, alkylsulfonamide, arylsulfonamide, alkylurea, arylurea, alkylcarbamate, arylcarbamate, alkoxy, substituted alkoxy, haloalkoxy, thioalkyl, thiohaloalkyl, carboxy, carboalkoxy, alkylcarboxamide, substituted alkylcarboxamide, dialkylcarboxamide or substituted dialkylcarboxamide; R₁₁ is hydrogen, alkyl or substituted alkyl;

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R₅ is hydrogen, halogen, hydroxy, alkyl or substituted alkyl;
represents a bond present or absent; and

W, X, Y and Z are independently or together -C(O)-, -C(S)-, -S-, -O- or
-NH- residues that form a 2,4-thiazolidinedione, 2-thioxo-4-thiazolidinedione,
isoxazolidinedione, 2,4-imidazolidinedione or 2-thioxo-4-imidazolidinedione
residue;

comprising the steps of:

1) coupling a first aryl residue with a second aryl residue to give a biaryl
carbonyl containing compound;

wherein the first aryl residue comprises a substituted or unsubstituted
residue having the structure:

\[
\begin{array}{c}
R_1 \\
\downarrow \\
R_2 \\
\downarrow \\
R_3 \\
\end{array}
\]

and wherein the second aryl residue has a carbonyl group and
comprises a substituted or unsubstituted residue having the structure:

\[
\begin{array}{c}
\downarrow \\
Ar \\
\downarrow \\
R_5 \\
\end{array}
\]

and wherein the biaryl carbonyl containing compound comprises a
substituted or unsubstituted residue having the structure:
and

2) condensing the biaryl carbonyl containing compound with an active methylene compound of the structure:

\[
\begin{array}{c}
\text{W} - \text{X} \\
\text{Y} \\
\text{Z}
\end{array}
\]

In another embodiments of the invention provides a process further comprising the step of reducing the benzylidene of Formula (XV) to form the benzyl compound of Formula (XVI):

\[
\begin{array}{c}
\text{W} - \text{X} \\
\text{Y} \\
\text{Z}
\end{array}
\]

A number of methods suitable for reducing benzylidene compounds to benzyl compounds (including hydrogenation, reaction with metal hydride reagents, or dissolving metal reductions) are known to those of skill in the art, and those methods may be applied in the methods of the instant invention.

The various organic group transformations utilized herein may be performed by a number of procedures other than those described above. References for other synthetic procedures that may be utilized for the synthetic steps leading to the compounds disclosed herein may be found in, for example, March, J., *Advanced Organic Chemistry*. 

One embodiment of the invention relates to the processes for making compounds of Formula I, where n is 0, which comprises coupling two aromatic rings to give a biaryl wherein one of the aryl rings contains a carbonyl moiety, preferably an aldehyde. The resulting biaryl product may be subsequently condensed with an active methylene compound, such as 2,4-thiazolidinedione, 2-thioxo-4-thiazolidinedione, 2,4-imidazolidinedione or 2-thioxo-4-imidazolidinedione to give a benzylidene compound of Formula (I) where - - - - - is a bond. In an optional step, the benzylidene compound may be reduced to give a benzyl compound of Formula (I) where - - - - - is absent.


\[
\begin{align*}
(XX) & \quad (XXI)
\end{align*}
\]

where \( R_{14} \) is either alkyl or hydrogen and \( R_{15} \) is a halide (such as, iodo, bromo, or chloro), triflate or diazonium tetrafluoroborate. Alternately, it is understood that the coupling groups may be reversed, such as the use of (XXII) and (XXIII), to achieve the same coupling product:
where R_{14} and R_{15} have the same meaning as described above. The preparation of the above mentioned precursors may be prepared by methods readily available to those skilled in the art. For example, the boronic ester may be prepared from an aryl halide by conversion into the corresponding aryl lithium, followed by treatment with a trialkyl borate. Preferably, the boronic ester is hydrolyzed to the boronic acid.

The coupling reaction may also be conducted between an arylzinc halide and an aryl halide or triflate. Alternately, the coupling reaction may also be executed using an aryl trialkyltin derivative and an aryl halide or triflate. These coupling methods are reviewed by Stanforth, *Tetrahedron* 54:263-303 (1998) and incorporated herein by reference. In general, the utilization of a specific coupling procedure is selected with respect to available precursors, chemoselectivity, regioselectivity and steric considerations.

Condensation of the biaryl carbonyl containing derivatives (e.g., Figure 3, compound (XXIV)) with a suitable active methylene compound, 2,4-thiazolidinedione, may be accomplished by the use of methods known in the art. For example, the biaryl carbonyl product from the coupling reaction may be condensed with an active methylene compound to give a benzylidene compound of Formula (I) (i.e., \(-\cdots\) is a bond) as described by Tietze and Beifuss, *Comprehensive Organic Synthesis* (Pergamon Press), 2:341-394, (1991), incorporated herein by reference. It is understood by those of skill in the art that intermediates having hydroxyl groups bound thereto may be formed during condensation of a biaryl carbonyl containing derivative and an active methylene compound, as shown below.
The hydroxyl groups of such intermediates are often eliminated (as water) during
the condensation reaction, to form the desired benzylidene compound. Nevertheless, the
conditions of the reaction may be modified for the isolation or further use of hydroxyl
containing intermediates, and such embodiments are within the scope of the invention.
Although the reaction shown above depicts the formation of the condensation
intermediate for the reaction between compound (XXIV) and an active methylene
compound, it is understood that a similar intermediate is within the scope of the
invention for compounds (XLV) and (XLII). Effective catalysts for the condensation
may be selected from ammonia, primary, secondary and tertiary amines, either as the free
base or the amine salt with an organic acid, such as acetic acid. Examples of catalysts
include pyrrolidine, piperidine, pyridine, diethylamine and the acetate salts thereof.
Inorganic catalysts may also be used for the condensation. Inorganic catalysts include,
but are not limited to, titanium tetrachloride and a tertiary base, such as pyridine; and
magnesium oxide or zinc oxide in an inert solvent system. This type of condensation can
be strongly solvent-dependent and it is understood that routine experimentation may be
necessary to identify the optimal solvent with a particular catalyst, preferable solvents
include ethanol, tetrahydrofuran, dioxane or toluene; or mixtures thereof.

The active methylene compound of the present invention may be 2,4-
thiazolidinedione, 2-thioxo-4-thiazolidinone, 2,4-imidazolidinedione or 2-thioxo-4-
imidazolidinedione. The resulting benzylidene (e.g., Figurem compound (XXXIII)) may
be reduced, if desired, to a compound of Formula (I) wherein - - - - - is absent (e.g.,
Figure 3, compound (XXX)).

In addition, various methods may be employed in the production of the
compounds disclosed herein wherein n = 1, representative examples are shown in Figure
4. Structures of compound (XL) may be prepared by methods known in the art. The acid, \( R_{30} = H \) or the ester, \( R_{30} = \text{aryl, alkyl or substituted alkyl} \), may be reduced to the corresponding benzyl alcohol (XLI) followed by oxidation to an aldehyde (XLII). Alternatively, ester (XL), \( R_{30} = \text{alkyl or substituted alkyl} \), may be reduced directly to the aldehyde via selective reductions, for example, DIBAL. Aldehyde (XLII) may be reacted with a metal reagent, such as a Grignard reagent, to give benzyl alcohol (XLIV) that can subsequently be converted to ketone (XLV) via an oxidation, such as a Swern oxidation, Corey oxidation with NCS or another suitable procedure described by Hudlicky, M, *Oxidations in Organic Chemistry*, ACS Monograph 186 (1990), incorporated herein by reference. In a similar manner as described above, compound (XLII) or compound (XLV) may be condensed with an active methylene of a heterocycle to give compound (XLVI). The reduced analogue (XLVII) may be prepared in a manner similar to the process described above using a benzyl halide derived from either benzyl alcohol (XLI) or reduction from compound (XLVI).

In addition, various methods may be employed in the production of the compounds disclosed herein wherein \( n \) is either 0 or 1 and \( m \) is 0, representative examples are shown in Figure 5. Utilizing, for example, compound (XLII) or (XXIV) the carbonyl may be converted to a cyanohydrin using methods known in the art. Such methods include, the use of acetone cyanohydrin, TMS-CN/ZnI\(_2\) (followed by hydrolysis of the TMS ether) and the like. The resulting alcohol of the cyanohydrin may be converted to a halide (where \( V = \text{Cl or Br} \)) with the use of thionyl chloride, thionyl bromide or the like, in the presence or absence of solvent. Conversion to compounds of Formula where \( m \) is equal to 0 may be prepared by the reaction of the (XLII b) or (XXIV b) with thiourea followed by hydrolysis.

**Using the Compositions**

The compounds of the present invention have been found to be active in one or more biological assays that correlate to or are representative of a human disease.

Inflammation is a biological response, such as, edema, swelling, pain, fever, redness or diminished function, and related physiological manifestations, that arise from tissue/cellular damage or insult. These clinical observations are the net result of one or
more inflammatory mediators released from the activation of the inflammatory cascade in response to the insult. Among the many inflammatory mediators that have been identified, two that have received considerable attention are tumor necrosis factor-alpha and nitric oxide synthase.

**TUMOR NECROSIS FACTOR-ALPHA**

Tumor necrosis factor-alpha (e.g., TNF-α) is a pleiotropic cytokine that is secreted primarily by monocytes and macrophages as a soluble homotrimer of 17 kD protein subunits in response to endotoxin or other stimuli (Smith, R. A. et al., J. Biol. Chem. 1987, 262, 6951-6954). However, the expression of TNF-α is not limited to only the monocyte/macrophage family, but also several human non-monocytic tumor cell lines, peripheral blood T lymphocytes, and a variety of B and T cell lines have shown to produce TNF-α. There has also been reported a membrane-bound 26 kD precursor form of TNF-α (Kriegler, M. et al., Cell 1988, 53, 45-53). TNF-α has been shown to play a beneficial role in destroying tumors, mediating responses to tissue injury, and protecting hosts from infections by various microorganisms. However, TNF-α has also been shown to be overexpressed in a number of physiological disorders (Pujol-Borrell et al., Nature 1987 326, 304-306; Oliff, Cell 1988 54, 141-142; Tracey et al., Nature 1987, 330, 662-664). There exists a growing body of data suggesting that TNF-α is a significant mediator of a variety of inflammatory and immunological responses, as well as in the pathogenesis of endotoxic and septic shock (reviewed by Tracey and Cerami, Ann. Rev. Med. 45, 491-503, 1994; Glauser et al. Clin. Infect Dis. 18, suppl. 2, 205-216, 1994).

TNF-α has been shown to promote the accumulation and activation of polymorphonuclear leukocytes by stimulating the endothelium to express adhesion molecules (T. H. Pohlmans et al., J. Immunol, 136, pp. 4548-4553, 1986) and to release secondary chemotactic cytokines such as IL-8 (R. M. Strieter et al., Science, 243, pp. 1467-1469, 1989). In addition, TNF-α can stimulate cells within the joint to synthesize and express the inducible cyclooxygenase enzyme (e.g., COX 2) and the inducible NO synthase enzyme (e.g., iNOS). The products of these enzymes, prostaglandins and nitric oxide, are important mediators of pain and inflammation. Also TNF-α can activate chondrocytes leading to the degradation of their own extracellular matrix and suppress synthesis of cartilage matrix components leading to cartilage destruction. Another effect
of TNF-α is in the regulation of the production of other cytokines. This has been demonstrated in cultures of dissociated RA synovial cells where blocking the activity of TNF-α can inhibit the secretion of IL-1 (F. M. Brennan et al., Lancet, 2, pp. 244-247, 1989) and therefore, inhibiting TNF-α should prevent the synthesis of other downstream cytokines such as IL-1. Lastly, TNF-α has been shown to be immunolocalised in both RA and OA synovial membranes (M. N. Farahat et al., Ann. Rheum. Dis., 52, pp. 870-875, 1993). Therefore, among the serious disease states related to the production or overproduction of TNF-α, a partial list includes the following: septic and endotoxic shock (reviewed by Tracey and Cerami, Ann. Rev. Med. 45, 491-503, 1994; Glauser et al. Clin. Infect Dis. 18, suppl. 2, 205-216, 1994); cachexia syndromes associated with bacterial infections (e.g., tuberculosis, meningitis), viral infections (e.g., AIDS), parasitic infections (e.g., malaria), and neoplastic disease; inflammatory bowel diseases and Crohn’s Disease; autoimmune disease, including some forms of arthritis (especially rheumatoid and degenerative forms); and adverse effects associated with treatment for the prevention of graft rejection.

Reduction in TNF-α levels can have clear beneficial effects in humans. This has been demonstrated by the approval of Racemide, an anti-TNF-α monoclonal antibody for the treatment of Crohn’s disease by Food and Drug Administration (e.g., FDA) in 1998. Another TNF-α inhibiting protein Enbrel was approved by the FDA in June 2000 to reduce the signs and symptoms of rheumatoid arthritis. TNF-α overproduction in other tissues has also been correlated with other diseases. An example is type 2 diabetes where overproduction of TNF-α in adipose tissue of obese patients may have an increase in insulin resistance. This is supported by the finding that mice lacking TNF-α function are protected from obesity induced insulin resistance (Kysal et al., Nature 389,619-614, 1997).

NITRIC OXIDE SYNTHASE

Nitric oxide synthases, are hemoproteins with a cytochrome “P450-like” active site, which catalyzes the oxidation of arginine to nitric oxide and citrulline. The short-lived nitric oxide fulfills a large range of biological functions as both a cellular messenger and a cytotoxic factor. There are three basic types of nitric oxide synthases: 1) a soluble

In addition, there is increasing data suggesting a connection between chronic inflammation and carcinogenic transformation (Kyriakis et al., 1996, J. Biol Chem.
271:24313-24316; Ferrell, J E, 1996, TIBS 21:460-466), one such study showed an
enhancement of rat urinary bladder tumorigenesis by lipopolysaccharide-induced
inflammation (Kawai et al., 1993, Cancer Res. 53:5172-5; Rosin et al., 1994, Cancer Res.
54 (7 Suppl):1929s-1933s; Choi et al., 1994, Gut 35:950-4). Based on the connection
between chronic inflammation and carcinogenic transformation, compounds that are
effective anti-inflammatory agents may also prove effective against cancer.
Compounds disclosed are useful in the inhibition of certain inflammatory
mediators, such as tumor necrosis factor-alpha and/or nitric oxide synthase. These
compounds may be useful in the treatment of diseases related to necrosis factor-alpha and
nitric oxide synthase.
A variety of assays may be performed to identify biological activity for TNF-α
and NOS. In the case of TNF-α, a TNFα inhibitor candidate, i.e. test compound, can be
found to inhibit TNF-α binding to a fusion protein that is composed of a TNF-α receptor
or a TNF-α-binding portion thereof, fused to an immunoglobulin molecule or a portion
thereof. In other assays, the ability of a test compound to inhibit TNF-α from binding to
an isolated TNF-α receptor is measured. Another assay is one where known cell
responses to TNF-α are measured in the presence and absence of putative TNF-α
inhibitors. For example, TNF–α has been shown to be cytotoxic to some cells, such as
WEHI cells, and assays can be used to measure the ability of a test compound to inhibit
TNF-α cytotoxicity. In some assays, specific non-lethal effects of TNF-α on control
cells are collected and used as an end point to evaluate the TNF-α inhibitory activity of a
test compound. Known effects of TNF-α on fibroblast cells include effects on
mitogenesis, IL-6 secretion, and HLA class II antigen induction. Comparisons can be
made between TNF-α's effect on fibroblasts in the presence or absence of a test
compound using these detectable phenotypic changes as endpoints. Similarly, known
effects of TNF-α on monocyte cells include effects on secretion of cytokines such as
GMCSF, IL-6 and IL-8. Comparisons can be made between TNF-α's effect on cytokine
secretion by monocytes in the presence or absence of a test compound. Additionally,
TNF-α is known to have effects on endothelial cell cytokine secretion and similar assays
may be designed and performed. Further, TNF–α is also known to effect adhesion

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molecule induction, such as ICAM-1, E-selectin, VCAM, and tissue factor production in endothelial cells. Comparisons can be made between TNF-α's effect on endothelial cells in the presence or absence of a test compound using these detectable phenotypic changes as endpoints as well. Likewise, TNF-α is known to effect neutrophils in specific ways.

Comparisons can be made between TNF-α's effect on neutrophils in the presence or absence of a test compound using activation, priming, degranulation and superoxide production as detectable endpoints for evaluation of TNF-α inhibitory activity. In another assay, U937 cells (human histiocytic lymphoma), in the presence of 12-O-tetradecanoylphorbo1 13-acetate (e.g., TPA), have been shown to induce secretion of TNF-α, and therefore a direct percent inhibition of the test compound on TNF-α activity can be determined by comparing cells treated with TPA in the presence and absence of test compound. These and other assays are well known to those having ordinary skill in the art. Such assays may be designed and performed routinely from readily available starting materials.

The enzyme nitric oxide synthase has a number of isoforms and compounds disclosed herein may be screened for nitric oxide synthetase activity by procedures based on those of Bredt and Snyder in Proc. Natl. Acad. Sci. (1990) 87, 682-685 and Forstermann et al. (1992) Eur. J. Pharm. 225,161-165. These assays rely on the ability to quantify the amount of 3 H-L-citrulline that is converted from H-L-arginine by the presence of nitric oxide synthetase. This can be accomplished by the cation exchange separation and quantified by liquid scintillation counting. A screen for neuronal nitric oxide synthase activity can be accomplished by isolating the enzyme from rat hippocampus or cerebellum. A screen for macrophage nitric oxide synthase activity can be accomplished by isolating the enzyme after induction by interferon-gamma. (IFN-gamma) and lipopolysaccharide (LPS) from the cultured murine macrophage cell line J774A-1. A screen for endothelial nitric oxide synthase activity can be accomplished by isolating the enzyme from human umbilical vein endothelial cells (HUVECs) by a procedure based on that of Pollock et al (1991) Proc. Nat. Acad. Sci., 88, 10480-10484. A screen for nitric oxide synthase can also be accomplishing using primary human chondrocytes in the presence of IL-β that induces NO production and quantified using the Griess Reagent system.
Compounds disclosed herein may have the ability to function as antidiabetic molecules. This activity may be demonstrated in animal models for type 2 diabetes, such as in the db/db or the KKA\textsuperscript{Y} mouse. In these models a compound is considered active if they are able to exhibit the ability to reduce glucose and triglyceride levels compared to controls. Compounds disclosed herein may be useful, for example, to modulate metabolism (such as, for example, lipid metabolism and carbohydrate metabolism) and may be able to treat type 2 diabetes. Modulation of lipid metabolism, for example, would include an increase of lipid content intracellularly or extracellularly. Modulation of lipid metabolism could also include a decrease of lipid content intracellularly or extracellularly. Modulation of lipid metabolism could also include the increase of one type of lipid containing particle such as high density lipoprotein (HDL) and or simultaneous decrease in low density lipoprotein (LDL). In one suitable animal model to measure such activity in vivo are young Sprague Dawley rats fed a high fat or high cholesterol diet. Modulation of metabolism may occur directly for example, through binding of the compounds disclosed herein with its cognate nuclear receptor, which directly affects an increase or decrease in lipid content by up-regulation or down-regulation of a gene involved in lipid metabolism. Modulation, for example, could be an increase in lipid metabolism, such that lipid metabolism is greater than that of a control. Modulation, also includes, for example, an increase in lipid metabolism, such that the lipid metabolism approaches that of a control. Likewise, modulation of lipid metabolism could be a decrease in lipid metabolism, such that the lipid metabolism is less than or decreasing towards a control. Carbohydrate metabolism may also be up-regulated or down-regulated to either approach the level of carbohydrate metabolism in a control or to deviate from the level of carbohydrate metabolism in a control. Changes in carbohydrate metabolism may directly or indirectly also result in changes of lipid metabolism and, similarly, changes in lipid metabolism may lead to changes in carbohydrate metabolism. An example is type 2 diabetes where an increase in free fatty acids in the patients leads to decreased cellular uptake and metabolism of glucose.

It is understood that a variety of lipid molecules may be modulated. The compounds disclosed herein may modulate a single type of lipid molecule, such as a triglyceride, or the compounds disclosed herein may modulate multiple types of lipid molecules.
molecules. The compounds disclosed herein may also modulate a single or variety of carbohydrate molecules. The compounds disclosed herein may modulate metabolism disorders, such as type 2 diabetes. Metabolism can be modulated by the compounds disclosed herein by, for example, decreasing the serum glucose levels and/or decreasing the serum triglyceride levels, relative to a control having serum glucose and/or triglyceride levels indicative of a mammal having type 2 diabetes. It is recognized that any decrease in serum glucose and/or triglyceride levels can benefit the mammal having type 2 diabetes.

These compounds may be characterized by their low molecular weights and physiological stability, and therefore, represent a class that may be implemented to prevent, alleviate, and/or otherwise, treat disorders of lipid and carbohydrate metabolism, such as obesity, dislipidemia, type 2 diabetes and other diseases related to type 2 diabetes. It is understood that treatment or prevention of type 2 diabetes may involve modulation of lipid or carbohydrate metabolism, such as the modulation of serum glucose or serum triglyceride levels.

An embodiment of the invention relates to the use of the compounds disclosed herein. The compounds disclosed herein may be either used singularly or plurally, and pharmaceutical compositions thereof for the treatment of mammalian diseases, particularly those related to humans. Compounds disclosed herein and compositions thereof may be administered by various methods including, for example, orally, enterally, parentally, topically, nasally, vaginally, ophthalmically, sublingually or by inhalation for the treatment of diseases related to lipid metabolism, carbohydrate metabolism, lipid and carbohydrate metabolism such as polycystic ovary syndrome, syndrome X, type 2 diabetes, including disorders related to type 2 diabetes such as, diabetic retinopathy, neuropathy, macrovascular disease or differentiation of adipocytes. Routes of administration and dosages known in the art may be found in Comprehensive Medicinal Chemistry, Volume 5, Hansch, C. Pergamon Press, 1990; incorporated herein by reference. The compositions may also be used as regulators in diseases of uncontrolled proliferation. The composition may be useful in the treatment of polycystic kidney disease and cancers such as, carcinomas, lymphomas, leukemias, and sarcomas. A representative but non-limiting list of cancers is lymphoma, Hodgkin’s Disease, myeloid
leukemia, bladder cancer, brain cancer, head and neck cancer, kidney cancer, lung cancers such as small cell lung cancer and non-small cell lung cancer, myeloma, neuroblastoma/glioblastoma, ovarian cancer, pancreatic cancer, prostate cancer, skin cancer, liver cancer, melanoma, colon cancer, cervical carcinoma, breast cancer, and epithelial cancer. Compounds disclosed herein may be used for the treatment of diseases and disorders such as neurodegenerative disorders, disorders of gastrointestinal motility, hypotension, septic shock, toxic shock syndrome, hemodialysis, IL-2 therapy such as in cancer patients, cachexia, and immunosuppression such as in transplant therapy. Compounds disclosed herein may be used for the treatment of diseases autoimmune and/or inflammatory indications including sunburn, eczema or psoriasis, respiratory conditions such as bronchitis, asthma, oxidant-induced lung injury, acute respiratory distress syndrome (ARDS), glomerulonephritis, restenosis, inflammatory sequelae of viral infections, myocarditis, heart failure, atherosclerosis, osteoarthritis, rheumatoid arthritis, septic arthritis, chronic or inflammatory bowel disease, ulcerative colitis, Crohn's disease, systemic lupus erythematosus (SLE), ocular conditions such as ocular hypertension, retinitis and uveitis, type 1 diabetes, type 2 diabetes, insulin-dependent diabetes mellitus and cystic fibrosis. Compounds disclosed herein may be useful in the treatment of hypoxia, hyperbaric oxygen convulsions and toxicity, dementia, Alzheimer's disease, Sydenham's chorea, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis (ALS), multiple sclerosis, epilepsy, Korsakoff's disease, imbecility related to cerebral vessel disorder, NO mediated cerebral trauma and related sequelae, ischemic brain edema (stroke), sleeping disorders, eating disorders such as anorexia, schizophrenia, depression, pre-menstrual syndrome (PMS), urinary incontinence, anxiety, drug and alcohol addiction, pain, migraine, emesis, tumor growth, immune complex disease, such as immunosuppressive agents, acute allograft rejection, infections caused by invasive microorganisms which produce NO, and for preventing or reversing tolerance to opiates and diazepines.

Although the compounds described herein may be administered as pure chemicals, it is preferable to present the active ingredient as a pharmaceutical composition. Thus another embodiment of the disclosed compounds is the use of a pharmaceutical composition comprising one or more compounds and/or a
pharmaceutically acceptable salt thereof, together with one or more pharmaceutically
acceptable carriers thereof and, optionally, other therapeutic and/or prophylactic
ingredients. The carrier(s) must be 'acceptable' in the sense of being compatible with the
other ingredients of the composition and not overly deleterious to the recipient thereof.

Pharmaceutical compositions include those suitable for oral, enteral, parental
(including intramuscular, subcutaneous and intravenous), topical, nasal, vaginal,
ophthalmic, sublingually or by inhalation administration. The compositions may,
where appropriate, be conveniently presented in discrete unit dosage forms and may be
prepared by any of the methods well known in the art of pharmacy. Such methods
include the step of bringing into association the active compound with liquid carriers,
solid matrices, semi-solid carriers, finely divided solid carriers or combination thereof,
and then, if necessary, shaping the product into the desired delivery system.

Pharmaceutical compositions suitable for oral administration may be presented as
discrete unit dosage forms such as hard or soft gelatin capsules, cachets or tablets each
containing a predetermined amount of the active ingredient; as a powder or as granules;
as a solution, a suspension or as an emulsion. The active ingredient may also be
presented as a bolus, electuary or paste. Tablets and capsules for oral administration may
contain conventional excipients such as binding agents, fillers, lubricants, disintegrants,
or wetting agents. The tablets may be coated according to methods well known in the
art., e.g., with enteric coatings.

Oral liquid preparations may be in the form of, for example, aqueous or oily
suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product
for constitution with water or other suitable vehicle before use. Such liquid preparations
may contain conventional additives such as suspending agents, emulsifying agents, non-
aqueous vehicles (which may include edible oils), or one or more preservative.

The compounds may also be formulated for parenteral administration (e.g., by
injection, for example, bolus injection or continuous infusion) and may be presented in
unit dose form in ampules, pre-filled syringes, small bolus infusion containers or in
multi-doses containers with an added preservative. The compositions may take such
forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may
contain formulation agents such as suspending, stabilizing and/or dispersing agents.
Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilization from solution, for constitution with a suitable vehicle, e.g., sterile, pyrogen-free water, before use.

For topical administration to the epidermis, the compounds may be formulated as ointments, creams or lotions, or as the active ingredient of a transdermal patch. Suitable transdermal delivery systems are disclosed, for example, in Fisher et al. (U.S. Patent No. 4,788,603, incorporated herein by reference) or Bawas et al. (U.S. Patent No. 4,931,279, 4,668,504 and 4,713,224; all incorporated herein by reference). Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilizing agents, dispersing agents, suspending agents, thickening agents, or coloring agents. The active ingredient may also be delivered via iontophoresis, e.g., as disclosed in U.S. Patent Nos. 4,140,122, 4383,529, or 4,051,842; incorporated herein by reference.

Compositions suitable for topical administration in the mouth include unit dosage forms such as lozenges comprising active ingredient in a flavored base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerin or sucrose and acacia; mucoadherent gels, and mouthwashes comprising the active ingredient in a suitable liquid carrier.

When desired, the above-described compositions may be adapted to provide sustained release of the active ingredient employed, e.g., by combination thereof with certain hydrophilic polymer matrices, e.g., comprising natural gels, synthetic polymer gels or mixtures thereof.

The pharmaceutical compositions according to the invention may also contain other adjuvants such as flavorings, coloring, antimicrobial agents, or preservatives.

It will be further appreciated that the amount of the compound, or an active salt or derivative thereof, required for use in treatment will vary not only with the particular salt selected but also with the route of administration, the nature of the condition being treated and the age and condition of the patient and will be ultimately at the discretion of the attendant physician or clinician.
In general, one of skill in the art understands how to extrapolate in vivo data obtained in a model organism, such as mouse, rat and the like, to another mammal, such as a human. These extrapolations are not simply based on the weights of the two organisms, but rather incorporate differences in metabolism, differences in pharmacological delivery, and administrative routes. Based on these types of considerations, a suitable dose will, in alternative embodiments, typically be in the range of from about 0.5 to about 100 mg/kg/day, from about 1 to about 75 mg/kg of body weight per day, from about 3 to about 50 mg per kilogram body weight of the recipient per day, or in the range of 6 to 90 mg/kg/day, most preferably in the range of 15 to 60 mg/kg/day.

The compound is conveniently administered in unit dosage form; for example, in alternative embodiments, containing 0.5 to 1000 mg, 5 to 750 mg, most conveniently, or 10 to 500 mg of active ingredient per unit dosage form.

One skilled in the art will recognize that dosage and dosage forms outside these typical ranges can be tested and, where appropriate, be used in the methods of this invention.

In separate embodiments, the active ingredient may be administered to achieve peak plasma concentrations of the active compound of from about 0.5 to about 75 μM, about 1 to 50 μM, or about 2 to about 30 μM. This may be achieved, for example, by the intravenous injection of a 0.05 to 5% solution of the active ingredient, optionally in saline, or orally administered as a bolus containing about 0.5-500 mg of the active ingredient. Desirable blood levels may be maintained by continuous infusion to provide about 0.01-5.0 mg/kg/hr or by intermittent infusions containing about 0.4-15 mg/kg of the active ingredients.

The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example, as two, three, four or more sub-doses per day. The sub-dose itself may be further divided, e.g., into a number of discrete loosely spaced administrations; such as multiple inhalations from an insufflator or by application of a plurality of drops into the eye.
While the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications and this application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure as come within known or customary practice within the art to which the invention pertains and as may be applied to the essential features hereinbefore set forth, and as follows in the scope of the appended claims.

The following examples are given to illustrate the invention and are not intended to be inclusive in any manner:

**Examples**

**Example 1:** 2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-methoxybenzylidene-2,4-thiazolidinedione, also referred to Compound 1 herein:

To a solution of toluene (10 mL) containing piperidine (0.1 mL) and acetic acid (0.1 mL) was added 3-methoxy-2-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)benzaldehyde (0.480 g, 1.42 mmol) and 2,4-thiazolidinedione (0.117 g, 1.42 mmol) and the solution was heated at reflux overnight with continuous removal of water using a Dean-Stark water separator. The reaction mixture was cooled to room temperature, diluted with EtOAc, washed with water and brine. After drying over MgSO₄ the mixture was filtered and evaporated. The resulting residue was purified on silica gel (2% MeOH in CH₂Cl₂) to give 0.356 g (57% yield) of the desire product. The product was further purified by recrystallization from aqueous ethanol: mp 125-130°C.

¹H NMR (500 MHz; DMSO-d₆): 8 1.11 (s, 3 H); 1.17 (s, 3 H); 1.27 (s, 3 H); 1.28 (s, 3 H); 1.64 (2 s, 4 H); 1.91 (s, 3 H); 3.73 (s, 3 H); 6.82 (s, 1 H); 7.16-7.22 (m, 3 H); 7.51 (d, J = 8.2 Hz, 1 H); 12.5 (br, 1 H).

The intermediate 3-methoxy-2-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)benzaldehyde was prepared as follows:

a. To a solution of o-vanillin (0.5 g, 3.28 mmol; i.e., 3-methoxy-2-hydroxybenzaldehyde) in dichloromethane (20 mL) was added pyridine (0.3 mL, 1.2 eq) and the solution cooled to 0°C. Triflic anhydride (0.65 mL, 1.2 eq) was added slowly and
the resulting reaction mixture was allowed to warm slowly to room temperature and
stirred for 3 hr. at room temperature. The solution was washed successively with water
and brine, dried over anhydrous magnesium sulfate, filtered and evaporated. The residue
was purified on silica gel (ethyl acetate/ hexane, 1:9) to give 0.437 g of 3-methoxy-2-
trifluoromethanesulfonfyl benzaldehyde (yield 47%). The product was used without
further purification.

b. A mixture of 3-methoxy-2-trifluoromethanesulfonfyl benzaldehyde (0.430
g, 1.51 mmol), (3,5,8,8-pentamethyl-5,6,7,8-tetrahydro-1 2-pyrol-2-yl) boronic acid
(0.740 g, 3.00 mmol) and potassium carbonate (0.835 g) in 1,2-dimethoxyethane (20
mL) and water (1 mL) was degassed with argon for 15 minutes. To this mixture was
added tetrakis(triphenylphosphine)palladium(0) (0.35 g, 0.3 mmol) and the resulting
mixture was heated at reflux under argon for 4 hours. The solution was cooled to room
temperature, diluted with ethyl acetate and washed successively with water and brine,
dried over anhydrous magnesium sulfate, filtered and evaporated. The residue was
chromatographed on silica gel (ethyl acetate/ hexane, 1:9) to give 0.48 g of 3-methoxy-2-
(3,5,8,8-pentamethyl-5,6,7,8-tetrahydro-1 2-pyrol-2-yl) benzaldehyde.

Example 2: 4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-
methoxybenzylidene-2,4-thiazolidinedione, referred to as Compound 2 herein.

Prepared in a similar manner to Example 1 in a 54% yield using 3-methoxy-4-
(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-1 2-pyrol-2-yl) benzaldehyde; mp 227-228°C.

\(^1\)H NMR (500 MHz; DMSO-d\(_6\)) 1.21 (s, 6 H), 1.26 (s, 6 H), 1.64 (s, 4 H), 2.00 (s, 3 H),
3.78 (s, 3 H), 7.01 (s, 1 H), 7.16 (s, 1 H), 7.22 (dd, J\(_1\) = 7.8 Hz, J\(_2\) = 1 Hz, 1 H), 7.24 (d, 
J = 7.8 Hz, 1 H), 7.30 (s, 1 H), 7.85 (s, 1 H), 12.75 (s, 1 H).

The intermediate 3-methoxy-4-(3,5,5,8,8-pentamethyl-5,6,7,8-
tetrahydro-1 2-pyrol-2-yl) benzaldehyde was prepared as follows:

a. To a solution of vanillin (1.0 g, 6.57 mmol) in dichloromethane (50 mL)
was added pyridine (0.6 mL, 7.76 mmol) and the solution cooled to 0°C. Triflic
anhydride (1.3 mL, 7.76 mmol) was added slowly and the reaction mixture warmed
slowly to room temperature and stirred overnight at room temperature. The solution was
washed successively with water and brine, dried over anhydrous magnesium sulfate,
filtered and evaporated. The residue was purified on silica gel (eluent: ethyl acetate/hexane, 1:9) to give 1.38 g of 3-methoxy-4-trifluoromethanesulfonyl benzaldehyde (yield 74%). $^1$H NMR (500 MHz; CDCl$_3$) 4.00 (s, 3 H); 7.41 (d, J = 8.0 Hz, 1 H), 7.50 (dd, J$_1$ = 2.0 Hz, J$_2$ = 8.0 Hz, 1 H), 7.56 (d, J = 2.0 Hz, 1 H), 9.98 (s, 1 H).

b. A mixture of 3-methoxy-4-trifluoromethanesulfonyl benzaldehyde (0.50 g, 1.76 mmol), (3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-1-naphthalen-2-yl) boronic acid (0.43 g, 1.76 mmol) and potassium carbonate (0.97 g, 7.04 mmol) in 1,2-dimethoxyethane (15 mL) and water (1 mL) was degassed with argon for 30 minutes. Tetrakis(triphenylphosphine)palladium(0) (0.20 g, 0.17 mmol) was added and the mixture heated at reflux under argon for 5 hours. The solution was cooled to room temperature, diluted with ethyl acetate and washed successively with water and brine, dried over anhydrous magnesium sulfate, filtered and evaporated. The residue was chromatographed on silica gel (Biotage, eluent: 0-30% ethyl acetate in hexane) to give 0.40 g of 4-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-methoxybenzaldehyde (67%). $^1$H NMR (500 MHz; CDCl$_3$) 1.27 (s, 6 H), 1.32 (s, 6 H), 1.70 (s, 4 H), 2.09 (s, 3 H), 3.85 (s, 3 H), 7.09 (s, 1 H), 7.16 (s, 1 H), 7.26 (s, 1 H), 7.35 (d, J = 7.5 Hz, 1 H); 7.47 (s, 1 H), 7.50 (d, J = 7.5 Hz, 1 H), 10.02 (s, 1 H).

**Example 3:** 2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-5-pyridylidene-2,4-thiazolidinedione, referred to as Compound 3 herein.

Prepared in a similar manner to Example 1 in a 53% yield using 2-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)pyridine-5-carboxaldehyde; mp 277°C (dec.).

$^1$H NMR (300 MHz; DMSO-d$_6$) 1.25 (s, 6 H), 1.27 (s, 6 H), 1.65 (s, 4 H), 2.31 (s, 3 H), 7.24 (s, 1 H), 7.37 (s, 1 H), 8.00 (dd, J$_1$ = 8.1 Hz, J$_2$ = 2.1 Hz, 1 H), 7.24 (d, J = 7.8 Hz, 1 H), 7.30 (s, 1 H), 7.85 (s, 1 H); 12.75 (s, 1 H). The intermediate 2-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)pyridine-5-carboxaldehyde was prepared as follows:

a. 2-Bromo-pyridine-5-carboxaldehyde.
To a suspension of 2,5-dibromopyridine (10.28 g, 0.043 mol) in dry ether (150 mL) cooled to –78°C under argon was added dropwise a solution of n-BuLi (17.4 mL, 0.043 mol, 2.5 M in hexanes) while maintaining an internal reaction temperature below –78°C. The resulting dark red suspension was stirred for 30 min. and a solution of DMF (4.0 mL, 0.0521 mol) in 5 mL dry ether was added dropwise. After 45 min. the bath was removed and the mixture was allowed to warm to RT. The mixture was cooled to 0°C and 1 N HCl was added and stirred for 15 min. The resulting layers were separated and the aqueous layer washed with ether (twice) and combined with the original organics. The organics were washed with water, brine and dried (MgSO₄). The mixture was filtered and evaporated to give a solid that was purified by column chromatography (silica gel, CH₂Cl₂) to afford the product as a white solid, 5.23 g (64.8% yield). ¹H NMR (300 MHz; CDCl₃) 7.69 (d, J = 8.0 Hz, 1 H), 8.03 (dd, J₁ = 8.0 Hz, J₂ = 2.0 Hz, 1 H), 8.84 (d, J = 2.0 Hz, 1 H), 10.10 (s, 1 H).

b. 2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)pyridine-5-carboxaldehyde.

A mixture of 2-Bromo-pyridine-5-carboxaldehyde (0.50 g, 2.69 mmol), (3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphtalen-2-yl) boronic acid (0.795 g, 3.23 mmol) and potassium carbonate (0.745 g, 5.38 mmol) in toluene (5 mL), EtOH (1 mL) and water (0.75 mL) was degassed with argon for 30 minutes. Tetrakis(triphenylphosphine)palladium(0) (0.062 g, 0.054 mmol) was added and the mixture heated at reflux under argon until complete consumption of starting material. The solution was cooled to room temperature, diluted with ethyl acetate and washed successively with water and brine, dried over anhydrous magnesium sulfate, filtered and evaporated. The residue was chromatographed on silica gel (Biotage, eluent: 10% ethyl acetate in hexane) to give 0.744 g of 2-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)pyridine-5-carboxaldehyde (93 %).

Example 4: 4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-hydroxybenzylidene-2,4-thiazolidinedione.
Prepared in a similar manner to Example 1 in a 58% yield using 3-hydroxy-4-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)benzaldehyde.

$^1$H NMR (300 MHz; DMSO-d$_6$) 1.21 (s, 6 H), 1.27 (s, 6 H), 1.64 (s, 4 H), 2.06 (s, 3 H), 3.78 (s, 3 H), 7.01 (s, 1 H), 7.10-7.20 (m, 4 H), 7.21 (s, 1 H), 9.85 (s, 1 H), 12.61 (s, 1 H).

The intermediate 3-hydroxy-4-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)benzaldehyde was prepared as follows:

a. To a solution of 3-methoxy-4-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)benzaldehyde (2.0 g, 5.94 mmol) in dichloromethane (60 mL) cooled to -78°C was added BBr$_3$ (1.12 mL) under argon. The solution was slowly warmed to RT and clearly poured into iced-water. The mixture was extracted with EtOAc, washed with water and brine, dried (MgSO$_4$), filtered and evaporated to give the crude product. The crude product was taken up into DMF (15 mL) and NaOAc (2.5 g) and the solution was heated to reflux and the temperature maintained overnight. The solution was cooled to RT, diluted with EtOAc and washed successively with water and brine, dried (MgSO$_4$), filtered and evaporated. The residue was purified on silica gel (eluent: ethyl acetate/hexane, 1:9) to give 1.19 g of 3-hydroxy-4-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)benzaldehyde (yield 62%).

Example 5: 4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-ethoxybenzylidene-2,4-thiazolidinedione.

Prepared in a similar manner to Example 1 in a 49% yield using 3-ethoxy-4-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)benzaldehyde, mp 240-241°C.

$^1$H NMR (300 MHz; DMSO-d$_6$) 1.22-1.27 (2s & t, 15 H), 1.64 (s, 4 H), 2.06 (s, 3 H), 4.11 (q, J = 7.2 Hz, 2 H), 7.06 (s, 1 H), 7.18 (s, 1 H), 7.20 (d, J = 10 Hz, 1 H), 7.28 (d, J = 8.0 Hz, 1 H), 7.30 (s, 1 H), 7.85 (s, 1 H), 12.64 (s, 1 H).

The intermediate 3-ethoxy-4-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)benzaldehyde was prepared in a similar manner as described in Example 2:

a. 3-Ethoxy-4-trifluoromethanesulfonfyl benzaldehyde.

To a solution of 4-hydroxy-3-ethoxybenzaldehyde (5.0 g, 30.09 mmol) in dichloromethane (100 mL) was added pyridine (2.92 mL, 36.11 mmol) and the solution
cooled to 0°C. Triflic anhydride (6.01 mL, 36.11 mmol) was added slowly and the reaction mixture warmed slowly to room temperature and stirred overnight. The mixture was washed successively with water and brine, dried over anhydrous magnesium sulfate, filtered and evaporated. The residue was purified on silica gel (eluent: ethyl acetate/hexane, 5:95) to give 4.89 g of 3-ethoxy-4-trifluoromethanesulfonyl benzaldehyde (yield 58%).

b. 3-ethoxy-4-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)benzaldehyde.

A mixture of 3-methoxy-4-trifluoromethanesulfonyl benzaldehyde (0.51 g, 1.81 mmol), (3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)boronic acid (0.534 g, 2.17 mmol) and potassium carbonate (0.50 g, 3.62 mmol) in toluene (5 mL), EtOH (1 mL) and water (0.75 mL) was degassed with argon for 30 minutes. Tetrais(triphenylphosphine)palladium(0) (0.042 g, 0.036 mmol) was added and the mixture heated at reflux under argon overnight. The solution was cooled to room temperature, diluted with ethyl acetate and washed successively with water and brine, dried over anhydrous magnesium sulfate, filtered and evaporated. The residue was chromatographed on silica gel (Biotage, eluent: 10% ethyl acetate in hexane) to give 0.40 g of 4-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-ethoxybenzaldehyde (67%).

Example 6: 4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-methylbenzylidene-2,4-thiazolidinedione.

Prepared in a similar manner as described in Example 1 in a 56% yield using the intermediate 3-methyl-4-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)benzaldehyde, mp 223-225°C. 1H NMR (300 MHz; DMSO-d6) 1.21 (s, 6 H), 1.27 (s, 3 H), 1.28 (s, 3 H), 1.65 (s, 4 H), 1.96 (s, 3 H), 2.06 (s, 3 H), 6.98 (s, 1 H), 7.23 (s, 1 H), 7.25 (d, J = 9 Hz, 1 H), 7.44 (d, J = 8 Hz, 1 H), 7.52 (s, 1 H), 7.78 (s, 1 H), 12.62 (s, 1 H).

The intermediate 3-methyl-4-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)benzaldehyde was prepared in a similar manner as described in Example 2 utilizing 4-hydroxy-3-methylbenzaldehyde; step a) 3-methoxy-4-trifluoromethanesulfonyl benzaldehyde (yield 47%) and step b) 3-methyl-4-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)benzaldehyde (yield 83%).
**Example 7:** 4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-methoxy-5-fluorobenzylidene-2,4-thiazolidinedione.

Prepared in a similar manner as described in Example 1; mp 209-211

$^1$H NMR (300 MHz; DMSO-d$_6$) 1.20 (s, 6 H), 1.28 (s, 6 H), 1.65 (s, 4 H), 1.98 (s, 3 H), 3.79 (s, 3 H), 7.04 (s, 1 H), 7.13 (d, J = 9.9 Hz, 1 H), 7.18 (d, J = 0.6 Hz, 1 H), 7.23 (s, 1 H), 7.84 (s, 1 H), 12.73 (s, 1 H).

**Example 8:** Inhibition of TNF-α: U937 cells (50,000 c/w per 96 well plate (i.e., wp)).

Growth medium (GM): RPMI containing 10% fetal calf serum (FCS) plus glutamine-pen-strep. Cells were grown in an atmosphere containing 6% CO$_2$. U937 cells are seeded in growth medium and after 4-6 hours cells are treated with a test compound at various concentrations in the presence of TPA (0.1 µM). Cells are incubated for about 16 hours under these conditions upon which the supernatants are transferred to a new 96 wp and the remaining cells are replenished with growth medium. A commercially available colorimetric (MTT) assay kit is used to determine cell density. A TNFα-ELISA kit (ENDOGEN) is used for quantification of TNF-α. A 1:10 dilution of each supernatant is analyzed with the ELISA kit. The kit was used following the manufacturer’s instructions.

Figure 1 show inhibition of TPA induced TNF-α production by Compounds 1, 2 and 7. For a control, cells were incubated with TPA only.

**Example 9:** Inhibition of iNOS: human chondrocytes (20,000 c/w per 96 well plate (wp)).

Growth condition: Cells were grown in Dulbecco’s Modified Eagles medium containing 10% fetal calf serum (FCS) plus glutamine-pen-strep. Cells are allowed to grow overnight and are then treated with the test compound in DME containing 1% FCS. After 5 hours of incubation with the test compound, IL-1β is added to the cells at a final concentration of 1 ng/ml. Cells are incubated for an additional 48 hours, the supernatants are transferred to a fresh 96 wp, and kept frozen until NO readings are carried out. A
colorimetric (MTT) assay is carried our to control for cell density. For this DME is added to the original plate containing the attached cells.

NO measurement:

1) A volume of 50 µl of the supernatant of the treated human chondrocytes is transferred to a 96 well plate and mixed with an equal volume of Greiss reagent.
2) After 10 minutes, the color of the reaction is read at 540 nm.
3) A sodium nitrite standard curve is established in parallel. The concentrations of Sodium Nitrite used were: 2.9; 7.8; 15.6; 31.25; 62.5; 125 (mM).

Figure 2 shows inhibition of iNOS by Compound 3. Control cells were grown in the presence of IL-1β in the absence of the test compound.

It will be apparent to those skilled in the art that various modifications and variations can be made in the present invention without departing from the scope or spirit of the invention. Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims.
We claim:
1. A compound of Formula (I):

   \[
   \text{(I)}
   \]

wherein:

- \( n \) and \( m \) are independently 0 or 1;
- \( R_1 \) and \( R_2 \) are 1) independently or together hydrogen, alkyl, substituted alkyl, haloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substituted alkoxy, hydroxyl, acyl, amino, mono-substituted amino, di-substituted amino, carboxy, carboalkoxy, alkylcarboxamide, substituted alkylcarboxamide, dialkylcarboxamide, substituted dialkylcarboxamide or haloalkoxy; or 2) \( R_1 \) and \( R_2 \) together with the aromatic ring bonded thereto form a cycloalkyl, substituted cycloalkyl, cycloalkenyl or substituted cycloalkeny residue that may optionally comprise 1 or 2 heteroatoms selected from O, S, NH or N-alkyl;

- \( R_3 \) and \( R_4 \) are independently or together hydrogen, alkyl, substituted alkyl, haloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, halogen, cyano, nitro, hydroxyl, acyloxy, amino, mono-substituted amino, di-substituted amino, alkylsulfonamide, arylsulfonamide, alkylurea, arylurea, alkylcarbamate, arylcarbamate, heteroaryl, alkoxy, substituted alkoxy, haloalkoxy, thioalkyl, thioheteroalkyl, carboxy, carboalkoxy, alkylcarboxamide, substituted alkylcarboxamide, dialkylcarboxamide or substituted dialkylcarboxamide;

- \( A \) is \(-\text{CR}_6\text{R}_7-\) where \( R_6 \) and \( R_7 \) are independently or together hydrogen, alkyl, substituted alkyl, alkoxy, substituted alkoxy or haloalkoxy; or \( R_6 \) and \( R_7 \)
together form a cycloalkyl residue that may optionally comprise 1 or 2 heteroatoms selected from O, S, NH and N-alkyl;

\[
\text{Ar is Formula (II), (III), (IV), (V) or (VI):}
\]

\[
\begin{align*}
\text{(II)} & \quad \begin{array}{c}
\begin{array}{c}
\text{R}_8 \\
\text{R}_9 \\
\text{R}_{10}
\end{array}
\end{array} \\
\text{(III)} & \quad \begin{array}{c}
\begin{array}{c}
\text{R}_8 \\
\text{R}_9 \\
\text{R}_{10}
\end{array}
\end{array} \\
\text{(IV)} & \quad \begin{array}{c}
\begin{array}{c}
\text{R}_8 \\
\text{R}_9
\end{array}
\end{array} \\
\text{(V)} & \quad \begin{array}{c}
\begin{array}{c}
\text{R}_9 \\
\text{R}_8
\end{array}
\end{array} \\
\text{(VI)} & \quad \begin{array}{c}
\begin{array}{c}
\text{R}_9 \\
\text{R}_8
\end{array}
\end{array}
\end{align*}
\]

where \(\text{R}_8, \text{R}_9\) and \(\text{R}_{10}\) are independently or together hydrogen, alkyl, substituted alkyl, haloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, halogen, cyano, nitro, hydroxyl, acyloxy, amino, mono-substituted amino, di-substituted amino, alkylamide, alkylsulfonamide, arylsulfonamide, alkylurea, aroylurea, alkylcarbamate, aroylurea, alkoxy, substituted alkoxy, haloalkoxy, thioalkyl, thiohaloalkyl, carboxy, carbaalkoxy, alkylcarboxamide, substituted alkylcarboxamide, dialkylcarboxamide or substituted dialkylcarboxamide;

\[
\text{R}_5 \text{ is hydrogen, halogen, hydroxy, alkyl or substituted alkyl;}
\]

\[
\text{\text{- - - - -} represents a bond present or absent; and}
\]

\[
\text{W, X, Y and Z are independently or together} \ -\text{C(O)-,} -\text{C(S)-,} -\text{S-,} -\text{O- or}
\]

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-NH-residues that together form a 2,4-thiazolidinedione, 2-thioxo-4-thiazolidinedione, isoxazolidinedione, 2,4-imidazolidinedione or 2-thioxo-4-imidazolidinedione residue;

or a pharmaceutically acceptable salt thereof.

2. A compound of claim 1 wherein \( n \) is 0.

3. A compound of claim 1 wherein \( n \) is 1.

4. A compound of claim 2 wherein \( m \) is 1.

5. A compound of claim 4 wherein \( R_1 \) and \( R_2 \) are 1) independently or together alkyl, substituted alkyl or hydroxyl; or 2) \( R_1 \) and \( R_2 \) together with the aromatic ring bonded thereto form a cycloalkyl or substituted cycloalkyl optionally comprising 1 or 2 heteroatoms selected from O, NH and N-alkyl; and

\[ \text{R}_3 \text{ and } \text{R}_4 \text{ are independently or together hydrogen, halogen, alkyl, substituted alkyl, haloalkyl, alkoxy, substituted alkoxy, haloalkoxy, amino, mono-} \]
\[ \text{substituted amino or di-substituted amino.} \]

6. A compound of claim 5 wherein \( W, X, Y \) and \( Z \) form a 2,4-thiazolidinedione, 2-thioxo-4-thiazolidinedione, 2-thioxo-4-imidazolidinedione or 2,4-imidazolidinedione residue.

7. A compound of claim 6 wherein \( \text{Ar} \) is Formula (VI), (VII) or (VIII):

\[ \begin{align*}
(\text{II}) & \quad (\text{III}) & \quad (\text{VI})
\end{align*} \]
wherein

\[ R_9 \text{ is alkyl, substituted alkyl, alkenyl, haloalkyl, hydroxy, acyloxy, halogen, alkoxy, substituted alkoxy, amino, mono-substituted amino, di-substituted amino, alkylamide or haloalkoxy; and} \]

5 \[ R_9 \text{ and } R_{10} \text{ are independent or together hydrogen, halogen, alkyl, substituted alkyl, haloalkyl, alkenyl, substituted alkenyl, alkoxy, hydroxy, amino, mono-substituted amino, di-substituted amino, alkylamide or haloalkoxy.} \]

8. A compound of claim 7 wherein \(-\text{-----}\) represents the bond is present and the compound has the Formula (XV):

![Formula XV](image)

9. A compound of claim 1 wherein \( R_1 \) and \( R_2 \) together with the aromatic ring bonded thereto form a substituted cycloalkyl; \( R_3 \) is methyl, ethyl, trifluoromethyl, methoxy or dimethylamino; and \( R_4 \) is hydrogen.

10. A compound of claim 1 wherein \( R_1 \) and \( R_2 \) together with the aromatic ring bonded thereto form a substituted cycloalkyl; \( R_3 \) is methyl, ethyl, trifluoromethyl, methoxy or dimethylamino; and \( R_4 \) is hydrogen form a residue, wherein the residue is selected from:

\[ 3,5,5,8,8\text{-pentamethyl-5,6,7,8\text{-tetrahydro-2\text{-naphthyl}},} \]

\[ 3\text{-ethyl-5,5,8,8\text{-tetramethyl-5,6,7,8\text{-tetrahydro-2\text{-naphthyl}},} \]

\[ 3\text{-trifluoromethyl-5,5,8,8\text{-tetramethyl-5,6,7,8\text{-tetrahydro-2\text{-naphthyl}},} \]

\[ 3\text{-methoxy-5,5,8,8\text{-tetramethyl-5,6,7,8\text{-tetrahydro-2\text{-naphthyl}}, or} \]

\[ 3\text{-dimethylamino-5,5,8,8\text{-tetramethyl-5,6,7,8\text{-tetrahydro-2\text{-naphthyl}.} \}

11. The compound of claim 2 present as:
2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-methoxybenzylidene-2,4-thiazolidinedione,
2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-trifluoromethoxybenzylidene-2,4-thiazolidinedione,
2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-dimethylaminobenzylidene-2,4-thiazolidinedione,
2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-chlorobenzylidene-2,4-thiazolidinedione,
2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-methylenbenzylidene-2,4-thiazolidinedione,
2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-ethylbenzylidene-2,4-thiazolidinedione,
2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-trifluoromethylbenzylidene-2,4-thiazolidinedione,
2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-ethoxybenzylidene-2,4-thiazolidinedione,
2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-methoxy-4-fluorobenzylidene-2,4-thiazolidinedione,
2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-methoxy-6-fluorobenzylidene-2,4-thiazolidinedione,
2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-isopropoxybenzylidene-2,4-thiazolidinedione or
2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-aminobenzylidene-2,4-thiazolidinedione; or a pharmaceutically acceptable salt thereof.

12. The compound of claim 2 present as:
2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-acetamidobenzylidene-2,4-thiazolidinedione,
2-(3-Methoxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-trifluoromethoxybenzylidene-2,4-thiazolidinedione,
2-(3-Dimethylamino-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-
trifluoromethoxybenzylidene-2,4-thiazolidinedione,
2-(3-Trifluoromethyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-
3-methoxybenzylidene-2,4-thiazolidinedione,
2-(3-Trifluoromethyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-
3-methylbenzylidene-2,4-thiazolidinedione,
2-(3-Trifluoromethyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-
3-ethylbenzylidene-2,4-thiazolidinedione,
2-(3-Trifluoromethyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-
3-trifluoromethoxybenzylidene-2,4-thiazolidinedione,
2-(3-Dimethylamino-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-
dimethylaminobenzylidene-2,4-thiazolidinedione,
2-(3-Trifluoromethyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-
3-chlorobenzylidene-2,4-thiazolidinedione,
2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-
acetoxybenzylidene-2,4-thiazolidinedione,
2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-
hydroxybenzylidene-2,4-thiazolidinedione or
2-(3-Trifluoromethyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-
3-dimethylaminobenzylidene-2,4-thiazolidinedione, or a pharmaceutically
acceptable salt thereof.

13. The compound of claim 2 present as:
4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-
methoxybenzylidene-2,4-thiazolidinedione,
4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-
trifluoromethoxybenzylidene-2,4-thiazolidinedione,
4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-
dimethylaminobenzylidene-2,4-thiazolidinedione,
4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-
chlorobenzylidene-2,4-thiazolidinedione,
4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthal)-3-methylbenzylidene-2,4-thiazolidinedione,
4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthal)-3-ethylbenzylidene-2,4-thiazolidinedione,
4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthal)-3-trifluoromethylbenzylidene-2,4-thiazolidinedione,
4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthal)-4-ethoxybenzylidene-2,4-thiazolidinedione,
4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthal)-3-methoxy-5-fluorobenzylidene-2,4-thiazolidinedione,
4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthal)-2-fluoro-3-methoxy-benzylidene-2,4-thiazolidinedione,
4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthal)-3-isopropoxybenzylidene-2,4-thiazolidinedione or
4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthal)-3-aminobenzylidene-2,4-thiazolidinedione; or a pharmaceutically acceptable salt thereof.

14. The compound of claim 2 present as:
4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthal)-3-acetamidobenzylidene-2,4-thiazolidinedione,
4-(3-Methoxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthal)-3-trifluoromethoxybenzylidene-2,4-thiazolidinedione,
4-(3-Dimethylamino-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthal)-3-trifluoromethoxybenzylidene-2,4-thiazolidinedione,
4-(3-Trifluoromethyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthal)-3-methoxybenzylidene-2,4-thiazolidinedione,
4-(3-Trifluoromethyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthal)-3-methylbenzylidene-2,4-thiazolidinedione,
4-(3-Trifluoromethyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthal)-3-ethylbenzylidene-2,4-thiazolidinedione,
4-(3-Trifluoromethyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-
3-trifluoromethoxybenzylidene-2,4-thiazolidinedione,
4-(3-Dimethylamino-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-
dimethylaminobenzylidene-2,4-thiazolidinedione,
4-(3-Trifluoromethyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-
3-chlorobenzylidene-2,4-thiazolidinedione,
4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-
acetoxybenzylidene-2,4-thiazolidinedione,
4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-
hydroxybenzylidene-2,4-thiazolidinedione or
4-(3-Trifluoromethyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-
3-dimethylaminobenzylidene-2,4-thiazolidinedione; or a pharmaceutically
acceptable salt thereof.

15. A compound of claim 2 present as:
2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-5-pyridylidene-
2,4-thiazolidinedione or
2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-methoxy-5-
pyridylidene-2,4-thiazolidinedione; or a pharmaceutically acceptable salt thereof.

16. A compound of claim 7 wherein ---- represents the bond is absent and the
compound has the Formula (XVI):

![Formula XVI]

17. The compound of claim 2 present as:
2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-methoxybenzyl-2,4-thiazolidinedione,
2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-trifluoromethoxybenzyl-2,4-thiazolidinedione,
2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-dimethylaminobenzyl-2,4-thiazolidinedione,
2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-chlorobenzyl-2,4-thiazolidinedione,
2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-methylbenzyl-2,4-thiazolidinedione,
2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-ethylbenzyl-2,4-thiazolidinedione,
2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-trifluoromethylbenzyl-2,4-thiazolidinedione,
2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-ethoxybenzyl-2,4-thiazolidinedione,
2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-methoxy-4-fluorobenzyl-2,4-thiazolidinedione,
2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-methoxy-6-fluorobenzyl-2,4-thiazolidinedione,
2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-isopropoxybenzyl-2,4-thiazolidinedione or
2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-aminobenzyl-2,4-thiazolidinedione; or a pharmaceutically acceptable salt thereof.

18. The compound of claim 2 present as:
2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-acetamidobenzyl-2,4-thiazolidinedione,
2-(3-Methoxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-trifluoromethoxybenzyl-2,4-thiazolidinedione,
2-(3-Dimethylamino-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-trifluoromethoxybenzyl-2,4-thiazolidinedione,
2-(3-Trifluoromethyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-methoxybenzyl-2,4-thiazolidinedione,
2-(3-Trifluoromethyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-methylbenzyl-2,4-thiazolidinedione,
2-(3-Trifluoromethyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-ethylbenzyl-2,4-thiazolidinedione,
2-(3-Trifluoromethyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-trifluoromethoxybenzyl-2,4-thiazolidinedione,
2-(3-Dimethylamino-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-dimethylaninobenzyl-2,4-thiazolidinedione,
2-(3-Trifluoromethyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-chlorobenzyl-2,4-thiazolidinedione,
2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-acetoxybenzyl-2,4-thiazolidinedione,
2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-hydroxybenzyl-2,4-thiazolidinedione or
2-(3-Trifluoromethyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-dimethylaninobenzyl-2,4-thiazolidinedione; or a pharmaceutically acceptable salt thereof.

19. The compound of claim 2 present as:
4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-methoxybenzyl-2,4-thiazolidinedione,
4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-trifluoromethoxybenzyl-2,4-thiazolidinedione,
4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-dimethylaninobenzyl-2,4-thiazolidinedione,
4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-chlorobenzyl-2,4-thiazolidinedione,
4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-methylbenzyl-2,4-thiazolidinedione,
4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-ethylbenzyl-2,4-thiazolidinedione,
4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-trifluoromethylbenzyl-2,4-thiazolidinedione,
4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-4-ethoxybenzyl-2,4-thiazolidinedione,
4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-methoxy-5-fluorobenzyl-2,4-thiazolidinedione,
4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-2-fluoro-3-methoxy-benzyl-2,4-thiazolidinedione or
4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-isopropoxybenzyl-2,4-thiazolidinedione; or a pharmaceutically acceptable salt thereof.

20. The compound of claim 2 present as:
4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-aminobenzyl-2,4-thiazolidinedione,
4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-acetamidobenzyl-2,4-thiazolidinedione,
4-(3-Methoxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-trifluoromethoxybenzyl-2,4-thiazolidinedione,
4-(3-Dimethylamino-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-trifluoromethoxybenzyl-2,4-thiazolidinedione,
4-(3-Trifluoromethyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-methoxybenzyl-2,4-thiazolidinedione,
4-(3-Trifluoromethyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-methylbenzyl-2,4-thiazolidinedione,
4-(3-Trifluoromethyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-ethylbenzyl-2,4-thiazolidinedione,
4-(3-Trifluoromethyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-trifluoromethoxybenzyl-2,4-thiazolidinedione,
4-(3-Dimethylamino-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-dimethylaminobenzyl-2,4-thiazolidinedione,
4-(3-Trifluoromethyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-chlorobenzyl-2,4-thiazolidinedione,
4-(3-Trifluoromethyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-dimethylaminobenzyl-2,4-thiazolidinedione,
4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-acetoxybenzyl-2,4-thiazolidinedione or
4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-hydroxybenzyl-2,4-thiazolidinedione; or a pharmaceutically acceptable salt thereof.

21. The compound of claim 2 present as:
2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-5-pyridyl-2,4-thiazolidinedione or
2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-methoxy-5-pyridyl-2,4-thiazolidinedione; or a pharmaceutically acceptable salt thereof.

22. A compound of claim 3 wherein R₁ and R₂ together with the aromatic ring bonded thereto form a cycloalkyl or substituted cycloalkyl optionally comprising 1 or 2 nitrogen heteroatoms; and R₃ is alkyl or substituted alkyl.

23. A compound of claim 22 wherein R₆ and R₇ are independently or together alkyl or R₆ and R₇ together form a cycloalkyl comprising 1 or 2 oxygen heteroatoms.

24. A compound of claim 23 wherein W, X, Y and Z form a 2,4-thiazolidinedione, 2-thioxo-4-thiazolidinedione, 2-thioxo-4-imidazolidinedione or 2,4-imidazolidinedione residue.
25. A compound of claim 3 wherein \( m = 1 \) represents the bond is present and the compound has the Formula:

\[
\begin{array}{c}
\text{R}_1 \\
\text{R}_2 \\
\text{R}_3 \\
\text{Ar} \\
\text{A} \\
\text{R}_5 \\
\text{W} \\
\text{X} \\
\text{Z} \\
\text{Y}
\end{array}
\]

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26. A compound of claim 3 wherein \( m = 1 \) represents the bond is absent and has the formula:

\[
\begin{array}{c}
\text{R}_1 \\
\text{R}_2 \\
\text{R}_3 \\
\text{Ar} \\
\text{A} \\
\text{R}_5 \\
\text{W} \\
\text{X} \\
\text{Z} \\
\text{Y}
\end{array}
\]

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27. A pharmaceutical composition comprising one or more compounds of claim 1 for administration in mammals for the treatment of a disease of uncontrolled cellular proliferation.

28. The pharmaceutical composition of claim 27, wherein the disease is cancer.

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29. The pharmaceutical composition of claim 28, wherein the cancer is carcinoma, lymphoma, leukemia, or sarcoma.

30. A pharmaceutical composition of claim 28, wherein the cancer is Hodgkin's Disease, myeloid leukemia, polycystic kidney disease, bladder cancer, brain cancer, head and neck cancer, kidney cancer, lung cancer, non-small cell lung
cancer, myeloma, neuroblastoma/glioblastoma, ovarian cancer, pancreatic cancer, prostate cancer, skin cancer, liver cancer, melanoma, colon cancer, cervical carcinoma, breast cancer, epithelial cancer, or leukemia.

31. A pharmaceutical composition of claim 28, wherein the cancer is breast cancer.

32. A pharmaceutical composition of claim 28, wherein the cancer is prostate cancer.

33. A pharmaceutical composition of claim 28, wherein the cancer is colon cancer.

34. A pharmaceutical composition comprising one or more compounds of claim 1 for administration in mammals for the treatment of an inflammatory disease.

35. A pharmaceutical composition of claim 34, wherein the inflammatory disease is osteoarthritis, rheumatoid arthritis, Crohn’s Disease, pulminary fibrosis, or Inflammatory Bowel Disease.

36. A pharmaceutical composition of claim 34 wherein the disease is osteoarthritis or rheumatoid arthritis.

37. A pharmaceutical composition comprising one or more compounds of claim 1 for administration in mammals for modulating lipid metabolism, carbohydrate metabolism, or lipid and carbohydrate metabolism.

38. A pharmaceutical composition of claim 37 wherein the administration treats type 2 diabetes, polycystic ovary syndrome or syndrome X.

39. A pharmaceutical composition of claim 37 wherein the administration treats type 2 diabetes.
40. A method of treating a disease of uncontrolled cellular proliferation comprising
administering to a mammal diagnosed as having a disease of uncontrolled cellular
proliferation the pharmaceutical composition of claim 27.

41. The method of claim 40 wherein the mammal is a human.

42. A method of treating an inflammatory disease comprising administering to a
mammal diagnosed as having an inflammatory disease the pharmaceutical
composition of claim 34.

43. The method of claim 42 wherein the mammal is a human.

44. The method of modulating lipid metabolism, carbohydrate metabolism or lipid
and carbohydrate metabolism comprising administering to a mammal diagnosed
as needing such modulation the pharmaceutical composition of claim 37.

45. The method of claim 44 wherein the mammal is a human.

46. A process for the preparation of a compound of the Formula (XV)

![Chemical Structure]

(XV)

wherein:

R₁ and R₂ are independently or together hydrogen, alkyl, substituted alkyl,
alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substituted
alkoxy, hydroxyl, acyl, amino, mono-substituted amino, di-substituted amino,
carboxy, carboalkoxy, alkylcarboxamide, substituted alkylcarboxamide,
dialkylicarboxamide, substituted dialkylicarboxamide or haloalkoxy; or R₁ and R₂ together with the aromatic ring form a cycloalkyl, substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl optionally comprising 1 or 2 heteroatoms selected from O, S, NH and N-alkyl;

R₃ and R₄ are independently or together hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, halogen, cyano, nitro, hydroxyl, acyloxy, amino, mono-substituted amino, di-substituted amino, alkylsulfonamide, arylsulfonamide, alkylurea, arylurea, alkylcarbamate, arylcarbamate, heteroaryl, alkoxy, substituted alkoxy, haloalkoxy, thioalkyl, thiohaloalkyl, carboxy, carboalkoxy, alkylicarboxamide, substituted alkylicarboxamide, dialkylicarboxamide or substituted dialkylicarboxamide;

Ar is Formula (II), (III), (IV), (V) or (VI):

where R₈, R₉ and R₁₀ are independently or together hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl,
halogen, cyano, nitro, hydroxyl, acyloxy, amino, mono-substituted amino, disubstituted amino, alkylamide, alkylsulfonamide, arylsulfonamide, alkylurea, arylurea, alkylcarbamate, arylcarbamate, alkoxy, substituted alkoxy, haloalkoxy, thioalkyl, thiohaloalkyl, carboxy, carboalkoxy, alkylcarboxamide, substituted alkylcarboxamide, dialkylcarboxamide or substituted dialkylcarboxamide; $R_{11}$ is hydrogen, alkyl or substituted alkyl;

$R_5$ is hydrogen, halogen, hydroxy, alkyl or substituted alkyl;

- - - - - represents a bond present or absent; and

$W$, $X$, $Y$ and $Z$ are independently or together $-\text{C(O)}-, -\text{C(S)}-, -\text{S}-, -\text{O}-$ or $-\text{NH}-$ residues that form a 2,4-thiazolidinedione, 2-thioxo-4-thiazolidinedione, isoxazolidinedione, 2,4-imidazolidinedione or 2-thioxo-4-imidazolidinedione residue;

comprising the steps of:

1) coupling a first aryl residue with a second aryl residue to give a biaryl carbonyl containing compound;

wherein the first aryl residue comprises a substituted or unsubstituted residue having the structure:

![Diagram of biaryl structure]

and wherein the second aryl residue has a carbonyl group and comprises a substituted or unsubstituted residue having the structure:
and wherein the biaryl carbonyl containing compound comprises a substituted or unsubstituted residue having the structure:

and

2) condensing the biaryl carbonyl containing compound with an active methylene compound of the structure:

\[
\begin{array}{c}
W \\
\hline \\
X \\
\hline \\
Y
\end{array}
\]

to give the benzylidene compound of Formula (XV).

47. A process of claim 46 further comprising the step of reducing the benzylidene to form the benzyl compound of Formula (XVI):

\[
\begin{array}{c}
R_1 \\
\hline \\
R_4 \\
\hline \\
Ar \\
\hline \\
R_2 \\
\hline \\
R_3 \\
\hline \\
R_5
\end{array}
\]

(XVI)
[Diagram of molecular structure with labeled atoms and groups]