ANTIOXIDANT INFLAMMATION MODULATORS: NOVEL DERIVATIVES OFoleanolic ACID

Title: ANTIOXIDANT INFLAMMATION MODULATORS: NOVEL DERIVATIVES OF OLEANOLIC ACID

Abstract: Disclosed herein are novel oleanolic acid derivatives. Methods of preparing these compounds are also disclosed. The oleanolic acid derivatives of this invention may be used for the treatment and prevention of many diseases, including cancer, neurological disorders, inflammation, and pathologies involving oxidative stress.
DESCRIPTION

ANTIOXIDANT INFLAMMATION MODULATORS:
NOVEL DERIVATIVES OF OLEANOLIC ACID

BACKGROUND OF THE INVENTION

The present application claims the benefit of priority to U.S. Provisional Application No. 61/046,352, filed April 18, 2008, the entire content of this application is incorporated herein by reference in its entirety.

I. Field of the Invention

The present disclosure relates generally to the fields of biology and medicine. More particularly, it concerns compounds and methods for the treatment and prevention of diseases such as those associated with oxidative stress and inflammation.

II. Description of Related Art

Many serious and intractable human diseases are associated with dysregulation of inflammatory processes, including diseases such as cancer, atherosclerosis, and diabetes, which were not traditionally viewed as inflammatory conditions. Similarly, autoimmune diseases such as rheumatoid arthritis, lupus, psoriasis, and multiple sclerosis involve inappropriate and chronic activation of inflammatory processes in affected tissues, arising from dysfunction of self vs. non-self recognition and response mechanisms in the immune system. In neurodegenerative diseases such as Alzheimer's and Parkinson's diseases, neural damage is correlated with activation of microglia and elevated levels of pro-inflammatory proteins such as inducible nitric oxide synthase (iNOS).

One aspect of inflammation is the production of inflammatory prostaglandins such as prostaglandin E, whose precursors are produced by the enzyme cyclo-oxygenase (COX-2). High levels of COX-2 are found in inflamed tissues. Consequently, inhibition of COX-2 is known to reduce many symptoms of inflammation and a number of important anti-inflammatory drugs (e.g., ibuprofen and celecoxib) act by inhibiting COX-2 activity. Recent research, however, has demonstrated that a class of cyclopentenone prostaglandins (e.g., 15-deoxy prostaglandin J2, a.k.a. PGJ2) plays a role in stimulating the orchestrated resolution of inflammation. COX-2 is also associated with the production of cyclopentenone prostaglandins. Consequently, inhibition of COX-2 may interfere with the full resolution of inflammation, potentially promoting the persistence of activated immune cells in tissues and
leading to chronic, "smoldering" inflammation. This effect may be responsible for the increased incidence of cardiovascular disease in patients using selective COX-2 inhibitors for long periods of time. Corticosteroids, another important class of anti-inflammatory drugs, have many undesirable side effects and frequently are not suitable for chronic use. Newer protein-based drugs, such as anti-TNF monoclonal antibodies, have proven to be effective for the treatment of certain autoimmune diseases such as rheumatoid arthritis. However, these compounds must be administered by injection, are not effective in all patients, and may have severe side effects. In many severe forms of inflammation (e.g., sepsis, acute pancreatitis), existing drugs are ineffective. In addition, currently available drugs do not have significant antioxidant properties, and are not effective in reducing oxidative stress associated with excessive production of reactive oxygen species and related molecules such as peroxynitrite. Accordingly, there is a pressing need for improved therapeutics with antioxidant and anti-inflammatory properties.

A series of synthetic triterpenoid analogs of oleanolic acid have been shown to be inhibitors of cellular inflammatory processes, such as the induction by IFN-γ of inducible nitric oxide synthase (iNOS) and of COX-2 in mouse macrophages. See Honda et al. (2000a); Honda et al. (2000b), and Honda et al. (2002), which are all incorporated herein by reference. For example, one of these, 2-cyano-3,12-dioxooleane-1,9(11)-dien-28-oic acid methyl ester (CDDO-Me), is currently in clinical trials for a variety of disorders related to inflammation, including cancer and diabetic nephropathy. The pharmacology of these molecules is complex, as they have been shown to affect the function of multiple protein targets and thereby modulate the function of several important cellular signaling pathways related to oxidative stress, cell cycle control, and inflammation (e.g., Dinkova-Kostova et al., 2005; Ahmad et al., 2006; Ahmad et al., 2008; Liby et al., 2007). Given that the biological activity profiles of the known oleanolic acid derivatives vary, and in view of the wide variety of diseases that may be treated with compounds having potent antioxidant and anti-inflammatory effects, it is desirable to synthesize new candidates for the treatment or prevention of disease.
SUMMARY OF THE INVENTION

In one aspect, the present disclosure provides new compounds with antioxidant and anti-inflammatory properties, methods for their manufacture, and methods for their use. Compounds covered by the generic or specific formulas below or specifically named may be referred to herein as "compounds of the invention," "compounds of the present disclosure," or "oleanolic acid derivatives."

In some aspects, the disclosure provides compounds of the formula:

\[
Y \text{ is cyano or } -C(\text{O})R_n, \text{ further wherein:}
\]

\[
R_n \text{ is:}
\]

- hydrogen, hydroxy, halo, amino, hydroxyamino, azido or mercapto; or
-alkyl\(_{\leq 12}\), alkenyl\(_{\leq 12}\), alkynyl\(_{\leq 12}\), aryl\(_{\leq 12}\), aralkyl\(_{\leq 12}\),
-heteroaryl\(_{\leq 12}\), heteroaralkyl\(_{\leq 12}\), alkoxy\(_{\leq 12}\), alkenyloxy\(_{\leq 12}\),
alcohol\(_{\leq 12}\), dialkylaminooxy\(_{\leq 12}\), alkoxyamino\(_{\leq 12}\),
alkylamino\(_{\leq 12}\), dialkylamino\(_{\leq 12}\), alkoxyamino\(_{\leq 12}\),
alkenylamino\(_{\leq 12}\), alkynylamino\(_{\leq 12}\), arylamino\(_{\leq 12}\),
aralkylamino\(_{\leq 12}\), heteroarylamino\(_{\leq 12}\), heteroaralkylamino\(_{\leq 12}\),
alcohol\(_{\leq 12}\), alkylsulfamino\(_{\leq 12}\), amido\(_{\leq 12}\),
alcohio\(_{\leq 12}\), alkenylthio\(_{\leq 12}\), alkynylthio\(_{\leq 12}\), arythio\(_{\leq 12}\),
aralkylthio\(_{\leq 12}\), heteroarylthio\(_{\leq 12}\), heteroaralkylthio\(_{\leq 12}\),
acylthio (C ≤ 12), alkylsilyl (C ≤ 12), or a substituted version of any of these groups;

$X_1$ is OR$_b$, NR$_b$R$_c$, or SR$_b$, wherein R$_b$ and R$_c$ are each independently:

- hydrogen or hydroxy;
- alkyl$_1$ (C ≤ 8), aryl$_1$ (C ≤ 8), alkenyl$_1$ (C ≤ 8), alkynyl$_1$ (C ≤ 8), aralkyl$_1$ (C ≤ 8), heteroaryl$_1$ (C ≤ 8), heteroaralkyl$_1$ (C ≤ 8), acyl$_1$ (C ≤ 8), alkoxycarbonyl$_1$ (C ≤ 8), alkoxycarbonylamino$_1$ (C ≤ 8), aralkoxy$_1$ (C ≤ 8), aralkylamine$_1$ (C ≤ 8), amido$_1$ (C ≤ 8), or a substituted version of any of these groups; or

a substituent convertible in vivo to hydrogen;

provided that R$_b$ is absent when the atom to which it is bound is part of a double bond, further provided that when R$_b$ is absent the atom to which it is bound is part of a double bond;

$R_1$ is:
- hydrogen, cyano, hydroxy, halo or amino; or
- alkyl$_1$ (C ≤ 8), alkenyl$_1$ (C ≤ 8), alkynyl$_1$ (C ≤ 8), aryl$_1$ (C ≤ 8), aralkyl$_1$ (C ≤ 8), heteroaryl$_1$ (C ≤ 8), heteroaralkyl$_1$ (C ≤ 8), acyl$_1$ (C ≤ 8), alkoxycarbonyl$_1$ (C ≤ 8), alkoxycarbonylamino$_1$ (C ≤ 8), aralkoxy$_1$ (C ≤ 8), aralkylamine$_1$ (C ≤ 8), amido$_1$ (C ≤ 8), or a substituted version of any of these groups;

$R_2$ is:
- hydroxy, halo, amino; or
- fluoroalkyl$_1$ (C ≤ 8), alkenyl$_1$ (C ≤ 8), alkynyl$_1$ (C ≤ 8), aryl$_1$ (C ≤ 8), heteroaryl$_1$ (C ≤ 8), acyl$_1$ (C ≤ 8), alkoxycarbonyl$_1$ (C ≤ 8), alkoxycarbonylamino$_1$ (C ≤ 8), aralkoxy$_1$ (C ≤ 8), aralkylamine$_1$ (C ≤ 8), amido$_1$ (C ≤ 8), or a substituted version of any of these groups;

$R_4$ and $R_5$ are each independently alkyl$_1$ (C ≤ 8) or substituted alkyl$_1$ (C ≤ 8); $R_6$ is hydrogen, hydroxy or oxo; and

$R_7$ is hydrogen or hydroxy;

$R_8$, $R_9$, $R_10$ and $R_{11}$ are each independently hydrogen, hydroxy, alkyl$_1$ (C ≤ 8), substituted alkyl$_1$ (C ≤ 8), alkoxycarbonyl$_1$ (C ≤ 8), or substituted alkoxycarbonyl$_1$ (C ≤ 8); or pharmaceutically acceptable salts, esters, hydrates, solvates, tautomers, prodrugs, or optical isomers thereof.

In some embodiments, $Y$ is cyano. In some variations of one or more of the above embodiments, $Y$ is -C(O)R$_a$. In some embodiments, $X_1$ is OR$_b$ and R$_b$ is absent. In some embodiments, R$_a$ is hydroxy. In some embodiments, R$_a$ is alkoxycarbonyl$_1$ (C ≤ 8), aralkoxy$_1$ (C ≤ 8), aralkylamine$_1$ (C ≤ 8), or a substituted version of any of these groups. In some embodiments, R$_a$ is
alkoxy(C2-6). In some embodiments, Rₐ is alkoxy(C1-5) or substituted alkoxy(C1-5). In some embodiments, Rₐ is alkoxy(C2-4) or substituted alkoxy(C2-4). In some embodiments, Rₐ is alkoxy(C1-4) or substituted alkoxy(C1-4). In some embodiments, Rₐ is alkoxy(C1-2) or substituted alkoxy(C1-2). In some embodiments, Rₐ is methoxy. In some embodiments, Rₐ is amino. In some embodiments, Rₐ is alkylamino(C1-6), alkoxyamino(C1-6), arylamino(C1-8), aralkylamino(C1-8), dialkylamino(C2-8), or a substituted version of any of these groups. In some embodiments, Rₐ is alkylamino(C2-6) or substituted alkylamino(C2-6). In some embodiments, Rₐ is alkylamino(C3-6). In some embodiments, Rₐ is alkylamino(C1-5), dialkylamino(C2-6), or a substituted version of either of these groups. In some embodiments, Rₐ is alkylamino(C2-4), dialkylamino(C2-5), or substituted version of either of these groups. In some embodiments, Rₐ is alkylamino(C1-4) or substituted alkylamino(C1-4). In some embodiments, Rₐ is alkylamino(C1-3). In some embodiments, Rₐ is methylvamin o or ethylamino. In some embodiments, Rₐ is substituted alkylamino(C1-3). In some embodiments, Rₐ is 2,2,2-trifluoroethylamino. In some embodiments, Rₐ is alkyl(C1-5), aryl(C₆H₅), aralkyl(C₆H₅), heteroaralkyl(C₆H₅), or a substituted version of any of these groups. In some embodiments, Rₐ is heteroaryl(C₁H₈) or substituted heteroaryl(C₁H₈). In some embodiments, Rₐ is imidazolyl. In some embodiments, Rₐ is -H. In some embodiments, R₁ is -H, -OH or -F. In some embodiments, R₁ is -H. In some embodiments, R₂ is -F. In some embodiments, R₂ is fluoroalkyl(C₆H₅). In some embodiments, R₂ is -CF₃. In some embodiments, R₂ is a substituted acyl(C₁₃). In some embodiments, R₂ is heteroaryl(C₁H₈) or substituted heteroaryl(C₁H₈). In some embodiments, R₂ is -C(=O)NHS(=O)₂CH₃. In some embodiments, R₄ and R₅ are each methyl. In some embodiments, R₆ and R₇ are both hydrogen. In some embodiments, R₈ and R₉ are each hydrogen. In some embodiments, R₁₀ and R₁₁ are each methyl.

In some embodiments, the compound is further defined as:

![Chemical Structure](image)

wherein:

Rₐ is:

hydrogen, hydroxy, halo or amino; or
alkyl\(_{(c \leq 6)}\), aryl\(_{(C \leq 8)}\), aralkyl\(_{(C \leq 8)}\), heteroaryl\(_{(C \leq 8)}\), alkoxy\(_{(C \leq 6)}\), aryloxy\(_{(C \leq 8)}\),

aralkoxy\(_{(C \leq 8)}\), alkylamino\(_{(C \leq 6)}\), alkoxyamino\(_{(C \leq 6)}\), alkoxyaminoo\(_{(C \leq 6)}\),
dialkylamino\(_{(C \leq 6)}\), arylamino\(_{(C \leq 8)}\), aralkylamino\(_{(C \leq 8)}\), heteroaryl-
amino\(_{(C \leq 6)}\), heteroarylamino\(_{(C \leq 8)}\), alkysulfonylamino\(_{(C \leq 6)}\), amido\(_{(C \leq 6)}\), or

a substituted version of any of these groups; and

\( R_2 \) is:

fluoro; or

fluorooalkyl\(_{(C \leq 8)}\), heteroaryl\(_{(C \leq 8)}\), acyl\(_{(C \leq 8)}\), or a substituted version of either of

these groups;

or pharmaceutically acceptable salts, esters, hydrates, solvates, tautomers, prodrugs, or optical

isomers thereof.

In another aspect, the disclosure provides compounds of the formula:

\[
\text{(III)}
\]

wherein:

\( R_a \) is azido, fluoro, hydroxyamino, alkoxyamino\(_{(C \leq 2)}\), substituted alkoxyamino\(_{(C \leq 2)}\),
or -NH-L-\( R_d \);

wherein:

\( L \) is alkanediyl\(_{(C \leq 8)}\); and

\( R_d \) is:

hydroxy; or

alkoxy\(_{(C \leq 18)}\), aryloxy\(_{(C \leq 18)}\), or acyloxy\(_{(C \leq 18)}\), or a substituted

version of any of these groups;

\( X_1 \) is \( OR_b, NR_b R_c, \) or \( SR_b \), wherein \( R_b \) and \( R_c \) are each independently:

hydrogen or hydroxy;
alkyl\(_{1,8}\), aryl\(_{1,8}\), aralkyl\(_{1,8}\), acyl\(_{1,8}\), alkoxy\(_{1,8}\), aryloxy\(_{1,8}\), acyloxy\(_{1,8}\), alkylamino\(_{1,8}\), arylamino\(_{1,8}\), amido\(_{1,8}\), or a substituted version of any of these groups; or a substituent convertible in vivo to hydrogen;

provided that \(R_b\) is absent when the atom to which it is bound is part of a double bond, further provided that when \(R_b\) is absent the atom to which it is bound is part of a double bond;

\(R_1\) is:

hydrogen, cyano, hydroxy, halo or amino; or

alkyl\(_{1,8}\), alkenyl\(_{1,8}\), alkynyl\(_{1,8}\), aryl\(_{1,8}\), aralkyl\(_{1,8}\), heteroaryl\(_{1,8}\), heteroaralkyl\(_{1,8}\), acyl\(_{1,8}\), alkoxy\(_{1,8}\), aryloxy\(_{1,8}\), acyloxy\(_{1,8}\), alkylamino\(_{1,8}\), arylamino\(_{1,8}\), amido\(_{1,8}\), or a substituted version of any of these groups;

\(R_2\) is:

hydroxy, cyano, halo or amino; or

fluoroalkyl\(_{1,8}\), alkenyl\(_{1,8}\), alkynyl\(_{1,8}\), aryl\(_{1,8}\), heteroaryl\(_{1,8}\), acyl\(_{1,8}\), alkoxy\(_{1,8}\), aryloxy\(_{1,8}\), acyloxy\(_{1,8}\), alkylamino\(_{1,8}\), arylamino\(_{1,8}\), amido\(_{1,8}\), or a substituted version of any of these groups;

\(R_4\) and \(R_5\) are each independently alkyl\(_{1,8}\) or substituted alkyl\(_{1,8}\);

\(R_6\) is hydrogen, hydroxy or oxo; and

\(R_7\) is hydrogen or hydroxy;

\(R_8, R_9, R_{10}\) and \(R_{11}\) are each independently hydrogen, hydroxy, alkyl\(_{1,8}\), substituted alkyl\(_{1,8}\), alkoxy\(_{1,8}\), or substituted alkoxy\(_{1,8}\);

or pharmaceutically acceptable salts, esters, hydrates, solvates, tautomers, prodrugs, or optical isomers thereof.

In some embodiments, \(X_1\) is OR\(_b\) and \(R_b\) is absent. In some embodiments, \(R_a\) is azido. In some embodiments, \(R_a\) is fluoro. In some embodiments, \(R_a\) is hydroxyamino. In some embodiments, \(R_a\) is alkoxyamino\(_{1,8}\). In some embodiments, \(R_a\) is -NH-L-R\(_b\). In some embodiments, \(R_d\) is hydroxy. In some embodiments, \(L\) is 1,2-ethanediyl. In some embodiments, \(R_1\) is -H. In some embodiments, \(R_2\) is -CN. In some embodiments, \(R_4\) and \(R_5\) are each methyl. In some embodiments, \(R_4\) and \(R_5\) is hydroxymethyl and the other is methyl. In some embodiments, \(R_6\) and \(R_7\) are each hydrogen. In some embodiments, \(R_6\) is hydroxy.
In some embodiments, \(R_6\) is oxo. In some embodiments, \(R_8\) and \(R_9\) are each hydrogen. In some embodiments, \(R_{10}\) and \(R_{11}\) are each methyl.

Examples of specific compounds provided by the present disclosure include:

\[
(4aS,6aR,6bS,8aR,12aR,14aR,14b<S)-\text{methyl-11-fiuro}-2,2,6a,6b,9,9,12a-heptamethyl-10,14-dioxo-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-octadecahydropicene-4a-carboxylate,
\]

\[
(4aS,6aR,6bS,8aR,12aS,14aR,14bS)-\text{methyl-2,2,6a,6b,9,9,12a-heptamethyl-10,14-dioxo-1-}(1\text{-tetrazol-5-yl})-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-octadecahydropicene-4a-carboxylate,
\]

\[
(4aS,6aR,6bS,8aR,12aS,14aR,14bS)-\text{methyl-11-}(\text{hydroxycarbamoyl})-2,2,6a,6b,9,9,12a-heptamethyl-10,14-dioxo-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-octadecahydropicene-4a-carboxylate,
\]

\[
(4aS,6aR,6bS,8aR,12aS,14aR,14bS)-\text{methyl-2,2,6a,6b,9,9,12a-heptamethyl-11-}(\text{methylsulfonylcarbamoyl})-10,14-dioxo-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-octadecahydropicene-4a-carboxylate,
\]

\[
(4aS,6aR,6bS,8aR,12aS,14aR,14bS)-11-cyano-N-hydroxy-2,2,6a,6b,9,9,12a-heptamethyl-10,14-dioxo-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-octadecahydropicene-4a-carboxamide,
\]

\[
(4aS,6aR,6bS,8aR,12aS,14aR,14bS)-11-cyano-N-methoxy-2,2,6a,6b,9,9,12a-heptamethyl-10,14-dioxo-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-octadecahydropicene-4a-carboxamide,
\]

\[
(4aS,6aR,6bS,8aR,12aS,14aR,14bS)-11-cyano-2,2,6a,6b,9,9,12a-heptamethyl-10,14-dioxo-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-octadecahydropicene-4a-carbonyl fluoride,
\]

\[
(4aS,6aR,6bS,8aR,12aR,14aR,14bS)-\text{methyl-1-}l\text{-cyano-2,2,6a,6b,9,9,12,12a-octamethyl-10,14-dioxo-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-octadecahydropicene-4a-carbonyl fluoride},
\]

\[
(4aS,6aR,6bS,8aR,12aS,14aR,14bS)-11-cyano-N-(2-hydroxyethyl)-2,2,6a,6b,9,9,12a-heptamethyl-10,14-dioxo-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-octadecahydropicene-4a-carboxamide,
\]

\[
(4aS,6aR,6bS,8aR,12aS,14aR,14bS)-11-cyano-N-(2-hydroxyethyl)-2,2,6a,6b,9,9,12a-heptamethyl-10,14-dioxo-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-octadecahydropicene-4a-carboxamide,
\]

\[
(4aS,6aR,6bS,8aR,12aS,14aR,14bS)-11-cyano-N-methoxy-2,2,6a,6b,9,9,12a-heptamethyl-10,14-dioxo-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-octadecahydropicene-4a-carboxamide,
\]

\[
(4aS,6aR,6bS,8aR,12aS,14aR,14bS)-11-cyano-2,2,6a,6b,9,9,12a-heptamethyl-10,14-dioxo-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-octadecahydropicene-4a-carbonyl azide,
\]
(4aS,6aR,6bS,8aR,12aS,14aR,14bS)-methyl-10-acetoxy-11-cyano-2,2,6a,6b,9,9,12a-heptamethyl-14-oxo-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,12,12a,14,14a,14b-octadecahydropicene-4a-carboxylate,

(4aS,6aR,6bS,8aR,9S,12aS,UaR,14bS)-methyl 11-cyano-9-(hydroxymethyl)-2,2,6a,6b,9,12a-hexamethyl-10,14-dioxo-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-octadecahydropicene-4a-carboxylate,

(4aS,6aR,6bS,8aR,9S,12aS,14aR,14bS)-methyl 11-cyano-9-((methoxymethoxy)methyl)-2,2,6a,6b,9,12a-hexamethyl-10,14-dioxo-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-octadecahydropicene-4a-carboxylate,

(4aS,6aR,6bS,8aR,12aS,14aR,14bS)-methyl 11-cyano-8-hydroxy-2,2,6a,6b,9,9,12a-heptamethyl-10,14-dioxo-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-octadecahydropicene-4a-carboxylate,

(4aS,6aR,6bS,8aR,12aS,14aR,14bS)-methyl 11-cyano-2,2,6a,6b,9,9,12a-heptamethyl-8,10,14-trioxo-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-octadecahydropicene-4a-carboxylate,

(4aS,6aR,6bS,8aR,12aR,14bS)-methyl 11-cyano-1,1,12-dihydroxy-2,2,6a,6b,9,9,12a-heptamethyl-10,14-dioxo-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-icosahydropicene-4a-carboxylate, and

(4aS,6aR,6bS,8aR,12aS,14aR,14bS)-methyl 2,2,6a,6b,9,9,12a-heptamethyl-10,14-dioxo-1-((trifluoromethyl))-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-octadecahydropicene-4a-carboxylate.

The present disclosure also contemplates a compound of the formula:

![Chemical Structure](image)

or pharmaceutically acceptable salts, hydrates, solvates, tautomers, or optical isomers thereof, in certain embodiments. In certain embodiments, the following particular compound is contemplated:
or pharmaceutically acceptable salts thereof, and substantially free from other optical isomers thereof.

Non-limiting examples of compounds provided by this invention include:

<table>
<thead>
<tr>
<th>Compound</th>
<th>IUPAC Number</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Image" /></td>
<td>63161 (402-05)</td>
</tr>
<tr>
<td><img src="image2.png" alt="Image" /></td>
<td>63162 (402-06)</td>
</tr>
<tr>
<td><img src="image3.png" alt="Image" /></td>
<td>63164 (402-08)</td>
</tr>
<tr>
<td><img src="image4.png" alt="Image" /></td>
<td>63129 (402-07)</td>
</tr>
<tr>
<td><img src="image5.png" alt="Image" /></td>
<td>63165 (402-09)</td>
</tr>
<tr>
<td><img src="image6.png" alt="Image" /></td>
<td>63166 (402-10)</td>
</tr>
<tr>
<td><img src="image7.png" alt="Image" /></td>
<td>63163 (402-11)</td>
</tr>
</tbody>
</table>
In some embodiments, compounds of the present disclosure are in the form of pharmaceutically acceptable salts. In other embodiments, compounds of the present disclosure are not be in the form of a pharmaceutically acceptable salts.

In some embodiments, compounds of the present disclosure can be esters of the above formulas. The ester may, for example, result from a condensation reaction between a hydroxy group of the formula and the carboxylic acid group of biotin.

In some embodiments, the compounds of the present disclosure can be present as a mixture of stereoisomers. In other embodiments, the compounds of the present disclosure are present as single stereoisomers.

In some embodiments, compounds of the present disclosure may be inhibitors of IFN-\(\gamma\)-induced nitrous oxide (NO) production in macrophages, for example, having an IC\(_{50}\) value of less than 0.2 \(\mu\)M.

Other general aspects of the present disclosure contemplate a pharmaceutical composition comprising as an active ingredient a compound of the present disclosure and a pharmaceutically acceptable carrier. The composition may, for example, be adapted for administration by a route selected from the group consisting of orally, intraarterially, intraarticularly, intracranially, intradermally, intramuscularly, intranasally, intraocularly, intrapericardially, intraperitoneally, intrapleurally, intraprostatically, intrarectally, intrathecally, intratracheally, intratumorally, intrapituitally, intravaginally, intravenously, intravesically, intravitreally, liposomally, locally, mucosally, orally, parenterally, rectally, subconjunctival, subcutaneously, sublingually, topically, transbuccally, transdermally, vaginally, in crèmes, in lipid compositions, via a catheter, via a lavage, via continuous infusion, via infusion, via inhalation, via injection, via local delivery, via localized perfusion, bathing target cells directly, or any combination thereof. In particular embodiments, the composition may be formulated for oral delivery. In particular embodiments, the composition is formulated as a hard or soft capsule, a tablet, a syrup, a suspension, a wafer, or an elixir. In certain embodiments, the soft capsule is a gelatin capsule. Certain compositions may comprise a protective coating, such as those compositions formulated for oral delivery. Certain compositions further comprise an agent that delays absorption, such as those compositions formulated for oral delivery. Certain compositions may further comprise an agent that enhances solubility or dispersibility, such as those compositions formulated for oral delivery. Certain compositions may comprise a compound
of the present disclosure, wherein the compound is dispersed in a liposome, an oil and water emulsion or a water and oil emulsion.

Yet another general aspect of the present disclosure contemplates a therapeutic method comprising administering a pharmaceutically effective compound of the present disclosure to a subject. The subject may, for example, be a human. These or any other methods of the present disclosure may further comprise identifying a subject in need of treatment.

Another method of the present disclosure contemplates a method of treating cancer in a subject, comprising administering to the subject a pharmaceutically effective amount of a compound of the present disclosure. The cancer may be any type of cancer, such as a carcinoma, sarcoma, lymphoma, leukemia, melanoma, mesothelioma, multiple myeloma, or seminoma. Other types of cancers include cancer of the bladder, blood, bone, brain, breast, central nervous system, colon, endometrium, esophagus, genitourinary tract, head, larynx, liver, lung, neck, ovary, pancreas, prostate, spleen, small intestine, large intestine, stomach, or testicle. In these or any other methods, the subject may be a primate. This or any other method may further comprise identifying a subject in need of treatment. The subject may have a family or patient history of cancer. In certain embodiments, the subject has symptoms of cancer. The compounds of the invention may be administered via any method described herein, such as locally. In certain embodiments, the compound is administered by direct intratumoral injection or by injection into tumor vasculature. In certain embodiments, the compounds may be administered systemically. The compounds may be administered intravenously, intra-arterially, intramuscularly, intraperitoneally, subcutaneously or orally, in certain embodiments.

In certain embodiments regarding methods of treating cancer in a subject, comprising administering to the subject a pharmaceutically effective amount of a compound of the present disclosure, the pharmaceutically effective amount is 0.1 - 1000 mg/kg. In certain embodiments, the pharmaceutically effective amount is administered in a single dose per day. In certain embodiments, the pharmaceutically effective amount is administered in two or more doses per day. The compound may be administered by contacting a tumor cell during ex vivo purging, for example. The method of treatment may comprise any one or more of the following: a) inducing cytotoxicity in a tumor cell; b) killing a tumor cell; c) inducing apoptosis in a tumor cell; d) inducing differentiation in a tumor cell; or e) inhibiting growth in a tumor cell. The tumor cell may be any type of tumor cell, such as a leukemia cell. Other types of cells include, for example, a bladder cancer cell, a breast cancer cell, a lung cancer
cell, a colon cancer cell, a prostate cancer cell, a liver cancer cell, a pancreatic cancer cell, a stomach cancer cell, a testicular cancer cell, a brain cancer cell, an ovarian cancer cell, a lymphatic cancer cell, a skin cancer cell, a brain cancer cell, a bone cancer cell, or a soft tissue cancer cell.

Combination treatment therapy is also contemplated by the present disclosure. For example, regarding methods of treating cancer in a subject, comprising administering to the subject a pharmaceutically effective amount of a compound of the present disclosure, the method may further comprise a treatment selected from the group consisting of administering a pharmaceutically effective amount of a second drug, radiotherapy, gene therapy, and surgery. Such methods may further comprise (1) contacting a tumor cell with the compound prior to contacting the tumor cell with the second drug, (2) contacting a tumor cell with the second drug prior to contacting the tumor cell with the compound, or (3) contacting a tumor cell with the compound and the second drug at the same time. The second drug may, in certain embodiments, be an antibiotic, anti-inflammatory, anti-neoplastic, anti-proliferative, anti-viral, immunomodulatory, or immunosuppressive. The second drug may be an alkylating agent, androgen receptor modulator, cytoskeletal disruptor, estrogen receptor modulator, histone-deacetylase inhibitor, HMG-CoA reductase inhibitor, prenyl-protein transferase inhibitor, retinoid receptor modulator, topoisomerase inhibitor, or tyrosine kinase inhibitor. In certain embodiments, the second drug is 5-azacytidine, 5-fluorouracil, 9-cis-retinoic acid, actinomycin D, altitretinoi, all-trans-retinoic acid, annamycin, axitinib, belinostat, bevacizumab, bexarotene, bosutinib, busulfan, capecitabine, carboplatin, carmustine, CD437, cediranib, cetuximab, chlorambucil, cisplatin, cyclophosphamide, cytarabine, dacarbazine, dasatinib, daunorubicin, decitabine, docetaxel, dolastatin-10, doxifluridine, doxorubicin, doxorubicin, eprirubicin, erlotinib, etoposide, etoposide, gefitinib, gemcitabine, gemtuzumab ozogamicin, hexamethylmelamine, idarubicin, ifosfamide, imatinib, irinotecan, isotretinoin, ixabepilone, laptatinib, LBH589, lomustine, mechlorethamine, melphalan, mercaptopurine, methotrexate, mitomycin, mitoxantrone, MS-275, neratinib, nilotinib, nitrosourea, oxaliplatin, paclitaxel, plicamycin, procarbazine, semaxanib, semustine, sodium butyrate, sodium phenylacetate, streptozocin, suberoylanilide hydroxamic acid, sunitinib, tamoxifen, teniposide, thiopeta, tioguanine, topotecan, TRAIL, trastuzumab, tretinoin, trichostatin A, valproic acid, valrubicin, vandetanib, vinblastine, vincristine, vindesine, or vinorelbine.

Methods of treating or preventing a disease with an inflammatory component in a subject, comprising administering to the subject a pharmaceutically effective amount of a...
compound of the present disclosure are also contemplated. The disease may be, for example, lupus or rheumatoid arthritis. The disease may be an inflammatory bowel disease, such as Crohn's disease or ulcerative colitis. The disease with an inflammatory component may be a cardiovascular disease. The disease with an inflammatory component may be diabetes, such as type 1 or type 2 diabetes. Compounds of the present disclosure may also be used to treat complications associated with diabetes. Such complications are well-known in the art and include, for example, obesity, hypertension, atherosclerosis, coronary heart disease, stroke, peripheral vascular disease, hypertension, nephropathy, neuropathy, myonecrosis, retinopathy and metabolic syndrome (syndrome X). The disease with an inflammatory component may be a skin disease, such as psoriasis, acne, or atopic dermatitis. Administration of a compound of the present disclosure in treatment methods of such skin diseases may be, for example, topical or oral.

The disease with an inflammatory component may be metabolic syndrome (syndrome X). A patient having this syndrome is characterized as having three or more symptoms selected from the following group of five symptoms: (1) abdominal obesity; (2) hypertriglyceridemia; (3) low high-density lipoprotein cholesterol (HDL); (4) high blood pressure; and (5) elevated fasting glucose, which may be in the range characteristic of Type 2 diabetes if the patient is also diabetic. Each of these symptoms is defined in the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III, or ATP III), National Institutes of Health, 2001, NIH Publication No. 01-3670, incorporated herein by reference. Patients with metabolic syndrome, whether or not they have or develop overt diabetes mellitus, have an increased risk of developing the macrovascular and microvascular complications that are listed above that occur with type 2 diabetes, such as atherosclerosis and coronary heart disease.

Another general method of the present disclosure entails a method of treating or preventing a cardiovascular disease in a subject, comprising administering to the subject a pharmaceutically effective amount of a compound of the present disclosure. The cardiovascular disease may be, for example, atherosclerosis, cardiomyopathy, congenital heart disease, congestive heart failure, myocarditis, rheumatic heart disease, valve disease, coronary artery disease, endocarditis, or myocardial infarction. Combination therapy is also contemplated for such methods. For example, such methods may further comprise administering a pharmaceutically effective amount of a second drug. The second drug may be, for example, a cholesterol lowering drug, an anti-hyperlipidemic, a calcium channel
blocker, an anti-hypertensive, or an HMG-CoA reductase inhibitor. Non-limiting examples of second drugs include amlodipine, aspirin, ezetimibe, felodipine, lacidipine, lercanidipine, nicardipine, nifedipine, nimodipine, nisoldipine or nitrendipine. Other non-limiting examples of second drugs include atenolol, bucindolol, carvedilol, clonidine, doxazosin, indoramin, labetalol, methyldopa, metoprolol, nadolol, oxprenolol, phenoxybenzamine, phentolamine, pindolol, prazosin, propranolol, terazosin, timolol or tolazoline. The second drug may be, for example, a statin, such as atorvastatin, cerivastatin, fluvastatin, lovastatin, mevastatin, pitavastatin, pravastatin, rosuvastatin or simvastatin.

Methods of treating or preventing a neurodegenerative disease in a subject, comprising administering to the subject a pharmaceutically effective amount of a compound of the present disclosure are also contemplated. The neurodegenerative disease may, for example, be selected from the group consisting of Parkinson's disease, Alzheimer's disease, multiple sclerosis (MS), Huntington's disease and amyotrophic lateral sclerosis. In particular embodiments, the neurodegenerative disease is Alzheimer's disease. In particular embodiments, the neurodegenerative disease is MS, such as primary progressive, relapsing-remitting secondary progressive or progressive relapsing MS. The subject may be, for example, a primate. The subject may be a human.

In particular embodiments of methods of treating or preventing a neurodegenerative disease in a subject, comprising administering to the subject a pharmaceutically effective amount of a compound of the present disclosure, the treatment suppresses the demyelination of neurons in the subject's brain or spinal cord. In certain embodiments, the treatment suppresses inflammatory demyelination. In certain embodiments, the treatment suppresses the transection of neuron axons in the subject's brain or spinal cord. In certain embodiments, the treatment suppresses the transection of neurites in the subject's brain or spinal cord. In certain embodiments, the treatment suppresses neuronal apoptosis in the subject's brain or spinal cord. In certain embodiments, the treatment stimulates the remyelination of neuron axons in the subject's brain or spinal cord. In certain embodiments, the treatment restores lost function after an MS attack. In certain embodiments, the treatment prevents a new MS attack. In certain embodiments, the treatment prevents a disability resulting from an MS attack.

One general aspect of the present disclosure contemplates a method of treating or preventing a disorder characterized by overexpression of iNOS genes in a subject, comprising administering to the subject a pharmaceutically effective amount of a compound of the present disclosure.
Another general aspect of the present disclosure contemplates a method of inhibiting IFN-γ-induced nitric oxide production in cells of a subject, comprising administering to said subject a pharmaceutically effective amount of a compound of the present disclosure.

Yet another general method of the present disclosure contemplates a method of treating or preventing a disorder characterized by overexpression of COX-2 genes in a subject, comprising administering to the subject a pharmaceutically effective amount of compound of the present disclosure.

Methods of treating renal/kidney disease (RKD) in a subject, comprising administering to the subject a pharmaceutically effective amount of a compound of the present disclosure are also contemplated. See U.S. Patent Application 12/352,473, which is incorporated by reference herein in its entirety. The RKD may result from, for example, a toxic insult. The toxic insult may result from, for example, an imaging agent or a drug. The drug may be a chemotherapeutic, for example. The RKD may result from ischemia/reperfusion injury, in certain embodiments. In certain embodiments, the RKD results from diabetes or hypertension. The RKD may result from an autoimmune disease. The RKD may be further defined as chronic RKD, or acute RKD.

In certain methods of treating renal/kidney disease (RKD) in a subject, comprising administering to the subject a pharmaceutically effective amount of a compound of the present disclosure, the subject has undergone or is undergoing dialysis. In certain embodiments, the subject has undergone or is a candidate to undergo kidney transplant. The subject may be a primate. The primate may be a human. The subject in this or any other method may be, for example, a cow, horse, dog, cat, pig, mouse, rat or guinea pig.

Also contemplated by the present disclosure is a method for improving glomerular filtration rate or creatinine clearance in a subject, comprising administering to the subject a pharmaceutically effective amount of a compound of the present disclosure.

Methods of synthesizing compounds of the present disclosure are also contemplated. In particular embodiments, such methods comprise a method of making a compound of the following formula:

![Chemical Structure](attachment:image.png)
comprising reacting a compound of formula

![Chemical Structure](image)

with diphenylphosphorylazide (DPPA) to form the first compound.

Kits are also contemplated by the present disclosure, such as a kit comprising: a compound of the present disclosure; and instructions which comprise one or more forms of information selected from the group consisting of indicating a disease state for which the compound is to be administered, storage information for the compound, dosing information and instructions regarding how to administer the compound. The kit may comprise a compound of the present disclosure in a multiple dose form.

Other general aspects of the present disclosure contemplate articles of manufacture. For example, an article of manufacture may comprise a compound of the present disclosure; and packaging materials. The packaging materials may comprise a container for housing the compound, in certain embodiments. The container may comprise, for example, a label indicating one or more members of the group consisting of a disease state for which the compound is to be administered, storage information, dosing information and/or instructions regarding how to administer the compound. In certain embodiments, the article of manufacture comprises the compound in a multiple dose form.

In some embodiments, the invention provides compounds useful for preventing and/or treating diseases or disorders whose pathology involves oxidative stress, inflammation, and/or dysregulation of inflammatory signaling pathways. In some variations, the diseases or disorders can be characterized by overexpression of inducible nitric oxide synthase (iNOS) and/or inducible cyclooxygenase (COX-2) in affected tissues. In some variations, the diseases or disorders can be characterized by overproduction of reactive oxygen species (ROS) or reactive nitrogen species (RNS) such as superoxide, hydrogen peroxide, nitric oxide or peroxynitrite in affected tissues. In some variations, the disease or disorder is characterized by excessive production of inflammatory cytokines or other inflammation-related proteins such as TNFα, IL-6, IL-1, IL-8, ICAM-I, VCAM-I, and VEGF. Such diseases or disorders may, in some embodiments, involve undesirable proliferation of certain cells, as in the case of cancer (e.g., solid tumors, leukemias, myelomas, lymphomas, and other
cancers), fibrosis associated with organ failure, or excessive scarring. Non-limiting examples of the disease or disorder include: lupus, rheumatoid arthritis, juvenile-onset diabetes, multiple sclerosis, psoriasis, and Crohn's disease. Further non-limiting examples include cardiovascular diseases, such as atherosclerosis, heart failure, myocardial infarction, acute coronary syndrome, restenosis following vascular surgery, hypertension, and vasculitis; neurodegenerative or neuromuscular diseases such as Alzheimer's disease, Parkinson's disease, Huntington's disease, ALS, and muscular dystrophy; neurological disorders such as epilepsy and dystonia; neuropsychiatric conditions such as major depression, bipolar disorder, post-traumatic stress disorder, schizophrenia, anorexia nervosa, ADHD, and autism-spectrum disorders; retinal diseases such as macular degeneration, diabetic retinopathy, glaucoma, and retinitis; chronic and acute pain syndromes, including inflammatory and neuropathic pain; hearing loss and tinnitus; diabetes and complications of diabetes, including metabolic syndrome, diabetic nephropathy, diabetic neuropathy, and diabetic ulcers; respiratory diseases such as asthma, chronic obstructive pulmonary disease, acute respiratory distress syndrome, and cystic fibrosis; inflammatory bowel diseases; osteoporosis, osteoarthritis, and other degenerative conditions of bone and cartilage; acute or chronic organ failure, including renal failure, liver failure (including cirrhosis and hepatitis), and pancreatitis; ischemia-reperfusion injury associated with thrombotic or hemorrhagic stroke, subarachnoid hemorrhage, cerebral vasospasm, myocardial infarction, shock, or trauma; complications of organ or tissue transplantation including acute or chronic transplant failure or rejection and graft-versus-host disease; skin diseases including atopic dermatitis and acne; sepsis and septic shock; excessive inflammation associated with infection, including respiratory inflammation associated with influenza and upper respiratory infections; mucositis associated with cancer therapy, including radiation therapy or chemotherapy; and severe burns.

Other objects, features and advantages of the present disclosure will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating specific embodiments of the invention, are given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description. Note that simply because a particular compound is ascribed to one particular generic formula doesn't mean that it cannot also belong to another generic formula.
BRIEF DESCRIPTION OF THE DRAWINGS

The following drawings form part of the present specification and are included to further demonstrate certain aspects of the present disclosure. The invention may be better understood by reference to one of these drawings in combination with the detailed description of specific embodiments presented herein.

FIGS. 1-11 and 22. Inhibition of NO Production. RAW264.7 macrophages were pre-treated with DMSO or drugs at various concentrations (nM) for 2 hours, then treated with 20 ng/ml IFNγ for 24 hours. NO concentration in media was determined using a Griess reagent system; cell viability was determined using WST-I reagent.

FIGS. 12, 16 and 19. Induction of HO-I. MDA-MB-435 human melanoma cells were treated with vehicle (DMSO) or the indicated compounds and concentrations for 16 hours. HO-I mRNA levels were quantified using qPCR and were normalized relative to a DMSO-treated sample run in parallel. Values are averages of duplicate wells. FIG. 12: 400 nM compound; FIG. 16: 160 nM compound; FIG. 19: 160 nM compound.

FIGS. 13, 17 and 20. Induction of TrxRl. MDA-MB-435 human melanoma cells were treated with vehicle (DMSO) or the indicated compounds and concentrations for 16 hours. Thioredoxin reductase-1 (TrxRl) mRNA levels were quantified using qPCR and were normalized relative to a DMSO-treated sample run in parallel. Values are averages of duplicate wells. FIG. 13: 400 nM compound; FIG. 17: 160 nM compound; FIG. 20: 160 nM compound.

FIGS. 14, 18 and 21. Induction of γ-GCS. MDA-MB-435 human melanoma cells were treated with vehicle (DMSO) or the indicated compounds and concentrations for 16 hours. γ-Glutamylcysteine synthetase (γ-GCS) mRNA levels were quantified using qPCR and were normalized relative to a DMSO-treated sample run in parallel. Values are averages of duplicate wells. FIG. 14: 400 nM compound; FIG. 18: 160 nM compound; FIG. 21: 160 nM compound.

FIG. 15. Induction of HO-I, TrxRl and γ-GCS. MDA-MB-435 cells were treated with vehicle (DMSO) or the indicated compounds at 400 nM for 16 hours. HO-I, TrxRl and actin protein levels were assayed by immunoblotting.
DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

Disclosed herein are, for example, new compounds with antioxidant and anti-inflammatory properties, methods for their manufacture, and methods for their use, including for the treatment and/or prevention of disease.

1. Definitions

As used herein, "hydrogen" means -H; "hydroxy" means -OH; "oxo" means =O; "halo" means independently -F, -Cl, -Br or -I; "amino" means -NH₂ (see below for definitions of groups containing the term amino, e.g., alkylamino); "hydroxyamino" means -NHOH; "nitro" means -NO₂; imino means =NH (see below for definitions of groups containing the term imino, e.g., alkylamino); "cyano" means -CN; "azido" means -N₃; "mercapto" means -SH; "thio" means =S; "sulfonamido" means -NHS(O)₂⁻ (see below for definitions of groups containing the term sulfonamido, e.g., alkylsulfonamido); "sulfonyl" means -S(O)₂⁻ (see below for definitions of groups containing the term sulfonyl, e.g., alkylsulfonyl); and "silyl" means -SiH₃ (see below for definitions of group(s) containing the term silyl, e.g., alkylsilyl).

For the groups below, the following parenthetical subscripts further define the groups as follows: "(Cn)" defines the exact number (n) of carbon atoms in the group. "(C≤n)" defines the maximum number (n) of carbon atoms that can be in the group, with the minimum number of carbon atoms in such at least one, but otherwise as small as possible for the group in question. E.g., it is understood that the minimum number of carbon atoms in the group "alkenyl_(C≤4)" is 2. For example, "alkoxy_(C≤2)io" designates those alkoxy groups having from 1 to 10 carbon atoms (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, or any range derivable therein (e.g., 3-10 carbon atoms)). (Cn-n') defines both the minimum (n) and maximum number (n') of carbon atoms in the group. Similarly, "alkyl(C≤2)io" designates those alkyl groups having from 2 to 10 carbon atoms (e.g., 2, 3, 4, 5, 6, 7, 8, 9, or 10, or any range derivable therein (e.g., 3-10 carbon atoms)).

The term "alkyl" when used without the "substituted" modifier refers to a non-aromatic monovalent group with a saturated carbon atom as the point of attachment, a linear or branched, cyclo, cyclic or acyclic structure, no carbon-carbon double or triple bonds, and no atoms other than carbon and hydrogen. The groups, -CH₃ (Me), -CH₂CH₃ (Et), -CH₂CH₂CH₃ (n-Pr), -CH(CH₃)₂ (iso-Pr), -CH(CH₂)₂ (cyclopropyl), -CH₂CH₂CH₂CH₃ (n-Bu), -CH(CH₃)CH₂CH₃ (sec-butyl), -CH₂CH(CH₃)₂ (iso-butyl), -C(CH₃)₃ (tert-butyl),...
-CH₂C(CH₃)₃ (neo-pentyl), cyclobutyl, cyclopentyl, cyclohexyl, and cyclohexylmethyl are non-limiting examples of alkyl groups. The term "substituted alkyl" refers to a non-aromatic monovalent group with a saturated carbon atom as the point of attachment, a linear or branched, cyclo, cyclic or acyclic structure, no carbon-carbon double or triple bonds, and at least one atom independently selected from the group consisting of N, O, F, Cl, Br, I, Si, P, and S. The following groups are non-limiting examples of substituted alkyl groups: -CH₂OH, -CH₂Cl, -CH₂Br, -CH₂SH, -CF₃, -CH₂CN, -CH₂C(O)H, -CH₂C(O)OH, -CH₂C(O)OCH₃, -CH₂C(O)NH₂, -CH₂C(O)NHCH₃, -CH₂C(O)CH₃, -CH₂OCH₃, -CH₂OCF₃, -CH₂OC(O)CH₃, -CH₂NH₂, -CH₂NHCH₃, -CH₂N(CH₃)₂, -CH₂CH₂Cl, -CH₂CH₂OH, -CH₂CF₃, -CH₂CH₂OC(O)CH₃, -CH₂CH₂NHCO₂C(CH₃)₃, and -CH₂Si(CH₃)₃.

The term "alkanediyl" when used without the "substituted" modifier refers to a non-aromatic divalent group, wherein the alkanediyl group is attached with two σ-bonds, with one or two saturated carbon atom(s) as the point(s) of attachment, a linear or branched, cyclo, cyclic or acyclic structure, no carbon-carbon double or triple bonds, and no atoms other than carbon and hydrogen. The groups, -CH₂- (methylene), -CH₂CH₂-, -CH₂C(CH₃)₂CH₂-, -CH₂CH₂CH₂-, and

are non-limiting examples of alkanediyl groups. The term "substituted alkanediyl" refers to a non-aromatic monovalent group, wherein the alkynediyl group is attached with two σ-bonds, with one or two saturated carbon atom(s) as the point(s) of attachment, a linear or branched, cyclo, cyclic or acyclic structure, no carbon-carbon double or triple bonds, and at least one atom independently selected from the group consisting of N, O, F, Cl, Br, I, Si, P, and S. The following groups are non-limiting examples of substituted alkanediyl groups: -CH(F)-, -CF₂-, -CH(Cl)-, -CH(OH)-, -CH(OCH₃)-, and -CH₂CH(Cl)-.

The term "alkenyl" when used without the "substituted" modifier refers to a monovalent group with a nonaromatic carbon atom as the point of attachment, a linear or branched, cyclo, cyclic or acyclic structure, at least one nonaromatic carbon-carbon double bond, no carbon-carbon triple bonds, and no atoms other than carbon and hydrogen. Non-limiting examples of alkenyl groups include: -CH=CH₂ (vinyl), -CH=CHCH₃, -CH=CHCH₂CH₃, -CH₂CH=CH₂ (allyl), -CH₂CH=CHCH₃, and -CH=CH-C₆H₅. The term "substituted alkenyl" refers to a monovalent group with a nonaromatic carbon atom as the point of attachment, at least one nonaromatic carbon-carbon double bond, no carbon-carbon triple bonds, a linear or branched, cyclo, cyclic or acyclic structure, and at least one atom
independently selected from the group consisting of N, O, F, Cl, Br, I, Si, P, and S. The groups, \(-\text{CH}=\text{CHF}, -\text{CH}=-\text{CHCl}\) and \(-\text{CH}=\text{CHBr}\), are non-limiting examples of substituted alkenyl groups.

The term "alkenediy1" when used without the "substituted" modifier refers to a non-aromatic divalent group, wherein the alkenediyl group is attached with two \(\sigma\)-bonds, with two carbon atoms as points of attachment, a linear or branched, cyclo, cyclic or acyclic structure, at least one nonaromatic carbon-carbon double bond, no carbon-carbon triple bonds, and no atoms other than carbon and hydrogen. The groups, \(-\text{CH}=\text{CH}-, -\text{CH}=\text{C(CHs)}\text{CH}_2\), \(-\text{CH}=\text{CHCH}_2\), and \(\text{CH} \equiv \text{C} = \text{CH} _2\), are non-limiting examples of alkenediyl groups. The term "substituted alkenediyl" refers to a non-aromatic divalent group, wherein the alkenediyl group is attached with two \(\sigma\)-bonds, with two carbon atoms as points of attachment, a linear or branched, cyclo, cyclic or acyclic structure, at least one nonaromatic carbon-carbon double bond, no carbon-carbon triple bonds, and at least one atom independently selected from the group consisting of N, O, F, Cl, Br, I, Si, P, and S. The following groups are non-limiting examples of substituted alkenediyl groups: \(-\text{CF}=\text{CH}-, -\text{C(OH)}=\text{CH}-, \text{and } -\text{CH}_2\text{C}=\text{C(CH}s\text{)}\text{CH}_2\text{C}=\text{C}\text{Cl}^{-}\).

The term "alkynyl" when used without the "substituted" modifier refers to a monovalent group with a nonaromatic carbon atom as the point of attachment, a linear or branched, cyclo, cyclic or acyclic structure, at least one carbon-carbon triple bond, and no atoms other than carbon and hydrogen. The groups, \(-\text{C}=\text{CH}, \text{C}=\text{CCH}_3, \text{C}=\text{CC} \equiv \text{H}_2\), and \(-\text{CH}_2\text{C}=\text{CCH}_3\), are non-limiting examples of alkynyl groups. The term "substituted alkynyl" refers to a monovalent group with a nonaromatic carbon atom as the point of attachment and at least one carbon-carbon triple bond, a linear or branched, cyclo, cyclic or acyclic structure, and at least one atom independently selected from the group consisting of N, O, F, Cl, Br, I, Si, P, and S. The group, \(-\text{C}=\text{CSi} (\text{CH}_3)_3\), is a non-limiting example of a substituted alkynyl group.

The term "alkynediyl" when used without the "substituted" modifier refers to a non-aromatic divalent group, wherein the alkynediyl group is attached with two \(\sigma\)-bonds, with two carbon atoms as points of attachment, a linear or branched, cyclo, cyclic or acyclic structure, at least one carbon-carbon triple bond, and no atoms other than carbon and hydrogen. The groups, \(-\text{C}=\text{C}, -\text{C}=\text{CCH}_2\), and \(-\text{C}=\text{CCH(CHs)}\), are non-limiting examples of alkynediyl groups. The term "substituted alkynediyl" refers to a non-aromatic divalent group, wherein the alkynediyl group is attached with two \(\sigma\)-bonds, with two carbon atoms as points of attachment, a linear or branched, cyclo, cyclic or acyclic structure, at least one carbon-carbon
triple bond, and at least one atom independently selected from the group consisting of N, O, F, Cl, Br, I, Si, P, and S. The groups - C≡CCFH- and - C≡CHCH(Cl)- are non-limiting examples of substituted alkynediyl groups.

The term "aryl" when used without the "substituted" modifier refers to a monovalent group with an aromatic carbon atom as the point of attachment, said carbon atom forming part of a six-membered aromatic ring structure wherein the ring atoms are all carbon, and wherein the monovalent group consists of no atoms other than carbon and hydrogen. Non-limiting examples of aryl groups include phenyl (Ph), methylphenyl, (dimethyl)phenyl, - C₆H₄CH₂CH₃ (ethylphenyl), - C₆H₄CH₂CH₂CH₃ (propylphenyl), - C₆H₄CH(CH₃), - C₆H₄CH(CH₂CH₃), - C₆H₄CH=CH₂ (vinylphenyl), - C₆H₄CH=CHCH₃, - C₆H₄C=CH, - C₆H₄C=CCH₃, naphthyl, and the monovalent group derived from biphenyl. The term "substituted aryl" refers to a monovalent group with an aromatic carbon atom as the point of attachment, said carbon atom forming part of a six-membered aromatic ring structure wherein the ring atoms are all carbon, and wherein the monovalent group further has at least one atom independently selected from the group consisting of N, O, F, Cl, Br, I, Si, P, and S. Non-limiting examples of substituted aryl groups include the groups: - C₆H₄F, - C₆H₄Cl, - C₆H₄Br, - C₆H₄I, - C₆H₄OH, - C₆H₄OCH₃, - C₆H₄OCH₂CH₃, - C₆H₄OC(O)CH₃, - C₆H₄NH₂, - C₆H₄NHCH₃, - C₆H₄N(CH₃)₂, - C₆H₄CH₂OH, - C₆H₄CH₂OC(O)CH₃, - C₆H₄CH₂NH₂, - C₆H₄CF₃, - C₆H₄CN, - C₆H₄CHO, - C₆H₄CHO, - C₆H₄C(O)CH₃, - C₆H₄C(O)C₆H₅, - C₆H₄CO₂H, - C₆H₄CO₂CH₃, - C₆H₄CONH₂, - C₆H₄CONHCH₃, and - C₆H₄CON(CH₃)₂.

The term "arenediyl" when used without the "substituted" modifier refers to a divalent group, wherein the arenediyl group is attached with two σ-bonds, with two aromatic carbon atoms as points of attachment, said carbon atoms forming part of one or more six-membered aromatic ring structure(s) wherein the ring atoms are all carbon, and wherein the monovalent group consists of no atoms other than carbon and hydrogen. Non-limiting examples of arenediyl groups include:

The term "substituted arenediyl" refers to a divalent group, wherein the arenediyl group is attached with two σ-bonds, with two aromatic carbon atoms as points of attachment, said carbon atoms forming part of one or more six-membered aromatic rings structure(s), wherein
the ring atoms are all carbon, and wherein the divalent group further has at least one atom independently selected from the group consisting of N, O, F, Cl, Br, I, Si, P, and S.

The term "aralkyl" when used without the "substituted" modifier refers to the monovalent group -alkanediyl-aryl, in which the terms alkanediyl and aryl are each used in a manner consistent with the definitions provided above. Non-limiting examples of aralkyls are: phenylmethyl (benzyl, Bn), 1-phenyl-ethyl, 2-phenyl-ethyl, indenyl and 2,3-dihydro-indenyl, provided that indenyl and 2,3-dihydro-indenyl are only examples of aralkyl in so far as the point of attachment in each case is one of the saturated carbon atoms. When the term "aralkyl" is used with the "substituted" modifier, either one or both the alkanediyl and the aryl is substituted. Non-limiting examples of substituted aralkyls are: (3-chlorophenyl)-methyl, 2-oxo-2-phenyl-ethyl (phenylcarbonylmethyl), 2-chloro-2-phenyl-ethyl, chromanyl where the point of attachment is one of the saturated carbon atoms, and tetrahydroquinolinyl where the point of attachment is one of the saturated atoms.

The term "heteroaryl" when used without the "substituted" modifier refers to a monovalent group with an aromatic carbon atom or nitrogen atom as the point of attachment, said carbon atom or nitrogen atom forming part of an aromatic ring structure wherein at least one of the ring atoms is nitrogen, oxygen or sulfur, and wherein the monovalent group consists of no atoms other than carbon, hydrogen, aromatic nitrogen, aromatic oxygen and aromatic sulfur. Non-limiting examples of aryl groups include acridinyl, furanyl, imidazoimidazolyl, imidazopyrazolyl, imidazopyridinyl, imidazopyrimidinyl, indolyl, indazolyl, methylpyridyl, oxazolyl, phenylimidazolyl, pyridyl, pyrrolyl, pyrimidyl, pyrazinyl, quinolyl, quinazolyl, quinoxalinyl, tetrahydroquinolinyl, thienyl, triazinyl, pyrrolopyridinyl, pyrrolopyrimidinyl, pyrrolopyrazinyl, pyrrolothiazinyl, pyrroloimidazolyl, chromenyl (where the point of attachment is one of the aromatic atoms), and chromanyl (where the point of attachment is one of the aromatic atoms). The term "substituted heteroaryl" refers to a monovalent group with an aromatic carbon atom or nitrogen atom as the point of attachment, said carbon atom or nitrogen atom forming part of an aromatic ring structure wherein at least one of the ring atoms is nitrogen, oxygen or sulfur, and wherein the monovalent group further has at least one atom independently selected from the group consisting of non-aromatic nitrogen, non-aromatic oxygen, non aromatic sulfur F, Cl, Br, I, Si, and P.

The term "heteroarenediyl" when used without the "substituted" modifier refers to a divalent group, wherein the heteroarenediyl group is attached with two σ-bonds, with an
aromatic carbon atom or nitrogen atom as the point of attachment, said carbon atom or nitrogen atom two aromatic atoms as points of attachment, said carbon atoms forming part of one or more six-membered aromatic ring structure(s) wherein the ring atoms are all carbon, and wherein the monovalent group consists of no atoms other than carbon and hydrogen.

Non-limiting examples of heteroarenediyl groups include:

\[ \text{Non-limiting examples include:} \]

The term "substituted heteroarenediyl" refers to a divalent group, wherein the heteroarenediyl group is attached with two \( \sigma \)-bonds, with two aromatic carbon atoms as points of attachment, said carbon atoms forming part of one or more six-membered aromatic rings structure(s), wherein the ring atoms are all carbon, and wherein the divalent group further has at least one atom independently selected from the group consisting of N, O, F, Cl, Br, I, Si, P, and S.

The term "heteroaralkyl" when used without the "substituted" modifier refers to the monovalent group -alkanediyl-heteroaryl, in which the terms alkanediyl and heteroaryl are each used in a manner consistent with the definitions provided above. Non-limiting examples of aralkyls are: pyridylmethyl, and thiethylmethyI. When the term "heteroaralkyl" is used with the "substituted" modifier, either one or both the alkanediyl and the heteroaryl is substituted.

The term "acyl" when used without the "substituted" modifier refers to a monovalent group with a carbon atom of a carbonyl group as the point of attachment, further having a linear or branched, cyclo, cyclic or acyclic structure, further having no additional atoms that are not carbon or hydrogen, beyond the oxygen atom of the carbonyl group. The groups, -CHO, -C(O)CH\(_3\) (acetyl, Ac), -C(O)CH\(_2\)CH\(_3\), -C(O)CH\(_2\)CH\(_2\)CH\(_3\), -C(O)CH(CH\(_3\))\(_2\), -C(O)CH(CH\(_2\))\(_2\), -C(O)C\(_6\)H\(_5\), -C(O)C\(_6\)H\(_4\)CH\(_3\), -C(O)C\(_6\)H\(_4\)CH\(_2\)CH\(_3\), -C(O)C\(_6\)H\(_3\)(CH\(_3\))\(_2\), and -C(O)CH\(_2\)C\(_6\)H\(_5\), are non-limiting examples of acyl groups. The term "acyl" therefore encompasses, but is not limited to groups sometimes referred to as "alkyl carbonyl" and "aryl carbonyl" groups. The term "substituted acyl" refers to a monovalent group with a carbon atom of a carbonyl group as the point of attachment, further having a linear or branched, cyclo, cyclic or acyclic structure, further having at least one atom, in addition to the oxygen of the carbonyl group, independently selected from the group consisting of N, O, F, Cl, Br, I, Si, P, and S. The groups, -C(O)CH\(_2\)F\(_3\), -CO\(_2\)H (carboxyl), -CO\(_2\)CH\(_3\) (methylcarboxyl), -CO\(_2\)CH\(_2\)CH\(_3\), -CO\(_2\)CH\(_2\)CH\(_2\)CH\(_3\), -CO\(_2\)C\(_6\)H\(_5\), -CO\(_2\)CH(CH\(_3\))\(_2\), -CO\(_2\)CH(CH\(_2\))\(_2\), -C(O)NH\(_2\) (carbamoyl), -C(O)NHCH\(_3\), -C(O)NHCH\(_2\)CH\(_3\), -CONHCH(CH\(_3\))\(_2\), -CONHCH(CH\(_2\))\(_2\),
-CON(CH₃)₂, -CONHCH₂CF₃, -CO-pyridyl, -COHmidazoyl, and -C(O)N₃, are non-limiting examples of substituted acyl groups. The term "substituted acyl" encompasses, but is not limited to, "heteroaryl carbonyl" groups.

The term "alkyldiene" when used without the "substituted" modifier refers to the divalent group =CRR', wherein the alkyldiene group is attached with one σ-bond and one π-bond, in which R and R' are independently hydrogen, alkyl, or R and R' are taken together to represent alkanediyl. Non-limiting examples of alkyldiene groups include: =CH₂, =CH(CH₂CH₃), and =C(CH₃)₂. The term "substituted alkyldiene" refers to the group =CRR', wherein the alkyldiene group is attached with one σ-bond and one π-bond, in which R and R' are independently hydrogen, alkyl, substituted alkyl, or R and R' are taken together to represent a substituted alkanediyl, provided that either one of R and R' is a substituted alkyl or R and R' are taken together to represent a substituted alkanediyl.

The term "alkoxy" when used without the "substituted" modifier refers to the group -OR, in which R is an alkyl, as that term is defined above. Non-limiting examples of alkoxy groups include: -OCH₃, -OCH₂CH₃, -OCH₂CH₂CH₃, -OCH(CH₃)₂, -OCH(CH₂)₂, -O-cyclopentyl, and -O-cyclohexyl. The term "substituted alkoxy" refers to the group -OR, in which R is a substituted alkyl, as that term is defined above. For example, -OCH₂CF₃ is a substituted alkoxy group.

Similarly, the terms "alkenyloxy", "alkynyloxy", "aryloxy", "aralkoxy", "heteroaryloxy", "heteroaralkoxy" and "acyloxy", when used without the "substituted" modifier, refers to groups, defined as -OR, in which R is alkenyl, alkynyl, aryl, aralkyl, heteroaryl, heteroaralkyl and acyl, respectively, as those terms are defined above. When any of the terms alkenyloxy, alkynyloxy, aryloxy, aralkyloxy and acyloxy is modified by "substituted," it refers to the group -OR, in which R is substituted alkenyl, alkynyl, aryl, aralkyl, heteroaryl, heteroaralkyl and acyl, respectively.

The term "alkylamino" when used without the "substituted" modifier refers to the group -NHR, in which R is an alkyl, as that term is defined above. Non-limiting examples of alkylamino groups include: -NHCH₃, -NHCH₂CH₃, -NHCH₂CH₂CH₃, -NHCH(CH₃)₂, -NHCH(CH₂)₂, -NHCH₂CH₂CH₂CH₃, -NHCH(CH₃)₂CH₂CH₃, -NHCH₂CH(CH₃)₂, -NHCH(CH₃)₃, -NH-cyclopentyl, and -NH-cyclohexyl. The term "substituted alkylamino" refers to the group -NHR, in which R is a substituted alkyl, as that term is defined above. For example, -NHCH₂CF₃ is a substituted alkylamino group.
The term "dialkylamino" when used without the "substituted" modifier refers to the group -NRR', in which R and R' can be the same or different alkyl groups, or R and R' can be taken together to represent an alkanediyl having two or more saturated carbon atoms, at least two of which are attached to the nitrogen atom. Non-limiting examples of dialkylamino groups include: -NHC(CH$_3$)$_3$, -N(CH$_3$)$_2$CH$_2$CH$_3$, -N(CH$_2$CH$_3$)$_2$, JV-pyrrolidinyl, and N-piperidinyl. The term "substituted dialkylamino" refers to the group -NRR', in which R and R' can be the same or different substituted alkyl groups, one of R or R' is an alkyl and the other is a substituted alkyl, or R and R' can be taken together to represent a substituted alkanediyl with two or more saturated carbon atoms, at least two of which are attached to the nitrogen atom.

The terms "alkoxyamino", "alkenylamino", "alkynylamino", "arylamino", "aralkylamino", "heteroarylamino", "heteroaralkylamino", and "alkylsulfonlamino" when used without the "substituted" modifier, refers to groups, defined as -NHR, in which R is alkoxy, alkenyl, alkynyl, aryl, aralkyl, heteroaryl, heteroaralkyl and alkylsulfonyl, respectively, as those terms are defined above. A non-limiting example of an arylamino group is -NHC6H5. When any of the terms alkoxyamino, alkenylamino, alkynylamino, arylamino, aralkylamino, heteroarylamino, heteroaralkylamino and alkylsulfonlamino is modified by "substituted," it refers to the group -NHR, in which R is substituted alkoxy, alkenyl, alkynyl, aryl, aralkyl, heteroaryl, heteroaralkyl and alkylsulfonyl, respectively.

The term "amido" (acylamino), when used without the "substituted" modifier, refers to the group -NHR, in which R is acyl, as that term is defined above. A non-limiting example of an acylamino group is -NHC(O)CH$_3$. When the term amido is used with the "substituted" modifier, it refers to groups, defined as -NHR, in which R is substituted acyl, as that term is defined above. The groups -NHC(O)OCH$_3$ and -NHC(O)NHCH$_3$ are non-limiting examples of substituted amido groups.

The term "alkylimino" when used without the "substituted" modifier refers to the group =NR, wherein the alkylimino group is attached with one σ-bond and one π-bond, in which R is an alkyl, as that term is defined above. Non-limiting examples of alkylimino groups include: =NCH$_3$, =NCH$_2$CH$_3$ and =N-cyclohexyl. The term "substituted alkylimino" refers to the group =NR, wherein the alkylimino group is attached with one σ-bond and one π-bond, in which R is a substituted alkyl, as that term is defined above. For example, =NCH$_2$CF$_3$ is a substituted alkylimino group.
Similarly, the terms "alkenylimino", "alknylimino", "arylimino", "aralkylimino", "heteroarylylimino", "heteroaralkylimino" and "acylimino", when used without the "substituted" modifier, refers to groups, defined as =NR, wherein the alkylimino group is attached with one σ-bond and one π-bond, in which R is alkenyl, alkynyl, aryl, aralkyl, heteroaryl, heteroaralkyl and acyl, respectively, as those terms are defined above. When any of the terms alkenylimino, alkynylimino, arylimino, aralkylimino and acylimino is modified by "substituted," it refers to the group =NR, wherein the alkylimino group is attached with one σ-bond and one π-bond, in which R is substituted alkenyl, alkynyl, aryl, aralkyl, heteroaryl, heteroaralkyl and acyl, respectively.

The term "fluoroalkyl" when used without the "substituted" modifier refers to an alkyl, as that term is defined above, in which one or more fluorines have been substituted for hydrogens. The groups, -CH₂F, -CF₃, and -CH₂CF₃ are non-limiting examples of fluoroalkyl groups. The term "substituted fluoroalkyl" refers to a non-aromatic monovalent group with a saturated carbon atom as the point of attachment, a linear or branched, cyclic or acyclic structure, at least one fluorine atom, no carbon-carbon double or triple bonds, and at least one atom independently selected from the group consisting of N, O, Cl, Br, I, Si, P, and S. The following group is a non-limiting example of a substituted fluoroalkyl: -CF₂CH₂Cl.

The term "alkythio" when used without the "substituted" modifier refers to the group -SR, in which R is an alkyl, as that term is defined above. Non-limiting examples of alkylthio groups include: -SCH₃, -SCH₂CH₃, -SCH₂CH₂CH₃, -SCH(CH₃)₂, -SCH(CH₂)₂, -S-cyclopentyl, and -S-cyclohexyl. The term "substituted alkylthio" refers to the group -SR, in which R is a substituted alkyl, as that term is defined above. For example, -SCH₂CF₃ is a substituted alkylthio group.

Similarly, the terms "alkenylthio", "alkynylthio", "arylthio", "aralkylthio", "heteroarylthio", "heteroaralkylthio", and "acylthio", when used without the "substituted" modifier, refers to groups, defined as -SR, in which R is alkenyl, alkynyl, aryl, aralkyl, heteroaryl, heteroaralkyl and acyl, respectively, as those terms are defined above. When any of the terms alkenylthio, alkynylthio, arylthio, aralkylthio, heteroarylthio, heteroaralkylthio, and acylthio is modified by "substituted," it refers to the group -SR, in which R is substituted alkenyl, alkynyl, aryl, aralkyl, heteroaryl, heteroaralkyl and acyl, respectively.

The term "thioacyl" when used without the "substituted" modifier refers to a monovalent group with a carbon atom of a thiocarbonyl group as the point of attachment,
further having a linear or branched, cyclo, cyclic or acyclic structure, further having no additional atoms that are not carbon or hydrogen, beyond the sulfur atom of the carbonyl group. The groups, -CHS, -C(S)CH$_3$, -C(S)CH$_2$CH$_3$, -C(S)CH$_2$CH$_2$CH$_3$, -C(S)CH(CH$_3$)$_2$, -C(S)CH(CH$_2$)$_2$, -C(S)C$_6$H$_5$, -C(S)C$_6$H$_5$CH$_3$, -C(S)C$_6$H$_5$CH$_2$CH$_3$, -C(S)C$_6$H$_5$CH$_2$CH$_2$H$_2$, and -C(S)CH$_2$C$_6$H$_5$, are non-limiting examples of thioacyl groups. The term "thioacyl" therefore encompasses, but is not limited to, groups sometimes referred to as "alkyl thiocarbonyl" and "aryl thiocarbonyl" groups. The term "substituted thioacyl" refers to a radical with a carbon atom as the point of attachment, the carbon atom being part of a thiacarbonyl group, further having a linear or branched, cyclo, cyclic or acyclic structure, further having at least one atom, in addition to the sulfur atom of the carbonyl group, independently selected from the group consisting of N, O, F, Cl, Br, I, Si, P, and S. The groups, -C(S)CH$_2$CF$_3$, -C(S)O$_2$H, -C(S)OCH$_3$, -C(S)OCH$_2$CH$_3$, -C(S)OCH$_2$CH$_2$CH$_3$, -C(S)OC$_6$H$_5$, -C(S)OCH(CH$_3$)$_2$, -C(S)OCH(CH$_2$)$_2$, -C(S)ONH$_2$, and -C(S)NHCH$_3$, are non-limiting examples of substituted thioacyl groups. The term "substituted thioacyl" encompasses, but is not limited to, "heteroaryl thiocarbonyl" groups.

The term "alkyl sulfonyl" when used without the "substituted" modifier refers to the group -S(O)$_2$R, in which R is an alkyl, as that term is defined above. Non-limiting examples of alkylsulfonyl groups include: -S(O)$_2$CH$_3$, -S(O)$_2$CH$_2$CH$_3$, -S(O)$_2$CH$_2$CH$_2$CH$_3$, -S(O)$_2$CH(CH$_3$)$_2$, -S(O)$_2$CH(CH$_2$)$_2$, -S(O)$_2$-cyclopentyl, and -S(O)$_2$-cyclohexyl. The term "substituted alkylsulfonyl" refers to the group -S(O)$_2$R, in which R is a substituted alkyl, as that term is defined above. For example, -S(O)$_2$CH$_2$CF$_3$ is a substituted alkylsulfonyl group.

Similarly, the terms "alkenyl sulfonyl", "alkynyl sulfonyl", "aryl sulfonyl", "aralkyl sulfonyl", "heteroarylsulfonyl", and "heteroaaryl sulfonyl" when used without the "substituted" modifier, refers to groups, defined as -S(O)$_2$R, in which R is alkenyl, alkynyl, aryl, aralkyl, heteroaryl, and heteroaaryl, respectively, as those terms are defined above. When any of the terms alkenyl sulfonyl, alkynyl sulfonyl, aryl sulfonyl, aralkyl sulfonyl, heteroarylsulfonyl, and heteroaaryl sulfonyl is modified by "substituted," it refers to the group -S(O)$_2$R, in which R is substituted alkenyl, alkynyl, aryl, aralkyl, heteroaryl and heteroaaryl, respectively.

The term "alkalammonium" when used without the "substituted" modifier refers to a group, defined as -NH$_2$R$, -NHRR' +$, or -NRR'R$'' +$, in which R, R', and R'' are the same or different alkyl groups, or any combination of two of R, R' and R'' can be taken together to represent an alkanediyl. Non-limiting examples of alkalammonium cation groups include:

-\(-\text{NH}_2(\text{CH}_3)^+\), \(-\text{NH}_2(\text{CH}_2\text{CH}_3)^+\), \(-\text{NH}_2(\text{CH}_2\text{CH}_2\text{CH}_3)^+\), \(-\text{NH}(\text{CH}_3)^+\), \(-\text{NH}(\text{CH}_2\text{CH}_3)^+\).
-NH(CH₂CH₂CH₃)₂⁺, -N(CH₃)₃⁺, -N(CH₃)(CH₂CH₃)₂⁺, -N(CH₃)₂(CH₂CH₃)⁺, -NH₂C(CH₃)₃⁺, -NH(cyclopentyl)₂⁺, and -NH₂(cyclohexyl)⁺. The term "substituted alkylammonium" refers -NH₂R⁺, -NHRRZ⁺, or -NR'R''⁺, in which at least one of R, R' and R" is a substituted alkyl or two of R, R' and R" can be taken together to represent a substituted alkanediyl. When more than one of R, R' and R" is a substituted alkyl, they can be the same of different. Any of R, R' and R" that are not either substituted alkyl or substituted alkanediyl, can be either alkyl, either the same or different, or can be taken together to represent a alkanediyl with two or more carbon atoms, at least two of which are attached to the nitrogen atom shown in the formula.

The term "alkylsulfonium" when used without the "substituted" modifier refers to the group -SRR⁺, in which R and R' can be the same or different alkyl groups, or R and R' can be taken together to represent an alkanediyl. Non-limiting examples of alkylsulfonium groups include: -SH(CH₃)⁺, -SH(CH₂CH₃)⁺, -SH(CH₂CH₂CH₃)⁺, -S(CH₃)₂⁺, -S(CH₂CH₃)₂⁺, -S(CH₂CH₂CH₃)₂⁺, -SH(cyclopentyl)⁺, and -SH(cyclohexyl)⁺. The term "substituted alkylsulfonium" refers to the group -SRR⁺, in which R and R' can be the same or different substituted alkyl groups, one of R or R' is an alkyl and the other is a substituted alkyl, or R and R' can be taken together to represent a substituted alkanediyl. For example, -SH(CH₂CF₃)⁺ is a substituted alkylsulfonium group.

The term "alkylsilyl" when used without the "substituted" modifier refers to a monovalent group, defined as -SiH₂R, -SiHRR', or -SiRR'R", in which R, R' and R" can be the same or different alkyl groups, or any combination of two of R, R' and R" can be taken together to represent an alkanediyl. The groups, -SiH₂CH₃, -SiH(CH₃)₂, -Si(CH₃)₃ and -Si(CH₃)₂C(CH₃)₂ are non-limiting examples of unsubstituted alkylsilyl groups. The term "substituted alkylsilyl" refers -SiH₂R, -SiHRR', or -SiRR'R", in which at least one of R, R' and R" is a substituted alkyl or two of R, R' and R" can be taken together to represent a substituted alkanediyl. When more than one of R, R' and R" is a substituted alkyl, they can be the same of different. Any of R, R' and R" that are not either substituted alkyl or substituted alkanediyl, can be either alkyl, either the same or different, or can be taken together to represent a alkanediyl with two or more saturated carbon atoms, at least two of which are attached to the silicon atom.

In addition, atoms making up the compounds of the present disclosure are intended to include all isotopic forms of such atoms. Isotopes, as used herein, include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include tritium and deuterium, and isotopes of
carbon include $^{13}$C and $^{14}$C. Similarly, it is contemplated that one or more carbon atom(s) of a compound of the present disclosure may be replaced by a silicon atom(s). Furthermore, it is contemplated that one or more oxygen atom(s) of a compound of the present disclosure may be replaced by a sulfur or selenium atom(s).

A compound having a formula that is represented with a dashed bond is intended to include the formulae optionally having zero, one or more double bonds. Thus, for example, the structure $\text{CH}_2$ includes the structures $\text{CH} \equiv \text{CH}$, $\text{CH} \equiv \text{CH} \equiv \text{CH}$, $\text{CH} \equiv \text{CH}_2$ and $\text{CH}_2 \equiv \text{CH}$. As will be understood by a person of skill in the art, no one such ring atom forms part of more than one double bond.

Any undefined valency on an atom of a structure shown in this application implicitly represents a hydrogen atom bonded to the atom.

A ring structure shown with an unconnected "R" group, indicates that any implicit hydrogen atom on that ring can be replaced with that R group. In the case of a divalent R group (e.g., oxo, imino, thio, alkylidene, etc.), any pair of implicit hydrogen atoms attached to one atom of that ring can be replaced by that R group. This concept is as exemplified below:

\[
\text{R} \quad \text{represents}
\]

As used herein, a "chiral auxiliary" refers to a removable chiral group that is capable of influencing the stereoselectivity of a reaction. Persons of skill in the art are familiar with such compounds, and many are commercially available.

The use of the word "a" or "an," when used in conjunction with the term "comprising" in the claims and/or the specification may mean "one," but it is also consistent with the meaning of "one or more," "at least one," and "one or more than one."

Throughout this application, the term "about" is used to indicate that a value includes the inherent variation of error for the device, the method being employed to determine the value, or the variation that exists among the study subjects.

The terms "comprise," "have" and "include" are open-ended linking verbs. Any forms or tenses of one or more of these verbs, such as "comprises," "comprising," "has,"
"having," "includes" and "including," are also open-ended. For example, any method that "comprises," "has" or "includes" one or more steps is not limited to possessing only those one or more steps and also covers other unlisted steps.

The term "effective," as that term is used in the specification and/or claims, means adequate to accomplish a desired, expected, or intended result.

The term "hydrate" when used as a modifier to a compound means that the compound has less than one (e.g., hemihydrate), one (e.g., monohydrate), or more than one (e.g., dihydrate) water molecules associated with each compound molecule, such as in solid forms of the compound.

As used herein, the term "IC_{50}" refers to an inhibitory dose which is 50% of the maximum response obtained.

An "isomer" of a first compound is a separate compound in which each molecule contains the same constituent atoms as the first compound, but where the configuration of those atoms in three dimensions differs.

As used herein, the term "patient" or "subject" refers to a living mammalian organism, such as a human, monkey, cow, sheep, goat, dog, cat, mouse, rat, guinea pig, or transgenic species thereof. In certain embodiments, the patient or subject is a primate. Non-limiting examples of human subjects are adults, juveniles, infants and fetuses.

"Pharmacologically acceptable" means that which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes that which is acceptable for veterinary use as well as human pharmaceutical use.

"Pharmacologically acceptable salts" means salts of compounds of the present disclosure which are pharmaceutically acceptable, as defined above, and which possess the desired pharmacological activity. Such salts include acid addition salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or with organic acids such as 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, 2-naphthalenesulfonic acid, 3-phenylpropionic acid, 4,4'-methylenebis(3-hydroxy-2-ene-1-carboxylic acid), 4-methylbicyclo[2.2.2]oct-2-ene-1-carboxylic acid, acetic acid, aliphatic mono- and dicarboxylic acids, aliphatic sulfuric acids, aromatic sulfuric acids, benzenesulfonic acid, benzoic acid, camphorsulfonic acid, carbonic acid, cinnamic acid, citric acid, cyclopentanepropionic acid, ethanesulfonic acid, fumaric acid, glucoheptonic acid, gluconic acid, glutamic acid, glycolic acid, heptanoic acid, hexanoic acid, hydroxynaphthoic acid, lactic acid, laurysulfuric acid, maleic acid, malic acid, malonic acid, and the like.

The term "includes" means that which includes but is not limited to the examples specifically mentioned.
acid, mandelic acid, methanesulfonic acid, muconic acid, o-(4-hydroxybenzoyl)benzoic acid, oxalic acid, \(\beta\)-chlorobenzenesulfonic acid, phenyl-substituted alkanoic acids, propionic acid, \(\beta\)-toluenesulfonic acid, pyruvic acid, salicylic acid, stearic acid, succinic acid, tartaric acid, tertiarybutylacetic acid, trimethylacetic acid, and the like. Pharmaceutically acceptable salts also include base addition salts which may be formed when acidic protons present are capable of reacting with inorganic or organic bases. Acceptable inorganic bases include sodium hydroxide, sodium carbonate, potassium hydroxide, aluminum hydroxide and calcium hydroxide. Acceptable organic bases include ethanolamine, diethanolamine, triethanolamine, tromethamine, JV-methylglucamine and the like. It should be recognized that the particular anion or cation forming a part of any salt of this invention is not critical, so long as the salt, as a whole, is pharmacologically acceptable. Additional examples of pharmaceutically acceptable salts and their methods of preparation and use are presented in Handbook of Pharmaceutical Salts: Properties, and Use (P. H. Stahl & C. G. Wermuth eds., Verlag Helvetica Chimica Acta, 2002).

As used herein, "predominantly one enantiomer" means that a compound contains at least about 85% of one enantiomer, or more preferably at least about 90% of one enantiomer, or even more preferably at least about 95% of one enantiomer, or most preferably at least about 99% of one enantiomer. Similarly, the phrase "substantially free from other optical isomers" means that the composition contains at most about 15% of another enantiomer or diastereomer, more preferably at most about 10% of another enantiomer or diastereomer, even more preferably at most about 5% of another enantiomer or diastereomer, and most preferably at most about 1% of another enantiomer or diastereomer.

"Prevention" or "preventing" includes: (1) inhibiting the onset of a disease in a subject or patient which may be at risk and/or predisposed to the disease but does not yet experience or display any or all of the pathology or symptomatology of the disease, and/or (2) slowing the onset of the pathology or symptomatology of a disease in a subject or patient which may be at risk and/or predisposed to the disease but does not yet experience or display any or all of the pathology or symptomatology of the disease.

"Prodrug" means a compound that is convertible in vivo metabolically into an inhibitor according to the present disclosure. The prodrug itself may or may not also have activity with respect to a given target protein. For example, a compound comprising a hydroxy group may be administered as an ester that is converted by hydrolysis in vivo to the hydroxy compound. Suitable esters that may be converted in vivo into hydroxy compounds include acetates, citrates, lactates, phosphates, tartrates, malonates, oxalates, salicylates,
propionates, succinates, fumarates, maleates, methylene-bis-β-hydroxynaphthoate, gentisates, isethionates, di-p-toluoyltartrates, methanesulfonates, ethanesulfonates, benzenesulfonates, \( \beta \)-toluenesulfonates, cyclohexylsulfamates, quinates, esters of amino acids, and the like. Similarly, a compound comprising an amine group may be administered as an amide that is converted by hydrolysis in vivo to the amine compound.

The term "saturated" when referring to an atom means that the atom is connected to other atoms only by means of single bonds.

A "stereoisomer" or "optical isomer" is an isomer of a given compound in which the same atoms are bonded to the same other atoms, but where the configuration of those atoms in three dimensions differs. "Enantiomers" are stereoisomers of a given compound that are mirror images of each other, like left and right hands. "Diastereomers" are stereoisomers of a given compound that are not enantiomers.

The invention contemplates that for any stereocenter or axis of chirality for which stereochemistry has not been defined, that stereocenter or axis of chirality can be present in its \( R \) form, \( S \) form, or as a mixture of the \( R \) and \( S \) forms, including racemic and non-racemic mixtures.

"Substituent convertible to hydrogen in vivo" means any group that is convertible to a hydrogen atom by enzymological or chemical means including, but not limited to, hydrolysis and hydrogenolysis. Examples include acyl groups, groups having an oxycarbonyl group, amino acid residues, peptide residues, \( o \)-nitrophenylsulfenyl, trimethylsilyl, tetrahydro-2-pyran-1-yl, diphenylphosphinyl, hydroxy or alkoxy substituents on imino groups, and the like. Examples of acyl groups include formyl, acetyl, trifluoroacetyl, and the like. Examples of groups having an oxycarbonyl group include ethoxycarbonyl, \( \text{tert} \)-butyloxycarbonyl \((-\text{COOC}(\text{CH}_3)_3\))\), benzyloxy carbonyl, \( p \)-methoxybenzyloxycarbonyl, vinylloxy carbonyl, \( \beta \)-(\( p \)-toluenesulfonyl)ethoxycarbonyl, and the like. Suitable amino acid residues include, but are not limited to, residues of Gly (glycine), Ala (alanine), Arg (arginine), Asn (asparagine), Asp (aspartic acid), Cys (cysteine), Glu (glutamic acid), His (histidine), He (isoleucine), Leu (leucine), Lys (lysine), Met (methionine), Phe (phenylalanine), Pro (proline), Ser (serine), Thr (threonine), Trp (tryptophan), Tyr (tyrosine), Val (valine), Nva (norvaline), Hse (homoserine), 4-Hyp (4-hydroxyproline), 5-Hyl (5-hydroxylysine), Orn (ornithine) and \( \beta \)-Ala.

Examples of suitable amino acid residues also include amino acid residues that are protected with a protecting group. Examples of suitable protecting groups include those typically employed in peptide synthesis, including acyl groups (such as formyl and acetyl),
arylmethyloxycarbonyl groups (such as benzyloxycarbonyl and p-nitrobenzyloxycarbonyl), tert-butoxycarbonyl groups (-C(O)OC(CH$_3$)$_3$), and the like. Suitable peptide residues include peptide residues comprising two to five, and optionally amino acid residues. The residues of these amino acids or peptides can be present in stereochemical configurations of the D-form, the L-form or mixtures thereof. In addition, the amino acid or peptide residue may have an asymmetric carbon atom. Examples of suitable amino acid residues having an asymmetric carbon atom include residues of Ala, Leu, Phe, Trp, Nva, Val, Met, Ser, Lys, Thr and Tyr. Peptide residues having an asymmetric carbon atom include peptide residues having one or more constituent amino acid residues having an asymmetric carbon atom. Examples of suitable amino acid protecting groups include those typically employed in peptide synthesis, including acyl groups (such as formyl and acetyl), arylmethylxycarbonyl groups (such as benzyloxycarbonyl and /?-nitrobenzyloxycarbonyl), tert-butoxycarbonyl groups (-C(O)OC(CH$_3$)$_3$), and the like. Other examples of substituents "convertible to hydrogen in vivo" include reductively eliminable hydrogenolyzable groups. Examples of suitable reductively eliminable hydrogenolyzable groups include, but are not limited to, arylsulfonyl groups (such as o-toluenesulfonyl); methyl groups substituted with phenyl or benzyloxy (such as benzyl, trityl and benzyloxymethyl); arylmethoxycarbonyl groups (such as benzyloxycarbonyl and o-methoxy-benzyloxycarbonyl); and haloethoxycarbonyl groups (such as β,β,β-trichloroethoxycarbonyl and β-iodoethoxycarbonyl).

"Therapeutically effective amount" or "pharmacologically effective amount" means that amount which, when administered to a subject or patient for treating a disease, is sufficient to effect such treatment for the disease.

"Treatment" or "treating" includes (1) inhibiting a disease in a subject or patient experiencing or displaying the pathology or symptomatology of the disease (e.g., arresting further development of the pathology and/or symptomatology), (2) ameliorating a disease in a subject or patient that is experiencing or displaying the pathology or symptomatology of the disease (e.g., reversing the pathology and/or symptomatology), and/or (3) effecting any measurable decrease in a disease in a subject or patient that is experiencing or displaying the pathology or symptomatology of the disease.

As used herein, the term "water soluble" means that the compound dissolves in water at least to the extent of 0.010 mole/liter or is classified as soluble according to literature precedence.

Other abbreviations used herein are as follows: DMSO, dimethyl sulfoxide; NO, nitric oxide; iNOS, inducible nitric oxide synthase; COX-2, cyclooxygenase-2; NGF, nerve growth
factor; IBMX, isobutylmethylxanthine; FBS, fetal bovine serum; GPDH, glycerol 3-phosphate dehydrogenase; RXR, retinoid X receptor; TGF-β, transforming growth factor-β; IFNγ or IFN-γ, interferon-γ; LPS, bacterial endotoxic lipopolysaccharide; TNFα or TNF-α, tumor necrosis factor-α; IL-1β, interleukin-1β; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; MTT, 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide; TCA, trichloroacetic acid; HO-I, inducible heme oxygenase.

The above definitions supersede any conflicting definition in any of the reference that is incorporated by reference herein. The fact that certain terms are defined, however, should not be considered as indicative that any term that is undefined is indefinite. Rather, all terms used are believed to describe the invention in terms such that one of ordinary skill can appreciate the scope and practice the present disclosure.

II. Synthetic Methods

Compounds of the present disclosure may be made using the methods outlined in the Examples section (Example 2 and 3). These methods can be further modified and optimized using the principles and techniques of organic chemistry as applied by a person skilled in the art. Such principles and techniques are taught, for example, in March’s Advanced Organic Chemistry: Reactions, Mechanisms, and Structure (2007), which is incorporated by reference herein.

III. Biological Activity of Oleanolic Acid Derivatives

Certain compounds of the present disclosure have been tested for inhibition of NO production, iNOS induction, Nrf2 target gene induction, inhibition of COX-2 induction, inhibition of STAT3 phosphorylation, suppression of IL-6 induced phosphorylation, inhibition of TNFα-induced IkBα degradation, inhibition of NF-κB activation, induction of HO-I, induction of TrxR1, induction of γ-GCS, and/or induction of ferritin heavy chain. The results of certain experiments are shown in the figures and in Tables Ia & Ib, below. The experimental details are provided in Example 1.

Table Ia: Suppression of IFNγ-induced NO production.

<table>
<thead>
<tr>
<th>Working ID</th>
<th>MW</th>
<th>RAW264.7 (20 ng/ml IFNγ)</th>
<th>WST-1 IC_{50}</th>
</tr>
</thead>
<tbody>
<tr>
<td>402-05</td>
<td>498.70</td>
<td>&gt; 200 nM</td>
<td>&gt; 200 nM</td>
</tr>
<tr>
<td>402-06</td>
<td>548.70</td>
<td>&gt; 200 nM</td>
<td>&gt; 200 nM</td>
</tr>
<tr>
<td>Working ID</td>
<td>MW</td>
<td>RAW264.7 (20 ng/ml IFNγ)</td>
<td></td>
</tr>
<tr>
<td>-----------</td>
<td>-------</td>
<td>-------------------------</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>NO IC₅₀</td>
<td>WST-1 IC₅₀</td>
</tr>
<tr>
<td>402-07</td>
<td>539.70</td>
<td>&gt; 200 nM</td>
<td>&gt; 200 nM</td>
</tr>
<tr>
<td>402-08</td>
<td>601.80</td>
<td>62 nM</td>
<td>&gt; 200 nM</td>
</tr>
<tr>
<td>402-09</td>
<td>506.70</td>
<td>4.2 nM</td>
<td>&gt; 200 nM</td>
</tr>
<tr>
<td>402-10</td>
<td>520.70</td>
<td>2.3 nM</td>
<td>&gt; 200 nM</td>
</tr>
<tr>
<td>402-11</td>
<td>516.70</td>
<td>2.5 nM</td>
<td>150 nM</td>
</tr>
<tr>
<td>402-22</td>
<td>519.70</td>
<td>&gt; 200 nM</td>
<td>&gt; 200 nM</td>
</tr>
<tr>
<td>402-40</td>
<td>534.70</td>
<td>17 nM</td>
<td>75 nM</td>
</tr>
<tr>
<td>402-47</td>
<td>549.74</td>
<td>&gt; 200 nM</td>
<td>&gt; 200 nM</td>
</tr>
<tr>
<td>402-55</td>
<td>493.65</td>
<td>~3 nM</td>
<td>100 nM</td>
</tr>
<tr>
<td>63301</td>
<td>521.69</td>
<td>~3.2 nM</td>
<td>~120 nM</td>
</tr>
<tr>
<td>63302</td>
<td>565.74</td>
<td>~18 nM</td>
<td>~100 nM</td>
</tr>
<tr>
<td>63307</td>
<td>521.69</td>
<td>~60 nM</td>
<td>&gt; 200 nM</td>
</tr>
<tr>
<td>63309</td>
<td>519.69</td>
<td>~12 nM</td>
<td>&gt; 200 nM</td>
</tr>
<tr>
<td>63316</td>
<td>539.70</td>
<td>~80 nM</td>
<td>&gt; 200 nM</td>
</tr>
<tr>
<td>63320</td>
<td>548.68</td>
<td>~12 nM</td>
<td>See FIG. 22</td>
</tr>
</tbody>
</table>
Table Ib: Induction of HO-I, TrxR1 and γ-GCS in Human Melanoma Cells.

<table>
<thead>
<tr>
<th>Compound Code</th>
<th>Nrf2 target gene induction in MDA-MB-435 cells at 160 nM*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HO-1</td>
</tr>
<tr>
<td>63165</td>
<td>19</td>
</tr>
<tr>
<td>63166</td>
<td>6</td>
</tr>
<tr>
<td>63177</td>
<td>0</td>
</tr>
</tbody>
</table>

* Data expressed as a percent of induction observed for 402 (see below for structure).

III. Diseases Associated with Inflammation and/or Oxidative Stress

Inflammation is a biological process that provides resistance to infectious or parasitic organisms and the repair of damaged tissue. Inflammation is commonly characterized by localized vasodilation, redness, swelling, and pain, the recruitment of leukocytes to the site of infection or injury, production of inflammatory cytokines such as TNF-α and IL-1, and production of reactive oxygen or nitrogen species such as hydrogen peroxide, superoxide and peroxynitrite. In later stages of inflammation, tissue remodeling, angiogenesis, and scar formation (fibrosis) may occur as part of the wound healing process. Under normal circumstances, the inflammatory response is regulated and temporary and is resolved in an orchestrated fashion once the infection or injury has been dealt with adequately. However, acute inflammation can become excessive and life-threatening if regulatory mechanisms fail. Alternatively, inflammation can become chronic and cause cumulative tissue damage or systemic complications.

Many serious and intractable human diseases involve dysregulation of inflammatory processes, including diseases such as cancer, atherosclerosis, and diabetes, which were not traditionally viewed as inflammatory conditions. In the case of cancer, the inflammatory processes are associated with tumor formation, progression, metastasis, and resistance to therapy. Atherosclerosis, long viewed as a disorder of lipid metabolism, is now understood to be primarily an inflammatory condition, with activated macrophages playing an important role in the formation and eventual rupture of atherosclerotic plaques. Activation of inflammatory signaling pathways has also been shown to play a role in the development of insulin resistance, as well as in the peripheral tissue damage associated with diabetic hyperglycemia. Excessive production of reactive oxygen species and reactive nitrogen species such as superoxide, hydrogen peroxide, nitric oxide, and peroxynitrite is a hallmark of
inflammatory conditions. Evidence of dysregulated peroxynitrite production has been reported in a wide variety of diseases (Szabo et al., 2007; Schulz et al., 2008; Forstermann, 2006; Pall, 2007).

Autoimmune diseases such as rheumatoid arthritis, lupus, psoriasis, and multiple sclerosis involve inappropriate and chronic activation of inflammatory processes in affected tissues, arising from dysfunction of self vs. non-self recognition and response mechanisms in the immune system. In neurodegenerative diseases such as Alzheimer's and Parkinson's diseases, neural damage is correlated with activation of microglia and elevated levels of pro-inflammatory proteins such as inducible nitric oxide synthase (iNOS). Chronic organ failure such as renal failure, heart failure, and chronic obstructive pulmonary disease is closely associated with the presence of chronic oxidative stress and inflammation, leading to the development of fibrosis and eventual loss of organ function.

Many other disorders involve oxidative stress and inflammation in affected tissues, including inflammatory bowel disease; inflammatory skin diseases; mucositis related to radiation therapy and chemotherapy; eye diseases such as uveitis, glaucoma, macular degeneration, and various forms of retinopathy; transplant failure and rejection; ischemia-reperfusion injury; chronic pain; degenerative conditions of the bones and joints including osteoarthritis and osteoporosis; asthma and cystic fibrosis; seizure disorders; and neuropsychiatric conditions including schizophrenia, depression, bipolar disorder, post-traumatic stress disorder, attention deficit disorders, autism-spectrum disorders, and eating disorders such as anorexia nervosa. Dysregulation of inflammatory signaling pathways is believed to be a major factor in the pathology of muscle wasting diseases including muscular dystrophy and various forms of cachexia.

A variety of life-threatening acute disorders also involve dysregulated inflammatory signaling, including acute organ failure involving the pancreas, kidneys, liver, or lungs, myocardial infarction or acute coronary syndrome, stroke, septic shock, trauma, severe burns, and anaphylaxis.

Many complications of infectious diseases also involve dysregulation of inflammatory responses. Although an inflammatory response can kill invading pathogens, an excessive inflammatory response can also be quite destructive and in some cases can be a primary source of damage in infected tissues. Furthermore, an excessive inflammatory response can also lead to systemic complications due to overproduction of inflammatory cytokines such as
TNF-α and IL-1. This is believed to be a factor in mortality arising from severe influenza, severe acute respiratory syndrome, and sepsis.

The aberrant or excessive expression of either iNOS or cyclooxygenase-2 (COX-2) has been implicated in the pathogenesis of many disease processes. For example, it is clear that NO is a potent mutagen (Tamir and Tannebaum, 1996), and that nitric oxide can also activate COX-2 (Salvemini et al., 1994). Furthermore, there is a marked increase in iNOS in rat colon tumors induced by the carcinogen, azoxymethane (Takahashi et al., 1997). A series of synthetic triterpenoid analogs of oleanolic acid have been shown to be powerful inhibitors of cellular inflammatory processes, such as the induction by IFN-γ of inducible nitric oxide synthase (iNOS) and of COX-2 in mouse macrophages. See Honda et al. (2000a); Honda et al. (2000b), and Honda et al. (2002), which are all incorporated herein by reference.

In one aspect, compounds of the invention are characterized by their ability to inhibit the production of nitric oxide in macrophage-derived RAW 264.7 cells induced by exposure to γ-interferon. They are further characterized by their ability to induce the expression of antioxidant proteins such as NQO1 and reduce the expression of pro-inflammatory proteins such as COX-2 and inducible nitric oxide synthase (iNOS). These properties are relevant to the treatment of a wide array of diseases involving oxidative stress and dysregulation of inflammatory processes including cancer, mucositis resulting from radiation therapy or chemotherapy, autoimmune diseases, cardiovascular diseases including atherosclerosis, ischemia-reperfusion injury, acute and chronic organ failure including renal failure and heart failure, respiratory diseases, diabetes and complications of diabetes, severe allergies, transplant rejection, graft-versus-host disease, neurodegenerative diseases, diseases of the eye and retina, acute and chronic pain, degenerative bone diseases including osteoarthritis and osteoporosis, inflammatory bowel diseases, dermatitis and other skin diseases, sepsis, burns, seizure disorders, and neuropsychiatric disorders.

Without being bound by theory, the activation of the antioxidant/anti-inflammatory Keapl/Nrf2/ARE pathway is believed to be implicated in both the anti-inflammatory and anti-carcinogenic properties of the present oleanolic acid derivatives.

In another aspect, compounds of the invention may be used for treating a subject having a condition caused by elevated levels of oxidative stress in one or more tissues. Oxidative stress results from abnormally high or prolonged levels of reactive oxygen species such as superoxide, hydrogen peroxide, nitric oxide, and peroxynitrite (formed by the reaction of nitric oxide and superoxide). The oxidative stress may be accompanied by either acute or
chronic inflammation. The oxidative stress may be caused by mitochondrial dysfunction, by activation of immune cells such as macrophages and neutrophils, by acute exposure to an external agent such as ionizing radiation or a cytotoxic chemotherapy agent (e.g., doxorubicin), by trauma or other acute tissue injury, by ischemia/reperfusion, by poor circulation or anemia, by localized or systemic hypoxia or hyperoxia, by elevated levels of inflammatory cytokines and other inflammation-related proteins, and/or by other abnormal physiological states such as hyperglycemia or hypoglycemia.

In animal models of many such conditions, stimulating expression of inducible heme oxygenase (HO-I), a target gene of the Nrf2 pathway, has been shown to have a significant therapeutic effect including models of myocardial infarction, renal failure, transplant failure and rejection, stroke, cardiovascular disease, and autoimmune disease (e.g., Sacerdoti et al, 2005; Abraham & Kappas, 2005; Bach, 2006; Araujo et al, 2003; Liu et al, 2006; Ishikawa et al, 2001; Kruger et al, 2006; Satoh et al, 2006; Zhou et al, 2005; Morse and Choi, 2005; Morse and Choi, 2002). This enzyme breaks free heme down into iron, carbon monoxide (CO), and biliverdin (which is subsequently converted to the potent antioxidant molecule, bilirubin).

In another aspect, compounds of this invention may be used in preventing or treating tissue damage or organ failure, acute and chronic, resulting from oxidative stress exacerbated by inflammation. Examples of diseases that fall in this category include: heart failure, liver failure, transplant failure and rejection, renal failure, pancreatitis, fibrotic lung diseases (cystic fibrosis and COPD, among others), diabetes (including complications), atherosclerosis, ischemia-reperfusion injury, glaucoma, stroke, autoimmune disease, autism, macular degeneration, and muscular dystrophy. For example, in the case of autism, studies suggest that increased oxidative stress in the central nervous system may contribute to the development of the disease (Chauhan and Chauhan, 2006).

Evidence also links oxidative stress and inflammation to the development and pathology of many other disorders of the central nervous system, including psychiatric disorders such as psychosis, major depression, and bipolar disorder; seizure disorders such as epilepsy; pain and sensory syndromes such as migraine, neuropathic pain or tinnitus; and behavioral syndromes such as the attention deficit disorders. See, e.g., Dickerson et al, 2007; Hanson et al, 2005; Kendall-Tackett, 2007; Lencz et al, 2007; Dudhgaonkar et al, 2006; Lee et al, 2007; Morris et al, 2002; Ruster et al, 2005; Melver et al, 2005; Sarchielli et al, 2006; Kawakami et al, 2006; Ross et al, 2003, which are all incorporated by reference herein. For example, elevated levels of inflammatory cytokines, including TNF, interferon-γ,
and IL-6, are associated with major mental illness (Dickerson et al., 2007). Microglial activation has also been linked to major mental illness. Therefore, downregulating inflammatory cytokines and inhibiting excessive activation of microglia could be beneficial in patients with schizophrenia, major depression, bipolar disorder, autism-spectrum disorders, and other neuropsychiatric disorders.

Accordingly, in pathologies involving oxidative stress alone or oxidative stress exacerbated by inflammation, treatment may comprise administering to a subject a therapeutically effective amount of a compound of this invention, such as those described above or throughout this specification. Treatment may be administered preventively, in advance of a predictable state of oxidative stress (e.g., organ transplantation or the administration of radiation therapy to a cancer patient), or it may be administered therapeutically in settings involving established oxidative stress and inflammation.

The compounds of the invention may be generally applied to the treatment of inflammatory conditions, such as sepsis, dermatitis, autoimmune disease and osteoarthritis. In one aspect, the compounds of this invention may be used to treat inflammatory pain and/or neuropathic pain, for example, by inducing Nrf2 and/or inhibiting NF-κB.

In one aspect, the compounds of the invention may be used to function as antioxidant inflammation modulators (AIMs) having potent anti-inflammatory properties that mimic the biological activity of cyclopentenone prostaglandins (cyPGs). In one embodiment, the compounds of the invention may be used to control the production of pro-inflammatory cytokines by selectively targeting regulatory cysteine residues (RCRs) on proteins that regulate the transcriptional activity of redox-sensitive transcription factors. Activation of RCRs by cyPGs or AIMs has been shown to initiate a pro-resolution program in which the activity of the antioxidant and cytoprotective transcription factor Nrf2 is potently induced, and the activities of the pro-oxidant and pro-inflammatory transcription factors NF-κB and the STATs are suppressed. This increases the production of antioxidant and reductive molecules (e.g., NQO1, HO-1, SOD1, and/or γ-GCS) and/or decreases oxidative stress and the production of pro-oxidant and pro-inflammatory molecules (e.g., iNOS, COX-2, and/or TNF-α).

In some embodiments, the compounds of the invention may be used in the treatment and prevention of diseases such as cancer, inflammation, Alzheimer's disease, Parkinson's disease, multiple sclerosis, autism, amyotrophic lateral sclerosis, autoimmune diseases such as rheumatoid arthritis, lupus, and MS, inflammatory bowel disease, all other diseases whose
pathogenesis is believed to involve excessive production of either nitric oxide or
prostaglandins, and pathologies involving oxidative stress alone or oxidative stress
exacerbated by inflammation.

Another aspect of inflammation is the production of inflammatory prostaglandins such
as prostaglandin E. These molecules promote vasodilation, plasma extravasation, localized
pain, elevated temperature, and other symptoms of inflammation. The inducible form of the
enzyme COX-2 is associated with their production, and high levels of COX-2 are found in
inflamed tissues. Consequently, inhibition of COX-2 may relieve many symptoms of
inflammation and a number of important anti-inflammatory drugs (e.g., ibuprofen and
celecoxib) act by inhibiting COX-2 activity. Recent research, however, has demonstrated that
a class of cyclopentenone prostaglandins (cyPGs) (e.g., 15-deoxy prostaglandin J2, a.k.a.
PGJ2) plays a role in stimulating the orchestrated resolution of inflammation (e.g., Rajakariar
et al., 2007). COX-2 is also associated with the production of cyclopentenone prostaglandins.
Consequently, inhibition of COX-2 may interfere with the full resolution of inflammation,
potentially promoting the persistence of activated immune cells in tissues and leading to
chronic, "smoldering" inflammation. This effect may be responsible for the increased
incidence of cardiovascular disease in patients using selective COX-2 inhibitors for long
periods of time.

In one aspect, the compounds of the invention may be used to control the production
of pro-inflammatory cytokines within the cell by selectively activating regulatory cysteine
residues (RCRs) on proteins that regulate the activity of redox-sensitive transcription factors.
Activation of RCRs by cyPGs has been shown to initiate a pro-resolution program in which the
activity of the antioxidant and cytoprotective transcription factor Nrf2 is potently induced and
the activities of the pro-oxidant and pro-inflammatory transcription factors NF-κB and the
STATs are suppressed. In some embodiments, this increases the production of antioxidant and
reductive molecules (NQO1, HO-1, SODI, γ-GCS) and decreases oxidative stress and the
production of pro-oxidant and pro-inflammatory molecules (iNOS, COX-2, TNF-α). In some
embodiments, the compounds of this invention may cause the cells that host the inflammatory
event to revert to a non-inflammatory state by promoting the resolution of inflammation and
limiting excessive tissue damage to the host.

A. Cancer

Further, the compounds of the present disclosure may be used to induce apoptosis in
tumor cells, to induce cell differentiation, to inhibit cancer cell proliferation, to inhibit an
inflammatory response, and/or to function in a chemopreventative capacity. For example, the invention provides new compounds that have one or more of the following properties: (1) an ability to induce apoptosis and differentiate both malignant and non-malignant cells, (2) an activity at sub-micromolar or nanomolar levels as an inhibitor of proliferation of many malignant or premalignant cells, (3) an ability to suppress the de novo synthesis of the inflammatory enzyme inducible nitric oxide synthase (iNOS), (4) an ability to inhibit NF-κB activation, and (5) an ability to induce the expression of heme oxygenase-1 (HO-I).

The levels of iNOS and COX-2 are elevated in certain cancers and have been implicated in carcinogenesis and COX-2 inhibitors have been shown to reduce the incidence of primary colonic adenomas in humans (Rostom et al., 2007; Brown and DuBois, 2005; Crowel et al., 2003). iNOS is expressed in myeloid-derived suppressor cells (MDSCs) (Angulo et al., 2000) and COX-2 activity in cancer cells has been shown to result in the production of prostaglandin E2 (PGE2), which has been shown to induce the expression of arginase in MDSCs (Sinha et al., 2007). Arginase and iNOS are enzymes that utilize L-arginine as a substrate and produce L-ornithine and urea, and L-citrulline and NO, respectively. The depletion of arginine from the tumor microenvironment by MDSCs, combined with the production of NO and peroxynitrite has been shown to inhibit proliferation and induce apoptosis of T cells (Bronte et al., 2003). Inhibition of COX-2 and iNOS has been shown to reduce the accumulation of MDSCs, restore cytotoxic activity of tumor-associated T cells, and delay tumor growth (Sinha et al., 2007; Mazzoni et al., 2002; Zhou et al., 2007).

Inhibition of the NF-κB and JAK/STAT signaling pathways has been implicated as a strategy to inhibit proliferation of cancer epithelial cells and induce their apoptosis. Activation of STAT3 and NF-κB has been shown to result in suppression of apoptosis in cancer cells, and promotion of proliferation, invasion, and metastasis. Many of the target genes involved in these processes have been shown to be transcriptionally regulated by both NF-κB and STAT3 (Yu et al., 2007).

In addition to their direct roles in cancer epithelial cells, NF-κB and STAT3 also have important roles in other cells found within the tumor microenvironment. Experiments in animal models have demonstrated that NF-κB is required in both cancer cells and hematopoietic cells to propagate the effects of inflammation on cancer initiation and progression (Greten et al., 2004). NF-κB inhibition in cancer and myeloid cells reduces the number and size, respectively, of the resultant tumors. Activation of STAT3 in cancer cells
results in the production of several cytokines (IL-6, IL-10) which suppress the maturation of tumor-associated dendritic cells (DC). Furthermore, STAT3 is activated by these cytokines in the dendritic cells themselves. Inhibition of STAT3 in mouse models of cancer restores DC maturation, promotes antitumor immunity, and inhibits tumor growth (Kortylewski et al., 2005).

B. Treatment of Multiple Sclerosis and Other Neurodegenerative Conditions

The compounds and methods of this invention may be used for treating patients for multiple sclerosis (MS). MS is known to be an inflammatory condition of the central nervous system (Williams et al., 1994; Merrill and Benvenist, 1996; Genain and Nauser, 1997). Based on several investigations, there is evidence suggesting that inflammatory, oxidative, and/or immune mechanisms are involved in the pathogenesis of Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and MS (Bagasra et al., 1995; McGeer and McGeer, 1995; Simonian and Coyle, 1996; Kalschmidt et al., 1997). Both reactive astrocytes and activated microglia have been implicated in causation of neurodegenerative disease (NDD) and neuroinflammatory disease (NID); there has been a particular emphasis on microglia as cells that synthesize both NO and prostaglandins as products of the respective enzymes, iNOS and COX-2. De novo formation of these enzymes may be driven by inflammatory cytokines such as interferon-γ or interleukin-1. In turn, excessive production of NO may lead to inflammatory cascades and/or oxidative damage in cells and tissues of many organs, including neurons and oligodendrocytes of the nervous system, with consequent manifestations in AD and MS, and possible PD and ALS (Coyle and Puttfarcken, 1993; Beal, 1996; Merrill and Benvenist, 1996; Simonian and Coyle, 1996; Vodovoz et al., 1996). Epidemiologic data indicate that chronic use of NSAID’s which block synthesis of prostaglandins from arachidonate, markedly lower the risk for development of AD (McGeer et al., 1996; Stewart et al., 1997). Thus, agents that block formation of NO and prostaglandins, may be used in approaches to prevention and treatment of NDD. Successful therapeutic candidates for treating such a disease typically require an ability to penetrate the blood-brain barrier. See, for example, U.S. Patent Publication 2009/0060873, which is incorporated by reference herein in its entirety.

C. Neuroinflammation

The compounds and methods of this invention may be used for treating patients with neuroinflammation. Neuroinflammation encapsulates the idea that microglial and astrocytic
responses and actions in the central nervous system have a fundamentally inflammation-like character, and that these responses are central to the pathogenesis and progression of a wide variety of neurological disorders. This idea originated in the field of Alzheimer's disease (Griffin et al., 1989; Rogers et al., 1988), where it has revolutionized our understanding of this disease (Akiyama et al., 2000). These ideas have been extended to other neurodegenerative diseases (Eikelenboom et al., 2002; Ishizawa and Dickson, 2001), to ischemic/toxic diseases (Gehrmann et al., 1995; Touzani et al., 1999), to tumor biology (Graeber et al., 2002) and even to normal brain development.

Neuroinflammation incorporates a wide spectrum of complex cellular responses that include activation of microglia and astrocytes and induction of cytokines, chemokines, complement proteins, acute phase proteins, oxidative injury, and related molecular processes. These events may have detrimental effects on neuronal function, leading to neuronal injury, further glial activation, and ultimately neurodegeneration.

D. Treatment of Renal Failure

The compounds and methods of this invention may be used for treating patients with renal failure. See U.S. Patent Application 12/352,473, which is incorporated by reference herein in its entirety. Another aspect of the present disclosure concerns new methods and compounds for the treatment and prevention of renal disease. Renal failure, resulting in inadequate clearance of metabolic waste products from the blood and abnormal concentrations of electrolytes in the blood, is a significant medical problem throughout the world, especially in developed countries. Diabetes and hypertension are among the most important causes of chronic renal failure, also known as chronic kidney disease (CKD), but it is also associated with other conditions such as lupus. Acute renal failure may arise from exposure to certain drugs (e.g., acetaminophen) or toxic chemicals, or from ischemia-reperfusion injury associated with shock or surgical procedures such as transplantation, and may result in chronic renal failure. In many patients, renal failure advances to a stage in which the patient requires regular dialysis or kidney transplantation to continue living. Both of these procedures are highly invasive and associated with significant side effects and quality of life issues. Although there are effective treatments for some complications of renal failure, such as hyperparathyroidism and hyperphosphatemia, no available treatment has been shown to halt or reverse the underlying progression of renal failure. Thus, agents that can improve compromised renal function would represent a significant advance in the treatment of renal failure.
Inflammation contributes significantly to the pathology of CKD. There is also a strong mechanistic link between oxidative stress and renal dysfunction. The NF-κB signaling pathway plays an important role in the progression of CKD as NF-κB regulates the transcription of MCP-I, a chemokine that is responsible for the recruitment of monocytes/macrophages resulting in an inflammatory response that ultimately injures the kidney (Wardle, 2001). The Keapl/Nrf2/ARE pathway controls the transcription of several genes encoding antioxidant enzymes, including heme oxygenase-1 (HO-I). Ablation of the Nrf2 gene in female mice results in the development of lupus-like glomerular nephritis (Yoh et al., 2001). Furthermore, several studies have demonstrated that HO-I expression is induced in response to renal damage and inflammation and that this enzyme and its products - bilirubin and carbon monoxide - play a protective role in the kidney (Nath et al., 2006).

The glomerulus and the surrounding Bowman's capsule constitute the basic functional unit of the kidney. Glomerular filtration rate (GFR) is the standard measure of renal function. Creatinine clearance is commonly used to measure GFR. However, the level of serum creatinine is commonly used as a surrogate measure of creatinine clearance. For instance, excessive levels of serum creatinine are generally accepted to indicate inadequate renal function and reductions in serum creatinine over time are accepted as an indication of improved renal function. Normal levels of creatinine in the blood are approximately 0.6 to 1.2 milligrams (mg) per deciliter (dl) in adult males and 0.5 to 1.1 milligrams per deciliter in adult females.

Acute kidney injury (AKI) can occur following ischemia-reperfusion, treatment with certain pharmacological agents such as cisplatin and rapamycin, and intravenous injection of radiocontrast media used in medical imaging. As in CKD, inflammation and oxidative stress contribute to the pathology of AKI. The molecular mechanisms underlying radiocontrast-induced nephropathy (RCN) are not well understood; however, it is likely that a combination of events including prolonged vasoconstriction, impaired kidney autoregulation, and direct toxicity of the contrast media all contribute to renal failure (Tumlin et al., 2006). Vasoconstriction results in decreased renal blood flow and causes ischemia-reperfusion and the production of reactive oxygen species. HO-I is strongly induced under these conditions and has been demonstrated to prevent ischemia-reperfusion injury in several different organs, including the kidney (Nath et al., 2006). Specifically, induction of HO-I has been shown to be protective in a rat model of RCN (Goodman et al., 2007). Reperfusion also induces an inflammatory response, in part though activation of NF-κB signaling (Nichols, 2004).
Targeting NF-κB has been proposed as a therapeutic strategy to prevent organ damage (Zingarelli et al., 2003).

E. Cardiovascular Disease

The compounds and methods of this invention may be used for treating patients with cardiovascular disease. See U.S. Patent Application 12/352,473, which is incorporated by reference herein in its entirety. Cardiovascular (CV) disease is among the most important causes of mortality worldwide, and is the leading cause of death in many developed nations. The etiology of CV disease is complex, but the majority of causes are related to inadequate or completely disrupted supply of blood to a critical organ or tissue. Frequently such a condition arises from the rupture of one or more atherosclerotic plaques, which leads to the formation of a thrombus that blocks blood flow in a critical vessel. Such thrombosis is the principal cause of heart attacks, in which one or more of the coronary arteries is blocked and blood flow to the heart itself is disrupted. The resulting ischemia is highly damaging to cardiac tissue, both from lack of oxygen during the ischemic event and from excessive formation of free radicals after blood flow is restored (a phenomenon known as ischemia-reperfusion injury). Similar damage occurs in the brain during a thrombotic stroke, when a cerebral artery or other major vessel is blocked by thrombosis. Hemorrhagic strokes, in contrast, involve rupture of a blood vessel and bleeding into the surrounding brain tissue. This creates oxidative stress in the immediate area of the hemorrhage, due to the presence of large amounts of free heme and other reactive species, and ischemia in other parts of the brain due to compromised blood flow. Subarachnoid hemorrhage, which is frequently accompanied by cerebral vasospasm, also causes ischemia/reperfusion injury in the brain.

Alternatively, atherosclerosis may be so extensive in critical blood vessels that stenosis (narrowing of the arteries) develops and blood flow to critical organs (including the heart) is chronically insufficient. Such chronic ischemia can lead to end-organ damage of many kinds, including the cardiac hypertrophy associated with congestive heart failure.

Atherosclerosis, the underlying defect leading to many forms of cardiovascular disease, occurs when a physical defect or injury to the lining (endothelium) of an artery triggers an inflammatory response involving the proliferation of vascular smooth muscle cells and the infiltration of leukocytes into the affected area. Ultimately, a complicated lesion known as an atherosclerotic plaque may form, composed of the above-mentioned cells combined with deposits of cholesterol-bearing lipoproteins and other materials (e.g., Hansson et al., 2006).
Pharmaceutical treatments for cardiovascular disease include preventive treatments, such as the use of drugs intended to lower blood pressure or circulating levels of cholesterol and lipoproteins, as well as treatments designed to reduce the adherent tendencies of platelets and other blood cells (thereby reducing the rate of plaque progression and the risk of thrombus formation). More recently, drugs such as streptokinase and tissue plasminogen activator have been introduced and are used to dissolve the thrombus and restore blood flow. Surgical treatments include coronary artery bypass grafting to create an alternative blood supply, balloon angioplasty to compress plaque tissue and increase the diameter of the arterial lumen, and carotid endarterectomy to remove plaque tissue in the carotid artery. Such treatments, especially balloon angioplasty, may be accompanied by the use of stents, expandable mesh tubes designed to support the artery walls in the affected area and keep the vessel open. Recently, the use of drug-eluting stents has become common in order to prevent post-surgical restenosis (renarrowing of the artery) in the affected area. These devices are wire stents coated with a biocompatible polymer matrix containing a drug that inhibits cell proliferation (e.g., paclitaxel or rapamycin). The polymer allows a slow, localized release of the drug in the affected area with minimal exposure of non-target tissues. Despite the significant benefits offered by such treatments, mortality from cardiovascular disease remains high and significant unmet needs in the treatment of cardiovascular disease remain.

As noted above, induction of HO-I has been shown to be beneficial in a variety of models of cardiovascular disease, and low levels of HO-I expression have been clinically correlated with elevated risk of CV disease. Compounds of the invention, therefore, may be used in treating or preventing a variety of cardiovascular disorders including but not limited to atherosclerosis, hypertension, myocardial infarction, chronic heart failure, stroke, subarachnoid hemorrhage, and restenosis.

**F. Diabetes**

The compounds and methods of this invention may be used for treating patients with diabetes. See U.S. Patent Application 12/352,473, which is incorporated by reference herein in its entirety. Diabetes is a complex disease characterized by the body's failure to regulate circulating levels of glucose. This failure may result from a lack of insulin, a peptide hormone that regulates both the production and absorption of glucose in various tissues. Deficient insulin compromises the ability of muscle, fat, and other tissues to absorb glucose properly, leading to hyperglycemia (abnormally high levels of glucose in the blood). Most commonly, such insulin deficiency results from inadequate production in the islet cells of the
pancreas. In the majority of cases this arises from autoimmune destruction of these cells, a condition known as type 1 or juvenile-onset diabetes, but may also be due to physical trauma or some other cause.

Diabetes may also arise when muscle and fat cells become less responsive to insulin and do not absorb glucose properly, resulting in hyperglycemia. This phenomenon is known as insulin resistance, and the resulting condition is known as Type 2 diabetes. Type 2 diabetes, the most common type, is highly associated with obesity and hypertension. Obesity is associated with an inflammatory state of adipose tissue that is thought to play a major role in the development of insulin resistance (e.g., Hotamisligil, 2006; Guilherme et al., 2008).

Diabetes is associated with damage to many tissues, largely because hyperglycemia (and hypoglycemia, which can result from excessive or poorly timed doses of insulin) is a significant source of oxidative stress. Chronic kidney failure, retinopathy, peripheral neuropathy, peripheral vasculitis, and the development of dermal ulcers that heal slowly or not at all are among the common complications of diabetes. Because of their ability to protect against oxidative stress, particularly by the induction of HO-1 expression, compounds of the invention may be used in treatments for many complications of diabetes. As noted above (Cai et al., 2005), chronic inflammation and oxidative stress in the liver are suspected to be primary contributing factors in the development of Type 2 diabetes. Furthermore, PPARγ agonists such as thiazolidinediones are capable of reducing insulin resistance and are known to be effective treatments for Type 2 diabetes.

The effect of treatment of diabetes may be evaluated as follows. Both the biological efficacy of the treatment modality as well as the clinical efficacy are evaluated, if possible. For example, because the disease manifests itself by increased blood sugar, the biological efficacy of the treatment therefore can be evaluated, for example, by observation of return of the evaluated blood glucose towards normal. Measurement of glycosylated hemoglobin, also called A1c or HbA1c, is another commonly used parameter of blood glucose control. Measuring a clinical endpoint which can give an indication of b-cell regeneration after, for example, a six-month period of time, can give an indication of the clinical efficacy of the treatment regimen.

G. Rheumatoid Arthritis

The compounds and methods of this invention may be used for treating patients with RA. Typically the first signs of rheumatoid arthritis (RA) appear in the synovial lining layer, with proliferation of synovial fibroblasts and their attachment to the articular surface at the
joint margin (Lipsky, 1998). Subsequently, macrophages, T cells and other inflammatory cells are recruited into the joint, where they produce a number of mediators, including the cytokines interleukin-1 (IL-1), which contributes to the chronic sequelae leading to bone and cartilage destruction, and tumour necrosis factor (TNF-α), which plays a role in inflammation (Dinarello, 1998; Arend and Dayer, 1995; van den Berg, 2001). The concentration of IL-1 in plasma is significantly higher in patients with RA than in healthy individuals and, notably, plasma IL-1 levels correlate with RA disease activity (Eastgate et al, 1988). Moreover, synovial fluid levels of IL-1 are correlated with various radiographic and histologic features of RA (Kahle et al, 1992; Rooney et al, 1990).

In normal joints, the effects of these and other proinflammatory cytokines are balanced by a variety of anti-inflammatory cytokines and regulatory factors (Burger and Dayer, 1995). The significance of this cytokine balance is illustrated in juvenile RA patients, who have cyclical increases in fever throughout the day (Prieur et al, 1987). After each peak in fever, a factor that blocks the effects of IL-1 is found in serum and urine. This factor has been isolated, cloned and identified as IL-1 receptor antagonist (IL-1ra), a member of the IL-1 gene family (Hannum et al, 1990). IL-1ra, as its name indicates, is a natural receptor antagonist that competes with IL-1 for binding to type I IL-1 receptors and, as a result, blocks the effects of IL-1 (Arend et al, 1998). A 10- to 100-fold excess of IL-1ra may be needed to block IL-1 effectively; however, synovial cells isolated from patients with RA do not appear to produce enough IL-1ra to counteract the effects of IL-1 (Firestein et al, 1994; Fujikawa et al, 1995).

H. Psoriatic Arthritis

The compounds and methods of this invention may be used for treating patients with psoriatic arthritis. Psoriasis is an inflammatory and proliferative skin disorder with a prevalence of 1.5-3%. Approximately 20% of patients with psoriasis develop a characteristic form of arthritis that has several patterns (Gladman, 1992; Jones et al, 1994; Gladman et al, 1995). Some individuals present with joint symptoms first but in the majority, skin psoriasis presents first. About one-third of patients have simultaneous exacerbations of their skin and joint disease (Gladman et al, 1987) and there is a topographic relationship between nail and distal interphalangeal joint disease (Jones et al, 1994; Wright, 1956). Although the inflammatory processes which link skin, nail and joint disease remain elusive, an immune-mediated pathology is implicated.
Psoriatic arthritis (PsA) is a chronic inflammatory arthropathy characterized by the association of arthritis and psoriasis and was recognized as a clinical entity distinct from rheumatoid arthritis (RA) in 1964 (Blumberg et al., 1964). Subsequent studies have revealed that PsA shares a number of genetic, pathogenic and clinical features with other spondyloarthropathies (SpAs), a group of diseases that comprise ankylosing spondylitis, reactive arthritis and enteropathic arthritis (Wright, 1979). The notion that PsA belongs to the SpA group has recently gained further support from imaging studies demonstrating widespread enthesitis in the, including PsA but not RA (McGonagle et al., 1999; McGonagle et al., 1998). More specifically, enthesitis has been postulated to be one of the earliest events occurring in the SpAs, leading to bone remodeling and ankylosis in the spine, as well as to articular synovitis when the inflamed entheses are close to peripheral joints. However, the link between enthesitis and the clinical manifestations in PsA remains largely unclear, as PsA can present with fairly heterogeneous patterns of joint involvement with variable degrees of severity (Marsal et al., 1999; Salvarani et al., 1998). Thus, other factors must be posited to account for the multifarious features of PsA, only a few of which (such as the expression of the HLA-B27 molecule, which is strongly associated with axial disease) have been identified. As a consequence, it remains difficult to map the disease manifestations to specific pathogenic mechanisms, which means that the treatment of this condition remains largely empirical.

Family studies have suggested a genetic contribution to the development of PsA (Moll and Wright, 1973). Other chronic inflammatory forms of arthritis, such as ankylosing spondylitis and rheumatoid arthritis, are thought to have a complex genetic basis. However, the genetic component of PsA has been difficult to assess for several reasons. There is strong evidence for a genetic predisposition to psoriasis alone that may mask the genetic factors that are important for the development of PsA. Although most would accept PsA as a distinct disease entity, at times there is a phenotypic overlap with rheumatoid arthritis and ankylosing spondylitis. Also, PsA itself is not a homogeneous condition and various subgroups have been proposed.

Increased amounts of TNF-α have been reported in both psoriatic skin (Ettehadi et al., 1994) and synovial fluid (Partsch et al., 1997). Recent trials have shown a positive benefit of anti-TNF treatment in both PsA (Mease et al., 2000) and ankylosing spondylitis (Brandt et al., 2000).
I. Reactive Arthritis

The compounds and methods of this invention may be used for treating patients with reactive arthritis. In reactive arthritis (ReA) the mechanism of joint damage is unclear, but it is likely that cytokines play critical roles. A more prevalent Th1 profile high levels of interferon gamma (IFN-γ) and low levels of interleukin 4 (IL-4) has been reported (Lahesmaa et al., 1992; Schlaak et al., 1992; Simon et al., 1993; Schlaak et al., 1996; Kotake et al., 1999; Ribbens et al., 2000), but several studies have shown relative predominance of IL-4 and IL-10 and relative lack of IFN-γ and tumour necrosis factor alpha (TNF-α) in the synovial membrane (Simon et al., 1994; Yin et al., 1999) and fluid (SF) (Yin et al., 1999; Yin et al., 1997) of reactive arthritis patients compared with rheumatoid arthritis (RA) patients. A lower level of TNF-α secretion in reactive arthritis than in RA patients has also been reported after ex vivo stimulation of peripheral blood mononuclear cells (PBMC) (Braun et al., 1999).

It has been argued that clearance of reactive arthritis-associated bacteria requires the production of appropriate levels of IFN-γ and TNF-α, while IL-10 acts by suppressing these responses (Autenrieth et al., 1994; Sieper and Braun, 1995). IL-10 is a regulatory cytokine that inhibits the synthesis of IL-12 and TNF-γ by activated macrophages (de Waal et al., 1991; Hart et al., 1995; Chomarat et al., 1995) and of IFN-γ by T cells (Macatonia et al., 1993).

J. Enteropathic Arthritis

The compounds and methods of this invention may be used for treating patients with enteropathic arthritis. Typically enteropathic arthritis (EA) occurs in combination with inflammatory bowel diseases (IBD) such as Crohn's disease or ulcerative colitis. It also can affect the spine and sacroiliac joints. Enteropathic arthritis involves the peripheral joints, usually in the lower extremities such as the knees or ankles. It commonly involves only a few or a limited number of joints and may closely follow the bowel condition. This occurs in approximately 11% of patients with ulcerative colitis and 21% of those with Crohn's disease. The synovitis is generally self-limited and non-deforming.

Enteropathic arthropathies comprise a collection of rheumatologic conditions that share a link to GI pathology. These conditions include reactive (i.e., infection-related) arthritis due to bacteria (e.g., Shigella, Salmonella, Campylobacter, Yersinia species, Clostridium difficile), parasites (e.g., Strongyloides stercoralis, Taenia saginata, Giardia lamblia, Ascaris lumbricoides, Cryptosporidium species), and spondyloarthropathies.
associated with inflammatory bowel disease (IBD). Other conditions and disorders include intestinal bypass (jejunoileal), arthritis, celiac disease, Whipple disease, and collagenous colitis.

K. Juvenile Rheumatoid Arthritis

The compounds and methods of this invention may be used for treating patients with JRA. Juvenile rheumatoid arthritis (JRA), a term for the most prevalent form of arthritis in children, is applied to a family of illnesses characterized by chronic inflammation and hypertrophy of the synovial membranes. The term overlaps, but is not completely synonymous, with the family of illnesses referred to as juvenile chronic arthritis and/or juvenile idiopathic arthritis in Europe.

Both innate and adaptive immune systems use multiple cell types, a vast array of cell surface and secreted proteins, and interconnected networks of positive and negative feedback (Lo et al., 1999). Furthermore, while separable in thought, the innate and adaptive wings of the immune system are functionally intersected (Fearon and Locksley, 1996), and pathologic events occurring at these intersecting points are likely to be highly relevant to our understanding of pathogenesis of adult and childhood forms of chronic arthritis (Warrington, et al, 2001).

Polyarticular JRA is a distinct clinical subtype characterized by inflammation and synovial proliferation in multiple joints (four or more), including the small joints of the hands (Jarvis, 2002). This subtype of JRA may be severe, because of both its multiple joint involvement and its capacity to progress rapidly over time. Although clinically distinct, polyarticular JRA is not homogeneous, and patients vary in disease manifestations, age of onset, prognosis, and therapeutic response. These differences very likely reflect a spectrum of variation in the nature of the immune and inflammatory attack that can occur in this disease (Jarvis, 1998).

L. Early Inflammatory Arthritis

The compounds and methods of this invention may be used for treating patients with early inflammatory arthritis. The clinical presentation of different inflammatory arthropathies is similar early in the course of disease. As a result, it is often difficult to distinguish patients who are at risk of developing the severe and persistent synovitis that leads to erosive joint damage from those whose arthritis is more self-limited. Such distinction is critical in order to target therapy appropriately, treating aggressively those with erosive disease and avoiding
unnecessary toxicity in patients with more self-limited disease. Current clinical criteria for
diagnosing erosive arthropathies such as rheumatoid arthritis (RA) are less effective in early
disease and traditional markers of disease activity such as joint counts and acute phase
response do not adequately identify patients likely to have poor outcomes (Harrison et al.,
1998). Parameters reflective of the pathologic events occurring in the synovium are most
likely to be of significant prognostic value.

Recent efforts to identify predictors of poor outcome in early inflammatory arthritis
have identified the presence of RA specific autoantibodies, in particular antibodies towards
citrullinated peptides, to be associated with erosive and persistent disease in early
inflammatory arthritis cohorts. On the basis of this, a cyclical citrullinated peptide (CCP) has
been developed to assist in the identification of anti-CCP antibodies in patient sera. Using
this approach, the presence of anti-CCP antibodies has been shown to be specific and
sensitive for RA, can distinguish RA from other arthropathies, and can potentially predict
persistent, erosive synovitis before these outcomes become clinically manifest. Importantly,
anti-CCP antibodies are often detectable in sera many years prior to clinical symptoms
suggesting that they may be reflective of subclinical immune events (Nielen et al., 2004;
Rantapaa-Dahlqvist et al., 2003).

M. Ankylosing Spondylitis

The compounds and methods of this invention may be used for treating patients with
ankylosing spondylitis. AS is a disease subset within a broader disease classification of
spondyloarthritis. Patients affected with the various subsets of spondyloarthropathy have
disease etiologies that are often very different, ranging from bacterial infections to
inheritance. Yet, in all subgroups, the end result of the disease process is axial arthritis.
Despite the early clinically differences seen in the various patient populations, many of them
end up nearly identical after a disease course of ten-to-twenty years. Recent studies suggest
the mean time to clinical diagnosis of ankylosing spondylitis from disease onset of disease is
7.5 years (Khan, 1998). These same studies suggest that the spondyloarthropathies may have
prevalence close to that of rheumatoid arthritis (Feldtkeller et al., 2003; Doran et al., 2003).

AS is a chronic systemic inflammatory rheumatic disorder of the axial skeleton with
or without extraskeletal manifestations. Sacroiliac joints and the spine are primarily affected,
but hip and shoulder joints, and less commonly peripheral joints or certain extra-articular
structures such as the eye, vasculature, nervous system, and gastrointestinal system may also
be involved. Its etiology is not yet fully understood (Wordsworth, 1995; Calin and Taurog,
It is strongly associated with the major histocompatibility class I (MHC I) HLA-B27 allele (Calin and Taurog, 1998). AS affects individuals in the prime of their life and is feared because of its potential to cause chronic pain and irreversible damage of tendons, ligaments, joints, and bones (Brewerton et al., 1973a; Brewerton et al., 1973b; Schlosstein et al., 1973).

AS may occur alone or in association with another form of spondyloarthropathy such as reactive arthritis, psoriasis, psoriatic arthritis, enthesitis, ulcerative colitis, irritable bowel disease, or Crohn's disease, in which case it is classified as secondary AS.

Typically, the affected sites include the discovertebral, apophyseal, costovertebral, and costotransverse joints of the spine, and the paravertebral ligamentous structures. Inflammation of the entheses, which are sites of musculotendinous and ligamentous attachment to bones, is also prominent in this disease (Calin and Taurog, 1998). The site of enthesitis is known to be infiltrated by plasma cells, lymphocytes, and polymorphonuclear cells. The inflammatory process frequently results in gradual fibrous and bony ankylosis, (Ball, 1971; Khan, 1990).

Delayed diagnosis is common because symptoms are often attributed to more common back problems. A dramatic loss of flexibility in the lumbar spine is an early sign of AS. Other common symptoms include chronic pain and stiffness in the lower back which usually starts where the lower spine is joined to the pelvis, or hip. Although most symptoms begin in the lumbar and sacroiliac areas, they may involve the neck and upper back as well.

Arthritis may also occur in the shoulder, hips and feet. Some patients have eye inflammation, and more severe cases must be observed for heart valve involvement.

The most frequent presentation is back pain, but disease can begin atypically in peripheral joints, especially in children and women, and rarely with acute iritis (anterior uveitis). Additional early symptoms and signs are diminished chest expansion from diffuse costovertebral involvement, low-grade fever, fatigue, anorexia, weight loss, and anemia. Recurrent back pain - often nocturnal and of varying intensity - is an eventual complaint, as is morning stiffness typically relieved by activity. A flexed or bent-over posture eases back pain and paraspinal muscle spasm; thus, some degree of kyphosis is common in untreated patients.

Systemic manifestations occur in 1/3 of patients. Recurrent, usually self-limited, acute iritis (anterior uveitis) rarely is protracted and severe enough to impair vision. Neurologic signs can occasionally result from compression radiculitis or sciatica, vertebral fracture or subluxation, and cauda equina syndrome (which consists of impotence, nocturnal urinary incontinence, diminished bladder and rectal sensation, and absence of ankle jerks). Cardiovascular manifestations can include aortic insufficiency, angina, pericarditis, and ECG
conduction abnormalities. A rare pulmonary finding is upper lobe fibrosis, occasionally with
cavitation that may be mistaken for TB and can be complicated by infection with Aspergillus.

AS is characterized by mild or moderate flares of active spondylitis alternating with
periods of almost or totally inactive inflammation. Proper treatment in most patients results in
minimal or no disability and in full, productive lives despite back stiffness. Occasionally, the
course is severe and progressive, resulting in pronounced incapacitating deformities. The
prognosis is bleak for patients with refractory iritis and for the rare patient with secondary
amyloidosis.

N. Ulcerative Colitis

The compounds and methods of this invention may be used for treating patients with
ulcerative colitis. Ulcerative colitis is a disease that causes inflammation and sores, called
ulcers, in the lining of the large intestine. The inflammation usually occurs in the rectum and
lower part of the colon, but it may affect the entire colon. Ulcerative colitis rarely affects the
small intestine except for the end section, called the terminal ileum. Ulcerative colitis may
also be called colitis or proctitis. The inflammation makes the colon empty frequently,
causing diarrhea. Ulcers form in places where the inflammation has killed the cells lining the
colon; the ulcers bleed and produce pus.

Ulcerative colitis is an inflammatory bowel disease (IBD), the general name for
diseases that cause inflammation in the small intestine and colon. Ulcerative colitis can be
difficult to diagnose because its symptoms are similar to other intestinal disorders and to
another type of IBD, Crohn's disease. Crohn's disease differs from ulcerative colitis because
it causes inflammation deeper within the intestinal wall. Also, Crohn's disease usually occurs
in the small intestine, although it can also occur in the mouth, esophagus, stomach, duodenum, large intestine, appendix, and anus.

Ulcerative colitis may occur in people of any age, but most often it starts between
ages 15 and 30, or less frequently between ages 50 and 70. Children and adolescents
sometimes develop the disease. Ulcerative colitis affects men and women equally and appears
to run in some families. Theories about what causes ulcerative colitis abound, but none have
been proven. The most popular theory is that the body's immune system reacts to a virus or a
bacterium by causing ongoing inflammation in the intestinal wall. People with ulcerative
colitis have abnormalities of the immune system, but doctors do not know whether these
abnormalities are a cause or a result of the disease. Ulcerative colitis is not caused by
emotional distress or sensitivity to certain foods or food products, but these factors may trigger symptoms in some people.

The most common symptoms of ulcerative colitis are abdominal pain and bloody diarrhea. Patients also may experience fatigue, weight loss, loss of appetite, rectal bleeding, and loss of body fluids and nutrients. About half of patients have mild symptoms. Others suffer frequent fever, bloody diarrhea, nausea, and severe abdominal cramps. Ulcerative colitis may also cause problems such as arthritis, inflammation of the eye, liver disease (hepatitis, cirrhosis, and primary sclerosing cholangitis), osteoporosis, skin rashes, and anemia. No one knows for sure why problems occur outside the colon. Scientists think these complications may occur when the immune system triggers inflammation in other parts of the body. Some of these problems go away when the colitis is treated.

A thorough physical exam and a series of tests may be required to diagnose ulcerative colitis. Blood tests may be done to check for anemia, which could indicate bleeding in the colon or rectum. Blood tests may also uncover a high white blood cell count, which is a sign of inflammation somewhere in the body. By testing a stool sample, the doctor can detect bleeding or infection in the colon or rectum. The doctor may do a colonoscopy or sigmoidoscopy. For either test, the doctor inserts an endoscope - a long, flexible, lighted tube connected to a computer and TV monitor - into the anus to see the inside of the colon and rectum. The doctor will be able to see any inflammation, bleeding, or ulcers on the colon wall. During the exam, the doctor may do a biopsy, which involves taking a sample of tissue from the lining of the colon to view with a microscope. A barium enema x ray of the colon may also be required. This procedure involves filling the colon with barium, a chalky white solution. The barium shows up white on x-ray film, allowing the doctor a clear view of the colon, including any ulcers or other abnormalities that might be there.

Treatment for ulcerative colitis depends on the seriousness of the disease. Most people are treated with medication. In severe cases, a patient may need surgery to remove the diseased colon. Surgery is the only cure for ulcerative colitis. Some people whose symptoms are triggered by certain foods are able to control the symptoms by avoiding foods that upset their intestines, like highly seasoned foods, raw fruits and vegetables, or milk sugar (lactose). Each person may experience ulcerative colitis differently, so treatment is adjusted for each individual. Emotional and psychological support is important. Some people have remissions - periods when the symptoms go away - that last for months or even years. However, most patients' symptoms eventually return. This changing pattern of the disease means one cannot
always tell when a treatment has helped. Some people with ulcerative colitis may need medical care for some time, with regular doctor visits to monitor the condition.

**O. Crohn's Disease**

The compounds and methods of this invention may be used for treating patients with Crohn's disease. Another disorder for which immunosuppression has been tried is Crohn's disease. Crohn's disease symptoms include intestinal inflammation and the development of intestinal stenosis and fistulas; neuropathy often accompanies these symptoms. Anti-inflammatory drugs, such as 5-aminosalicylates (e.g., mesalamine) or corticosteroids, are typically prescribed, but are not always effective (reviewed in Botoman et al, 1998).

Immunosuppression with cyclosporine is sometimes beneficial for patients resistant to or intolerant of corticosteroids (Brynskov et al, 1989).

Efforts to develop diagnostic and treatment tools against Crohn's disease have focused on the central role of cytokines (Schreiber, 1998; van Hogezaand and Verspaget, 1998). Cytokines are small secreted proteins or factors (5 to 20 kD) that have specific effects on cell-to-cell interactions, intercellular communication, or the behavior of other cells. Cytokines are produced by lymphocytes, especially T$_H$1 and T$_H$2 lymphocytes, monocytes, intestinal macrophages, granulocytes, epithelial cells, and fibroblasts (reviewed in Rogler and Andus, 1998; Galley and Webster, 1996). Some cytokines are pro-inflammatory (e.g., TNF-α, IL-1(α and β), IL-6, IL-8, IL-12, or leukemia inhibitory factor [LIF]); others are anti-inflammatory (e.g., IL-1 receptor antagonist, IL-4, IL-IO, IL-11, and TGF-β). However, there may be overlap and functional redundancy in their effects under certain inflammatory conditions.

In active cases of Crohn's disease, elevated concentrations of TNF-α and IL-6 are secreted into the blood circulation, and TNF-α, IL-1, IL-6, and IL-8 are produced in excess locally by mucosal cells (id.; Funakoshi et al, 1998). These cytokines can have far-ranging effects on physiological systems including bone development, hematopoiesis, and liver, thyroid, and neuropsychiatric function. Also, an imbalance of the IL-1 β/IL-Ira ratio, in favor of pro-inflammatory IL-1β, has been observed in patients with Crohn's disease (Rogler and Andus, 1998; Saiki et al, 1998; Dionne et al, 1998; but see Kuboyama, 1998). One study suggested that cytokine profiles in stool samples could be a useful diagnostic tool for Crohn's disease (Saiki et al, 1998).

Treatments that have been proposed for Crohn's disease include the use of various cytokine antagonists (e.g., IL-Ira), inhibitors (e.g., of IL-1β converting enzyme and
antioxidants) and anti-cytokine antibodies (Rogler and Andus, 1998; van Hogezaand and Verspaget, 1998; Reimund et al, 1998; Lugering et al, 1998; McAlindon et al, 1998). In particular, monoclonal antibodies against TNF-α have been tried with some success in the treatment of Crohn's disease (Targan et al, 1997; Stack et al, 1997; van Dullemen et al, 1995). These compounds may be used in combination therapy with compounds of the present disclosure.

Another approach to the treatment of Crohn's disease has focused on at least partially eradicating the bacterial community that may be triggering the inflammatory response and replacing it with a non-pathogenic community. For example, U.S. Patent 5,599,795 discloses a method for the prevention and treatment of Crohn's disease in human patients. Their method was directed to sterilizing the intestinal tract with at least one antibiotic and at least one anti-fungal agent to kill off the existing flora and replacing them with different, select, well-characterized bacteria taken from normal humans. Borody taught a method of treating Crohn's disease by at least partial removal of the existing intestinal microflora by lavage and replacement with a new bacterial community introduced by fecal inoculum from a disease-screened human donor or by a composition comprising Bacteroides and Escherichia coli species. (U.S. Patent 5,443,826).

P. Systemic Lupus Erythematosus

The compounds and methods of this invention may be used for treating patients with SLE. There has also been no known cause for autoimmune diseases such as systemic lupus erythematosus. Systemic lupus erythematosus (SLE) is an autoimmune rheumatic disease characterized by deposition in tissues of autoantibodies and immune complexes leading to tissue injury (Kotzin, 1996). In contrast to autoimmune diseases such as MS and type 1 diabetes mellitus, SLE potentially involves multiple organ systems directly, and its clinical manifestations are diverse and variable (reviewed by Kotzin and O'Dell, 1995). For example, some patients may demonstrate primarily skin rash and joint pain, show spontaneous remissions, and require little medication. At the other end of the spectrum are patients who demonstrate severe and progressive kidney involvement that requires therapy with high doses of steroids and cytotoxic drugs such as cyclophosphamide (Kotzin, 1996).

The serological hallmark of SLE, and the primary diagnostic test available, is elevated serum levels of IgG antibodies to constituents of the cell nucleus, such as double-stranded DNA (dsDNA), single-stranded DNA (ss-DNA), and chromatin. Among these autoantibodies, IgG anti-dsDNA antibodies play a major role in the development of lupus
glomerulonephritis (GN) (Hahn and Tsao, 1993; Ohnishi et al., 1994). Glomerulonephritis is
a serious condition in which the capillary walls of the kidney's blood purifying glomeruli
become thickened by accretions on the epithelial side of glomerular basement membranes.
The disease is often chronic and progressive and may lead to eventual renal failure.

5 **Q. Irritable Bowel Syndrome**

The compounds and methods of this invention may be used for treating patients with
Irritable bowel syndrome (IBS). IBS is a functional disorder characterized by abdominal pain
and altered bowel habits. This syndrome may begin in young adulthood and can be
associated with significant disability. This syndrome is not a homogeneous disorder. Rather,
subtypes of IBS have been described on the basis of the predominant symptom—diarrhea,
constipation, or pain. In the absence of "alarm" symptoms, such as fever, weight loss, and
gastrointestinal bleeding, a limited workup is needed. Once a diagnosis of IBS is made, an
integrated treatment approach can effectively reduce the severity of symptoms. IBS is a
common disorder, although its prevalence rates have varied. In general, IBS affects about
15% of US adults and occurs about three times more often in women than in men (Jailwala et
al., 2000).

IBS accounts for between 2.4 million and 3.5 million visits to physicians each year. It
not only is the most common condition seen by gastroenterologists but also is one of the most
common gastrointestinal conditions seen by primary care physicians (Everhart et al., 1991;
Sandler, 1990).

IBS is also a costly disorder. Compared with persons who do not have bowel
symptoms, persons with IBS miss three times as many workdays and are more likely to report
being too sick to work (Drossman et al., 1993; Drossman et al., 1997). Moreover, those with
IBS incur hundreds of dollars more in medical charges than persons without bowel disorders
(talley et al., 1995).

No specific abnormality accounts for the exacerbations and remissions of abdominal
pain and altered bowel habits experienced by patients with IBS. The evolving theory of IBS
suggests dysregulation at multiple levels of the brain-gut axis. Dysmotility, visceral
hypersensitivity, abnormal modulation of the central nervous system (CNS), and infection
have all been implicated. In addition, psychosocial factors play an important modifying role.
Abnormal intestinal motility has long been considered a factor in the pathogenesis of IBS.
Transit time through the small intestine after a meal has been shown to be shorter in patients
with diarrhea-predominant IBS than in patients who have the constipation-predominant or
pain-predominant subtype (Cann et al., 1983).

In studies of the small intestine during fasting, the presence of both discrete, clustered
contractions and prolonged, propagated contractions has been reported in patients with IBS
(Kellow and Phillips, 1987). They also experience pain with irregular contractions more often
than healthy persons (Kellow and Phillips, 1987; Horwitz and Fisher, 2001)

These motility findings do not account for the entire symptom complex in patients
with IBS; in fact, most of these patients do not have demonstrable abnormalities (Rothstein,
2000). Patients with IBS have increased sensitivity to visceral pain. Studies involving
balloon distention of the rectosigmoid colon have shown that patients with IBS experience
pain and bloating at pressures and volumes much lower than control subjects (Whitehead et
al., 1990). These patients maintain normal perception of somatic stimuli.

Multiple theories have been proposed to explain this phenomenon. For example,
receptors in the viscera may have increased sensitivity in response to distention or
intraluminal contents. Neurons in the dorsal horn of the spinal cord may have increased
excitability. In addition, alteration in CNS processing of sensations may be involved
(Drossman et al., 1997). Functional magnetic resonance imaging studies have recently shown
that compared with control subjects, patients with IBS have increased activation of the
anterior cingulate cortex, an important pain center, in response to a painful rectal stimulus
(Mertz et al., 2000).

Increasingly, evidence suggests a relationship between infectious enteritis and
subsequent development of IBS. Inflammatory cytokines may play a role. In a survey of
patients with a history of confirmed bacterial gastroenteritis (Neal et al., 1997), 25% reported
persistent alteration of bowel habits. Persistence of symptoms may be due to psychological
stress at the time of acute infection (Gwee et al., 1999).

Recent data suggest that bacterial overgrowth in the small intestine may have a role in
IBS symptoms. In one study (Pimentel et al., 2000), 157 (78%) of 202 IBS patients referred
for hydrogen breath testing had test findings that were positive for bacterial overgrowth. Of
the 47 subjects who had follow-up testing, 25 (53%) reported improvement in symptoms (i.e.,
abdominal pain and diarrhea) with antibiotic treatment.

IBS may present with a range of symptoms. However, abdominal pain and altered
bowel habits remain the primary features. Abdominal discomfort is often described as crampy
in nature and located in the left lower quadrant, although the severity and location can differ
greatly. Patients may report diarrhea, constipation, or alternating episodes of diarrhea and

63
constipation. Diarrheal symptoms are typically described as small-volume, loose stools, and stool is sometimes accompanied by mucus discharge. Patients also may report bloating, fecal urgency, incomplete evacuation, and abdominal distention. Upper gastrointestinal symptoms, such as gastroesophageal reflux, dyspepsia, or nausea, may also be present (Lynn and Friedman, 1993).

Persistence of symptoms is not an indication for further testing; it is a characteristic of IBS and is itself an expected symptom of the syndrome. More extensive diagnostic evaluation is indicated in patients whose symptoms are worsening or changing. Indications for further testing also include presence of alarm symptoms, onset of symptoms after age 50, and a family history of colon cancer. Tests may include colonoscopy, computed tomography of the abdomen and pelvis, and barium studies of the small or large intestine.

R. Sjogren's Syndrome

The compounds and methods of this invention may be used for treating patients with SS. Primary Sjogren's syndrome (SS) is a chronic, slowly progressive, systemic autoimmune disease, which affects predominantly middle-aged women (female-to-male ratio 9:1), although it can be seen in all ages including childhood (Jonsson et al., 2002). It is characterized by lymphocytic infiltration and destruction of the exocrine glands, which are infiltrated by mononuclear cells including CD4+, CD8+ lymphocytes and B-cells (Jonsson et al., 2002). In addition, extraglandular (systemic) manifestations are seen in one-third of patients (Jonsson et al., 2001).

The glandular lymphocytic infiltration is a progressive feature (Jonsson et al., 1993), which, when extensive, may replace large portions of the organs. Interestingly, the glandular infiltrates in some patients closely resemble ectopic lymphoid microstructures in the salivary glands (denoted as ectopic germinal centers) (Salomonsson et al., 2002; Xanthou et al., 2001). In SS, ectopic GCs are defined as T and B cell aggregates of proliferating cells with a network of follicular dendritic cells and activated endothelial cells. These GC-like structures formed within the target tissue also portray functional properties with production of autoantibodies (anti-Ro/SSA and anti-La/SSB) (Salomonsson and Jonsson, 2003).

In other systemic autoimmune diseases, such as RA, factors critical for ectopic GCs have been identified. Rheumatoid synovial tissues with GCs were shown to produce chemokines CXCL13, CCL21 and lymphotoxin (LT)-β (detected on follicular center and mantle zone B cells). Multivariate regression analysis of these analytes identified CXCL13 and LT-β as the solitary cytokines predicting GCs in rheumatoid synovitis (Weyand and
Goronzy, 2003). Recently CXCL13 and CXCR5 in salivary glands has been shown to play an essential role in the inflammatory process by recruiting B and T cells, therefore contributing to lymphoid neogenesis and ectopic GC formation in SS (Salomonsson et al, 2002).

S. Psoriasis

The compounds and methods of this invention may be used for treating patients with psoriasis. Psoriasis is a chronic skin disease of scaling and inflammation that affects 2 to 2.6 percent of the United States population, or between 5.8 and 7.5 million people. Although the disease occurs in all age groups, it primarily affects adults. It appears about equally in males and females. Psoriasis occurs when skin cells quickly rise from their origin below the surface of the skin and pile up on the surface before they have a chance to mature. Usually this movement (also called turnover) takes about a month, but in psoriasis it may occur in only a few days. In its typical form, psoriasis results in patches of thick, red (inflamed) skin covered with silvery scales. These patches, which are sometimes referred to as plaques, usually itch or feel sore. They most often occur on the elbows, knees, other parts of the legs, scalp, lower back, face, palms, and soles of the feet, but they can occur on skin anywhere on the body. The disease may also affect the fingernails, the toenails, and the soft tissues of the genitals and inside the mouth. While it is not unusual for the skin around affected joints to crack, approximately 1 million people with psoriasis experience joint inflammation that produces symptoms of arthritis. This condition is called psoriatic arthritis.

Psoriasis is a skin disorder driven by the immune system, especially involving a type of white blood cell called a T cell. Normally, T cells help protect the body against infection and disease. In the case of psoriasis, T cells are put into action by mistake and become so active that they trigger other immune responses, which lead to inflammation and to rapid turnover of skin cells. In about one-third of the cases, there is a family history of psoriasis. Researchers have studied a large number of families affected by psoriasis and identified genes linked to the disease. People with psoriasis may notice that there are times when their skin worsens, then improves. Conditions that may cause flareups include infections, stress, and changes in climate that dry the skin. Also, certain medicines, including lithium and beta blockers, which are prescribed for high blood pressure, may trigger an outbreak or worsen the disease.
T. Infectious diseases

Compounds of the present disclosure may be useful in the treatment of infectious diseases, including viral and bacterial infections. As noted above, such infections may be associated with severe localized or systemic inflammatory responses. For example, influenza may cause severe inflammation of the lung and bacterial infection can cause the systemic hyperinflammatory response, including the excessive production of multiple inflammatory cytokines, that is the hallmark of sepsis. In addition, compounds of the invention may be useful in directly inhibiting the replication of viral pathogens. Previous studies have demonstrated that related compounds such as CDDO can inhibit the replication of HIV in macrophages (Vazquez et al., 2005). Other studies have indicated that inhibition of NF-kappa B signaling may inhibit influenza virus replication, and that cyclopentenone prostaglandins may inhibit viral replication (e.g., Mazur et al., 2007; Pica et al., 2000).

IV. Pharmaceutical Formulations and Routes of Administration

The compounds of the present disclosure may be administered by a variety of methods, e.g., orally or by injection (e.g. subcutaneous, intravenous, intraperitoneal, etc.). Depending on the route of administration, the active compounds may be coated in a material to protect the compound from the action of acids and other natural conditions which may inactivate the compound. They may also be administered by continuous perfusion/infusion of a disease or wound site.

To administer the therapeutic compound by other than parenteral administration, it may be necessary to coat the compound with, or co-administer the compound with, a material to prevent its inactivation. For example, the therapeutic compound may be administered to a patient in an appropriate carrier, for example, liposomes, or a diluent. Pharmaceutically acceptable diluents include saline and aqueous buffer solutions. Liposomes include water-in-oil-in-water CGF emulsions as well as conventional liposomes (Strejan et al., 1984).

The therapeutic compound may also be administered parenterally, intraperitoneally, intraspinally, or intracerebrally. Dispersions can be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations may contain a preservative to prevent the growth of microorganisms.

Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. In all cases, the composition must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the
conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (such as, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, sodium chloride, or polyalcohols such as mannitol and sorbitol, in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate or gelatin.

Sterile injectable solutions can be prepared by incorporating the therapeutic compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the therapeutic compound into a sterile carrier which contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying which yields a powder of the active ingredient (i.e., the therapeutic compound) plus any additional desired ingredient from a previously sterile-filtered solution thereof.

The therapeutic compound can be orally administered, for example, with an inert diluent or an assimilable edible carrier. The therapeutic compound and other ingredients may also be enclosed in a hard or soft shell gelatin capsule, compressed into tablets, or incorporated directly into the subject's diet. For oral therapeutic administration, the therapeutic compound may be incorporated with excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. The percentage of the therapeutic compound in the compositions and preparations may, of course, be varied. The amount of the therapeutic compound in such therapeutically useful compositions is such that a suitable dosage will be obtained.

It is especially advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subjects to be treated; each unit
containing a predetermined quantity of therapeutic compound calculated to produce the
desired therapeutic effect in association with the required pharmaceutical carrier. The
specification for the dosage unit forms of the invention are dictated by and directly dependent
on (a) the unique characteristics of the therapeutic compound and the particular therapeutic
effect to be achieved, and (b) the limitations inherent in the art of compounding such a
therapeutic compound for the treatment of a selected condition in a patient.

The therapeutic compound may also be administered topically to the skin, eye, or
mucosa. Alternatively, if local delivery to the lungs is desired the therapeutic compound may
be administered by inhalation in a dry-powder or aerosol formulation.

Active compounds are administered at a therapeutically effective dosage sufficient to
treat a condition associated with a condition in a patient. A "therapeutically effective
amount" preferably reduces the amount of symptoms of the condition in the infected patient
by at least about 20%, more preferably by at least about 40%, even more preferably by at
least about 60%, and still more preferably by at least about 80% relative to untreated subjects.

For example, the efficacy of a compound can be evaluated in an animal model system that
may be predictive of efficacy in treating the disease in humans, such as the model systems
shown in the examples and drawings.

The actual dosage amount of a compound of the present disclosure or composition
comprising a compound of the present disclosure administered to a subject may be
determined by physical and physiological factors such as age, sex, body weight, severity of
condition, the type of disease being treated, previous or concurrent therapeutic interventions,
idiopathy of the subject and on the route of administration. These factors may be determined
by a skilled artisan. The practitioner responsible for administration will typically determine
the concentration of active ingredient(s) in a composition and appropriate dose(s) for the
individual subject. The dosage may be adjusted by the individual physician in the event of
any complication.

An effective amount typically will vary from about 0.001 mg/kg to about 1,000
mg/kg, from about 0.01 mg/kg to about 750 mg/kg, from about 100 mg/kg to about 500
mg/kg, from about 1.0 mg/kg to about 250 mg/kg, from about 10.0 mg/kg to about 150 mg/kg
in one or more dose administrations daily, for one or several days (depending, of course, on
the mode of administration and the factors discussed above). Other suitable dose ranges
include 1 mg to 10,000 mg per day, 100 mg to 10,000 mg per day, 500 mg to 10,000 mg per
day, and 500 mg to 1,000 mg per day. In some particular embodiments, the amount is less
than 10,000 mg per day with a range, for example, of 750 mg to 9,000 mg per day.
The effective amount may be less than 1 mg/kg/day, less than 500 mg/kg/day, less than 250 mg/kg/day, less than 100 mg/kg/day, less than 50 mg/kg/day, less than 25 mg/kg/day or less than 10 mg/kg/day. It may alternatively be in the range of 1 mg/kg/day to 200 mg/kg/day. For example, regarding treatment of diabetic patients, the unit dosage may be an amount that reduces blood glucose by at least 40% as compared to an untreated subject. In another embodiment, the unit dosage is an amount that reduces blood glucose to a level that is ± 10% of the blood glucose level of a non-diabetic subject.

In other non-limiting examples, a dose may also comprise from about 1 microgram/kg/body weight, about 5 microgram/kg/body weight, about 10 microgram/kg/body weight, about 50 microgram/kg/body weight, about 100 microgram/kg/body weight, about 200 microgram/kg/body weight, about 350 microgram/kg/body weight, about 500 microgram/kg/body weight, about 1 milligram/kg/body weight, about 5 milligram/kg/body weight, about 10 milligram/kg/body weight, about 50 milligram/kg/body weight, about 100 milligram/kg/body weight, about 200 milligram/kg/body weight, about 350 milligram/kg/body weight, about 500 milligram/kg/body weight, or about 1,000 mg/kg/body weight or more per administration, and any range derivable therein. In non-limiting examples of a derivable range from the numbers listed herein, a range of about 5 mg/kg/body weight to about 100 mg/kg/body weight, about 5 microgram/kg/body weight to about 500 milligram/kg/body weight, etc., can be administered, based on the numbers described above.

In certain embodiments, a pharmaceutical composition of the present disclosure may comprise, for example, at least about 0.1% of a compound of the present disclosure. In other embodiments, the compound of the present disclosure may comprise between about 2% to about 75% of the weight of the unit, or between about 25% to about 60%, for example, and any range derivable therein.

Single or multiple doses of the agents are contemplated. Desired time intervals for delivery of multiple doses can be determined by one of ordinary skill in the art employing no more than routine experimentation. As an example, subjects may be administered two doses daily at approximately 12 hour intervals. In some embodiments, the agent is administered once a day.

The agent(s) may be administered on a routine schedule. As used herein a routine schedule refers to a predetermined designated period of time. The routine schedule may encompass periods of time which are identical or which differ in length, as long as the schedule is predetermined. For instance, the routine schedule may involve administration
twice a day, every day, every two days, every three days, every four days, every five days, every six days, a weekly basis, a monthly basis or any set number of days or weeks there-between. Alternatively, the predetermined routine schedule may involve administration on a twice daily basis for the first week, followed by a daily basis for several months, etc. In other embodiments, the invention provides that the agent(s) may taken orally and that the timing of which is or is not dependent upon food intake. Thus, for example, the agent can be taken every morning and/or every evening, regardless of when the subject has eaten or will eat.

V. Combination Therapy

In addition to being used as a monotherapy, the compounds of the present disclosure may also find use in combination therapies. Effective combination therapy may be achieved with a single composition or pharmacological formulation that includes both agents, or with two distinct compositions or formulations, at the same time, wherein one composition includes the oleanolic acid derivative according to the methods of this invention, and the other includes the second agent(s). Alternatively, the therapy may precede or follow the other agent treatment by intervals ranging from minutes to months.

Various combinations may be employed, such as when a compound of the present disclosure is "A" and "B" represents a secondary agent, non-limiting examples of which are described below:

A/B/A  B/A/B  B/B/A  A/A/B  A/BBB  B/A/A  A/B/B/B  B/A/B/B  B/B/B/A  B/A/A/B  A/A/A/B  B/A/A/A  A/B/A/A  A/A/B/A

Administration of the compounds of the present disclosure to a patient will follow general protocols for the administration of pharmaceuticals, taking into account the toxicity, if any, of the drug. It is expected that the treatment cycles would be repeated as necessary.

Beta interferons may be suitable secondary agents. These are medications derived from human cytokines which help regulate the immune system. They include interferon β-lb and interferon β-la. Betaseron has been approved by the FDA for relapsing forms of secondary progressive MS. Furthermore, the FDA has approved the use of several β-interferons as treatments for people who have experienced a single attack that suggests multiple sclerosis, and who may be at risk of future attacks and developing definite MS. For
example, risk of MS may be suggested when an MRI scan of the brain shows lesions that predict a high risk of conversion to definite MS.

Glatiramer acetate is a further example of a secondary agent that may be used in a combination treatment. Glatiramer is presently used to treat relapsing remitting MS. It is made of four amino acids that are found in myelin. This drug is reported to stimulate T cells in the body's immune system to change from harmful, pro-inflammatory agents to beneficial, anti-inflammatory agents that work to reduce inflammation at lesion sites.

Another potential secondary agent is mitoxantrone, a chemotherapy drug used for many cancers. This drug is also FDA-approved for treatment of aggressive forms of relapsing remitting MS, as well as certain forms of progressive MS. It is given intravenously, typically every three months. This medication is effective, but is limited by cardiac toxicity. Novantrone has been approved by the FDA for secondary progressive, progressive-relapsing, and worsening relapsing-remitting MS.

Another potential secondary agent is natalizumab. In general, natalizumab works by blocking the attachment of immune cells to brain blood vessels, which is a necessary step for immune cells to cross into the brain, thus reducing the immune cells' inflammatory action on brain neurons. Natalizumab has been shown to significantly reduce the frequency of attacks in people with relapsing MS.

In the case of relapsing remitting MS, patients may be given intravenous corticosteroids, such as methylprednisolone, as a secondary agent, to end the attack sooner and leave fewer lasting deficits.

Other common drugs for MS that may be used in combination with the oleanolic acid derivatives include immunosuppressive drugs such as azathioprine, cladribine and cyclophosphamide.

It is contemplated that other anti-inflammatory agents may be used in conjunction with the treatments of the current invention. Other COX inhibitors may be used, including arylcarboxylic acids (salicylic acid, acetylsalicylic acid, diflunisal, choline magnesium trisalicylate, salicylate, benorylate, flufenamic acid, mefenamic acid, meclofenamic acid and triflumic acid), arylalkanoic acids (diclofenac, fenclofenac, alclofenac, fentiazac, ibuprofen, flurbiprofen, ketoprofen, naproxen, fenoprofen, fenbufen, suprofen, indoprofen, tiaprofenic acid, benoxaprofen, piroprofen, tolmetin, zomepirac, clopinac, indomethacin and sulindac) and enolic acids (phenylbutazone, oxyphenbutazone, azapropazone, feprazone, piroxicam, and isoxicam. See also U.S. Pat. No. 6,025,395, which is incorporated herein by reference.
Histamine H2 receptor blocking agents may also be used in conjunction with the compounds of the current invention, including cimetidine, ranitidine, famotidine and nizatidine.

Treatment with acetylcholinesterase inhibitors such as tacrine, donepezil, metrifonate and rivastigmine for the treatment of Alzheimer's and other disease in conjunction with the compounds of the present disclosure is contemplated. Other acetylcholinesterase inhibitors may be developed which may be used once approved include rivastigmine and metrifonate. Acetylcholinesterase inhibitors increase the amount of neurotransmitter acetylcholine at the nerve terminal by decreasing its breakdown by the enzyme cholinesterase.

MAO-B inhibitors such as selegilene may be used in conjunction with the compounds of the current invention. Selegilene is used for Parkinson's disease and irreversibly inhibits monoamine oxidase type B (MAO-B). Monoamine oxidase is an enzyme that inactivates the monoamine neurotransmitters norepinephrine, serotonin and dopamine.

Dietary and nutritional supplements with reported benefits for treatment or prevention of Parkinson's, Alzheimer's, multiple sclerosis, amyotrophic lateral sclerosis, rheumatoid arthritis, inflammatory bowel disease, and all other diseases whose pathogenesis is believed to involve excessive production of either nitric oxide (NO) or prostaglandins, such as acetyl-L-carnitine, octacosanol, evening primrose oil, vitamin B6, tyrosine, phenylalanine, vitamin C, L-dopa, or a combination of several antioxidants may be used in conjunction with the compounds of the current invention.

For the treatment or prevention of cancer, compounds of the invention may be combined with one or more of the following: radiation, chemotherapy agents (e.g., cytotoxic agents such as anthracyclines, vincristine, vinblastin, microtubule-targeting agents such as paclitaxel and docetaxel, 5-FU and related agents, cisplatin and other platinum-containing compounds, irinotecan and topotecan, gemcitabine, temozolomide, etc.), targeted therapies (e.g., imatinib, bortezomib, bevacizumab, rituximab), or vaccine therapies designed to promote an enhanced immune response targeting cancer cells.

For the treatment or prevention of autoimmune disease, compounds of the invention may be combined with one or more of the following: corticosteroids, methotrexate, anti-TNF antibodies, other TNF-targeting protein therapies, and NSAIDs. For the treatment of prevention of cardiovascular diseases, compounds of the invention may be combined with antithrombotic therapies, anticholesterol therapies such as statins (e.g., atorvastatin), and surgical interventions such as stenting or coronary artery bypass grafting. For the treatment of osteoporosis, compounds of the invention may be combined with antiresorptive agents
such as bisphosphonates or anabolic therapies such as teriparatide or parathyroid hormone. For the treatment of neuropsychiatric conditions, compounds of the invention may be combined with antidepressants (e.g., imipramine or SSRIs such as fluoxetine), antipsychotic agents (e.g., olanzapine, sertindole, risperidone), mood stabilizers (e.g., lithium, valproate semisodium), or other standard agents such as anxiolytic agents. For the treatment of neurological disorders, compounds of the invention may be combined with anticonvulsant agents (e.g., valproate semisodium, gabapentin, phenytoin, carbamazepine, and topiramate), antithrombotic agents (e.g., tissue plasminogen activator), or analgesics (e.g., opioids, sodium channel blockers, and other antinociceptive agents).

For the treatment of disorders involving oxidative stress, compounds of the present disclosure may be combined with tetrahydrobiopterin (BH4) or related compounds. BH4 is a cofactor for constitutive forms of nitric oxide synthase, and may be depleted by reactions with peroxynitrite. Peroxynitrite is formed by the reaction of nitric oxide and superoxide. Thus, under conditions of oxidative stress excessive levels of superoxide can deplete normal, beneficial levels of nitric oxide by converting NO to peroxynitrite. The resulting depletion of BH4 by reaction with peroxynitrite results in the "uncoupling" of nitric oxide synthases so that they form superoxide rather than NO. This adds to the oversupply of superoxide and prolongs the depletion of NO. Addition of exogenous BH4 can reverse this uncoupling phenomenon, restoring the production of NO and reducing the level of oxidative stress in tissues. This mechanism is expected to complement the actions of compounds of the invention, which reduce oxidative stress by other means, as discussed above and throughout this invention.

VI. Examples

The following examples are included to demonstrate preferred embodiments of the invention. It should be appreciated by those of skill in the art that the techniques disclosed in the examples which follow represent techniques discovered by the inventor to function well in the practice of the invention, and thus can be considered to constitute preferred modes for its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention.
Example 1 - Methods and Materials

Nitric Oxide production and cell viability. RAW264.7 macrophages were pretreated with DMSO or drugs for 2 hours, then treated with recombinant mouse IFNγ (Sigma) for 24 hours. NO concentration in media was determined using the Griess reagent system (Promega). Cell viability was determined using WST-I reagent (Roche).

Nrf2 target gene induction. MDA-MB-435 human melanoma cells were treated with vehicle (DMSO) or the indicated compounds and concentrations for 16 hours. HO-I, thioredoxin reductase-1 (TrxR1), γ-glutamylcysteine synthetase (γ-GCS), and ferritin heavy chain mRNA levels were quantified using qPCR and were normalized relative to a DMSO-treated sample run in parallel. Values are averages of duplicate wells. Primer sequences are as follows.

HO-I FW: TCCGATGGGTCTTACACTC (SEQ ID NO:1),
HO-I REV: TAGGCTCCTCCTCCTTTCC (SEQ ID NO:2),
TrxR1 FW: GCAGCACTGAGTGTCAAAA (SEQ ID NO:3),
TrxR1 REV: GGTCACCTGCTCAATTGCT (SEQ ID NO:4),
γ-GCS FW: GCTGTGGCTACTGGATT (SEQ ID NO:5),
γ-GCS REV ATCTGCCTCAATGACACCATT (SEQ ID NO:6),
Ferritin HC FW: ATGAGCAGGTGAAGCCATC (SEQ ID NO:7),
Ferritin HC REV: TAAAGGAAACCCCAACATGC (SEQ ID NO:8),
S9 FW: GATTACATCCTGGCCTGAA (SEQ ID NO:9),
S9 REV: GAGCGCAGAGAGAAGTCGAT (SEQ ID NO:10).

Comparison Compounds. In some of the experiments (e.g., FIGS. 13 - 21), certain compounds of this invention were compared with other compounds, such as those shown here:

**Aqueous Solubility Determination.** The following procedure was used to obtain the aqueous solubility results summarized in Example 4. Step 1. Determination of optimal UV/vis wavelengths and generation of standard curves for a compound of interest:

1. For eight standard calibration curves (one plate), prepare 34 mL of 50:50 (v:v) universal buffer:acetonitrile in a 50 mL tube.
(2) Using a multichannel pipet, dispense (in µL) the buffer: acetonitrile in a deep well plate as follows:

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(3) Using a multichannel pipet, dispense DMSO into the same plate as follows:

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td></td>
<td></td>
<td></td>
<td>12</td>
<td>12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td></td>
<td></td>
<td></td>
<td>12</td>
<td>12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td></td>
<td></td>
<td></td>
<td>15</td>
<td>15</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D</td>
<td></td>
<td></td>
<td></td>
<td>15</td>
<td>15</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E</td>
<td></td>
<td></td>
<td></td>
<td>15</td>
<td>15</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td></td>
<td></td>
<td></td>
<td>15</td>
<td>15</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G</td>
<td></td>
<td></td>
<td></td>
<td>15</td>
<td>15</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H</td>
<td></td>
<td></td>
<td></td>
<td>15</td>
<td>15</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(4) Add 10 mM compound in DMSO into the plates as follows:

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>15 µL cmpd1</td>
<td>15 µL cmpd1</td>
<td>8 µL cmpd1</td>
<td>8 µL cmpd1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>15 µL cmpd2</td>
<td>15 µL cmpd2</td>
<td>8 µL cmpd2</td>
<td>8 µL cmpd2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>15 µL cmpd3</td>
<td>15 µL cmpd3</td>
<td>8 µL cmpd3</td>
<td>8 µL cmpd3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>15 µL cmpd4</td>
<td>15 µL cmpd4</td>
<td>8 µL cmpd4</td>
<td>8 µL cmpd4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>15 µL cmpd5</td>
<td>15 µL cmpd5</td>
<td>8 µL cmpd5</td>
<td>8 µL cmpd5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>15 µL cmpd6</td>
<td>15 µL cmpd6</td>
<td>8 µL cmpd6</td>
<td>8 µL cmpd6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G</td>
<td>15 µL cmpd7</td>
<td>15 µL cmpd7</td>
<td>8 µL cmpd7</td>
<td>8 µL cmpd7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>15 µL cmpd8</td>
<td>15 µL cmpd8</td>
<td>8 µL cmpd8</td>
<td>8 µL cmpd8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
(5) Mix columns 1 and 2 by pipetting each up and down 10 times. Mix columns 3 and 4 by pipetting up and down 10 times. Serially dilute as follows (pipet up and down 10 times after each transfer):

<p>| | | | | | | | | | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>B</td>
<td>C</td>
<td>D</td>
<td>E</td>
<td>F</td>
<td>G</td>
<td>H</td>
<td>A</td>
<td>B</td>
<td>C</td>
<td>D</td>
<td>E</td>
<td>F</td>
</tr>
</tbody>
</table>

100 µL → 100 µL → 100 µL

Note columns 11 and 12 contain DMSO only and so compound should not be transferred to these wells.

(6) Cover plate with lid and shake (200-300 rpm) at room temperature for 20 minutes.

(V) Mix all wells by pipetting up and down 10 times.

(8) Transfer 120 µL from each well to a UV transparent plate. Cover and shake for 3-5 minutes. Remove any bubbles in the wells using a pipet.

(9) Read from 220 nm to 500 nm at 10 nm increments on a spectrophotometer (e.g., SpectraMax®).


**Consumables:** Millipore™ Multiscreen® Solubility Filter Plate #MSSLBPC10

Greiner® 96 well disposable UV-Star analysis plate, VWR#655801

Greiner® 96 well polypropylene V-bottom collection plate, VWR#651201

**Universal Aqueous Buffer:**

(a) To prepare 500 mL of universal buffer, add the following: 250 mL Nanopure water; 1.36 mL (45 mM) ethanolamine; 3.08 g (45 mM) potassium dihydrogen phosphate; 2.21 g (45 mM) potassium acetate; thoroughly mix.
(b) Adjust pH to 7.4 with HCl and q.s. to 500 µL with 0.15 M KCl.

(c) Filter to remove particulates and reduce bacterial growth.

(d) Store at 4°C in the dark.

Solubility Protocol:

(a) Add 285 µL of Universal Aqueous Buffer to desired wells of the Millipore™ Multiscreen® Solubility filter plate.

(b) Add 15 µL of 10 mM compound in DMSO to the appropriate wells. Add 15 µL of 100% DMSO only to 6 wells of the filter plate for blanks.

(c) Using a multichannel pipet, mix wells by pipetting up and down 10 times. Be careful not to touch the filters in the plate with the tips.

(d) Cover and gently shake (200-300 rpm) filter plate for 90 minutes at room temperature.

(e) Vacuum filter the aqueous solution from the Multiscreen® solubility filter plate into a polypropylene V-bottom plate.

(f) Transfer 60 µL of filtrate to a UV transparent plate (Greiner® UV-Star Analysis Plate).

(g) Add 60 µL of acetonitrile to each well and mix by pipetting up and down 10 times.

(h) Cover and gently shake for 3-5 minutes. Remove any bubbles with a pipet.

(i) Measure the absorbance of each well in the plate on the spectrophotometer (UV/vis) at the desired wavelength. For compounds in a plate with different absorbance peaks, set the spectrophotometer to read a spectrum (e.g., from 220 nm to 460 nm).

(j) Identify concentration using measured absorbance for each compound and the predetermined standard curve (see Step 1).
Example 2 - Synthesis of Oleanolic Acid Derivatives

Scheme 1:

Reagents and conditions for Scheme 1: (a) 30% H₂O₂, 10% NaOH, rt, 85%; (b) KHF₂, 140 °C, 18 h, 51%.

Compound 402-05 was synthesized from compound 1 (Honda et al., 2000b) in two steps (Scheme 1). Compound 1 was treated with hydrogen peroxide under basic conditions to give epoxide 2 in 85% yield. Using the methodology developed by Sakagami et al. 2007, compound 2 was reacted with KHF₂ at 140 °C to give the vinyl fluoride 402-05 in 51% yield.
Scheme 2:

\[ \text{402-04} \xrightarrow{a} \text{3} \xrightarrow{b} \text{402-06} \]
Reagents and conditions for Scheme 2: (a) NH₄Cl, NaN₃, 150 °C, 2 h, 24%; (b) DDQ, 80 °C, 20 min, 44%.

The synthesis of compound 402-06 started from compound 402-04 (Honda et al., 2000b) (Scheme 2). 402-04 was reacted with excess NaN₃ in the presence of NH₄Cl, under the Buchanan reaction conditions (Buchanan et al., 1992) to give the corresponding tetrazole derivative 3 in 24% yield. Compound 3 was then oxidized with DDQ to give compound 402-06 in 44% yield.
Reagents and conditions for Scheme 3: (a) oxalyl chloride, DMF, 0 °C to rt, 2 h; (b) NH₂OH-HCl, Et₃N, rt, 2 h, 44%.

Acid 4 (Honda et ah, 2000b) was transformed to the corresponding acid chloride 5, which was then reacted with NH₂OH to give hydroxamic acid 402-07 in 44% yield (Scheme 3).

Scheme 4:

Reagents and conditions for Scheme 4: (a) MeSO₂NH₂, NaH, 0 °C to rt, 20 h, 24%.

The acid chloride 5 reacted with the sodium salt of methyl sulfonamide to give compound 402-08 in 24% yield (Scheme 4).

Scheme 5:

Reagents and conditions for Scheme 5: (a) (i) oxalyl chloride, DMF, 0 °C to rt, 2 h; (ii) NH₂OH-HCl, Et₃N, rt, 2 h, 68% (for 402-09); NH₂OMe-HCl, Et₃N, rt, 2 h, 64% (for 402-10).

Acid 6 (Honda et ah, 2000b) was transformed to the corresponding acid chloride, which was then reacted with NH₂OH to give hydroxyamide 402-09 in 68% yield (Scheme 5). By using NH₂OMe, compound 402-10 (64%) was obtained from compound 6 using the same method (Scheme 5).
Scheme 6:

Reagents and conditions for Scheme 6: (a) DPPA, Et$_3$N, 0 °C to rt, 6 h, 90%.

Acid 6 (Honda et al., 2000b) was treated with DPPA and Et$_3$N to give the corresponding azide 402-11 in 90% yield (Scheme 6).

Scheme 7:

Reagents and conditions for Scheme 7: (a) CuI, MeLi, 0 °C to rt, 2 h, 63%; (b) (i) LDA, -78 °C, 45 min; (ii) TsCN, 30 min, 67%; (c) (i) PhSeCl, pyridine, 0 °C to rt, 2 h; (ii) 30% H$_2$O$_2$, 0 °C, 40 min, 49%.

Compound 402-22 was synthesized from compound 1 (Honda et al., 2000b) in 3 steps (Scheme 7). Compound 1 was treated with Me$_2$CuLi to give the Michael addition product 7 in 63% yield. Compound 7 was then reacted with LDA and TsCN to introduce the 2-cyano group and give compound 8 (67% yield). Oxidation to the enone was attempted using DDQ (Honda et al., 2000b) or 1,3-dibromo-5,5-dimethylhydantoin and pyridine, but no desired
product was obtained. Under the Sharpless reaction conditions (Sharpless et al., 1973), compound 8 was reacted with PhSeCl, followed by H₂O₂ oxidation, to give compound 402-22 in 49% yield.

Scheme 8:

Reagents and conditions for Scheme 8: (a) Ac₂O, pyridine, DMAP, rt, 10 min, 81%.

402-04 (Honda et al., 2000b) (exists as a mixture of enol and ketone forms) was treated with Ac₂O/pyridine to give acetate 402-47 in 81% yield.

Scheme 9:

Reagents and conditions for Scheme 9: (a) (i) (COCl)₂, CH₂Cl₂, rt, 16h (ii) 9-BBN, rt, 4h (iii) MeOH (iv) 2-ethanolamine, 38%.

Compound 402-40 was synthesized from acid 6. Compound 6 was first converted to the acid chloride. Reduction of the acid chloride by 9-BBN was attempted, followed by sequential quench of the reaction by methanol and then 2-ethanolamine. No reduction of the acid chloride occurred, but the unreacted acid chloride did react with the 2-ethanolamine quench to give amide 402-40 in 38% yield.
Scheme 10:

Reagents and conditions for Scheme 10: (a) DAST, CH₂Cl₂, rt, 7 h, 94%. Treatment of acid 6 with DAST gave acyl fluoride 402-55 in 94% yield.
Reagents and conditions for Scheme 11: (a) (i) Na$_2$PdCl$_4$, NaOAc, AcOH, rt, 72 h; (ii) Ac$_2$O, Et$_3$N, DMAP, CH$_2$Cl$_2$, rt, 1 h; (iii) Pb(OAc)$_4$, pyridine, AcOH, THF, -78 °C to rt, 18 h; (iv) Na$_2$CO$_3$, MeOH, rt, 22 h, 4.7% (for 10a from 9), 57% (for 10b from 9). The synthesis of compound 9 is reported in Honda et al. (2004).
Scheme 12:
Reagents and conditions for Scheme 12: (a) NH$_4$OAc, TiCl$_3$, THF, rt, 2 h, 76%; (b) MOMCl, /-Pr$_2$NEt, CH$_2$Cl$_2$, rt, 14 h, 77%; (c) (i) HCO$_2$Me, NaOMe, O °C, 1 h; (ii) NH$_2$OH·HCl, EtOH, H$_2$O, 55 °C, 20 h, 68%; (d) NaOMe, MeOH, 55 °C, 2 h, 100%; (e) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, O°C, 1 h; (ii) pyridine, 55 °C, 4 h, 76%; (f) 4 N HCl(aq), THF, rt, 72 h, 85%.
Scheme 13a:
Reagents and conditions for Schemes 13a & 13b: (a) TMSCHN₂, MeOH, toluene, 0 °C, 15 min, 85%; (b) Ac₂O, BF₃·Et₂O, CH₂Cl₂, rt, 1 h, 72%; (c) 30% H₂O₂, HCO₂H, THF, rt, 40 h, 65%; (d) 48% HBr(aq), Br₂, CH₃CN, 35 °C, 19 h, 82%; (e) (i) 10% NaOH(aq), THF, EtOH, 0 °C, 2.5 h; (ii) TPAP, NMO, 4A MS, CH₂Cl₂, rt, 30 min, 90%; (f) 20% NaOH(aq), EtOH, 80 °C, 15 min, 88%; (g) (i) HCO₂Me, NaOMe, rt, 1.5 h; (ii) NH₂OH·HCl, EtOH, H₂O, 55 °C, 14 h, 87%; (h) NaOMe, MeOH, 55 °C, 1.5 h, 93%; (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, 0 °C, 1 h; (ii) pyridine, 55 °C, 4.5 h, 73%; (j) Dess-Martin periodinane, NaHCO₃, CH₂Cl₂, 0 °C, 2 h, 89%.

Scheme 14:

Reagents and conditions for Scheme 14: (a) RuCl₃·xHCl, NaIO₄, 0 °C, 5 min, 71%.
Reagents and conditions to Scheme 15: (a) I₂, pyridine, 65 °C, 20 h, 77%; (b) FSO₂CF₂CO₂Me, CuI, HMPA, 70 °C, 6 h, 83%. The synthesis of compound 1 is reported in Honda et al (2000b), which is incorporated herein by reference.

**Example 3 - Characterization of Oleanolic Acid Derivatives**

**Compound 2**: 30% H₂O₂ (aq) (200 μL, 2.0 mmol) and 10% NaOH (aq) solution were added successively to a solution of compound 1 (Honda et al, 2000b) (200 mg, 0.42 mmol) in MeOH (5 mL). The mixture was stirred at room temperature until compound 1 was completely consumed by TLC analysis. EtOAc was added, and the mixture was washed with water, 5% Na₂S₂O₃ (aq) solution, and dried with MgSO₄. After concentration, the residue obtained was purified by column chromatography (silica gel, 5% EtOAc in CH₂Cl₂) to give product 2 (175 mg, 85%) as a white solid: ¹H NMR (400 MHz, CDCl₃) δ 6.12 (s, 1H), 3.92 (d, 1H, J = 4.4 Hz), 3.70 (s, 3H), 3.44 (d, 1H, J = 4.4 Hz), 3.05 (m, 1H), 2.93 (d, 1H, J = 4.4 Hz), 2.09 (m, 1H), 1.81-1.96 (m, 2H), 1.44-1.74 (m, 8H), 1.22-1.37 (m, 4H), 1.26 (s, 3H), 1.20 (s, 3H), 1.14 (s, 3H), 1.10 (s, 3H), 1.05 (s, 3H), 1.01 (s, 3H), 0.90 (s, 3H).

**Compound 402-05**: A mixture of epoxide 2 (75 mg, 0.15 mmol), KH₂F₂ (240 mg, 3.08 mmol), and ethylene glycol (2.0 mL) was heated at 140 °C for 18 h, and then cooled to room temperature. Water was added, and the mixture was extracted with CH₂Cl₂. The combined extracts were washed with water and dried with MgSO₄. After concentration, the residue obtained was purified by column chromatography (silica gel, 3% EtOAc in CH₂Cl₂) to give product 402-05 (38 mg, 51%) as a white solid: ¹H NMR (400 MHz, CDCl₃) δ 6.91 (d, 1H, J = 15.6 Hz), 5.89 (s, 1H), 3.69 (s, 3H), 3.02 (m, 1H), 2.90 (d, 1H, J = 4.4 Hz), 1.64-1.94 (m, 8H), 1.50-1.59 (m, 3H), 1.49 (d, 3H, J = 0.8 Hz), 1.30 (s, 3H), 1.25 (s, 3H), 1.15-1.36 (m, 4H), 1.14 (s, 3H), 1.00 (s, 3H), 0.99 (s, 3H), 0.89 (s, 3H); m/z 499.3 (M+).

**Compound 3**: A mixture of compound 402-04 (Honda et al, 2000b) (50 mg, 0.099 mmol), NH₄Cl (8.0 mg, 0.15 mmol), and NaN₃ (33 mg, 0.50 mmol) in DMF (0.5 mL) was heated at 150 °C for 2 h. After cooling to room temperature, EtOAc and 1 N HCl (aq) solution were added successively. The organic phase was separated and washed with water, then dried with MgSO₄ and concentrated. The residue obtained was purified by column chromatography (silica gel, 5% to 7% acetone in CH₂Cl₂) to give product 3 (13 mg, 24%): ¹H NMR (400 MHz, CDCl₃) δ 10.97 (bs, 1H), 6.33 (s, 1H), 3.78 (s, 3H), 3.70 (m, 1H), 2.94-3.05 (m, 4H), 2.57 (d, 1H, J = 16.0 Hz), 1.36 (s, 3H), 1.35 (s, 3H), 1.27 (s, 6H), 0.98 (s, 3H), 0.76 (s, 3H), 0.70-1.85 (m, 14H), 0.33 (s, 3H). Compound 3 was contaminated with some unknown impurities and was used in the next step without further purification.
**Compound 402-06:** DDQ (5.5 mg, 0.024 mmol) was added to a solution of compound 3 (13 mg, 0.024 mmol) in benzene (1 mL). After refluxing for 20 min, the reaction mixture was cooled to room temperature and purified by column chromatography (silica gel, 10% to 20% acetone in CH₂Cl₂) to give product **402-06** (5.7 mg, 44%): ¹H NMR (400 MHz, CDCl₃) δ 8.85 (s, 1H), 6.24 (s, 1H), 3.71 (s, 3H), 3.06 (m, 1H), 2.94 (d, 1H, J = 4.4 Hz), 1.47-1.96 (m, 12H), 1.36 (s, 3H), 1.31 (s, 3H), 1.26 (s, 6H), 1.18-1.40 (m, 3H), 1.02 (s, 3H), 1.01 (s, 3H), 0.90 (s, 3H); m/z 549.3 (M+).

**Compound 402-07:** Oxalyl chloride (48 µL, 0.57 mmol) and DMF (2 µL, catalytic) were added successively to a solution of compound 4 (100 mg, 0.19 mmol) in CH₂Cl₂ (2 mL) at 0 °C. After stirring at room temperature for 2 h, the solvent was removed by nitrogen purge to give acid chloride 5 as a light yellow foam solid. Compound 5 was dissolved in THF (2 mL) and then added to a solution of NH₂OH-Cl (40 mg, 0.57 mmol), Et₃N (106 µL, 0.76 mmol), and water (0.4 mL) in THF (2 mL) at room temperature. After stirring for 2 h, EtOAc was added, and the mixture was washed with water, dried with MgSO₄, and concentrated. The residue obtained was purified by column chromatography (silica gel, 33% EtOAc and 1% AcOH in hexanes) to give product **402-07** (45 mg, 44%): ¹H NMR (400 MHz, CDCl₃) δ 10.96 (bs, 1H), 8.59 (s, 1H), 6.21 (s, 1H), 3.70 (s, 3H), 3.05 (m, 1H), 2.92 (d, 1H, J = 4.8 Hz), 1.48-1.96 (m, 12H), 1.43 (s, 3H), 1.32 (s, 3H), 1.21 (s, 3H), 1.18 (s, 3H), 1.16-1.37 (m, 3H), 1.01 (s, 6H), 0.90 (s, 3H); m/z 540.3 (M+).

**Compound 402-08:** MeSO₂NH₂ (40 mg, 0.42 mmol) in THF (1.5 mL) was added to a suspension of NaH (60% in mineral oil, 33 mg, 0.83 mmol) in THF (0.5 mL) at 0 °C. After stirring for 30 min at room temperature, the mixture was cooled to 0 °C, and a solution of compound 5 (115 mg, 0.21 mmol) in THF (2 mL) was added. After stirring at ambient temperature for 20 h, NH₄Cl (aq) solution was added. The mixture was extracted with CH₂Cl₂. The combined extracts were washed with 1 N HCl (aq) and water, then dried with MgSO₄ and concentrated. The residue obtained was purified by column chromatography (silica gel, 33% to 40% EtOAc in hexanes) to give product **402-08** (30 mg, 24%): ¹H NMR (400 MHz, CDCl₃) δ 11.19 (bs, 1H), 8.73 (s, 1H), 6.16 (s, 1H), 3.70 (s, 3H), 3.35 (s, 3H), 3.05 (m, 1H), 2.93 (d, 1H, J = 4.4 Hz), 1.64-1.94 (m, 8H), 1.48-1.60 (m, 3H), 1.45 (s, 3H), 1.33 (s, 3H), 1.24 (s, 3H), 1.20 (s, 3H), 1.17-1.36 (m, 4H), 1.01 (s, 3H), 1.00 (s, 3H), 0.90 (s, 3H); m/z 602.3 (M+).

**Compound 402-09:** Using the procedure described for the synthesis of compound **402-07** from compound 4, compound **402-09** (70 mg, 68%) was produced from compound 6.
(Honda et al., 2000b) (100 mg, 0.20 mmol) and NH₂OH-HCl (40 mg, 0.58 mmol). ¹H NMR (400 MHz, CDCl₃) δ 8.91 (bs, 1H), 8.04 (s, 1H), 7.43 (bs, 1H), 6.02 (s, 1H), 3.02 (m, 1H), 2.89 (d, 1H, J = 4.8 Hz), 2.02 (m, 1H), 1.48-1.90 (m, HH), 1.46 (s, 3H), 1.32 (s, 3H), 1.24 (s, 3H), 1.18-1.38 (m, 3H), 1.16 (s, 3H), 1.01 (s, 3H), 0.99 (s, 3H), 0.91 (s, 3H); m/z 507.3.

Compound 402-10: Using the procedure described for the synthesis of compound 402-07 from compound 4, compound 402-10 (68 mg, 64%) was produced from compound 6 (Honda et al., 2000b) (100 mg, 0.20 mmol) and NH₂OMe-HCl (50 mg, 0.60 mmol). ¹H NMR (400 MHz, CDCl₃) δ 8.53 (s, 1H), 8.04 (s, 1H), 5.99 (s, 1H), 3.77 (s, 3H), 3.09 (d, 1H, J = 4.8 Hz), 2.84 (m, 1H), 1.99 (m, 1H), 1.50-1.90 (m, 9H), 1.49 (s, 3H), 1.37 (s, 3H), 1.26 (s, 3H), 1.18-1.38 (m, 5H), 1.17 (s, 3H), 1.02 (s, 3H), 1.00 (s, 3H), 0.91 (s, 3H); m/z 521.3.

Compound 402-11: Et₃N (8.44 mL, 60.7 mmol) and DPPA (2.50 g, 9.08 mmol) were added successively to a solution of compound 6 (1.49 g, 3.03 mmol) in toluene (30 mL) at 0 °C. After stirring at room temperature for 6 h, the solvent was removed by evaporation to give an oil, which was purified by column chromatography (silica gel, 0 to 10% EtOAc in CH₂Cl₂) to give azide 402-11 (1.41 g, 90%) as a white foam solid: ¹H NMR (400 MHz, CDCl₃) δ 8.03 (s, 1H), 5.98 (s, 1H), 2.98 (m, 1H), 2.93 (d, 1H, J = 4.8 Hz), 1.66-1.96 (m, 8H), 1.49 (s, 3H), 1.46-1.62 (m, 3H), 1.36 (s, 3H), 1.26 (s, 3H), 1.18-1.34 (m, 4H), 1.18 (s, 3H), 1.01 (s, 3H), 1.00 (s, 3H), 0.91 (s, 3H); m/z 517.3 (M+I), 489.3 (M-N₃+I).

Compound 7: A suspension of CuI (165 mg, 0.86 mmol) in THF (3 mL) was treated with MeLi (1.6 M in Et₂O, 1.08 mL, 1.73 mmol) at 0 °C. After 1 h, a solution of compound 1 (200 mg, 0.42 mmol) in THF (1 mL) was added. After stirring at room temperature for 2 h, the reaction was quenched with NH₄Cl (aq) solution. The reaction mixture was extracted with EtOAc, and the combined extracts were washed with water, dried with MgSO₄, and concentrated. The residue obtained was purified by column chromatography (silica gel, 0% to 50% EtOAc in hexanes) to give product 7 (130 mg, 63%): ¹H NMR (400 MHz, CDCl₃) δ 5.88 (s, 1H), 3.70 (s, 3H), 3.07 (m, 1H), 3.01 (dd, 1H, J = 5.6, 16.4 Hz), 2.48 (m, 1H), 2.22 (dd, 1H, J = 2.4, 16.4 Hz), 1.44 (s, 3H), 1.41-1.96 (m, 12H), 1.32 (s, 3H), 1.13 (s, 3H), 1.12-1.37 (m, 4H), 1.09 (s, 3H), 1.03 (s, 3H), 1.00 (s, 3H), 0.90 (d, 3H, J = 5.6 Hz), 0.89 (s, 3H).

Compound 8: n-BuLi (2.5 M in hexanes, 77 µL, 0.19 mmol) was added to diisopropylamine (29 µL, 0.20 mmol) in THF (0.5 mL) at -78 °C. After stirring at 0 °C for 30 min, the mixture was cooled again to -78 °C, and compound 7 (64 mg, 0.13 mmol) in THF (0.5 mL) was added dropwise. After stirring for 45 min at -78 °C, TsCN (47 mg, 0.26 mmol) in THF (0.5 mL) was added. After stirring for another 30 min, NH₄Cl (aq) solution was added.
added to quench the reaction. The mixture was extracted with EtOAc, and the combined extracts were washed with water, dried with MgSO₄, and concentrated. The residue obtained was purified by column chromatography (silica gel, 0% to 40% EtOAc in CH₂Cl₂) to give product 8 (64 mg, 67%).

**Compound 402-22:** Pyridine (35 μL, 0.43 mmol) was added to PhSeCl (52 mg, 0.27 mmol) in CH₂Cl₂ (2 mL) at 0 °C. After stirring for 15 min, compound 8 (35 mg, 0.067 mmol) in CH₂Cl₂ (2 mL) was added. After stirring for 1 h at 0 °C, the reaction mixture was warmed to room temperature and stirred for another 1 h. The reaction mixture was washed with 2 N HCl (aq) (2 x 5 mL) and 30% H₂O₂ (70 μL, 0.70 mmol) was added at 0 °C. After stirring for 40 min at 0 °C, EtOAc was added. The mixture was washed with water, dried with MgSO₄, and concentrated. The residue obtained was purified by column chromatography (silica gel, 0% to 50% EtOAc in hexanes) to give product 402-22 (17 mg, 49%) as a white foam solid: ¹H NMR (400 MHz, CDCl₃) δ 5.25 (s, 1H), 3.69 (s, 3H), 3.01 (m, 1H), 2.88 (d, 1H, J = 4.8 Hz), 2.08 (m, 1H), 1.56 (s, 3H), 1.48-1.96 (m, 9H), 1.31 (s, 3H), 1.09 (s, 3H), 1.09 (s, 3H), 1.13-1.42 (m, 5H), 1.02 (s, 3H), 0.99 (s, 3H), 0.88 (s, 3H); m/z 520.3 (M+1).

**Compound 402-47:** DMAP (5 mg, 0.041 mmol) was added to a mixture of 402-04 (125 mg, 0.25 mmol), acetic anhydride (0.23 mL, 2.5 mmol) and pyridine (1 mL). After stirring at room temperature for 10 min, NaHCO₃ (aq) solution was added and stirred for 5 min. The mixture was extracted with EtOAc, and the combined extracts were washed with NaHCO₃ (aq) solution, 1 N HCl (aq), and water, then dried with MgSO₄ and concentrated. The residue obtained was purified by column chromatography (silica gel, 0% to 50% EtOAc in hexanes) to give compound 402-47 (110 mg, 81%) as a white foam solid: ¹H NMR (400 MHz, CDCl₃) δ 5.78 (s, 1H), 3.69 (s, 3H), 3.03 (m, 1H), 2.90 (d, 1H, J = 4.4 Hz), 2.58 (d, 1H, J = 16.4 Hz), 2.39 (d, 1H, J = 16.4 Hz), 2.29 (s, 3H), 1.80-1.94 (m, 2H), 1.56-1.76 (m, 6H), 1.44-1.54 (m, 2H), 1.30 (s, 3H), 1.26 (s, 3H), 1.14-1.42 (m, 5H), 1.13 (s, 3H), 1.02 (s, 3H), 1.00 (s, 6H), 0.90 (s, 3H); m/z 550.3 (M+1).

**Compound 402-40:** To a magnetically-stirred solution of compound 6 (Honda et al, 2000b) (2.00 g, 4.07 mmol) in CH₂Cl₂ (15 mL) under a nitrogen atmosphere was added dropwise over 30 min a solution of oxalyl chloride (1.04 g, 8.19 mmol) in CH₂Cl₂ (4 mL). Gas evolution was observed after each drop, but no exotherm was noted. After stirring the yellow reaction solution for 16 h at -18-22 °C, a sample (~3 drops) of the solution was quenched in a CH₂Cl₂/CH₃OH (95/5) solution (~1.2 mL) and warmed just to reflux. TLC
(silica gel, CH_{2}CVMEOH (1/1): showed a major product spot (R_f 0.8) corresponding to a spot from authentic RTA-402 methyl ester. Only a trace of compound 6 was present just off the baseline. The reaction solution was concentrated by rotary evaporation, and the residue dried under vacuum to give light tan solids (2.2 g) identified as the acid chloride of compound 6 from the 1H NMR spectrum. To a magnetically-stirred solution of this acid chloride of compound 6 (0.30g, 0.59 mmol) in anhydrous THF (7.5 mL) at room temperature was added dropwise a solution of ethanolamine (0.08 g, 1.31 mmol) in CH_{2}Cl_{2} (~20 mL). After stirring at room temperature for 30 min, the reaction mixture was quenched in 5% HCl (~20 mL). The CH_{2}Cl_{2} layer was washed with water (~20 mL) and dried (MgSO_{4}). The filtrate was concentrated to a resin which generated a crystalline foam upon drying under high vacuum. The foam obtained was purified by column chromatography (silica gel, 100% EtOAc) to give 402-40 (0.12 g, 38% yield) as an off-white solid: 1H NMR (400 MHz, CDCl_{3}) \( \delta \) 8.15 (s, 1H), 6.54 (br, 1H), 6.05 (s, 1H), 3.71 (m, 2H), 3.47 (m, 2H), 3.21 (br, 1H), 3.08 (m, 1H), 2.92 (br d, 1H, \( J = 13.2 \) Hz), 1.99 (m, 2H), 1.20-2.02 (m, 13H), 1.50 (s, 3H), 1.37 (s, 3H), 1.26 (s, 3H), 1.17 (s, 3H), 1.03 (s, 3H), 0.99 (s, 3H), 0.90 (s, 3H); m/z 535.35 (M+1).

**Compound 402-55:** A mixture of compound 6 (Honda et al, 2000b) (252 mg, 0.51 mmol) and (diethylamino)sulfur trifluoride (0.12 mL, 0.9 mmol, 1.8 equiv) in chloroform (7.0 mL) was stirred at ambient temperature for 6.5 h. The reaction was diluted with chloroform (20 mL) and quenched with water (20 mL). The mixture was partitioned, and the CH_{2}Cl_{2} layer was washed with brine (20 mL) and dried (MgSO_{4}). The filtrate was concentrated and the residue purified by preparative TLC using hexanes/ethyl acetate (65/35), to give 402-55 (239 mg, 94% yield) as a pale yellow solid: 1H NMR (400 MHz, CDCl_{3}) \( \delta \) 8.03 (s, 1H), 5.99 (s, 1H), 3.00 (br, 1H), 2.95 (m, 1H), 2.01 (m, 2H), 1.22-1.83 (m, yyH), 1.50 (s, 3H), 1.39 (s, 3H), 1.26 (s, 3H), 1.18 (s, 3H), 1.03 (s, 3H), 1.01 (s, 3H), 0.93 (s, 3H); m/z 535.43 (M+1+CH_{3}CN).

**Compound 10a and 10b:** Na_{2}PdCl_{2} (1.80 g, 6.12 mmol) was added to a solution of compound 9 (2.77 g, 5.56 mmol) and NaOAc (0.51 g, 6.14 mmol) in AcOH (225 mL) at room temperature. After stirring for 72 h, the reaction mixture was poured onto ice (1000 g). The mixture was kept at room for 3 h, after which, the light brown precipitate was collected by filtration, which was washed with water. The wet cake was then dissolved in CH_{2}Cl_{2}, and transferred to a separatory funnel, which was washed with water. The organic extract was separated, then dried over Na_{2}SO_{4}, filtered and concentrated to give crude palladium complex (3.82 g) as a brown foam solid.
Et₃N (1.30 mL, 9.34 mmol), Ac₂O (1.00 mL, 10.58 mmol), and DMAP (18 mg, 0.15 mmol) were added to a solution of crude palladium complex (3.82 g) in CH₂Cl₂ (200 mL) at room temperature. After stirring for 1 h, the reaction was transferred to a separatory funnel, which was then washed with NaHCO₃(aq) solution and water. The organic extract was separated, which was dried over MgSO₄, filtered, and concentrated to give crude acetate as a brown foam solid.

Pyridine (0.5 mL, 6.20 mmol) was added to a solution of the crude acetate in THF (245 mL) at room temperature. After stirring for 15 min, the reaction was cooled to -78 °C, and a solution of Pb(OAc)₄ (3.06 g, 6.90 mmol) in AcOH (100 mL) was added. After stirring at room temperature for 18 h, the reaction mixture was cooled to 0 °C, and a solution of NaOH (3.60 g, 90 mmol) and NaBH₄ (261 mg, 6.87 mmol) in water (90 mL) was added. After stirring at room temperature for another 15 min, the reaction mixture was filtered through a pad of celite, which was washed with EtOAc. The combined filtrate and washes were treated with a suspension of NaHCO₃ (150 g) in water (100 mL). After stirring at room temperature for 1.5 h, the reaction mixture was transferred to a separatory funnel, which was extracted with EtOAc. The combined organic extracts were washed with NaHCO₃(aq) solution, water, and brine, then dried over MgSO₄, filtered and concentrated. The crude product was purified by column chromatography (silica gel, 0% to 50% EtOAc in hexanes) to give diacetate (2.20 g) as a white foam solid: m/z 598.4 (M+).

A mixture of diacetate (2.20 g, 3.68 mmol) and Na₂CO₃ (1.75 g, 16.51 mmol) in MeOH (185 mL) was stirred at room temperature for 22 h, after which, MeOH was removed by evaporation under vacuum. The residue was mixed with CH₂Cl₂ (100 mL) and 10% AcOH(aq) (30 mL). After stirring for 5 min, the reaction mixture was transferred to a separatory funnel, which was extracted with CH₂Cl₂. The combined organic extracts were washed with NaHCO₃(aq) solution and water, then dried over MgSO₄, filtered and concentrated. The crude product was purified by column chromatography (silica gel, 0% to 50% EtOAc in hexanes) to give product 10a (135 mg, 4.7% yield) as a white foam solid: m/z 514.3 (M+). From the column, product 10b (1.63 g, 57% yield) was also obtained as a white foam solid: m/z 514.3 (M+).

**Compound 11**: TiCl₃ (-10 wt.% in 20-30 wt.% hydrochloric acid(aq), 2.95 mL, 2.28 mmol) was added to a solution of NH₄OAc (1.95 g, 25.32 mmol) in water (15 mL) at room temperature. After stirring for 5 min, compound 10a (117 mg, 0.23 mmol) in THF (10 mL) was added over 10 min. The reaction mixture was stirred at room temperature for 2 h, after which, it was transferred to a separatory funnel, which was extracted with EtOAc. The
combined organic extracts were washed with NaHCO₃(aq) solution, then dried over MgSO₄, filtered and concentrated. The crude product was purified by column chromatography (silica gel, 0% to 50% EtOAc in hexanes) to give product 11 (87 mg, 76% yield) as a white foam solid: m/z 568.4 (M+1).

**Compound 12:** MOMCl (33 µL, 0.35 mmol) was added to a solution of compound 11 (74 mg, 0.15 mmol) and Hunig's base (100 µL, 0.57 mmol) in CH₂Cl₂ (0.6 mL) at room temperature. After stirring for 14 h, the reaction was quenched by adding NaHCO₃(aq) solution. After stirring for another 5 min, the reaction mixture was transferred to a separatory funnel, which was extracted with EtOAc. The combined organic extracts were washed with NaHCO₃(aq) solution, then dried over MgSO₄, filtered and concentrated. The crude product was purified by column chromatography (silica gel, 0% to 50% EtOAc in hexanes) to give product 12 (62 mg, 77% yield) as a white foam solid: m/z 543.4 (M+1).

**Compound 13:** NaOMe (25 w/w% solution in MeOH, 0.26 mL, 1.13 mmol) was added to a solution of compound 12 (40 mg, 0.074 mmol) in ethyl formate (0.18 mL, 2.23 mmol) at 0 °C. After stirring for at 0 °C for 1 h, t-BuOMe (5 mL) and 1N HCl(aq) (1.10 mL, 1.10 mmol) were added sequentially. After stirring for another 5 min, the reaction mixture was transferred to a separatory funnel, which was extracted with EtOAc. The combined organic extracts were washed with water. The organic layer was separated, which was dried over MgSO₄, filtered, and concentrated. The crude product was mixed with NH₂OH-HCl (7.7 mg, 0.11 mmol), water (0.15 mL) and EtOH (1.5 mL). The reaction mixture was heated at 55 °C for 20 h, after which, it was diluted with EtOAc, and transferred to a separatory funnel, which was then washed with water. The organic extract was separated, which was dried over MgSO₄, filtered and concentrated. The crude product was purified by column chromatography (silica gel, 0% to 40% EtOAc in hexanes) to give product 13 (29 mg, 68% yield) as a white foam solid: m/z 568.3 (M+1).

**Compound 14:** NaOMe (25 w/w% solution in MeOH, 20 µL, 0.087 mmol) was added to a solution of compound 13 (42 mg, 0.074 mmol) in MeOH (0.75 mL) at room temperature. The reaction was then heated to 55 °C, and stirred for 2 h. After cooling to 0 °C, t-BuOMe (10 mL) and 1N HCl(aq) (1 mL) were added, and stirred for 5 min. The reaction mixture was transferred to a separatory funnel, which was extracted with EtOAc. The combined organic extracts were washed with water, dried over MgSO₄, filtered, and concentrated to give product 14 (43 mg, 100% yield) as a white foam solid: m/z 568.4 (M+1). Compound 14 is an isomeric mixture of C3 ketone and enol forms.
**Compound 63302:** To a solution of compound 14 (43 mg, 0.075 mmol) in DMF (0.75 mL) was added 1,3-dibromo-5,5-dimethylhydantion (12 mg, 0.042 mmol) at 0 °C, and the reaction was stirred at 0 °C for 1 h. Pyridine (18 µL, 0.22 mmol) was then added, and the mixture was heated at 55 °C for 4 h. After cooling to room temperature, the reaction was diluted with EtOAc, and was transferred to a separatory funnel, which was then washed with Na$_2$SO$_3$(aq) solution, IN HCl(aq), and water. The organic layer was separated, which was dried over MgSO$_4$, filtered, and concentrated. The crude product was purified by column chromatography (silica gel, 0% to 40% EtOAc in hexanes) to give product 63302 (33 mg, 76% yield) as a white foam solid: $^1$H NMR (400 MHz, CDCl$_3$) δ 7.97 (s, 1H), 5.94 (s, 1H), 4.51 (s, 2H), 3.70 (s, 3H), 3.66 (d, 1H, J = 10.0 Hz), 3.50 (d, 1H, J = 10.0 Hz), 3.30 (s, 3H), 3.04 (m, 1H), 2.92 (d, 1H, J = 4.8 Hz), 1.81-1.94 (m, 5H), 1.64-1.76 (m, 4H), 1.55 (s, 3H), 1.49-1.62 (m, 2H), 1.34 (s, 3H), 1.27 (s, 3H), 1.14-1.36 (m, 4H), 1.00 (s, 6H), 0.90 (s, 3H); m/z 566.3 (M+).

**Compound 63301:** 4N HCl(aq) (1.0 mL, 4.0 mmol) was added to a solution of compound 63302 (27 mg, 0.048 mmol) in THF (2.0 mL) at room temperature. After stirring for 48 h, additional 4N HCl(aq) (1.0 mL, 4.0 mmol) was added. After another 24 h, the reaction was diluted with EtOAc, and was transferred to a separatory funnel, which was then washed with water. The organic layer was separated, which was dried over MgSO$_4$, filtered, and concentrated. The crude product was purified by column chromatography (silica gel, 0% to 50% EtOAc in hexanes) to give product 63301 (22 mg, 85% yield) as a white foam solid: $^1$H NMR (400 MHz, CDCl$_3$) δ 8.07 (s, 1H), 5.97 (s, 1H), 3.80 (dd, 1H, J = 3.6, 11.2 Hz), 3.70 (s, 3H), 3.69 (dd, 1H, J = 8.0, 11.2 Hz), 3.04 (m, 1H), 2.94 (d, 1H, J = 4.8 Hz), 2.10 (dd, 1H, J = 3.6, 8.0 Hz), 1.81-1.94 (m, 5H), 1.51-1.75 (m, 6H), 1.52 (s, 3H), 1.34 (s, 3H), 1.33 (s, 3H), 1.14-1.38 (m, 4H), 1.01 (s, 3H), 1.00 (s, 3H), 0.90 (s, 3H); m/z 522.3 (M+).

**Compound 15:** (Trimethylsilyl)diazomethane (2.0 M solution in Et$_2$O, 2.64 mL, 5.28 mmol) was added to a solution of sumaresinolic acid (500 mg, 1.06 mmol) in toluene (7.5 mL) and MeOH (2.5 mL) at 0 °C. After stirring at 0 °C for 15 min, the reaction was quenched by adding AcOH (0.6 mL). After stirring for another 5 min, the reaction mixture was diluted with EtOAc, and transferred to a separatory funnel, which was washed with NaHCO$_3$(aq) solution and water. The organic extract was separated, dried over MgSO$_4$, filtered, and concentrated. The crude product was purified by column chromatography (silica gel, 0% to 40% EtOAc in hexanes) to give product 15 (440 mg, 85% yield) as a white solid: m/z 487.3 (M+).
Compound 16: Ac$_2$O (172 µL, 1.82 mmol) was added to a solution of compound 15 (172 mg, 0.36 mmol) in CH$_2$Cl$_2$ (1.80 mL) at room temperature. After stirring for 5 min, BF$_3$OEt$_2$ (86 µL, 0.70 mmol) was added drop-wise. The reaction mixture was stirred at room temperature for 1 h, after which, it was cooled to 0 °C. Water and NaHCO$_3$(aq) solution were added sequentially. After stirring for another 5 min, the reaction was transferred to a separatory funnel, which was extracted with EtOAc. The combined organic extracts were washed with NaHCO$_3$(aq) solution, then dried over MgSO$_4$, filtered, and concentrated. The crude product was purified by column chromatography (silica gel, 0% to 15% EtOAc in hexanes) to give product 16 (133 mg, 72% yield) as a white foam solid: m/z 511.3 (M-AcOH+1).

Compound 17: 30% H$_2$O$_2$(aq) (0.53 mL, 5.19 mmol) was added to a solution of compound 16 (203 mg, 0.36 mmol) and formic acid (3.0 mL) in THF (6.0 mL) at room temperature. After stirring for 40 h, the reaction was quenched by adding 10% Na$_2$SO$_3$(aq) solution (20 mL). After stirring for another 5 min, the reaction mixture was transferred to a separatory funnel, which was extracted with EtOAc. The combined organic extracts were washed with NaHCO$_3$(aq) solution and water, then dried over MgSO$_4$, filtered, and concentrated. The crude product was purified by column chromatography (silica gel, 0% to 20% EtOAc in hexanes) to give product 17 (137 mg, 65% yield) as a white foam solid: m/z 587.4 (M+).

Compound 18: 48% HBr(aq) (11 µL, 0.098 mmol) was added to a solution of compound 17 (137 mg, 0.23 mmol) in MeCN (4.7 mL) at room temperature, and the reaction was heated to 35 °C. Bromine (1.0 M solution in MeCN, 0.28 mL, 0.28 mmol) was then added. The red reaction mixture was stirred at 35 °C for 18 h, after which, additional bromine (1.0 M solution in MeCN, 0.28 mL, 0.28 mmol) was added over 5 min. After another 1 h, the reaction was cooled to room temperature, which was then diluted with EtOAc, and transferred to a separatory funnel. The reaction mixture was washed with water, NaHCO$_3$(aq) solution, and Na$_2$SO$_3$(aq) solution. The organic extract was separated, which was dried over MgSO$_4$, filtered, and concentrated. The crude product was purified by column chromatography (silica gel, 0% to 20% EtOAc in hexanes) to give product 18 (112 mg, 82% yield) as a white foam solid: m/z 584.8 (M+).

Compound 19: 10% NaOH(aq) solution (0.40 mL, 1.00 mmol) was added to a solution of compound 18 (112 mg, 0.19 mmol) in THF (0.5 mL) and MeOH (0.5 mL) at 0 °C. After stirring at 0 °C for 2.5 h, and then at room temperature for 1 h, the reaction was quenched by adding IN HCl(aq) (1.05 mL). After stirring for another 5 min, the reaction
mixture was diluted with EtOAc, and transferred to a separatory funnel, which was washed with water. The organic extract was separated, which was dried over MgSO₄, filtered, and concentrated to give crude C3-alcohol (105 mg, 100%) as a white foam solid: m/z 543.4 (M+1).

The crude C3-alcohol (105 mg, 0.19 mmol), 4A molecular sieves (200 mg), NMO (49 mg, 0.418 mmol) and CH₂Cl₂ (10 mL) were mixed together. After stirring for 5 min, TPAP (9 mg, 0.025 mmol) was added. After another 25 min, the reaction was quenched by adding Na₂S0₃(aq) solution, and then transferred to a separatory funnel, which was extracted with CH₂Cl₂. The combined organic extracts were washed with water, then dried over MgSO₄, filtered, and concentrated. The crude product was purified by column chromatography (silica gel, 0% to 30% EtOAc in hexanes) to give product 19 (95 mg, 90% yield) as a white solid: m/z 522.3 (M+1).

**Compound 20:** 20% NaOH(aq) solution (1.10 mL, 5.50 mmol) was added to a solution of compound 19 (60 mg, 0.11 mmol) in EtOH (4.5 mL) at room temperature. The reaction was then heated at reflux for 15 min. After cooling to room temperature, the reaction mixture was diluted with t-BuOMe, and transferred to a separatory funnel, which was washed with IN HCl(aq) and water. The organic extract was separated, dried over MgSO₄, filtered, and concentrated. The crude product was purified by column chromatography (silica gel, 0% to 12% EtOAc in CH₂Cl₂) to give product 20 (49 mg, 88% yield) as a white solid: m/z 499.3 (M+1).

**Compound 21:** Using the procedure described for the synthesis of compound 13 from compound 12, compound 21 (44 mg, 87% yield) was produced from compound 20 (48 mg, 0.096 mmol) as a white foam solid: m/z 524.3.

**Compound 22:** Using the procedure described for the synthesis of compound 14 from compound 13, compound 22 (37 mg, 93% yield) was produced from compound 21 (40 mg, 0.076 mmol) as a white foam solid: m/z 524.3. Compound 22 is an isomeric mixture of C3 ketone and enol forms.

**Compound 63307:** Using the procedure described for the synthesis of compound 63302 from compound 14, compound 63307 (27 mg, 73% yield) was produced from compound 22 (37 mg, 0.070 mmol) as a white solid: ¹H NMR (400 MHz, CDCl₃) δ 7.90 (s, 1H), 5.97 (s, 1H), 4.67 (s, br, 1H), 3.70 (s, 3H), 3.06 (m, 1H), 2.98 (d, 1H, J = 4.8 Hz), 1.85 (s, 3H), 1.62 (s, 3H), 1.46 (s, 3H), 1.33 (s, 3H), 1.12-1.96 (m, 14H), 1.01 (s, 3H), 0.95 (s, 3H), 0.90 (s, 3H); m/z 522.3.
Compound 63309: NaHC\(\delta\)\(_3\) (7.6 mg, 0.090 mmol) and Dess-Martin periodinane (11.6 mg, 0.027 mmol) were added sequentially to a solution of compound 63307 (9.5 mg, 0.018 mmol) in CH\(_2\)Cl\(_2\) (0.36 mL) at 0 °C. After stirring at 0 °C for 2 h, the reaction was quenched by adding 10% Na\(_2\)SO\(_4\)(aq) solution. After stirring at ambient temperature for another 5 min, the reaction mixture was transferred to a separatory funnel, which was extracted with EtOAc. The combined organic extracts were washed with NaHCO\(_3\)(aq) solution and water, then dried over MgSO\(_4\), filtered, and concentrated. The crude product was purified by preparative TLC plate (silica gel, eluted with 14% EtOAc in CH\(_2\)Cl\(_2\)) to give product 24 (195 mg, 77% yield) as a white foam solid: m/z 606.9 (M+1).

Compound 63316: A solution of 23 (100 mg, 0.20 mmol) in MeCN (1.0 mL) and EtOAc (1.0 mL) was added to a solution of RuClyxHCl (11 mg, 0.053 mmol) and NaIO\(_4\) (80 mg, 0.37 mmol) in water (0.5 mL) at 0 °C. After stirring at 0 °C for 5 min, the reaction mixture was poured onto 10% Na\(_2\)SO\(_3\)(aq) solution (20 mL). After stirring at ambient temperature for 2 min, the reaction mixture was transferred to a separatory funnel, which was extracted with EtOAc. The combined organic extracts were filtered through a pad of celite, which was washed with additional EtOAc. The combined filtrate and washes were dried over MgSO\(_4\), filtered, and concentrated. The crude product was purified by column chromatography (silica gel, 0% to 25% EtOAc in hexanes) to give product 63316 (76 mg, 71% yield) as a white foam solid: \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.72 (s, 1H), 5.83 (s, 1H), 3.70 (s, 3H), 3.07 (m, 1H), 2.98 (d, 1H, \(J = 4.8\) Hz), 2.85 (s, 1H), 2.68 (d, 1H, \(J = 17.2\) Hz), 2.29 (d, 1H, \(J = 17.6\) Hz), 1.55 (s, 3H), 1.44 (s, 3H), 1.42 (s, 3H), 1.35 (s, 3H), 1.13-1.98 (m, 10 H), 1.08 (s, 3H), 1.00 (s, 3H), 0.90 (s, 3H); m/z 520.3 (M+1).

Compound 24: A mixture of compound 1 (200 mg, 0.42 mmol), iodine (211 mg, 0.83 mmol) and pyridine (0.10 mL, 1.24 mmol) in THF (4 mL) was heated at reflux for 20 h. After cooling to room temperature, the reaction mixture was diluted with EtOAc, and transferred to a separatory funnel, which was washed with water, Na\(_2\)SO\(_3\)(aq) solution, 1 N HCl(aq), and water. The organic extract was separated, dried over MgSO\(_4\), filtered and concentrated. The crude product was purified by column chromatography (silica gel, 0% to 30% EtOAc in hexanes) to give product 24 (195 mg, 77% yield) as a white foam solid: m/z 606.9 (M+1).
**Compound 63320:** A mixture of the compound 24 (80 mg, 0.13 mmol) and CuI (63 mg, 0.33 mmol) in dry DMF (5 mL) was heated to 70 °C under Ar. FSO₂CF₂CO₂Me (0.25 mL, 1.96 mmol) and hexamethylphosphoramide (0.38 mL, 2.18 mmol) were then added sequentially. The reaction mixture was heated at 70 °C for 6 h, after which it was cooled to room temperature, and quenched with NH₄Cl(aq) solution. After stirring for another 5 min, the reaction mixture was transferred to a separatory funnel, which was extracted with EtOAc. The combined organic extracts were washed with water, Na₂SO₄(aq) solution, 1 N HCl(aq), and water, then dried over MgSO₄, filtered and concentrated. The crude product was purified by column chromatography (silica gel, 0% to 25% EtOAc in hexanes) to give product 63320 (60 mg, 83% yield) as a white foam solid: ¹H NMR (400 MHz, CDCl₃) δ 7.81 (s, 1H), 6.01 (s, 1H), 3.69 (s, 3H), 3.04 (m, 1H), 2.93 (d, 1H, J = 4.8 Hz), 1.80-1.94 (m, 2H), 1.62-1.79 (m, 6H), 1.48-1.60 (m, 3H), 1.43 (s, 3H), 1.32 (s, 3H), 1.20 (s, 3H), 1.17 (s, 3H), 1.16-1.30 (m, 4H), 1.02 (s, 3H), 0.99 (s, 3H), 0.89 (s, 3H); m/z 549.3 (M+1).

**Example 4 - Aqueous Solubility of Oleanolic Acid Derivatives**

The aqueous solubility of the compounds shown here was determined using the procedures outlined in Example 1.

<table>
<thead>
<tr>
<th>Compound ID(s)</th>
<th>Structure</th>
<th>Aqueous Solubility (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>63097 (402)</td>
<td><img src="image1" alt="Structure" /></td>
<td>1.46</td>
</tr>
<tr>
<td>63102 (dh404)</td>
<td><img src="image2" alt="Structure" /></td>
<td>0.06</td>
</tr>
<tr>
<td>Compound ID(s)</td>
<td>Structure</td>
<td>Aqueous Solubility (μM)</td>
</tr>
<tr>
<td>---------------</td>
<td>-----------</td>
<td>-------------------------</td>
</tr>
<tr>
<td>63198</td>
<td><img src="image1.png" alt="Image" /></td>
<td>163.6</td>
</tr>
<tr>
<td>63202</td>
<td><img src="image2.png" alt="Image" /></td>
<td>1.89</td>
</tr>
<tr>
<td>63208</td>
<td><img src="image3.png" alt="Image" /></td>
<td>9.49</td>
</tr>
<tr>
<td>63214</td>
<td><img src="image4.png" alt="Image" /></td>
<td>112.2</td>
</tr>
<tr>
<td>63219</td>
<td><img src="image5.png" alt="Image" /></td>
<td>13.58</td>
</tr>
<tr>
<td>Compound ID(s)</td>
<td>Structure</td>
<td>Aqueous Solubility (µM)</td>
</tr>
<tr>
<td>---------------</td>
<td>-----------</td>
<td>------------------------</td>
</tr>
<tr>
<td>63221</td>
<td><img src="image1" alt="Structure 1" /></td>
<td>8.78</td>
</tr>
<tr>
<td>63226</td>
<td><img src="image2" alt="Structure 2" /></td>
<td>0.71</td>
</tr>
<tr>
<td>63231</td>
<td><img src="image3" alt="Structure 3" /></td>
<td>1.23</td>
</tr>
<tr>
<td>63232</td>
<td><img src="image4" alt="Structure 4" /></td>
<td>0.75</td>
</tr>
<tr>
<td>63237</td>
<td><img src="image5" alt="Structure 5" /></td>
<td>5.16</td>
</tr>
</tbody>
</table>
All of the methods disclosed and claimed herein can be made and executed without undue experimentation in light of the present disclosure. While the compositions and methods of this invention have been described in terms of preferred embodiments, it will be apparent to those of skill in the art that variations may be applied to the methods and in the steps or in the sequence of steps of the method described herein without departing from the concept, spirit and scope of the invention. More specifically, it will be apparent that certain agents which are both chemically and physiologically related may be substituted for the agents described herein while the same or similar results would be achieved. All such similar substitutes and modifications apparent to those skilled in the art are deemed to be within the spirit, scope and concept of the invention as defined by the appended claims.
REFERENCES

The following references, and those listed in the Appendix, to the extent that they provide exemplary procedural or other details supplementary to those set forth herein, are specifically incorporated herein by reference.

U.S. Patent 5,443,826

U.S. Patent 5,599,795

U.S. Patent 6,025,395

U.S. Patent 6,974,801

U.S. Patent Application 12/352,473

U.S. Provisional Application No. 61/046,332

U.S. Provisional Application No. 61/046,342

U.S. Provisional Application No. 61/046,363

U.S. Provisional Application No. 61/046,366

U.S. Provisional Application No. 61/111,333

U.S. Provisional Application No. 61/111,269

U.S. Provisional Application No. 61/111,294

U.S. Patent Publication 2009/0060873


Galley and Webster, Br. J. Anaesth., 77:1 1-16, 1996.


Vodovotz et al, In; Handbook of Experimental Immunology, Volumes I-IV, 1996.


CLAIMS

1. A compound of the formula:

wherein:

Y is cyano or \(-\text{C(O)R}_a\), further wherein:

\(\text{R}_a\) is:

hydrogen, hydroxy, halo, amino, hydroxyamino, azido or mercapto; or

alkyl_{(C \leq 12)}, alkenyl_{(C \leq 12)}, alkynyl_{(C \leq 12)}, aryl_{(C \leq 12)}, aralkyl_{(C \leq 12)},

heteroaryl_{(C \leq 12)}, heteroaralkyl_{(C \leq 12)}, alkoxy_{(C \leq 12)}, alkenyl-

\text{oxy}_{(C \leq 12)}, \text{alkynloxy}_{(C \leq 12)}, \text{aryloxy}_{(C \leq 12)}, \text{aralkoxy}_{(C \leq 12)},

heteroaryloxy_{(C \leq 12)}, heteroaralkoxy_{(C \leq 12)}, \text{acyloxy}_{(C \leq 12)},

\text{alkylamino}_{(C \leq 12)}, \text{dialkylamino}_{(C \leq 12)}, \text{alkoxyamino}_{(C \leq 12)},

\text{alkenylamino}_{(C \leq 12)}, \text{alkynylamino}_{(C \leq 12)}, \text{arylamino}_{(C \leq 12)},

\text{aralkylamino}_{(C \leq 12)}, \text{heteroarylamino}_{(C \leq 12)}, \text{heteroaralkyl-

\text{amino}_{(C \leq 12)}, \text{alkylsulfonylamino}_{(C \leq 12)}, \text{amido}_{(C \leq 12)},

\text{alkylthio}_{(C \leq 12)}, \text{alkenylthio}_{(C \leq 12)}, \text{alkynylthio}_{(C \leq 12)},

\text{arythio}_{(C \leq 12)}, \text{aralkylthio}_{(C \leq 12)}, \text{heteroarylthio}_{(C \leq 12)},

\text{heteroaralkylthio}_{(C \leq 12)}, \text{acylthio}_{(C \leq 12)}, \text{alkylsilyl}_{(C \leq 12)}\), or a

substituted version of any of these groups;

\(X_1\) is \(\text{OR}_b, \text{NR}_b\text{R}_c\), or \(\text{SR}_b\), wherein \(\text{R}_b\) and \(\text{R}_c\) are each independently:

hydrogen or hydroxy;
alkyl\(_{(C\leq 8)}\), aryl\(_{(C\leq 8)}\), aralkyl\(_{(C\leq 8)}\), acyl\(_{(C\leq 8)}\), alkoxy\(_{(C\leq 8)}\), aryloxy\(_{(C\leq 8)}\), acyloxy\(_{(C\leq 8)}\), alkylamino\(_{(C\leq 8)}\), arylamino\(_{(C\leq 8)}\), amido\(_{(C\leq 8)}\), or a substituted version of any of these groups; or

a substituent convertible in vivo to hydrogen;

5 provided that \(R_b\) is absent when the atom to which it is bound is part of a double bond, further provided that when \(R_b\) is absent the atom to which it is bound is part of a double bond;

\[R_1\] is:
hydrogen, cyano, hydroxy, halo or amino; or

alkyl\(_{(C\leq 8)}\), alkenyl\(_{(C\leq 8)}\), alkynyl\(_{(C\leq 8)}\), aryl\(_{(C\leq 8)}\), aralkyl\(_{(C\leq 8)}\), heteroaryl\(_{(C\leq 8)}\), heteroaralkyl\(_{(C\leq 8)}\), acyl\(_{(C\leq 8)}\), alkoxy\(_{(C\leq 8)}\), aryloxy\(_{(C\leq 8)}\), acyloxy\(_{(C\leq 8)}\), alkylamino\(_{(C\leq 8)}\), arylamino\(_{(C\leq 8)}\), amido\(_{(C\leq 8)}\), or a substituted version of any of these groups;

\[R_2\] is:
hydroxy, halo, amino; or

fluoroalkyl\(_{(C\leq 8)}\), alkenyl\(_{(C\leq 8)}\), alkynyl\(_{(C\leq 8)}\), aryl\(_{(C\leq 8)}\), heteroaryl\(_{(C\leq 8)}\), acyl\(_{(C\leq 8)}\), alkoxy\(_{(C\leq 8)}\), aryloxy\(_{(C\leq 8)}\), acyloxy\(_{(C\leq 8)}\), alkylamino\(_{(C\leq 8)}\), arylamino\(_{(C\leq 8)}\), amido\(_{(C\leq 8)}\), or a substituted version of any of these groups;

\[R_4\] and \(R_5\) are each independently alkyl\(_{(C\leq 8)}\) or substituted alkyl\(_{(C\leq 8)}\);

\(R_6\) is hydrogen, hydroxy or oxo; and

\(R_7\) is hydrogen or hydroxy;

\(R_8, R_9, R_10\) and \(R_{11}\) are each independently hydrogen, hydroxy, alkyl\(_{(C\leq 8)}\), substituted alkyl\(_{(C\leq 8)}\), alkoxy\(_{(C\leq 8)}\) or substituted alkoxy\(_{(C\leq 8)}\); or pharmaceutically acceptable salts, esters, hydrates, solvates, tautomers, prodrugs, or optical isomers thereof.

2. The compound of claim 1, wherein \(Y\) is cyano.

3. The compound of claim 1, wherein \(Y\) is \(-\text{C(O)}R_a\).

4. The compound of claim 1, wherein \(X_1\) is OR\(_b\) and \(R_b\) is absent.

5. The compound of claim 3, wherein \(R_a\) is hydroxy.
6. The compound of claim 3, wherein $R_a$ is alkoxy$_{(C\leq 6)}$, aryloxy$_{(C\leq 8)}$, aralkyloxy$_{(C\leq 8)}$, or a substituted version of any of these groups.

7. The compound of claim 6, wherein $R_a$ is alkoxy$_{(C_{2-6})}$.

8. The compound of claim 6, wherein $R_a$ is alkoxy$_{(C_{1-5})}$ or substituted alkoxy$_{(C_{1-5})}$.

9. The compound of claim 8, wherein $R_a$ is alkoxy$_{(C_{2-4})}$ or substituted alkoxy$_{(C_{2-4})}$.

10. The compound of claim 9, wherein $R_a$ is alkoxy$_{(C_{1-4})}$ or substituted alkoxy$_{(C_{1-4})}$.

11. The compound of claim 10, wherein $R_a$ is alkoxy$_{(C_{1,2})}$ or substituted alkoxy$_{(C_{1,2})}$.

12. The compound of claim 11, wherein $R_a$ is methoxy.

13. The compound of claim 3, wherein $R_a$ is amino.

14. The compound of claim 3, wherein $R_a$ is alkylamino$_{(C_{1-6})}$, alkoxyamino$_{(C_{1-6})}$, arylamino$_{(C_{1-8})}$, aralkylamino$_{(C_{1-8})}$, dialkylamino$_{(C_{2-8})}$, or a substituted version of any of these groups.

15. The compound of claim 14 wherein $R_a$ is alkylamino$_{(C_{2-6})}$ or substituted alkylamino$_{(C_{2-6})}$.

16. The compound of claim 15, wherein $R_a$ is alkylamino$_{(C_{3-6})}$.

17. The compound of claim 14, wherein $R_a$ is alkylamino$_{(C_{1-5})}$, dialkylamino$_{(C_{2-6})}$, or a substituted version of either of these groups.

18. The compound of claim 17, wherein $R_a$ is alkylamino$_{(C_{2-4})}$, dialkylamino$_{(C_{2-5})}$, or substituted version of either of these groups.

19. The compound of claim 17, wherein $R_a$ is alkylamino$_{(C_{1-4})}$ or substituted alkylamino$_{(C_{1-4})}$.

20. The compound of claim 19, wherein $R_a$ is alkylamino$_{(C_{1-3})}$.

21. The compound of claim 20, wherein $R_a$ is methylamino or ethylamino.

22. The compound of claim 17, wherein $R_a$ is substituted alkylamino$_{(C_{1-3})}$.
23. The compound of claim 22, wherein $R_a$ is 2,2,2-trifluoroethylamino.

24. The compound of claim 3, wherein $R_a$ is alkyl$_{(C1-5)}$, aryl$_{(C8)}$, aralkyl$_{(C8)}$, heteroaralkyl$_{(C8)}$, or a substituted version of any of these groups.

25. The compound of claim 3, wherein $R_a$ is heteroaryl$_{(C1-8)}$ or substituted heteroaryl$_{(C1-8)}$.

26. The compound of claim 25, wherein $R_a$ is imidazoyl.

27. The compound of claim 3, wherein $R_a$ is -H.

28. The compound of claim 1, wherein $R_1$ is -H, -OH or -F.

29. The compound of claim 1, wherein $R_1$ is -H.

30. The compound of claim 1, wherein $R_2$ is -F.

31. The compound of claim 1, wherein $R_2$ is fluoroalkyl$_{(C8)}$.

32. The compound of claim 31, wherein $R_2$ is -CF$_3$.

33. The compound of claim 1, wherein $R_2$ is a substituted acyl$_{(C1-3)}$.

34. The compound of claim 1, wherein $R_2$ is heteroaryl$_{(C1-6)}$ or substituted heteroaryl$_{(C1-6)}$.

35. The compound of claim 33, wherein $R_2$ is -C(=O)NHS(=O)$_2$CH$_3$.

36. The compound of claim 1, wherein $R_4$ and $R_5$ are each methyl.

37. The compound of claim 1, wherein one of $R_4$ and $R_5$ is hydroxymethyl and the other is methyl.

38. The compound of claim 1, wherein $R_6$ and $R_7$ are both hydrogen.

39. The compound of claim 1, wherein $R_8$ and $R_9$ are each hydrogen.

40. The compound of claim 1, wherein $R_{10}$ and $R_{11}$ are each methyl.
41. The compound according to claim 1, further defined as:

\[
R_a \text{ is:}
\]

1. hydrogen, hydroxy, halo or amino; or
2. alkyl\((C_\leq 8)\), aryl\((C_\leq 8)\), aralkyl\((C_\leq 8)\), heteroaryl\((C_\leq 8)\), alkoxy\((C_\leq 8)\), aryloxy\((C_\leq 8)\),
3. alkoxy\((C_\leq 8)\), alkylamino\((C_\leq 8)\), alkoxyamino\((C_\leq 8)\),
4. alkoxyamino\((C_\leq 6)\), dialkylamino\((C_\leq 6)\), arylamino\((C_\leq 8)\),
5. aralkylamino\((C_\leq 8)\), heteroarylamino\((C_\leq 6)\), heteroarylamino\((C_\leq 8)\),
6. alkylsulfonylamino\((C_\leq 8)\), amido\((C_\leq 6)\), or a substituted version of any of these groups; and

\[
R_2 \text{ is:}
\]

1. fluoro; or
2. fluoroalkyl\((C_\leq 8)\), heteroaryl\((C_\leq 8)\), acyl\((C_\leq 8)\), or a substituted version of either of these groups;
3. or pharmaceutically acceptable salts, esters, hydrates, solvates, tautomers, prodrugs, or optical isomers thereof.

42. The compound of claim 41, further defined as:

or pharmaceutically acceptable salts, hydrates, solvates, tautomers, or optical isomers thereof.
43. The compound of claim 42, further defined as:

![Chemical structure](image1)

or pharmaceutically acceptable salts thereof, and substantially free from other optical isomers thereof.

44. The compound of claim 41, further defined as:

![Chemical structure](image2)

or pharmaceutically acceptable salts, hydrates, solvates, tautomers, or optical isomers thereof.

45. The compound of claim 44, further defined as:

![Chemical structure](image3)

or pharmaceutically acceptable salts thereof, and substantially free from other optical isomers thereof.
46. The compound of claim 41, further defined as:

or pharmaceutically acceptable salts, hydrates, solvates, tautomers, or optical isomers thereof.

47. The compound of claim 46, further defined as:

or pharmaceutically acceptable salts thereof, and substantially free from other optical isomers thereof.

48. The compound of claim 41, further defined as:

or pharmaceutically acceptable salts, hydrates, solvates, tautomers, or optical isomers thereof.
49. The compound of claim 48, further defined as:

or pharmaceutically acceptable salts thereof, and substantially free from other optical isomers thereof.

50. The compound of claim 41, further defined as:

or pharmaceutically acceptable salts, hydrates, solvates, tautomers, or optical isomers thereof.

51. The compound of claim 50, further defined as:

or pharmaceutically acceptable salts thereof, and substantially free from other optical isomers thereof.
52. A compound of the formula:

\[
\text{R}_a \text{ is azido, fluoro, hydroxyamino, alkoxyamino } (\text{C } \leq 12), \text{ substituted alkoxy-amino } (\text{C } \leq 12), \text{ or -NH-L-Ra;}
\]

wherein:

\[
\text{L is alkanediyl } (\text{C } \leq 8); \text{ and}
\]

\[
\text{R}_d \text{ is:}
\]

hydroxy; or

\[
\text{alkoxy } (\text{C } \leq 18), \text{ arloxy } (\text{C } \leq 18)^*, \text{ or acyloxy } (\text{C } \leq 18), \text{ or a substituted version of any of these groups;}
\]

\[
\text{X}_1 \text{ is OR}_b, \text{ NR}_bR_c, \text{ or SR}_b, \text{ wherein } R_b \text{ and } R_c \text{ are each independently:}
\]

hydrogen or hydroxy;

\[
\text{alkyl } (\text{C } \leq 8), \text{ aryl } (\text{C } \leq 8), \text{ aralkyl } (\text{C } \leq 8), \text{ acyl } (\text{C } \leq 8), \text{ alkoxy } (\text{C } \leq 8), \text{ aryloxy } (\text{C } \leq 8),
\]

acyloxyv (C≤8), alkylamino (C≤8), arylamino (C≤8), amido (C≤8), or a substituted version of any of these groups; or

a substituent convertible \textit{in vivo} to hydrogen;

provided that \text{R}_b \text{ is absent when the atom to which it is bound is part of a double bond, further provided that when } \text{R}_b \text{ is absent the atom to which it is bound is part of a double bond;}

\[
\text{R}_1 \text{ is:}
\]

hydrogen, cyano, hydroxy, halo or amino; or

\[
\text{alkyl } (\text{C } \leq 8), \text{ alkenyl } (\text{C } \leq 8), \text{ alkynyl } (\text{C } \leq 8), \text{ aryl } (\text{C } \leq 8), \text{ aralkyl } (\text{C } \leq 8), \text{ heteroaryl } (\text{C } \leq 8),
\]

heteroaralkyl (C≤8), acyl (C≤8), alkoxy (C≤8), aryloxy (C≤8),
acyloxy\(_{(C \leq 8)}\), alkylamino\(_{(C \leq 8)}\), arylamino\(_{(C \leq 8)}\), amido\(_{(C \leq 8)}\), or a substituted version of any of these groups;

\(R_2\) is:

- hydroxy, cyano, halo or amino; or
- fluoroalkyl\(_{(C \leq 8)}\), alkenyl\(_{(C \leq 8)}\), alkynyl\(_{(C \leq 8)}\), aryl\(_{(C \leq 8)}\), heteroaryl\(_{(C \leq 8)}\),
- acyl\(_{(C \leq 8)}\), alkoxy\(_{(C \leq 8)}\), aryl oxy\(_{(C \leq 8)}\), acyloxy\(_{(C \leq 8)}\), alkylamino\(_{(C \leq 8)}\), arylamino\(_{(C \leq 8)}\), amido\(_{(C \leq 8)}\), or a substituted version of any of these groups;

\(R_4\) and \(R_5\) are each independently alkyl\(_{(C \leq 8)}\) or substituted alkyl\(_{(C \leq 8)}\);

\(R_6\) is hydrogen, hydroxy or oxo; and

\(R_7\) is hydrogen or hydroxy;

\(R_s, R_9, Ri\) and \(R_n\) are each independently hydrogen, hydroxy, alkyl\(_{(C \leq 8)}\), substituted alkyl\(_{(C \leq 8)}\), alkoxy\(_{(C \leq 8)}\) or substituted alkoxy\(_{(C \leq 8)}\);

or pharmaceutically acceptable salts, esters, hydrates, solvates, tautomers, prodrugs, or optical isomers thereof.

53. The compound of claim 52, wherein \(X_1\) is OR\(_b\) and \(R_b\) is absent.

54. The compound of claim 52, wherein \(R_a\) is azido.

55. The compound of claim 52, wherein \(R_a\) is fluoro.

56. The compound of claim 52, wherein \(R_a\) is hydroxyamino.

57. The compound of claim 52, wherein \(R_a\) is alkoxyamino\(_{(C \leq 8)}\).

58. The compound of claim 52, wherein \(R_a\) is -NH-L-R\(_d\).

59. The compound of claim 58, wherein \(R_d\) is hydroxy.

60. The compound of claim 58, wherein \(L\) is 1,2-ethanediyl.

61. The compound of claim 52, wherein \(R_1\) is -H.

62. The compound of claim 52, wherein \(R_2\) is -CN.

63. The compound of claim 52, wherein \(R_4\) and \(R_5\) are each methyl.
64. The compound of claim 52, wherein one of $R_4$ and $R_5$ is hydroxymethyl and the other is methyl.

65. The compound of claim 52, wherein $R_6$ and $R_7$ are each hydrogen.

66. The compound of claim 52, wherein $R_6$ is hydroxy.

67. The compound of claim 52, wherein $R_6$ is oxo.

68. The compound of claim 1, wherein $R_8$ and $R_9$ are each hydrogen.

69. The compound of claim 1, wherein $R_{10}$ and $R_{11}$ are each methyl.

70. The compound of claim 52, further defined as:

![Chemical Structure]

or pharmaceutically acceptable salts, hydrates, solvates, tautomers, or optical isomers thereof.

71. The compound of claim 70 further defined as:

![Chemical Structure]

or pharmaceutically acceptable salts thereof, and substantially free from other optical isomers thereof.
72. The compound according to claim 52, further defined as:

\[
\text{wherein } R_a \text{ is azido, fluoro, hydroxyamino, alkoxyamino}_{(C_6H_{12})} \text{ or substituted alkoxyamino}_{(C_6H_{12})};
\]

or pharmaceutically acceptable salts, esters, hydrates, solvates, tautomers, prodrugs, or optical isomers thereof.

73. The compound of claim 72, further defined as:

\[
\text{or pharmaceutically acceptable salts, hydrates, solvates, tautomers, or optical isomers thereof.}
\]

74. The compound of claim 73, further defined as:

\[
\text{or pharmaceutically acceptable salts thereof, and substantially free from other optical isomers thereof.}
\]
75. The compound of claim 72, further defined as:

![Chemical Structure](image1)

...or pharmaceutically acceptable salts, hydrates, solvates, tautomers, or optical isomers thereof.

76. The compound of claim 75, further defined as:

![Chemical Structure](image2)

...or pharmaceutically acceptable salts thereof, and substantially free from other optical isomers thereof.

77. The compound of claim 72, further defined as:

![Chemical Structure](image3)

...or pharmaceutically acceptable salts, hydrates, solvates, tautomers, or optical isomers thereof.
78. The compound of claim 77, further defined as:

![Compound Image]

or pharmaceutically acceptable salts thereof, and substantially free from other optical isomers thereof.

79. The compound of claim 72, further defined as:

![Compound Image]

or pharmaceutically acceptable salts, hydrates, solvates, tautomers, or optical isomers thereof.

80. The compound of claim 79, further defined as:

![Compound Image]

or pharmaceutically acceptable salts thereof, and substantially free from other optical isomers thereof.
81. A compound of the formula:

or pharmaceutically acceptable salts, hydrates, solvates, tautomers, or optical isomers thereof.

82. The compound of claim 81, further defined as:

or pharmaceutically acceptable salts thereof, and substantially free from other optical isomers thereof.

83. A compound of the formula:

or pharmaceutically acceptable salts, hydrates, solvates, tautomers, or optical isomers thereof.
84. The compound of claim 83 further defined as:

or pharmaceutically acceptable salts thereof, and substantially free from other optical isomers thereof.

85. A compound of the formula:

or pharmaceutically acceptable salts, hydrates, solvates, tautomers, or optical isomers thereof.

86. The compound of claim 85 further defined as:

or pharmaceutically acceptable salts thereof, and substantially free from other optical isomers thereof.
87. A compound of the formula:

![Chemical structure 1]

or pharmaceutically acceptable salts, hydrates, solvates, tautomers, or optical isomers thereof.

88. The compound of claim 87 further defined as:

![Chemical structure 2]

or pharmaceutically acceptable salts thereof, and substantially free from other optical isomers thereof.

89. A compound of the formula:

![Chemical structure 3]

or pharmaceutically acceptable salts, hydrates, solvates, tautomers, or optical isomers thereof.
90. The compound of claim 89 further defined as:

![Chemical structure](image)

or pharmaceutically acceptable salts thereof, and substantially free from other optical isomers thereof.

91. A compound of the formula:

![Chemical structure](image)

or pharmaceutically acceptable salts, hydrates, solvates, tautomers, or optical isomers thereof.

92. The compound of claim 91 further defined as:

![Chemical structure](image)

or pharmaceutically acceptable salts thereof, and substantially free from other optical isomers thereof.

93. A compound selected from the group consisting of:

\[(4aS,6aR,6bS,8aR,12aR,14aR,14bS)-methyl-11-fluoro-2,2,6a,6b,9,9,12a,14a,14b-10,14-dioxo-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-octadecahydropicene-4a-carboxylate,\]
(4aS,6aR,6bS,8aR,12aS,14aR,14bS)-methyl-2,2,6a,6b,9,9,12a-heptamethyl-10,14-dioxo-1-(1H-tetrazol-5-yl)-1,2,3,4,4a,5,6,6a,6b,7,7,8,8a,9,10,12a,14,14a,14b-octadecahydropicene-4a-carboxylate,

(4aS,6aR,6bS,8aR,12aS,14aR,14bS)-methyl-11-(hydroxycarbamoyl)-2,2,6a,6b,9,9,12a-heptamethyl-10,14-dioxo-1,2,3,4,4a,5,6,6a,6b,7,7,8,8a,9,10,12a,14,14a,14b-octadecahydropicene-4a-carboxylate,

(4aS,6aR,6bS,8aR,12aS,14aR,14bS)-methyl-2,2,6a,6b,9,9,12a-heptamethyl-11-(methylsulfonylcarbamoyl)-10,14-dioxo-1,2,3,4,4a,5,6,6a,6b,7,7,8,8a,9,10,12a,14,14a,14b-octadecahydropicene-4a-carboxylate,

(4aS,6aR,6bS,8aR,12aS,14aR,14bS)-l-cyano-N-hydroxy-2,2,6a,6b,9,9,12a-heptamethyl-10,14-dioxo-1,2,3,4,4a,5,6,6a,6b,7,7,8,8a,9,10,12a,14,14a,14b-octadecahydropicene-4a-carboxamide,

(4aS,6aR,6bS,8aR,12aS,14aR,14bS)-l-cyano-N-methoxy-2,2,6a,6b,9,9,12a-heptamethyl-10,14-dioxo-1,2,3,4,4a,5,6,6a,6b,7,7,8,8a,9,10,12a,14,14a,14b-octadecahydropicene-4a-carboxamide,

(4aS,6aR,6bS,8aR,12aS,14aR,14bS)-l-cyano-2,2,6a,6b,9,9,12a-octamethyl-10,14-dioxo-1,2,3,4,4a,5,6,6a,6b,7,7,8,8a,9,10,12a,14,14a,14b-octadecahydropicene-4a-carboxylate,

(4aS,6aR,6bS,8aR,12aS,14aR,14bS)-l-cyano-2,2,6a,6b,9,9,12a-heptamethyl-10,14-dioxo-1,2,3,4,4a,5,6,6a,6b,7,7,8,8a,9,10,12a,14,14a,14b-octadecahydropicene-4a-carbonyl azide,

(4aS,6aR,6bS,8aR,12aS,14aR,14bS)-methyl-1-cyano-2,2,6a,6b,9,9,12a-octamethyl-10,14-dioxo-1,2,3,4,4a,5,6,6a,6b,7,7,8,8a,9,10,12a,14,14a,14b-octadecahydropicene-4a-carboxylate,

(4aS,6aR,6bS,8aR,12aS,14aR,14bS)-l-cyano-N-(2-hydroxyethyl)-2,2,6a,6b,9,9,12a-heptamethyl-10,14-dioxo-1,2,3,4,4a,5,6,6a,6b,7,7,8,8a,9,10,12a,14,14a,14b-octadecahydropicene-4a-carbonyl fluoride,

(4aS,6aR,6bS,8aR,12aS,14aR,14bS)-methyl-2,2,6a,6b,9,9,12a-heptamethyl-14-oxo-1,2,3,4,4a,5,6,6a,6b,7,7,8,8a,9,10,12a,14,14a,14b-octadecahydropicene-4a-carboxylate,
A compound of the formula:

![Chemical Structure Diagram]

or pharmaceutically acceptable salts, hydrates, solvates, tautomers, or optical isomers thereof.
95. The compound of claim 94, further defined as:

![Chemical Structure](image)

or pharmaceutically acceptable salts thereof, and substantially free from other optical isomers thereof.

96. The compound according to any one of claims 1-95, wherein the compound is in the form of a pharmaceutically acceptable salt.

97. The compound according to any one of claims 1-95, wherein the compound is not a salt.

98. The compound according to any one of claims 1-41 and 52-72, wherein the compound is in the form of an ester.

99. The compound of claim 98, wherein the ester results from a condensation reaction between a hydroxy group of the formula and the carboxylic acid group of biotin.

100. The compound according to any one of claims 1-41 and 52-72, wherein the compound is present as a mixture of stereoisomers.

101. The compound according to any one of claims 1-41 and 52-72, wherein the compound is present as a single stereoisomer.

102. The compound of any of claims 1-80 and 93, wherein the compound is effective for inhibiting IFN-γ-induced NO production in macrophages, further wherein the compound has an IC50 value of less than 0.2 µM.

103. A pharmaceutical composition comprising as an active ingredient a compound according to any one of claims 1-95 and a pharmaceutically acceptable carrier.

104. The pharmaceutical composition of claim 103, wherein the composition is adapted for administration by a route selected from the group consisting of orally, intraadiposally, intraarterially, intraarticularly, intracranially, intradermally, intralesionally,
intramuscularly, intranasally, intraocularally, intrapericardially, intraperitoneally, intrapleurally, intraprostatically, intrarectally, intrathecially, intravesically, intravitreally, liposomally, locally, mucosally, orally, parenterally, rectally, subconjunctival, subcutaneously, sublingually, topically, transbuccally, transdermally, vaginally, in crèmes, in lipid compositions, via a catheter, via a lavage, via continuous infusion, via infusion, via inhalation, via injection, via local delivery, via localized perfusion, bathing target cells directly, or any combination thereof.

105. The composition of claim 104, wherein the composition is formulated for oral delivery.

106. The composition of claim 105, wherein the composition is formulated as a hard or soft capsule, a tablet, a syrup, a suspension, a wafer, or an elixir.

107. The composition of claim 106, wherein the soft capsule is a gelatin capsule.

108. The composition of claim 105, further comprising a protective coating.

109. The composition of claim 105, further comprising an agent that delays absorption.

110. The composition of claim 105, further comprising an agent that enhances solubility or dispersibility.

111. The composition of claim 103, wherein the compound is dispersed in a liposome, an oil and water emulsion or a water and oil emulsion.

112. A therapeutic method comprising administering a pharmaceutically effective compound of any one of claims 1-95 to a subject.

113. The method of claim 112, wherein the subject is a human.


115. A method of treating cancer in a subject, comprising administering to the subject a pharmaceutically effective amount of a compound according to any of claims 1-95.
116. The method of claim 115, wherein the cancer is a carcinoma, sarcoma, lymphoma, leukemia, melanoma, mesothelioma, multiple myeloma, or seminoma.

117. The method of claim 115, wherein the cancer is of the bladder, blood, bone, brain, breast, central nervous system, colon, endometrium, esophagus, genitourinary tract, head, larynx, liver, lung, neck, ovary, pancreas, prostate, spleen, small intestine, large intestine, stomach, or testicle.

118. The method of claim 115, wherein the subject is a primate.

119. The method of claim 115, wherein the subject is a human.

120. The method of claim 115, further comprising identifying a subject in need of treatment.

121. The method of claim 120, wherein the subject has a family or patient history of cancer.

122. The method of claim 115, wherein the subject has symptoms of cancer.

123. The method of claim 115, wherein the compound is administered locally.

124. The method of claim 123, wherein the compound is administered by direct intratumoral injection or by injection into tumor vasculature.

125. The method of claim 115, wherein the compound is administered systemically.

126. The method of claim 125, wherein the compound is administered intravenously, intra-arterially, intramuscularly, intraperitoneally, subcutaneously or orally.

127. The method of claim 115, wherein the pharmaceutically effective amount is 0.1 - 1000 mg/kg.

128. The method of claim 127, wherein the pharmaceutically effective amount is administered in a single dose per day.

129. The method of claim 127, wherein the pharmaceutically effective amount is administered in two or more doses per day.
130. The method of claim 115, wherein the compound is administered by contacting a tumor cell during ex vivo purging.

131. The method of claim 115, wherein the method comprises:
   a) inducing cytotoxicity in a tumor cell;
   b) killing a tumor cell;
   c) inducing apoptosis in a tumor cell;
   d) inducing differentiation in a tumor cell; or
   e) inhibiting growth in a tumor cell.

132. The method of claim 131, wherein the tumor cell is a leukemia cell.

133. The method of claim 131, wherein the tumor cell is a bladder cancer cell, a breast cancer cell, a lung cancer cell, a colon cancer cell, a prostate cancer cell, a liver cancer cell, a pancreatic cancer cell, a stomach cancer cell, a testicular cancer cell, a brain cancer cell, an ovarian cancer cell, a lymphatic cancer cell, a skin cancer cell, a brain cancer cell, a bone cancer cell, or a soft tissue cancer cell.

134. The method of claim 115, further comprising a treatment selected from the group consisting of administering a pharmaceutically effective amount of a second drug, radiotherapy, gene therapy, and surgery.

135. The method of claim 134, further comprising (1) contacting a tumor cell with the compound prior to contacting the tumor cell with the second drug, (2) contacting a tumor cell with the second drug prior to contacting the tumor cell with the compound, or (3) contacting a tumor cell with the compound and the second drug at the same time.

136. The method of claim 134, wherein the second drug is an antibiotic, anti-inflammatory, anti-neoplastic, anti-proliferative, anti-viral, immunomodulatory, or immunosuppressive.

137. The method of claim 134, wherein the second drug is an alkylating agent, androgen receptor modulator, cytoskeletal disruptor, estrogen receptor modulator, histone-deacetylase inhibitor, HMG-CoA reductase inhibitor, prenyl-protein transferase
inhibitor, retinoid receptor modulator, topoisomerase inhibitor, or tyrosine kinase inhibitor.

138. The method of claim 134, wherein the second drug is 5-azacitidine, 5-fluorouracil, 9-cis-retinoic acid, actinomycin D, alitretinoin, all-trans-retinoic acid, annamycin, axitinib, belinostat, bevacizumab, bexarotene, bosutinib, busulfan, capecitabine, carboplatin, carmustine, CD437, cediranib, cetuximab, chlorambucil, cisplatin, cyclophosphamide, cytarabine, dacarbazine, dasatinib, daunorubicin, decitabine, docetaxel, dolastatin-10, doxifluridine, doxorubicin, epirubicin, erlotinib, etoposide, gefitinib, gemcitabine, gemtuzumab ozogamicin, hexamethylmelamine, idarubicin, ifosfamide, imatinib, irinotecan, isotretinoin, ixabepilone, lapatinib, LBH589, lomustine, mechlorethamine, melphalan, mercaptopurine, methotrexate, mitomycin, mitoxantrone, MS-275, neratinib, nilotinib, nitrosourea, oxaliplatin, paclitaxel, plicamycin, procarbazine, semaxanib, semustine, sodium butyrate, sodium phenylacetate, streptozotocin, suberoylanilide hydroxamic acid, sunitinib, tamoxifen, teniposide, thiopeta, thioquanine, topotecan, TRAIL, trastuzumab, tretinoin, trichostatin A, valproic acid, valrubicin, vandetanib, vinblastine, vincristine, vindesine, or vinorelbine.

139. A method of treating or preventing a disease with an inflammatory component in a subject, comprising administering to the subject a pharmaceutically effective amount of a compound of any of claims 1-95.

140. The method of claim 139, wherein the disease is lupus or rheumatoid arthritis.

141. The method of claim 139, wherein the disease is an inflammatory bowel disease.

142. The method of claim 141, wherein the inflammatory bowel disease is Crohn's disease or ulcerative colitis.

143. The method of claim 139, wherein the disease with an inflammatory component is a cardiovascular disease.

144. The method of claim 139, wherein the disease with an inflammatory component is diabetes.

145. The method of claim 144, wherein the diabetes is type 1 diabetes.
146. The method of claim 144, wherein the diabetes is type 2 diabetes.

147. The method of claim 144, wherein the pharmaceutically effective amount of the also effectively treats one or more complications associated with diabetes.

148. The method of claim 147, wherein the complications are selected from the group consisting of obesity, hypertension, atherosclerosis, coronary heart disease, stroke, peripheral vascular disease, hypertension, nephropathy, neuropathy, myonecrosis, retinopathy and metabolic syndrome (syndrome X).

149. The method of claim 139, wherein the disease with an inflammatory component is metabolic syndrome (syndrome X).

150. The method of claim 139, wherein the disease with an inflammatory component is a skin disease.

151. The method of claim 150, wherein the administration is topical or oral.

152. The method of claim 150, wherein the skin disease is psoriasis, acne, or atopic dermatitis.

153. A method of treating or preventing a cardiovascular disease in a subject, comprising administering to the subject a pharmaceutically effective amount of a compound of any of claims 1-95.

154. The method of claim 153, wherein the cardiovascular disease is atherosclerosis, cardiomyopathy, congenital heart disease, congestive heart failure, myocarditis, rheumatic heart disease, valve disease, coronary artery disease, endocarditis, or myocardial infarction.

155. The method of claim 153, further comprising administering a pharmaceutically effective amount of a second drug.

156. The method of claim 155, wherein the second drug is a cholesterol lowering drug, an anti-hyperlipidemic, a calcium channel blocker, an anti-hypertensive, or an HMG-CoA reductase inhibitor.
157. The method of claim 156, wherein the second drug is amlodipine, aspirin, ezetimibe, felodipine, lacidipine, lercanidipine, nicardipine, nifedipine, nimodipine, nisoldipine or nitrendipine.

158. The method of claim 156, wherein the second drug is atenolol, bucindolol, carvedilol, clonidine, doxazosin, indoramin, labetalol, methyldopa, metoprolol, nadolol, oxprenolol, phenoxybenzamine, phentolamine, pindolol, prazosin, propranolol, terazosin, timolol or tolazoline.

159. The method of claim 155, wherein the second drug is a statin.

160. The method of claim 159, wherein the statin is atorvastatin, cerivastatin, fluvastatin, lovastatin, mevastatin, pitavastatin, pravastatin, rosuvastatin or simvastatin.

161. A method of treating or preventing a neurodegenerative disease in a subject, comprising administering to the subject a pharmaceutically effective amount of a compound of any of claims 1-95.

162. The method of claim 161, wherein said neurodegenerative disease is selected from the group consisting of Parkinson's disease, Alzheimer's disease, multiple sclerosis (MS), Huntington's disease and amyotrophic lateral sclerosis.

163. The method of claim 162, wherein said neurodegenerative disease is Alzheimer's disease.

164. The method of claim 162, wherein said neurodegenerative disease is MS.

165. The method of claim 164, wherein the MS is primary progressive, relapsing-remitting secondary progressive or progressive relapsing.

166. The method of claim 164, wherein the treatment suppresses the demyelination of neurons in the subject's brain or spinal cord.

167. The method of claim 166, wherein the treatment suppresses inflammatory demyelination.

168. The method of claim 164, wherein the treatment suppresses the transection of neuron axons in the subject's brain or spinal cord.
169. The method of claim 164, wherein the treatment suppresses the transection of neurites in the subject's brain or spinal cord.

170. The method of claim 164, wherein the treatment suppresses neuronal apoptosis in the subject's brain or spinal cord.

171. The method of claim 164, wherein the treatment stimulates the remyelination of neuron axons in the subject's brain or spinal cord.

172. The method of claim 164, wherein the treatment restores lost function after an MS attack.

173. The method of claim 164, wherein the treatment prevents a new MS attack.

174. The method of claim 164, wherein the treatment prevents a disability resulting from an MS attack.

175. The method of claim 164, wherein the subject is a primate.

176. The method of claim 175, wherein the primate is a human.

177. A method of treating or preventing a disorder characterized by overexpression of iNOS genes in a subject, comprising administering to the subject a pharmaceutically effective amount of a compound according to any of claims 1-95.

178. A method of inhibiting IFN-γ-induced nitric oxide production in cells of a subject, comprising administering to said subject a pharmaceutically effective amount of a compound of any of claims 1-95.

179. A method of treating or preventing a disorder characterized by overexpression of COX-2 genes in a subject, comprising administering to the subject a pharmaceutically effective amount of compound of any of claims 1-95.

180. A method of treating renal/kidney disease (RKD) in a subject, comprising administering to the subject a pharmaceutically effective amount of a compound of any of claims 1-95.

181. The method of claim 180, wherein the RKD results from a toxic insult.
182. The method of claim 181, wherein the toxic insult results from an imaging agent or a drug.

183. The method of claim 182, wherein the drug is a chemotherapeutic.

184. The method of claim 180, wherein the RKD results from ischemia/reperfusion injury.

185. The method of claim 180, wherein the RKD results from diabetes or hypertension.

186. The method of claim 180, wherein the RKD results from an autoimmune disease.

187. The method of claim 180, wherein the RKD is chronic RKD.

188. The method of claim 180, wherein the RKD is acute RKD.

189. The method of claim 180, wherein the subject has undergone or is undergoing dialysis.

190. The method of claim 180, wherein the subject has undergone or is a candidate to undergo kidney transplant.

191. The method of claim 180, wherein the subject is a primate.

192. The method of claim 191, wherein the primate is a human.

193. The method of claim 180, wherein the subject is a cow, horse, dog, cat, pig, mouse, rat or guinea pig.

194. A method for improving glomerular filtration rate or creatinine clearance in a subject, comprising administering to the subject a pharmaceutically effective amount of a compound of any of claims 1-95.

195. A method of making a first compound defined as:
comprising reacting a compound of formula

with diphenylphosphorylazide (DPPA) to form the first compound.

196. A kit comprising:

- a compound of any one of claims 1-95; and
- instructions which comprise one or more forms of information selected from the group consisting of indicating a disease state for which the compound is to be administered, storage information for the compound, dosing information and instructions regarding how to administer the compound.

197. The kit according to claim 196, wherein the kit comprises the compound in a multiple dose form.

198. An article of manufacture comprising:

- a compound of any one of claims 1-95; and
- packaging materials.

199. The article of manufacture according to claim 198, wherein the packaging materials comprise a container for housing the compound.

200. The article of manufacture according to claim 199, wherein the container comprises a label indicating one or more members of the group consisting of a disease state for which the compound is to be administered, storage information, dosing information and/or instructions regarding how to administer the compound.

201. The article of manufacture according to claim 198, wherein the article of manufacture comprises the compound in a multiple dose form.
FIG. 1
FIG. 3
FIG. 4
FIG. 6
FIG. 7
FIG. 8
FIG. 9
FIG. 10

[Graph showing 402-55 nM response to different concentrations of IFNγ (20 ng/ml)].
FIG. 11
FIG. 13
FIG. 15
FIG. 16
FIG. 20

[Graph showing fold change in TrxR for different samples, with error bars indicating variability.]
FIG. 22