Title: CYTOKINE INHIBITORS

Abstract: The present invention provides low molecular weight compounds useful as cytokine inhibitors, and compositions thereof. In particular, compounds of the invention are useful as anti-inflammatory agents. There are further provided methods for the preparation of such agents and their use in preventing or treating conditions mediated by cytokines, such as for example arthritis, pain, cardiovascular disease and cancer.
CYTOKINE INHIBITORS

RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application No. 60/884,571, entitled “Cytokine Inhibitors”, filed January 11, 2007, and U.S. Provisional Application No. 60/950,091, entitled “Cytokine Inhibitors”, filed July 16, 2007, the entire contents of which are incorporated herein by reference. This application is related to U.S. Application No. 10/939,324, filed September 10, 2004, entitled “Cytokine Inhibitors”, International Application No. PCT/US2006/006682, filed February 23, 2006, entitled “Cytokine Inhibitors and Their Use in Therapy”, and International Application No. PCT/US2007/070547, filed June 8, 2007, entitled “Therapy using Cytokine Inhibitors,” the entire contents of each of which is incorporated by reference.

FIELD OF THE INVENTION

[0002] The present invention relates to low molecular weight compounds and compositions thereof, useful as cytokine inhibitors, and their preparation. The invention further relates to methods of treating, preventing, modifying and managing a variety of conditions, including cytokine-mediated disorders or related disorders, which comprise the administration of a cytokine inhibitor, alone or in combination with known therapeutics. The invention also relates to pharmaceutical compositions and dosing regimens using the disclosed compounds, optionally in conjunction with other therapies, for the treatment of a variety of conditions, including autoimmune diseases, inflammatory diseases, cardiovascular diseases, cancer, and the like.

BACKGROUND OF THE INVENTION

[0003] The functioning of the immune system is finely balanced by the activities of pro-inflammatory and anti-inflammatory mediators or cytokines. Some cytokines promote inflammation and are called pro-inflammatory cytokines, whereas other cytokines suppress the activity of pro-inflammatory cytokines and are referred to as anti-inflammatory cytokines. For example, IL-4, IL-10, and IL-13 are potent activators of B lymphocytes, but are also potent anti-inflammatory agents. They are anti-inflammatory cytokines by virtue of their
ability to suppress genes for pro-inflammatory cytokines such as IL-1, TNF, and chemokines (C.A. Dinarello, Chest. 2000, 118, 503).

[0004] Unregulated activities of these mediators can lead to the development of serious inflammatory conditions. For example, autoimmune diseases arise when immune system cells (lymphocytes, macrophages) become sensitized against the "self". Lymphocytes as well as macrophages are usually under control in this system. However, a misdirection of the system toward the body's own tissues may happen in response to still unexplained triggers. One hypothesis is that lymphocytes recognize an antigen which mimics the "self" and a cascade of activation of different components of the immune system takes place, ultimately leading to tissue destruction. Genetic predisposition has also been postulated to be responsible for autoimmune disorders.

[0005] Tumor necrosis factor-α (TNF-α) and interleukin-1 (IL-1) are pro-inflammatory cytokines that mediate inflammatory responses associated with infectious agents and other cellular stresses. Overproduction of cytokines such as IL-1 and TNF-α is believed to underlie the progression of many inflammatory diseases including rheumatoid arthritis (RA), Crohn's disease, inflammatory bowel disease, multiple sclerosis, endotoxin shock, osteoporosis, Alzheimer's disease, congestive heart failure, and psoriasis among others (Dinarello, C.A. et al., Rev. Infect. Diseases 1984, 6, 51; Salituro et al., Curr. Med. Chem. 1999, 6, 807; Henry et al., Drugs Fut. 1999, 24,1345). Recent data from clinical trials support the use of protein antagonists of cytokines, for example soluble TNF-α receptor fusion protein (etanercept) (Moreland et al., Ann. Intern. Med. 1999, 130, 478) or the monoclonal TNFα antibody (infliximab), for the treatment of rheumatoid arthritis, Crohn’s disease, juvenile chronic arthritis and psoriatic arthritis (Rankin et al., Br. J. Rheumatol. 1995, 34, 334; Galadari et al. Int J Dermatol. 2003, 42,231; Reimold, Am J Med Sci. 2003, 325(2), 75). Thus, the reduction of pro-inflammatory cytokines such as TNF-α (also referred to as TNFa) and interleukin-1β (IL-1b) has become an accepted therapeutic approach for potential drug intervention in these conditions.

**SUMMARY OF THE INVENTION**

[0006] The present invention provides low molecular weight compounds and pharmaceutical compositions thereof. In particular, compounds of the invention are useful
for a variety of applications including, e.g., as cytokine release inhibitory agents. There are further provided methods for the preparation of such compounds and for the use of these compounds alone, in mixtures thereof, or in mixtures with other therapeutic agents, in the preparation of medicaments for use in treating various disease states. For example, methods are provided for the use of compounds of the invention in the prevention and treatment of various disorders mediated by cytokines such as inflammatory, cardiovascular, and autoimmune disorders, cancer, pain, and others.

[0007] Thus, there are provided in accordance with one aspect of the invention a compound of Formula I:

![Formula I](image)

stereoisomers thereof, tautomers thereof, solvates thereof, prodrugs thereof, and pharmaceutically acceptable salts thereof, wherein:

G is phenyl or pyrazolyl, wherein G is substituted by one or more R¹, R² or R³;
X is C(O) or C(S);
Ar is (Y)-naphthyl;
Y is C(O) or C(NOR);
L-Q is selected from:
1) –O-(C₁₋₄ alkyl)-Q, wherein Q is CN, O-(C₁₋₄ alkyl)-OR, N(C₁₋₄ alkyl-OR)₂,
2) ![Diagrams](image) or ![Diagrams](image) or ![Diagrams](image) or ![Diagrams](image)
each R¹ is independently F, Cl, Br, I, NR₂, CN, or a substituted or unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl or heterocyclylalkyl group;

each R² is independently F, Cl, Br, I, CN, NO₂, a substituted or unsubstituted alkyl, heterocyclyl, or heterocyclylalkyl group, OR', C(O)R'', C(O)OR', C(O)NR'₂, NR'₂, NRC(O)R'', NR'₂C(O)OR'', NR'SO₂R'', NR'₂C(O)NR'₂, NR'₂C(S)NR'₂, S(O)₃R'', or SO₂NR'₂;

each R³ is independently a substituted or unsubstituted alkyl, alkenyl, or alkynyl group, or an O(C₁₋₄ alkyl) group, wherein each alkyl group is optionally partially or fully halogenated;

R⁴ is a substituted or unsubstituted C₁₋₄ alkyl, NH-(C₁₋₄ alkyl), NH-aralkyl, or NH-heterocyclylalkyl group;

R⁵ is selected from substituted or unsubstituted -NH-(C₁₋₄ alkyl) group or a substituted or unsubstituted heterocyclyl selected from:
R² is selected from a substituted or un-substituted C₁-₄ alkyl, heterocyclyl, NH-(C₁-₄ alkyl), NH-alkylaryl, or NH-heterocyclylalkyl group;

R' is selected from F or Cl, or a substituted or un-substituted NH-(C₂-₈ alkyl) group;

each R is independently hydrogen or a substituted or un-substituted C₁-₄ alkyl group;

each R' is independently hydrogen, or a substituted or un-substituted alkyl, cycloalkyl, cycloalkylalkyl, aryl, heterocyclyl, aralkyl, or heterocyclylalkyl group;

each R'' is independently a substituted or un-substituted alkyl, cycloalkyl, cycloalkylalkyl, aryl, heterocyclyl, aralkyl or heterocyclylalkyl group; and

each m is independently 0, 1 or 2.

[0008] In some embodiments of compounds of Formula I, G is

![Diagram](image)

[0009] In other embodiments of compounds of Formula I, Ar is

![Diagram](image)

[0010] In other embodiments of compounds of Formula I, L-Q is O-(C₂-₃ alkyl)-Q, and Q is -N(C₂-₃ alkyl-OR)₂,

![Diagram](image)

[0011] In some such embodiments, L-Q is
[0012] In some embodiments of compounds of Formula I, L-Q is

and $R^4$ is a substituted or unsubstituted C$_{1-4}$ alkyl or -NH-(C$_{1-5}$ alkyl) group. In some such embodiments, $R^4$ is

[0013] In some embodiments of compounds of Formula I, L-Q is

and $R^5$ is selected from substituted or unsubstituted

[0014] In some other embodiments of compounds of Formula I, L-Q is
and R^6 is
\[
\frac{1}{2}\text{CH}_3 \quad \text{or} \quad \frac{1}{2}\text{N}\text{-}N^+\text{-}
\]

[0015] In other embodiments of compounds of Formula I, L-Q is
\[
\frac{1}{2}\text{N}\text{-}R^7
\]
and R^7 is F, or a 3,3-dimethylbutan-1-amine-1-yl group.

[0016] In some embodiments of compounds of Formula I, R^1 is a substituted or unsubstituted C_{1-6} alkyl, or heterocyclyl group. For example, R^1 is a substituted or unsubstituted methyl, isopropyl, tert-butyl, isobutyl, sec-butyl, neopentyl, cyclohexyl, pyrrolidinyl, piperidinyl, piperazinyl, oxazepanyl, morpholinyl, or thiomorpholinyl group.

[0017] In some embodiments of compounds of Formula I, R^2 is a substituted or unsubstituted (C_{1-6} alkyl), heterocyclyl, or heterocyclylalkyl group, F, Br, CN, C(O)NR^2, C(O)R^3, S(O)mR^3, NR^3SO_2R^3, or SO_2NR^3. For example, R^2 is F, Br, CN, CF_3, imidazolyl, triazolyl, tetrazolyl, C(O)NH_2, C(O)NH(C_{1-6} alkyl), C(O)NH(C_{3-6} cycloalkyl), C(O)NH(heterocyclyl), C(O)NH(heterocyclylalkyl), (CH_2)_1,1-heterocyclylalkyl), C(O)-heterocyclyl, NHSO_2(C_{1-6} alkyl), NHSO_2(C_{3-6} cycloalkyl), NHSO_2(heterocyclyl), SO_2NH(C_{1-6} alkyl), SO_2N(C_{1-6} alkyl)_2, wherein each C_{1-6} alkyl, C_{3-6} cycloalkyl, heterocyclyl, and heterocyclylalkyl group is substituted or unsubstituted. In some such embodiments, the C_{1-6} alkyl or C_{3-6} cycloalkyl group is a methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, sec-butyl, isobutyl, neopentyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, wherein the alkyl or cycloalkyl group is optionally substituted by OH or N(C_{1-3} alkyl)_2. In others, the heterocyclyl group is a pyrrolidinyl, piperidinyl, piperazinyl, azepanyl, or 3,8-diazabicyclo[3.2.1]octanyl group. In still others, the heterocyclylalkyl group is a (CH_2)_1,3-pyrrolidinyl, (CH_2)_1,3-piperidinyl, (CH_2)_1,3-piperazinyl, (CH_2)_1,3-furanyl, (CH_2)_1,3-oxazolyl, or (CH_2)_1,3-isoxazolyl group. In some such embodiments, the heterocyclyl and heterocyclylalkyl group is substituted with a substituent selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, sec-butyl, isobutyl, neopentyl, (CH_2)_1,3-cyclopropyl, (CH_2)_1,3-cyclobutyl, (CH_2)_1,3-cyclopentyl,
(CH₂)₃-cyclohexyl, (CH₂)₂-OH, (CH₂)₃NH(C₁-₃ alkyl), (CH₂)₃N(C₁-₃ alkyl)₂, and (CH₂)₃-pyrrolidinyl.

[0018] In some embodiments of compounds of Formula I, R³ is a substituted or unsubstituted C₁-₄ alkyl or O(C₁-₄ alkyl) group, or is a partially or fully halogenated O(C₁-₂ alkyl) group.

[0019] In some embodiments of compounds of Formula I, G is phenyl and R¹ a substituted or unsubstituted methyl, isopropyl, tert-butyl, isobutyl, sec-butyl, neopentyl, cyclohexyl, pyrrolidinyl, piperidinyl, piperazinyl, oxazepanyl, morpholinyl, or thiomorpholinyl group. In some such embodiments, R² is a substituted or unsubstituted (C₁-₆ alkyl) or heterocyclylalkyl group, F, Br, CN, C(O)NR‘₂, C(O)R‘₃, S(O)₃R‘₄, NR‘SO₂R‘₅, or SO₂NR‘₂. For example, R² is F, Br, CN, CF₃, imidazoyl, triazolyl, tetrazolyl, C(O)NH₂, C(O)NH(C₁-₆ alkyl), C(O)NH(C₅-₆ cycloalkyl), C(O)NH(heterocyclyl), C(O)NH(heterocyclylalkyl), (CH₂)₁₋₃-heterocyclylalkyl, C(O)-heterocyclyl, NHCO₂(C₁-₆ alkyl), NH₃(C₅-₆ cycloalkyl), NHCO₂(heterocyclyl), SO₂NH(C₁-₆ alkyl), SO₂N(C₁-₆ alkyl)₂, wherein each C₁-₆ alkyl, C₅-₆ cycloalkyl, heterocyclyl, and heterocyclylalkyl group is substituted or unsubstituted. In some such embodiments, the C₁-₆ alkyl or C₅-₆ cycloalkyl group is a methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, sec-butyl, isobutyl, neopentyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl. In others, the heterocyclyl group is a pyrrolidinyl, piperidinyl, piperazinyl, azepanyl, or 3,8-diazabicyclo[3.2.1]octanyl group. In still others, the heterocyclylalkyl group is a (CH₂)₁₋₃-pyrrolidinyl, (CH₂)₁₋₃-piperidinyl, (CH₂)₁₋₃-piperazinyl, (CH₂)₁₋₃-furanyl, (CH₂)₁₋₃-oxazolyl, or (CH₂)₁₋₃-isoxazolyl group. In some such embodiments, the C₁-₆ alkyl, C₅-₆ cycloalkyl, heterocyclyl, and heterocyclylalkyl group is substituted with methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, sec-butyl, isobutyl, neopentyl, (CH₂)₀₋₃-cyclopropyl, (CH₂)₀₋₃-cyclobutyl, (CH₂)₀₋₃-cyclopentyl, (CH₂)₀₋₃-cyclohexyl, (CH₂)₀₋₃-OH, (CH₂)₀₋₃NH(C₁-₃ alkyl), (CH₂)₀₋₃N(C₁-₃ alkyl)₂, or (CH₂)₀₋₃-pyrrolidinyl. In some such embodiments, R² is a substituted or unsubstituted C₁-₄ alkyl or O(C₁-₄ alkyl) group, or is a partially or fully halogenated O(C₁-₂ alkyl) group.

[0020] Where features or aspects of the invention are described in terms of Markush groups or other grouping of alternatives, those skilled in the art will recognize that the
invention is also thereby described in terms of any individual member or subgroup of members of the Markush group or other group. By way of illustration and not limitation, Table 1 sets forth various combinations of substituents of Formula 1 as described herein. Thus, e.g., combination 1006 describes those embodiments in which G is phenyl and L-Q is O-(C₃-₄ alkyl)- N(C₃-₄ alkyl-OR)₂.

Table 1: Exemplary combinations of G and L-Q for Formula 1.

<table>
<thead>
<tr>
<th>G</th>
<th>Phenyl</th>
<th>Pyrazolyl</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>O-(C₃-₄ alkyl)-CN</td>
<td>1000</td>
<td>1001</td>
<td>1002</td>
</tr>
<tr>
<td>O-(C₃-₄ alkyl)-O-(C₃-₄ alkyl)-OR</td>
<td>1003</td>
<td>1004</td>
<td>1005</td>
</tr>
<tr>
<td>O-(C₃-₄ alkyl)- N(C₃-₄ alkyl-OR)₂</td>
<td>1006</td>
<td>1007</td>
<td>1008</td>
</tr>
<tr>
<td>O-(C₂-₃ alkyl)- N(C₂-₃ alkyl-OR)₂</td>
<td>1009</td>
<td>1010</td>
<td>1011</td>
</tr>
<tr>
<td>O-(C₃-₄ alkyl)</td>
<td>1012</td>
<td>1013</td>
<td>1014</td>
</tr>
<tr>
<td>O-(C₃-₄ alkyl)</td>
<td>1015</td>
<td>1016</td>
<td>1017</td>
</tr>
<tr>
<td>O-(C₃-₄ alkyl)</td>
<td>1018</td>
<td>1019</td>
<td>1020</td>
</tr>
<tr>
<td>O-(C₃-₄ alkyl)</td>
<td>1021</td>
<td>1022</td>
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<td>1034</td>
<td>1035</td>
</tr>
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</table>
[0021] Table 2 sets forth various combinations of substituents X and Y of Formula I. Thus, e.g., combination 2000 describes those embodiments in which X is C(O) and Y is C(O). Further, those skilled in the art will understand that a combination of substituents is permissible only if such a combination results in a chemically stable compound, and that any combination from Table 1, describing G and L-Q, may be combined with any combination from Table 2, describing X and Y. For example, combination 1006 from Table 1 and combination 2000 from Table 2 describe those embodiments of Formula I in which G is phenyl, L-Q is O-(C\textsubscript{1-4} alkyl)- N(C\textsubscript{1-4} alkyl-OR\textsubscript{2})\textsubscript{2}, X is C(O) and Y is C(O). Each G and L-Q in the tables is understood to be optionally substituted as described herein. Moreover, each value of R\textsuperscript{1} (F, Cl, Br, I, NR\textsubscript{2}, CN, or a substituted or unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl or heterocyclylalkyl group) may be combined with any combination from Table 1 or Table 2 or any pair of combinations from the two tables. Thus, e.g., it will be understood that combination 2000 describes those embodiments
in which R₁ is F, X is C(O) and Y is C(O), as well as those where R₁ is –NR₂, X is C(O) and Y is C(O), etc.

<table>
<thead>
<tr>
<th>Y</th>
<th>C(O)</th>
<th>C(NOR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C(O)</td>
<td>2000</td>
<td>2001</td>
</tr>
<tr>
<td>C(S)</td>
<td>2002</td>
<td>2003</td>
</tr>
</tbody>
</table>

[0022] In another embodiment, the cytokine inhibitor is selected from List 1.

**List 1.**

N-(5-tert-butyl-2-methoxy-3-(methylsulfonamido)phenyl)-2-(hydroxyimino)-2-(4-(2-(pyrrolidin-1-yl)pyrimidin-4-ylamino)naphthalen-1-yl)acetamide;

N-(5-tert-butyl-2-methoxy-3-(methylsulfonamido)phenyl)-2-hydroxy-2-(4-(2-(pyrrolidin-1-yl)pyrimidin-4-ylamino)naphthalen-1-yl)acetamide;

N-(5-tert-butyl-2-methoxy-3-(methylsulfonamido)phenyl)-2-(4-(3-cyanopropoxy)naphthalen-1-yl)-2-oxoacetamide;

N-(5-tert-butyl-2-methoxy-3-(propylsulfonamido)phenyl)-2-(4-(3-cyanopropoxy)naphthalen-1-yl)-2-oxoacetamide;

N-(5-tert-butyl-2-methoxy-3-(methylsulfonamido)phenyl)-2-(4-(2-(2-methoxyethoxy)ethoxy)naphthalen-1-yl)-2-oxoacetamide;

N-(5-tert-butyl-2-methoxy-3-(propylsulfonamido)phenyl)-2-(4-(2-(2-methoxyethoxy)ethoxy)naphthalen-1-yl)-2-oxoacetamide;

2-(4-bromonaphthalen-1-yl)-N-(3-tert-butyl-5-cyanophenyl)-2-oxoacetamide;

N-(3-tert-butyl-5-cyanophenyl)-2-oxo-2-(4-(2-(pyrrolidin-1-yl)pyrimidin-4-ylamino)naphthalen-1-yl)acetamide;

N-(3-fluoro-5-morpholinophenyl)-2-oxo-2-(4-(2-(pyrrolidin-1-yl)pyrimidin-4-ylamino)naphthalen-1-yl)acetamide;

N-(3-tert-butyl-5-cyanophenyl)-2-(4-(2-morphinoethoxy)naphthalen-1-yl)-2-oxoacetamide;
N-(3-fluoro-5-morpholinophenyl)-2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-o xoacetamide;
N-(5-tert-butyl-3-cyano-2-methoxyphenyl)-2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2 oxoacetamide;
N-(3-tert-butyl-1-p-tolyl-1H-pyrazol-5-yl)-2-oxo-2-(4-(2-(pyrrolidin-1-yl)pyrimidin-4 ylamino)naphthalen-1-yl)acetamide;
N-(3-tert-butyl-1-m-tolyl-1H-pyrazol-5-yl)-2-oxo-2-(4-(2-(pyrrolidin-1-yl)pyrimidin-4 ylamino)naphthalen-1-yl)acetamide;
N-(3-cyano-5-morpholinophenyl)-2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2 oxoacetamide;
N-(3-morpholino-5-(trifluoromethyl)phenyl)-2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2 oxoacetamide;
2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxo-N-(3-(piperidin-1-yl)-5-(trifluoromethyl)phenyl)acetamide;
2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxo-N-(3-(pyrrolidin-1-yl)-5-(trifluoromethyl)phenyl)acetamide;
N-(3-bromo-5-tert-butyl-2-methoxyphenyl)-2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2 oxoacetamide;
N-(5-tert-butyl-2-methoxyphenyl)-2-oxo-2-(4-(2-(pyrrolidin-1-yl)pyrimidin-4 ylamino)naphthalen-1-yl)acetamide;
5-tert-butyl-2-methoxy-3-(2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamido)-N (oxazol-2-yl)methyl)benzamide;
5-tert-butyl-2-methoxy-N-(5-methylfuran-2-yl)methyl)-3-(2-(4-(2 morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamido)benzamide;
N-(3-cyano-5-(piperidin-1-yl)phenyl)-2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2 oxoacetamide;
N-(3-cyano-5-(pyrrolidin-1-yl)phenyl)-2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2 oxoacetamide;
N-(5-tert-butyl-3-cyano-2-methoxyphenyl)-2-oxo-2-(4-(2,2,6,6-tetramethylmorpholino)ethoxy)naphthalen-1-yl)acetamide;
2-(4-(2-(8-oxa-3-aza-bicyclo[3.2.1]octan-3-yl)ethoxy)naphthalen-1-yl)-N-(5-tert-butyl-2 methoxy-3-(methylsulfonamido)phenyl)-2-oxoacetamide;
2-(4-(2-(8-oxa-3-aza-bicyclo[3.2.1]octan-3-yl)ethoxy)naphthalen-1-yl)-N-(5-tert-butyl-3-cyano-2-methoxyphenyl)-2-oxoacetamide;
N-(5-tert-butyl-2-methoxy-3-(1H-tetrazol-5-yl)phenyl)-2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamide;
N-(5-tert-butyl-2-methoxy-3-(methylsulfonamido)phenyl)-2-(4-(2-(4-methylpiperazin-1-yl)pyrimidin-4-ylamino)naphthalen-1-yl)-2-oxoacetamide;
2-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-2-oxo-N-(4-(2-(2,2,6,6-tetramethylmorpholino)ethoxy)naphthalen-1-yl)acetamide;
N-(4-(2-(8-oxa-3-aza-bicyclo[3.2.1]octan-3-yl)ethoxy)naphthalen-1-yl)-2-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-2-oxoacetamide;
N-(5-tert-butyl-2-methoxy-3-(methylsulfonamido)phenyl)-2-oxo-2-(4-(2,2,6,6-tetramethylmorpholino)pyrimidin-4-ylamino)naphthalen-1-yl)acetamide;
N-(5-tert-butyl-2-methoxy-3-(methylsulfonamido)phenyl)-2-oxo-2-(4-(2-(piperazin-1-yl)pyrimidin-4-ylamino)naphthalen-1-yl)acetamide;
N-(5-tert-butyl-2-methoxy-3-(methylsulfonamido)phenyl)-2-oxo-2-(4-(4-(piperazin-1-yl)pyrimidin-2-ylamino)naphthalen-1-yl)acetamide;
N-(5-tert-butyl-3-cyano-2-methoxyphenyl)-2-oxo-2-(4-(2,2,6,6-tetramethylmorpholino)pyrimidin-4-ylamino)naphthalen-1-yl)acetamide;
2-(4-(2-(8-oxa-3-aza-bicyclo[3.2.1]octan-3-yl)pyrimidin-4-ylamino)naphthalen-1-yl)-N-(5-tert-butyl-3-cyano-2-methoxyphenyl)-2-oxoacetamide;
N-(5-tert-butyl-3-cyano-2-methoxyphenyl)-2-(4-(2-(3,3-dimethylbutylamino)pyridin-4-ylamino)naphthalen-1-yl)-2-oxoacetamide;
N-(5-tert-butyl-3-cyano-2-methoxyphenyl)-2-(4-(2-(2,6-dimethylpiperidin-1-yl)ethylamino)pyridin-4-ylamino)naphthalen-1-yl)-2-oxoacetamide;
N-(5-tert-butyl-3-cyano-2-methoxyphenyl)-2-oxo-2-(4-(pyridin-4-ylamino)naphthalen-1-yl)acetamide;
N-(5-tert-butyl-2-methoxy-3-(methylsulfonamido)phenyl)-2-(4-(2-(3,5-dimethylpiperazin-1-yl)pyrimidin-4-ylamino)naphthalen-1-yl)-2-oxoacetamide;
N-(5-tert-butyl-2-methoxy-3-(methylsulfonamido)phenyl)-2-(4-(4-(3,5-dimethylpiperazin-1-yl)pyrimidin-2-ylamino)naphthalen-1-yl)-2-oxoacetamide;
N-(5-tert-Butyl-3-methanesulfonylamino-2-methoxy-phenyl)-2-[4-(2-(10-oxa-4-aza-tricyclo[5.2.1.02,6]dec-4-yl)-ethoxy]-naphthalen-1-yl]-2-oxo-acetamide;
N-(5-tert-Butyl-3-cyano-2-methoxy-phenyl)-2-(4-[2-(10-oxa-4-aza-tricyclo[5.2.1.02,6]dec-4-
yl)-ethoxy]-naphthalen-1-yl)-2-oxo-acetamide;
N-(5-tert-butyl-2-methoxy-3-(methylsulfonamido)phenyl)-2-(4-(2-(3,3-
dimethylbutylamino)pyridin-4-ylamino)naphthalen-1-yl)-2-oxoacetamide;
-2-(4-(2-(bis(2-hydroxyethyl)amino)ethoxy)-naphthalen-1-yl)-N-(5-tert-butyl-2-methoxy-3-
(methylsulfonamido)phenyl)-2-oxoacetamide;
4-(2-(4-(2-(5-tert-butyl-2-methoxy-3-(methylsulfonamido)phenylamino)-2-
-oxoacetyl)naphthalen-1-yloxy)ethyl)morpholine 4-oxide;
N-(5-tert-butyl-3-cyano-2-methoxyphenyl)-2-(4-(2-methylpyridin-4-yl)naphthalen-1-yl)-2-
oxoacetamide;
N-(5-tert-butyl-3-cyano-2-methoxyphenyl)-2-oxo-2-(4-(pyridin-4-yl)naphthalen-1-
yl)acetamide;
N-(5-tert-butyl-3-cyano-2-methoxyphenyl)-2-oxo-2-(4-(pyridin-3-yl)naphthalen-1-
yl)acetamide
N-(5-tert-butyl-3-cyano-2-methoxyphenyl)-2-(4-(6-methoxypyridin-3-yl)naphthalen-1-yl)-2-
oxoacetamide;
N-(5-tert-butyl-3-cyano-2-methoxyphenyl)-2-(4-(6-fluoropyridin-3-yl)naphthalen-1-yl)-2-
oxoacetamide;
N-(5-tert-butyl-3-cyano-2-methoxyphenyl)-2-(4-(2-(4-methylpiperazin-1-yl)pyridin-4-
yl)naphthalen-1-yl)-2-oxoacetamide;
-2-(4-(2-(bis(2-methoxyethyl)amino)ethoxy)naphthalen-1-yl)-N-(5-tert-butyl-2-methoxy-3-
(methylsulfonamido)phenyl)-2-oxoacetamide;
N-(5-tert-butyl-3-cyano-2-methoxyphenyl)-2-(4-(6-(methylamino)pyridin-3-yl)naphthalen-1-
yl)-2-oxoacetamide;
N-(5-tert-butyl-3-cyano-2-methoxyphenyl)-2-(4-(6-(3,3-dimethylbutylamino)pyridin-3-
yl)naphthalen-1-yl)-2-oxoacetamide;
N-(5-tert-butyl-2-methoxy-3-(4-methylpiperazine-1-sulfonamido)phenyl)-2-(4-(2-
morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamide;
N-(3-tert-butyl-5-(4-methylpiperazin-1-yl)methyl)phenyl)-2-oxo-2-(4-(pyridin-3-
yl)naphthalen-1-yl)acetamide;
N-(5-tert-butyl-3-cyano-2-methoxyphenyl)-2-oxo-2-(4-(2-(pyrrolidin-1-yl)pyrimidin-4-
yl)amino)naphthalen-1-yl)acetamide;
N-(5-tert-butyl-3-cyano-2-methoxyphenyl)-2-(4-(2-((4-methyl-1,4-diazepan-1-yl)pyrimidin-4-ylamino)naphthalen-1-yl)-2-oxoacetamide;  
N-(5-tert-butyl-3-cyano-2-methoxyphenyl)-2-(4-(2-((4-morpholino-piperidin-1-yl)pyrimidin-4-ylamino)naphthalen-1-yl)-2-oxoacetamide;  
(E)-2-(4-(2-(8-oxa-3-aza-bicyclo[3.2.1]octan-3-yl)ethoxy)naphthalen-1-yl)-N-(5-tert-butyl-3-cyano-2-methoxyphenyl)-2-(hydroxyimino)acetamide;  
(E)-2-(4-(2-(8-oxa-3-aza-bicyclo[3.2.1]octan-3-yl)pyrimidin-4-ylamino)naphthalen-1-yl)-N-(5-tert-butyl-3-cyano-2-methoxyphenyl)-2-(hydroxyimino)acetamide;  
N-(5-tert-butyl-2-methoxy-3-(methylsulfonamido)phenyl)-2-oxo-2-(4-(2,2,6,6-tetramethylmorpholino)ethoxy)naphthalen-1-yl)acetamide;  
N-(5-tert-butyl-2-methoxyphenyl)-2-(4-(2-(cyclopropylamino)pyridin-4-ylamino)naphthalen-1-yl)-2-oxoacetamide;  
N-(5-tert-butyl-2-methoxyphenyl)-2-(4-(2-(3,3-dimethylbutylamino)pyridin-4-ylamino)naphthalen-1-yl)-2-oxoacetamide;  
N-(5-tert-butyl-2-methoxyphenyl)-2-(4-(2-(2,6-dimethylpiperidin-1-yl)ethyamino)pyridin-4-ylamino)naphthalen-1-yl)-2-oxoacetamide;  
N-(5-tert-butyl-2-methoxyphenyl)-2-(4-(2-methylpyridin-4-ylamino)naphthalen-1-yl)-2-oxoacetamide;  
N-(5-tert-butyl-3-cyano-2-methoxyphenyl)-2-(4-(2-methylpyridin-4-ylamino)naphthalen-1-yl)-2-oxoacetamide;  
2-(4-(2-(benzylamino)pyridin-4-ylamino)naphthalen-1-yl)-N-(5-tert-butyl-2-methoxyphenyl)-2-oxoacetamide;  
(S)-N-(5-tert-butyl-2-methoxyphenyl)-2-oxo-2-(4-(2-(1-phenylethylamino)pyridin-4-ylamino)naphthalen-1-yl)acetamide;  
2-(4-(2-(benzylamino)pyridin-4-ylamino)naphthalen-1-yl)-N-(5-tert-butyl-3-cyano-2-methoxyphenyl)-2-oxoacetamide;  
(S)-N-(5-tert-butyl-3-cyano-2-methoxyphenyl)-2-oxo-2-(4-(2-(1-phenylethylamino)pyridin-4-ylamino)naphthalen-1-yl)acetamide;  
N-(5-tert-butyl-2-methoxy-3-(piperazine-1-carbonyl)phenyl)-2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamide;  
N-(5-tert-butyl-2-methoxy-3-(4-methylpiperazine-1-carbonyl)phenyl)-2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamide;
N-(5-tert-butyl-3-(4-isopropylpiperazine-1-carboxyl)-2-methoxyphenyl)-2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamide;
N-(5-tert-butyl-3-(4-(cyclopropylmethyl)piperazine-1-carboxyl)-2-methoxyphenyl)-2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamide;
N-(5-tert-butyl-3-(4-(2-hydroxyethyl)piperazine-1-carboxyl)-2-methoxyphenyl)-2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamide;
N-(5-tert-butyl-2-methoxy-3-(4-methyl-1,4-diazepane-1-carboxyl)phenyl)-2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamide;
(R)-N-(5-tert-butyl-3-(3-(dimethylamino)pyrrolidine-1-carboxyl)-2-methoxyphenyl)-2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamide;
5-tert-butyl-2-methoxy-N-(1-methylpiperidin-4-yl)-3-(2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamido)benzamide;
(S)-N-(5-tert-butyl-3-cyano-2-methoxyphenyl)-2-oxo-2-(4-(1-phenylethylamino)pyrimidin-4-ylamino)naphthalen-1-yl)acetamide;
N-(3-(3,8-diaza-bicyclo[3.2.1]octane-3-carboxyl)-5-tert-butyl-2-methoxyphenyl)-2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamide;
N-(5-tert-butyl-3-cyano-2-methoxyphenyl)-2-(4-(2-cyclopropylamino)pyrimidin-4-ylamino)naphthalen-1-yl)-2-oxoacetamide;
5-tert-butyl-2-methoxy-3-(2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamido)N-(piperidin-4-yl)benzamide;
5-tert-butyl-2-methoxy-3-(2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamido)N-(piperidin-3-yl)benzamide;
N-(5-tert-butyl-2-methoxyphenyl)-2-(4-(2-cyclopropylamino)pyrimidin-4-ylamino)naphthalen-1-yl)-2-oxoacetamide;
5-tert-butyl-N-((1-ethylpyrrolidin-2-yl)methyl)-2-methoxy-3-(2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamido)benzamide;
5-tert-butyl-2-methoxy-N-((1-methylpiperidin-4-yl)methyl)-3-(2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamido)benzamide;
(S)-N-(5-tert-butyl-2-methoxy-3-(2-(pyrrolidin-1-ylmethyl)pyrrolidine-1-carboxyl)phenyl)-2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamide;
N-(5-tert-butyl-3-(2-(dimethylamino)methyl)piperidine-1-carboxyl)-2-methoxyphenyl)-2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamide;
5-tert-butyl-2-methoxy-3-(2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamido)-N-(2-pyrrolidin-1-yl)ethyl benzamide;
5-tert-butyl-2-methoxy-N-((1-methylpiperidin-2-yl)methyl)-3-(2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamido)benzamide;
3-tert-butyl-5-(2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamido)-N-(piperidin-3-yl)benzamide;
3-tert-butyl-5-(2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamido)-N-(2-pyrrolidin-2-yl)ethyl benzamide;
3-tert-butyl-N-(2-(methylamino)ethyl)-5-(2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamido)benzamide;
3-tert-butyl-N-(2-(diethylamino)ethyl)-5-(2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamido)benzamide;
N-(5-tert-butyl-3-(1H-imidazol-1-yl)-2-methoxyphenyl)-2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamide;
N-(5-tert-butyl-2-methoxy-3-(4-methyl1H-imidazol-1-yl)phenyl)-2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamide;
2-(4-(2-(8-oxa-3-aza-bicyclo[3.2.1]octan-3-yl)pyrimidin-4-ylamino)naphthalen-1-yl)-N-(5-tert-butyl-2-methoxy-3-(methylsulfonamido)phenyl)-2-oxoacetamide;
N-(3-azido-5-tert-butyl-2-methoxyphenyl)-2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamide;
N-(5-tert-butyl-2-methoxy-3-(1H-1,2,3-triazol-1-yl)phenyl)-2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamide;
N-(5-tert-butyl-3-(4-(hydroxymethyl)-1H-1,2,3-triazol-1-yl)-2-methoxyphenyl)-2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamide;
N-(5-tert-butyl-2-methoxy-3-(4-(trimethylsilyl)-1H-1,2,3-triazol-1-yl)phenyl)-2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamide;
N-(5-tert-butyl-3-(N,N-dimethylsulfamoyl)-2-methoxyphenyl)-2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamide;
N-(3-tert-butyl-5-(methylsulfonamido)phenyl)-2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamide;
N-(5-tert-butyl-2-methoxy-3-(methylsulfonfyl)phenyl)-2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamide;
N-((2-(8-oxa-3-aza-bicyclo[3.2.1]octan-3-yl)ethoxy)naphthalen-1-yl)-2-(5-tert-butyl-2-methylfuran-3-yl)-2-oxoacetamide;
(E)-N-((2-(8-oxa-3-aza-bicyclo[3.2.1]octan-3-yl)ethoxy)naphthalen-1-yl)-2-(5-tert-butyl-2-methylfuran-3-yl)-2-(hydroxyimino)acetamide;
(Z)-N-((2-(8-oxa-3-aza-bicyclo[3.2.1]octan-3-yl)ethoxy)naphthalen-1-yl)-2-(5-tert-butyl-2-methylfuran-3-yl)-2-(hydroxyimino)acetamide;
(Z)-N-((2-(8-oxa-3-aza-bicyclo[3.2.1]octan-3-yl)ethoxy)naphthalen-1-yl)-2-(3-tert-butyl-1-methyl-1H-pyrrozol-5-yl)-2-(hydroxyimino)acetamide;
(E)-N-((2-(8-oxa-3-aza-bicyclo[3.2.1]octan-3-yl)ethoxy)naphthalen-1-yl)-2-(3-tert-butyl-1-methyl-1H-pyrrozol-5-yl)-2-(hydroxyimino)acetamide
N-(5-tert-butyl-2-methoxy-3-(methylsulfonamido)phenyl)-2-oxo-2-(4-(2-(piperidin-1-yl)ethoxy)naphthalen-1-yl)acetamide;
2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-N-(naphthalen-2-yl)-2-oxoacetamide;
N-(5-isopropyl-2-methoxyphenyl)-2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamide;
2-(5-tert-butyl-2-methoxy-3-(methylsulfonamido)phenyl)-N-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamide; and

tautomers thereof, solvates thereof, prodrugs thereof, and pharmaceutically acceptable salts thereof.

[0023] In some embodiments, the compounds of the invention at a concentration of 10 μM inhibit induced TNFα-release from a cell by about 50% or greater than 50%.

[0024] In another aspect, there are provided compounds of Formula II:

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   \[ \text{N} \]
   \[ \text{X} \]
   \[ \text{N}^\text{P} \]
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Formula II

wherein X is CN, CF₃, or a halogen (such as F, Br or Cl); and Pₙ is H or an amine protecting group, such as a Boc group. Compounds of Formula II are useful intermediates in the synthesis of various cytokine inhibitors described herein (see Examples).
In another aspect, the invention provides compositions comprising a compound as described herein and a pharmaceutically acceptable carrier.

In yet another aspect, the invention provides methods of treating disorders mediated by cytokines, including but not limited to inflammatory disorders, autoimmune disorders, cardiovascular disorders, cancer and pain. The methods include administering to a subject in need of such treatment a therapeutically effective amount of a compound as described herein. In some such embodiments, the cytokine-mediated disorder is a p38 MAPK-mediated disorder. In other embodiments, the cytokine is selected from TNFa, IL-1, IL-6, IL-8, GM-CSF, and IFN-gamma, or a combination of any two or more thereof. In others, the cytokine is TNFa or IL-1. In some embodiments, the method further includes administration of additional therapeutic ingredients (hereafter referred to as ingredient A), as described herein.

Cytokine-mediated disorders include rheumatoid arthritis, osteoarthritis, Crohn's disease, ulcerative colitis, psoriatic arthritis, traumatic arthritis, rubella arthritis, inflammatory bowel disease, multiple sclerosis, graft versus host disease, systemic lupus erythematosus, toxic shock syndrome, irritable bowel syndrome, muscle degeneration, allograft rejections, pancreatitis, insulinitis, glomerulonephritis, diabetic nephropathy, renal fibrosis, chronic renal failure, gout, leprosy, acute synovitis, Reiter's syndrome, gouty arthritis, Behcet's disease, spondylitis, endometriosis, non-articular inflammatory conditions, such as intervertebral disk syndrome conditions, bursitis, tendonitis, tenosynovitis or fibromyalgic syndrome; and acute or chronic pain, including but not limited to neurological pain, neuropathies, polyneuropathies, diabetes-related polyneuropathies, trauma, migraine, tension and cluster headache, Horton's disease, varicose ulcers, neuralgias, musculo-skeletal pain, osteo-traumatic pain, fractures, algodystrophy, spondylarthitis, fibromyalgia, phantom limb pain, back pain, vertebral pain, post-surgery pain, herniated intervertebral disc-induced sciatica, cancer-related pain, vascular pain, visceral pain, childbirth-related pain, or HIV-related pain.

Other cytokine-mediated disorders are stroke, chronic heart failure, endotoxemia, reperfusion injury, ischemia reperfusion, myocardial ischemia, restenosis, thrombosis, angiogenesis, coronary heart disease, coronary artery disease, acute coronary
syndrome, Takayasu arteritis, cardiac failure such as heart failure, cardiomyopathy, myocarditis, vasculitis, vascular restenosis, valvular disease or coronary artery bypass; hypercholesteremia, diseases or conditions related to blood coagulation or fibrinolysis, such as for example, acute venous thrombosis, pulmonary embolism, thrombosis during pregnancy, hemorrhagic skin necrosis, acute or chronic disseminated intravascular coagulation (DIC), clot formation from surgery, long bed rest or long periods of immobilization, venous thrombosis, fulminant meningococcemia, acute thrombotic strokes, acute coronary occlusion, acute peripheral arterial occlusion, massive pulmonary embolism, axillary vein thrombosis, massive iliofemoral vein thrombosis, occluded arterial or venous cannulae, cardiomyopathy, venoocclusive disease of the liver, hypotension, decreased cardiac output, decreased vascular resistance, pulmonary hypertension, diminished lung compliance, leucopenia or thrombocytopenia; or atherosclerosis. Yet others are allergic conjunctivitis, uveitis, glaucoma, optic neuritis, retinal ischemia, diabetic retinopathy, laser induced optic damage, or surgery or trauma-induced proliferative vitreoretinopathy. Cytokine-mediated disorders further include allergic rhinitis, asthma, adult respiratory distress syndrome, chronic pulmonary inflammation, chronic obstructive pulmonary disease, obliterative bronchiolitis, emphysema, bronchitis, mucus hypersecretion, silicosis, SARS infection and respiratory tract inflammation. Also included are psoriasis, pemphigus, eczema, atopic dermatitis, contact dermatitis, or acne. Yet other cytokine-mediated disorders are Guillain-Barre syndrome, Parkinson’s disease, Huntington’s disease, Alzheimer’s disease, amyotrophic lateral sclerosis, multiple sclerosis and other demyelinating diseases, viral and bacterial meningitis, CNS trauma, spinal cord injury, seizures, convulsions, olivopontocerebellar atrophy, AIDS dementia complex, MERRF and MELAS syndromes, Leber’s disease, Wernicke’s encephalopathy, Rett syndrome, homocysteinuria, hyperprolinemia, hyperhomocysteinemia, nonketotic hyperglycemia, hydroxybutyric aminoaciduria, sulfite oxidase deficiency, combined systems disease, lead encephalopathy, Tourett's syndrome, hepatic encephalopathy, drug addiction, drug tolerance, drug dependency, depression, anxiety, schizophrenia, aneurism, or epilepsy. In another aspect of the invention, the cytokine-mediated disorders include bone resorption diseases such as osteopetrosis, osteoporosis, or osteoarthritis. Also included are diabetes, systemic cachexia, cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome (AIDS), obesity, anorexia or bulimia nervosa. Additionally, the cytokine-mediated disease can be sepsis, HIV infection,
HCV infection, malaria, infectious arthritis, leishmaniasis, Lyme disease, cancer, including but not limited to breast cancer, colon cancer, lung cancer, prostatic cancer, multiple myeloma, acute myelogenous leukemia, myelodysplastic syndrome, non-Hodgkins lymphoma, osteosarcoma or follicular lymphoma, Castleman’s disease, or drug resistance. In some embodiments, the cytokine-mediated disorder is rheumatoid arthritis, osteoarthritis, Crohn’s Disease, ulcerative colitis, inflammatory bowel disease, diabetes, psoriatic arthritis, psoriasis, pemphigus, chronic obstructive pulmonary disease, pain, atherosclerosis, ischemia reperfusion, restenosis, acute coronary syndrome, heart failure, multiple myeloma, follicular lymphoma or osteosarcoma.

[0029] In some embodiments of the invention, the cytokine mediated disorder is a neutrophil-mediated disorder, such as, for example, bronchial asthma, rhinitis, influenza, stroke, myocardial infarction, thermal injury, adult respiratory distress syndrome (ARDS), multiple organ injury secondary to trauma, acute glomerulonephritis, dermatoses with acute inflammatory components, acute purulent meningitis, hemodialysis, leukopheresis, granulocyte transfusion associated syndromes, or necrotizing enterocolitis.

[0030] In some embodiments of the invention, the cytokine mediated disorder is or results from abnormal bleeding, an abscess, actinie reticuloid syndrome, acute confusional migraine, acute confusional senile dementia, acute hepatocellular injury, acute tubular necrosis, adenohypophyseal diseases, adenovirus infections, adhesions, adhesive capsulitis, adenitis, agammaglobulinemia, allergy, alopecia, fibrosing alveolitis, amyloidosis, angioplasty, angor pectoris, antiphospholipid syndrome, arteriosclerotic dementia, arteritis temporal, arthropod-borne encephalitis, asphyxia, atopic hypersensitivity, atrial fibrillation, beaver fever, biliary cirrhosis, bone loss, bronchiolitis, cancer of endocrine gland, cancer of larynx, candidiasis, small cell lung carcinoma, cardiac hypertrophy, cardiac surgery, cardiomegaly, carditis, carotid angioplasty, carotid endarterectomy, carotid stents, carotid ulcer, celiac disease, cirrhosis, colitis, colitis granulomatous, coronary artery bypass graft, coronary artery bypass surgery, cortical cataracts, corticosteroid-resistant asthma, degenerative joint disease, dermatitis, diarrhea, erectile neuropathy, erectile vasculopathy, (particularly diabetic erectile neuropathy and vasculopathy) dry eye, dyslipidemia (including hyperlipidemia (increased lipids), hypercholesterolemia (increased cholesterol), hyperglyceridemia (increased glycerides), hypertriglyceridemia (increased triglycerides),

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hyperlipoproteinemia (increased lipoproteins), hyperchylomicronemia (increased chylomicrons), combined hyperlipidemia (increased LDL and triglycerides), familial hypercholesterolemia (hypercholesterolemia due to a defect on chromosome 19 (19p13.1-13.3)), hypolipoproteinemia (decreased lipoproteins), hypcholesterolemia (decreased cholesterol), abetalipoproteinemia (decreased beta lipoproteins), and Tangier disease (decreased high density lipoprotein), dyspnea, edema, end-stage renal disease, epstein-barr virus infections, fever, follicular thyroid carcinoma, gastroenteritis, heart attack, heart bypass surgery, heart surgery, heart transplantation, hepatitis A, hepatitis B, hepatitis C, chronic hepatitis, insulin resistance, kidney failure, kidney transplantation, adult chronic leukemia, liver cirrhosis, liver transplantation, meningitis, bacterial meningitis, myeloproliferative disorders, myopathies, myositis, neonatal-onset multisystem inflammatory disease, nephritis, neuromuscular disorders, neuropathy, obliterative bronchiolitis, oral cancer, percutaneous coronary intervention, periodontal bone loss, peripheral nerve disorders, neuropathy, peritoneal dialysis, pleural disease, pneumonitis, polymyositis, posterior capsular opacification, pruritus (including ocular, skin and general pruritus), pulmonary fibrosis, renal cancer, renal dialysis, scleroderma, septic arthritis, Sjogren's syndrome, ankylosing spondylitis, Still's disease, sympathetic ophthalmia, toxemia, tuberculosis, urticaria, viral hepatitis, or Wegener's granulomatosis.

[0031] In another aspect of the invention, there are provided methods of reducing levels of a cytokine in a subject. The methods comprise administering to a subject, such as a subject in need thereof, an amount of a compound as described herein or a stereoisomer, tautomer, solvate, prodrug, or pharmaceutically acceptable salt thereof, effective to reduce a level of a cytokine relative to the level prior to administration of the compound. In some embodiments, the reduction in cytokine levels is at least 10%, at least 30%, at least 50%, or at least 90%. In some embodiments the subject suffers from or is at risk for a cytokine mediated disorder, as described herein. In some embodiments, the cytokine is selected from TNFa, IL-1, IL-6, IL-8, GM-CSF, IFN-gamma, or a combination of any two or more thereof. In others, the cytokine is TNFa or IL-1. In some embodiments, the cytokine level is measured in the subject or samples from the subject, e.g., tissue or bodily fluids such as the subject’s blood. In others, cytokine level is measured in the subject’s synovium. In still others, the cytokine level is measured in the subject’s skin. In some embodiments of the
invention, the method further includes administration of additional therapeutic ingredients (hereafter referred to as ingredient A), as described herein.

[0032] In yet another aspect of the invention, there are provided methods of reducing the level of a cytokine released from a cell in response to a pro-inflammatory stimulus. The methods comprise exposing a cell to an amount of a compound as described herein, or a stereoisomer, tautomer, solvate, prodrug, or pharmaceutically acceptable salt thereof, effective to reduce the level of cytokine released from the cell in response to a pro-inflammatory stimulus relative to the level of released cytokine prior to contacting the cell with the compound. In some embodiments, the reduction in cytokine levels is at least 10%, at least 30%, at least 50%, or at least 90%. In some embodiments, the pro-inflammatory stimulus results from the presence of TNFa, IL-1, IL-6, IL-8, GM-CSF, IFN-gamma, LPS, or a combination of any two or more thereof. In other embodiments, the cytokine level is the level of TNFa, IL-1, IL-6, IL-8, GM-CSF, IFN-gamma, or a combination of any two or more thereof. In some embodiments of the invention, the method further includes exposing the cell to additional therapeutic ingredients (hereafter referred to as ingredient A), as described herein.

[0033] In yet another aspect of the invention, there are provided methods of inhibiting p38 activity. The methods comprise contacting p38 with an amount of a compound as described herein or a stereoisomer, tautomer, solvate, prodrug, or pharmaceutically acceptable salt thereof effective to inhibit p38 activity, the phosphorylation of p38, or both. In some embodiments, the inhibition of p38 activity or phosphorylation of p38 is at least 10%, at least 30%, at least 50%, or at least 90%. The p38 may be isolated such as in a cell-free in vitro system, a cellular preparation or it may be in a cell. In some other embodiments, the p38 is in a subject. In some embodiments, the subject suffers from, or is at risk for, a cytokine mediated disorder as described herein. In some embodiments of the invention wherein the p38 is in a subject, the method further includes administration of additional therapeutic ingredients (hereafter referred to as ingredient A) to the subject, as described herein.

[0034] In another aspect of the invention, there are provided methods of reducing the activity of a pro-inflammatory mediator. The methods comprise administering to a subject,
such as a subject in need thereof, an amount of a compound as described herein or a stereoisomer, tautomer, solvate, prodrug, or pharmaceutically acceptable salt thereof effective to reduce the activity of a pro-inflammatory mediator relative to the activity prior to the administration of the compound. In some embodiments, the reduction in pro-inflammatory mediator activity is at least 10%, at least 30%, at least 50%, or at least 90%. In certain embodiments, the subject suffers from or is at risk for a cytokine mediated disorder as described herein. In some embodiments, the reduction in activity results from a decrease in circulating levels of a pro-inflammatory mediator relative to the circulating levels prior to administration of the compound as described herein. In some such embodiments, the decrease in circulating pro-inflammatory mediator level is at least 10%, at least 30%, at least 50%, or at least 90%. In some such embodiments, the pro-inflammatory mediator is a prostaglandin or a leukotriene, or a combination of two or more thereof. In some other embodiments, the reduction in activity results from an inhibition of the production of a pro-inflammatory mediator. In some such embodiments, the inhibition of pro-inflammatory mediator production is at least 10%, at least 30%, at least 50%, or at least 90%. In some such embodiments, the pro-inflammatory mediator is a prostaglandin, leukotriene, COX-2, NO-synthase, or a combination of any two or more thereof. In some embodiments of the invention, the method further includes administration of additional therapeutic ingredients (hereafter referred to as ingredient A), as described herein.

[0035] In another aspect of the invention, there are provided methods of reducing the circulating levels of C-Reactive Protein or Rheumatoid Factor, or both. The methods comprise administering to a subject, such as a subject in need thereof, an amount of compound as described herein or a stereoisomer, tautomer, solvate, prodrug, or pharmaceutically acceptable salt thereof effective to reduce the circulating levels of C-Reactive Protein or Rheumatoid Factor, or both, in the subject's blood relative to the level prior to the administration of the compound. In some embodiments, the circulating C-Reactive Protein levels before administration are higher than about 2.87 mg/l. In some embodiments, the reduction in circulating level is at least 10%, at least 30%, at least 50%, or at least 90%. In some embodiments, the subject suffers from, or is at risk for, a cytokine mediated disorder as described herein. In certain embodiments of the invention, the method further includes administration of additional therapeutic ingredients (hereafter referred to as
ingredient A), as described herein, for example, the method further includes administration of methotrexate

[0036] In yet another aspect of the invention, there are provided methods of reducing at least one indicium of rheumatoid arthritis. The methods comprise administering to a subject exhibiting one or more indicia of rheumatoid arthritis, an amount of a compound as described herein or a stereoisomer, tautomer, solvate, prodrug, or pharmaceutically acceptable salt thereof, effective to reduce at least one of the indicia to a level below that which exists prior to the administration of the compound, wherein the indicia are selected from erythrocyte sedimentation rate (ESR), number of painful and tender joints, level of joint pain, joint tenderness, Ritchie articular index, duration of morning stiffness, joint immobility, joint swelling, and/or circulating C-reactive protein level. In some embodiments of the invention, the method further includes administration of additional therapeutic ingredients (hereafter referred to as ingredient A), as described herein.

[0037] Also provided are methods of reducing the number or severity of clinical signs of psoriasis. The methods comprise administering to a subject exhibiting one or more clinical signs of psoriasis an amount of a compound as described herein or a stereoisomer, tautomer, solvate, prodrug, or pharmaceutically acceptable salt thereof, effective to reduce the number or severity of clinical signs of psoriasis relative to those present in the subject prior to the administration of the compound, wherein the clinical signs of psoriasis are the percentage of total body surface area (BSA) affected by psoriasis, psoriasis plaque thickness, level of lymphocytes within psoriatic lesions, epidermal thickness, T-cell infiltration, pathological epidermal hyperplasia, cell-mediated immunity reactions, tetanus antibody response, lymphocyte subpopulations, or any two or more thereof. In some embodiments, one or more of the clinical signs of psoriasis, especially BSA, is reduced by at least 10%, by at least 30%, by at least 50%, by at least 70% or by at least 90%. In some embodiments of the invention, the method further includes administration of additional therapeutic ingredients (hereafter referred to as ingredient A), as described herein.

[0038] Combination therapy employing cytokine inhibitors of the invention in combination with additional ingredient(s) (hereinafter referred to as "ingredient A") provides a beneficial therapeutic effect, particularly an additive or over-additive effect or an overall
reduction of side effects of therapy. Such a beneficial therapeutic effect is desirable in the treatment of cytokine-mediated disorders as described herein, and in particular in the treatment of rheumatoid arthritis, Crohn's disease and psoriasis, and in the other methods described herein. Thus, in one aspect, the invention provides methods that further include administering to a subject one or more, typically one, of the ingredients A described herein together with one or more, typically one, compound of the invention. In some embodiments, the methods are for treating cytokine-mediated disorders or conditions. In some embodiments, a combination of any two or more ingredients A are administered with a compound as described herein. An additive or over-additive (e.g. synergistic) effect of the pharmaceutical combinations according to the invention provides for dose reduction, side-effect reduction and/or interval extension when compared to the individual compounds of the invention alone, or ingredient A alone. The effects mentioned above are observed both when the two substances are administered simultaneously in a single formulation and when they are administered successively in separate formulations. In the case of ingredient A being an injectable, especially a biological agent, other benefits of adding the compound of the invention may be seen, such as, for example, cost reduction by way of interval and/or dose reduction.

[0039] A variety of ingredients A are contemplated for use in the combinations of the invention. For example, non-steroidal anti-inflammatory drugs (NSAIDs), which are widely used for the treatment of inflammation, pain and fever, may be used. Such NSAIDs include acetaminophen, aspirin, ibuprofen, choline magnesium salicylate, choline salicylate, diclofenac, diflunisal, etodolac, fenoprofen calcium, flurbiprofen, indomethacin, ketoprofen, carprofen, indoprofen, ketorolac tromethamine, magnesium salicylate, meclofenamate sodium, mefenamic acid, oxaprozin, piroxicam, sodium salicylate, sulindac, tolmetin, meloxicam, rofecoxib, celecoxib, etoricoxib, valdecoxib, nabumetone, naproxen, lomoxicam, nimesulide, indoprofen, remifenvzone, salsalate, tiaprofenic acid, flosulide, and the like, or a combination of two or more thereof.

[0040] Angiogenesis inhibitors may serve as ingredient A, such as VEGF inhibitors, taxol, pentoxifylline and/or thalidomide.
[0041] Biological agents shall be understood to mean any natural or artificial/synthetic biological molecule or fragment thereof as known in the art, such as antibodies, proteins, fusion proteins, receptors, nucleic acids, lipids, carbohydrates, and the like. Therefore, ingredient A includes biological agents, such as etanercept, infliximab, alefacept, adalimumab, efalizumab, anakinra, IL-1RA, alpha-interferon, interferon beta 1-B, CTLA-4, and other antibodies or receptor constructs directed against TNFα, IL-1β, LFA-1, or C5.

[0042] Also within the scope of the invention for ingredient A are steroids, such as glucocorticoids, and vitamin D3 and analogs thereof (cholecalciferols), alone (the latter being used mostly for psoriasis) or in combination. Steroids include budesonide, dexamethasone, fluocinonide, hydrocortisone, betamethasone, halobetasol (ulobetasol), methylprednisolone, prednisolone, prednisone, clobetasone, deflazacort, fluocinolone acetonide, fluticasone, triamcinolone acetonide, mometasone and difluocortolone. Among vitamin D3 derivatives are calcipotriol, tacalcitol, maxacalcitol, and tacrolimus, the calcitropic hormones, 1α2,5-dihydroxyvitamin D3, and parathyroid hormone-related peptide.

[0043] Many types of immunomodulatory, immunosuppressive or cytotoxic drugs can be used in combination with the compounds as described herein. Exemplary agents include hydroxychloroquine, D-penicillamine, sulfasalazine, auranofin, gold sodium thiomalate, minocycline, dapsone, chlorambucil, mercaptopurine, tacrolimus, sirolimus, pimecrolimus, mycophenolate mofetil, cyclosporine, leflunomide, methotrexate, azathioprine, cyclophosphamide, macrolides, ascomycin, hydroxyurea, 6-thioguanine, (Orfános C E., 1999, Cutis 64 (5):347); alefacept, leflunomide, infliximab, etanercept, efalizumab, anti-CD4, anti-CD25, peptide T, LFA3TIP, alicaforsen, DAB389, CTLA-4Ig, anti-CD80, for example IDEC-114 or ABX-IL8, DAB-IL-2, IL-10, anti-TAC, basiliximab and daclizumab. In addition, agents or therapies which act on other targets or immune mediated products are suitable as the ingredient A. These include, for example, inhibitors of protein tyrosine kinases (PTKs) such as epidermal growth factor receptor (EGFR), E-selectin inhibitors, and therapies widely used for psoriasis such as anthralin, coal tar, phototherapies including ultraviolet B (UVB) or psoralens ultraviolet A (PUVA), photodynamic therapy and laser therapy.
Retinoid therapy can also be used as ingredient A. Thus, for example, becarotene, acitretin, etretinate, tazarotene, hydroxyurea, 6-thioguanine and phototherapies are suitable additional ingredients. (Orfanos C E., 1999, Cutis 64(5):347-53; see also Saurat J H., 1999, J.Am.Acad.Derm. 41(3 Pt 2):S2-6).

Ingredients A useful in the invention further include small molecule inhibitors directed against enzymes involved in signal transduction pathways or to cell adhesion molecules like LFA-1 or ICAM-1.

Statins and HMG-CoA reductase inhibitors may also be employed as ingredients A including, e.g., atorvastatin (LIPITOR, TORVAST), fluvastatin (LESCOL), lovastatin (MEVACOR, ALTOCOR), mevastatin, pitavastatin (LIVALO, PITAVA), pravastatin (PRAVACHOL, SELEKTINE, LIPOSTAT), rosuvastatin (CRESTOR), or simvastatin (ZOCOR, LIPEX). Other ingredients A contemplated for use in methods of the invention include fibrates, such as bezafibrate (e.g., BEZALIP), ciprofibrate (e.g., MODALIM), clofibrate, clinofibrate, gemfibrozil (e.g., LOPID), or fenofibrate; cholesterol absorption inhibitors, such as, ezetimibe (e.g., ZETIA); nicotinic acid; bile acid sequestrants, such as cholestyramine (QUESTRAN) and colestipol (COLESTID); and/or plant sterol-containing products and ω3-fatty acids. Also contemplated are the combination of two or more of the above, for example the combination of ezetimibe/simvastatin (VYTORIN or INEGY). Combination therapy with the above ingredients A is contemplated for use in any method of the invention including treatment of the cytokine-mediated disorders and conditions as well as in the methods described in the related applications, U.S. Application No. 10/939,324, International Application PCT/US2006/042679, International Application PCT/US2006/048803, and International Application No. PCT/US2006/006682, each of which is herein incorporated by reference in its entirety.

In another aspect, there are provided the above-mentioned combinations comprising ingredient A and one or more compounds as described herein, typically in therapeutically effective amounts, for use as pharmaceutical compositions with anti-cytokine activity. Moreover, combinations comprising ingredient A and a compound as described herein can be used for preparing a pharmaceutical composition for the treatment and/or prevention of a cytokine-mediated disorder or condition. The pharmaceutical preparations,
containing as the active substance one or more compound combinations comprising ingredient(s) A and the compound as described herein may further include the pharmaceutically acceptable derivatives thereof, and may be optionally combined with a conventional excipient, carrier, or combination thereof.

[0048] In psoriasis, known combination treatments have been effective and are used as rotation therapy for maintenance of remission or if the subject is refractory to usual systemic products. Most of the combinations are with different modes of action either to improve efficacy or to reduce side effects by reduction of the dosage. See Van de Kerkhof, P. 1997 Clinics in Dermatology, 15:831, which showed the effect of topical steroids or vitamin D with systemic agents. Two combinations which are widely accepted include ultraviolet B (UVB) or psoralens ultraviolet A (PUVA), each optionally administered with retinoids, methotrexate, or the combination of cyclosporine and retinoids.

[0049] A typical combination for treating psoriasis is the compound as described herein compound in combination with immunotherapy drugs which include cyclosporine, pimecrolimus, tacrolimus, ascomycin, anti-CD4, anti-CD25, peptide T, LFA3TIP, DAB389, CTLA-4Ig, E-selectin inhibitors, alefacept, infliximab, etanercept, efalizumab, and those disclosed in Griffiths, Christopher E. M., 1998 Hospital Medicine, Vol 59 No 7, and the obvious variants thereof. Another typical combination for treating psoriasis is the compound as described herein with methotrexate (MTX). It is expected this combination will be effective because of the good tolerability of MTX in the short term and because of the acceptability if maintenance of remission is obtained with good quality of life. Another typical combination for treating psoriasis is the compound as described herein with cyclosporine, especially because of cyclosporine’s efficiency for induction of remission. Another embodiment of the invention comprises administration in the following sequence: induction with the compound as described herein and cyclosporine, followed by continuation with after decrease of dosing and discontinuation of cyclosporine. Another typical combination for treating psoriasis is the compound as described herein in combination with retinoids. Retinoids provide minimal efficacy with potential Cyt P450 interactions and risk of teratogenicity, and this would be alleviated by continuation of therapy with the compound as described herein. Yet another typical combination for treating psoriasis is the compound as described herein, in combination with ingredients A selected from steroids, such as
glucocorticosteroids, vitamin D analogs, retinoids and dithranol. In some such combination treatments, the steroids and retinoids can be administered topically. A more typical combination for treating psoriasis is a compound as described herein with vitamin D derivatives, most typically calcipotriol or tacalcitol. Another typical combination for treating psoriasis is the compound as described herein in combination with macrolides, most typically with ascomycin analogues, administered topically, and even more typically with those available orally such as pimecrolimus. Another typical combination for treating psoriasis is the compound as described herein in combination with cell adhesion molecule inhibitors, such as anti-LFA3, and/or anti-LFA1. This includes adhesion molecule blockage by recombinant fusion proteins like alefacept, anti-LFA3-IgCl, or by anti-CD11 monoclonal antibodies, efalizumab, and the obvious variants thereof. Cell adhesion molecule inhibitors appear to provide an acceptable response rate with limited tolerability problems. Combination with a compound as described herein could avoid the disadvantage of their injectable form, with CAM inhibitors being used intermittently. Another embodiment of the invention comprises administration in the following sequence: induction with a compound as described herein and CAM inhibitors, followed by maintenance treatment with the compound as described herein alone and retreatment with CAM inhibitors in case of significant relapse.

Another typical combination for treating psoriasis is the compound as described herein with another anti-TNFa ingredient. A typical embodiment is one wherein the other anti-TNFa ingredient is selected from infliximab or etanercept, typically infliximab. Infliximab is believed to have a higher rate of response for induction of remission, which recently was suggested to be maintained on the long term. Within the scope of the invention is the use of topical or general antisense inhibitors of TNFa, such as alisaforsen, in combination with a compound as described herein. Another typical combination for treating psoriasis is the compound as described herein with anti-CD4, anti-CD80 (IDEC-114 or ABX-IL8), DAB IL-2, DAB385 IL-2, CTLA4-Ig, IL-10, the IL2 receptor inhibitors such as daclizumab (anti-TAC), or basiliximab. (See Tutrone, “Biologic Therapy for Psoriasis, A Brief History, I,” “Biologic Therapy for Psoriasis, 2001, 68, 331; Ben-Bassat, “Biological activity of tyrosine kinase inhibitors: Novel agents for psoriasis therapy,” Current Opinion in Investigational Drugs, 2001, 2 (11), 1539; Salim. et. al., “Targeting interleukin-2 as a treatment for psoriasis,” Current Opinion in Investigational Drugs, 2001, 2(11), 1546).
The combinations described above can also be used to reduce the number or severity of the clinical indicia of psoriasis.

Any of the above mentioned combinations within the scope of the invention may be tested by animal models known in the art. Reference in this regard may be made to: Schon, Michael P. 1999 Animal models of Psoriasis--What can we learn from them, The Society for Investigative Dermatology--Reviews, 12, No. 4, 405-410.

In rheumatoid arthritis, combination of immunosuppressive or immunomodulatory agents is a long and well established therapeutic paradigm. Combination partners may be selected from various therapeutic entities. Their identification is either based on empirical data supported by evolving knowledge about the underlying mechanisms or based on a well defined mode of action. These agents are generally referred to as Disease Modifying Antirheumatic Drugs (DMARDs) or Slow Acting Antirheumatic Drugs (SAARDs). Apart from the combinations listed below, combination of the compound as described herein, with one or more agents classified as DMARD/SAARD or NSAID and/or steroids, are contemplated in this invention.

A typical combination for treating rheumatoid arthritis is the compound as described herein combined with one or more of the following immunosuppressive, immunomodulatory, or cytostatic drugs, such as, for example, hydroxychloroquine, D-penicillamine, sulfasalazine, auranofin, gold sodium thiomolate, minocycline, dapsone, chlorambucil, mercaptopurine, tacrolimus, sirolimus, mycophenolate mofetil, cyclosporine, leflunomide, methotrexate, azathioprine or cyclophosphamide. Another typical combination for treating rheumatoid arthritis is the compound as described herein combined with angiogenesis inhibitors, such as compounds directed against VEGF, taxol, pentoxifylline, thalidomide, interferon beta-1B and alpha-interferon. Yet another typical combination for treating rheumatoid arthritis is the compound as described herein in combination with inhibitors of cell adhesion, such as inhibitors of LFA-1 or inhibitors of ICAM-1.

Another typical combination for treating rheumatoid arthritis is the compound as described herein combined with anti-TNFa antibodies or TNFa-receptor antagonists such as etanercept, infliximab, adalimumab (D2E7), or biological agents such as CTLA-4, or biological agents directed against targets such as CD-4, LFA-1, IL-6, ICAM-1, C5, or IL-1
receptor. In another embodiment the compound as described herein is combined with infliximab alone or infliximab and methotrexate. Another typical combination for treating rheumatoid arthritis is the compound as described herein in combination with IL-1 receptor antagonists, such as anakinra (KINERET). Yet another typical combination for treating rheumatoid arthritis is the compound as described herein combined with NSAIDs, including acetaminophen, aspirin, ibuprofen, choline magnesium salicylate, choline salicylate, diclofenac, diflunisal, etodolac, fenoprofen calcium, flurbiprofen, indomethacin, ketoprofen, carprofen, indoheptin, ketorolac tromethamine, magnesium salicylate, meclofenamate sodium, mefenamic acid, oxaprozin, piroxicam, sodium salicylate, sulindac, tolnetin, meloxicam, rofecoxib, celecoxib, etoricoxib, valdecoxib, nabumetone, naproxen, lomoxicam, nimesulide, indoprofen, remifentanil, salicylate, tiaprofenic acid, flosulide, and the like. Another typical combination for treating rheumatoid arthritis is the compound as described herein combined with steroids, such as glucocorticosteroids, for example, betamethasone, dexamethasone, methylprednisolone, prednisolone, and deflazacort.

[0056] The combinations described above can also be used to reduce at least one of the indicia of rheumatoid arthritis.


[0058] In Crohn's disease, the following groups of drugs combined with the compound as described herein may be effective: steroids such as budesonide, 5-ASA drugs like mesalamine, immunosuppressants, biological agents and adhesion molecule inhibitors. A typical combination for treating Crohn's disease is the compound as described herein with one or more of the following: steroids including all those listed herein, 5-ASA, methotrexate and azathioprine. Another typical combination for treating Crohn's disease is the compound as described herein combined with IL-1 receptor antagonists, such as anakinra (KINERET). Yet another typical combination for treating Crohn's disease is the compound as described herein with anti-TNFα antibodies or TNFα-receptor antagonists, such as etanercept, infliximab, adalimumab (D2E7), or biological agents such as CTLA-4, or biological agents.
directed against targets such as CD-4, LFA-1, IL-6, ICAM-1, or C5. In another embodiment the compound as described herein is combined with infliximab and methotrexate. More typically, the compound as described herein is combined with infliximab. Another typical combination for treating Crohn's disease is the compound as described herein combined with IL-10, alicafosren (anti ICAM 1), or antegren (VCAM receptor antagonist).

[0059] In another aspect of the invention, there are provided methods of increasing the HDL-levels of a subject. The methods comprise administering to a subject, such as a subject in need thereof, an amount of a compound as described herein, or a stereoisomer, tautomer, solvate, prodrug, or pharmaceutically acceptable salt thereof, effective to increase the HDL-level of the subject relative to the level prior to the administration of the compound. In some embodiments, the compound is a p38 inhibitor. In certain embodiments, the subject suffers from or is at risk for a cytokine mediated disorder as described herein. In some embodiments, the HDL level prior to administration is less than about 70 mg/dl, less than about 65 mg/ml, less than about 60 mg/dl, less than about 55 mg/dl, less than about 50 mg/dl, less than about 45 mg/dl or less than about 40 mg/dl. For example, the HDL level prior to administration is less than about 55 mg/dl. In some embodiments, the HDL is HDL2, while in others it is HDL3. In other embodiments, the subject has an LDL level less than about 150 mg/ml.

[0060] In some embodiments of methods for increasing HDL levels in a subject, the subject is at risk of a vascular event, for example, one or more of thrombotic disorder, myocardial infarction, angina, stroke, transient ischemic attack, thrombotic re-occlusion subsequent to a coronary intervention procedure and/or a disorder in which at least one major coronary artery exhibits greater than 50% stenosis. In some such embodiments, the vascular event is a cardiovascular event or a cerebrovascular event. In some embodiments, a reduction of the occurrence or severity of the vascular event occurs, relative to a subject who is at risk of a vascular event who has not been administered the compound as described herein. In still other embodiments, the subject is suffering from or is at risk of suffering from diabetes, insulin resistance, or metabolic syndrome.

[0061] In some embodiments, the methods of increasing HDL-levels in a subject additionally comprise administration of statins or HMG-CoA reductase inhibitors, such as,
atorvastatin (LIPITOR, TORVAST), fluvastatin (LESCOL), lovastatin (MEVACOR, ALTOCOR), mevastatin, pitavastatin (LIVALO, PITAVA), pravastatin (PRAVACHOL, SELEKTINE, LIPOSTAT), rosuvastatin (CRESTOR), or simvastatin (ZOCOR, LIPEX); fibrates, such as, gemfibrozil, fenofibrate, bezafibrate, ciprofibrate, clofibrate, or clinofibrate; bile acid sequestrants, such as, cholestyramine (QUESTTRAN), cholesterol absorption inhibitors, such as colestipol (COLESTID), or ezetimibe (ZETIA); niacin; plant sterol-containing products; ω3-fatty acids; or combinations of two or more thereof, for example ezetimibe/simvastatin (VYTORIN or INEGY). In some embodiments, the HDL level of the subject is increased by at least about 5%, by at least about 7%, by at least about 10%, or by at least about 15%. For example, the HDL level of the subject is increased by at least about 12%. In other embodiments the HDL level of the subject may be increased by about 5% to about 20%.

[0062] In another aspect, there are provided methods of increasing Apo-A1-levels of a subject. The methods comprise administering to a subject, such as a subject in need thereof, an amount of a compound as described herein, or a stereoisomer, tautomer, solvate, prodrug, or pharmaceutically acceptable salt thereof, effective to increase the Apo-A1-level of the subject relative to the level prior to the administration of the compound. In some embodiments, the Apo-A1-level is increased by at least about 5% or by at least about 10%. In some other embodiments, the subject's HDL level prior to administration is less than about 70 mg/dl, less than about 65 mg/dl, less than about 60 mg/dl, less than about 55 mg/dl, less than about 50 mg/dl, less than about 45 mg/dl or less than about 40 mg/dl. In other embodiments, the HDL level prior to administration is less than about 55 mg/dl; or the subject's LDL level prior to administration is less than about 150 mg/ml. In some embodiments, the subject is at risk of a vascular event, for example, one or more of thrombotic disorder, myocardial infarction, angina, stroke, transient ischemic attack, thrombotic re-occlusion subsequent to a coronary intervention procedure and a disorder in which at least one major coronary artery exhibits greater than 50% stenosis. For example, the vascular event can be a cardiovascular event or a cerebrovascular event. In some embodiments, a reduction of the occurrence or severity of the vascular event occurs, relative to a subject who is at risk of a vascular event who has not been administered the compound as described herein. In other embodiments, the subject is suffering from or is at risk of suffering from diabetes, insulin resistance, or metabolic syndrome. In some embodiments, the HDL
level of the subject is increased by at least about 5%, by at least about 7%, by at least about 10%, or by at least about 15%. For example, the HDL level of the subject is increased by at least about 12%. In other embodiments the HDL level of the subject may be increased by about 5% to about 20%.

[0063] In another aspect, there are provided methods of decreasing or preventing from increasing the systolic or diastolic blood pressure of a subject in need thereof. The methods comprise administering to a subject an amount of a compound effective to decrease or to prevent from increasing the systolic or diastolic blood pressure of the subject relative to the blood pressure prior to the administration of the compound, wherein the compound is as described herein or a stereoisomer, tautomer, solvate, prodrug, or pharmaceutically acceptable salt thereof. In some embodiments, the blood pressure is the systolic blood pressure. In others, the blood pressure is the diastolic blood pressure. In some embodiments, the subject’s systolic blood pressure prior to administration is above 140 mm Hg, and the diastolic blood pressure prior to administration of the compound is above 90 mm Hg. In others, the diastolic blood pressure prior to administration of the compound is higher than 85 mm Hg. In some embodiments, the decrease in systolic or diastolic blood pressure, or both, is at least about 5 mm Hg, at least about 3 mm Hg or at least about 2 mm Hg. In some other embodiments, the subject’s HDL level prior to administration is less than about 70 mg/dl, less than about 65 mg/dl, less than about 60 mg/dl, less than about 55 mg/dl, less than about 50 mg/dl, less than about 45 mg/dl or less than about 40 mg/dl. In other embodiments, the HDL level prior to administration is less than about 55 mg/dl; or the subject’s LDL level prior to administration is less than about 150 mg/ml. In some embodiments, the subject is at risk of a vascular event, for example, one or more of thrombotic disorder, myocardial infarction, angina, stroke, transient ischemic attack, thrombotic re-occlusion subsequent to a coronary intervention procedure and a disorder in which at least one major coronary artery exhibits greater than 50% stenosis. For example, the vascular event may be a cardiovascular event or a cerebrovascular event. In some embodiments, the present methods produce a reduction of the occurrence or severity of the vascular event in the subject, relative to a subject who is at risk of a vascular event who has not been administered a compound described herein. In other embodiments, the subject is suffering from or is at risk of suffering from diabetes, insulin resistance, or metabolic syndrome. In some embodiments, the HDL level of the subject may be increased by at least
about 5%, by at least about 7%, by at least about 10%, or by at least about 15%. For example, the HDL level of the subject is increased by at least about 12%. In other embodiments the HDL level of the subject may be increased by about 5% to about 20%.

[0064] Compounds disclosed herein, such as cytokine inhibitors, may be used in combination therapy with one or more anti-hypertensive agents, for example, ACE inhibitors, calcium channel blockers, aldosterone antagonists, angiotensin II antagonists, diuretics, benzothiazepine derivatives, beta blocking agents, dihydropyridine derivatives, potassium-sparing agents, urologicals, sulfonamides, or thiazides. Examples include benazepril, enalapril, lisinopril, quinapril, captopril, ramipril, spironolactone, olmesartan, valsartan, telmisartan, valsartan, losartan, irbesartan, diltiazem, verapamil, trandolapril, atenolol, bisoprolol, metoprolol, toprol, tenoretic, amlodipine, nifedipine, felodipine, nisoldipine, triamterene, furosemide, lasix, prazosin, propanolol, hydrochlorothiazide, or combinations of two or more thereof.

[0065] In another aspect, there are provided methods of decreasing or preventing an elevation in PAI-1 levels. The methods comprise administering to a subject at risk for increased PAI-1 levels (for example in a subject suffering from, or at risk of obesity, metabolic syndrome or inflammatory conditions) an amount of a compound effective to decrease or prevent an elevation in the PAI-1-level of the subject relative to the level in the untreated subject, wherein the compound is as described herein, or a stereoisomer, tautomer, solvate, prodrug, or pharmaceutically acceptable salt thereof.

[0066] In yet another aspect of the invention, there are provided methods of decreasing the triglyceride-level of a subject. The methods comprise administering to a subject, such as a subject in need thereof, an amount of a compound as described herein, or a stereoisomer, tautomer, solvate, prodrug, or pharmaceutically acceptable salt thereof, effective to decrease the triglyceride-level of the subject relative to the level prior to the administration of the compound as described herein. In some embodiments, the triglyceride-level prior to administration is above 500 mg/dl, above 200 mg/dl, or above 150 mg/dl. For example, the triglyceride-level prior to administration is above 200 mg/dl. In certain embodiments, the subject suffers from or is at risk for a cytokine mediated disorder as described herein. In other embodiments, the subject is at risk of a vascular event, for
example, one or more of thrombotic disorder, myocardial infarction, angina, stroke, transient ischemic attack, thrombotic re-occlusion subsequent to a coronary intervention procedure and a disorder in which at least one major coronary artery exhibits greater than 50% stenosis. In some such embodiments, the vascular event is a cardiovascular event or a cerebrovascular event. In some embodiments, a reduction of the occurrence or severity of the vascular event occurs, relative to a subject who is at risk of a vascular event who has not been administered the compound as described herein In some embodiments of the invention, the method additionally comprises administration of statins or HMG-CoA reductase inhibitors, such as, atorvastatin (LIPITOR, TORVAST), fluvastatin (LESCOL), lovastatin (MEVACOR, ALTOCOR), mevastatin, pitavastatin (LIVALO, PITAVA), pravastatin (PRAVACHOL, SELEKTINE, LIPOSTAT), rosuvastatin (CRESTOR), or simvastatin (ZOCOR, LIPEX); fibrates, such as, gemfibrozil, fenofibrate, bezafibrate, ciprofibrate, clofibrate, or clinofibrate; bile acid sequestrants, such as, cholestyramine (QUESTRAN); cholesterol absorption inhibitors, such as, colestipol (COLESTID), or ezetimibe (ZETIA); niacin; plant sterol-containing products; ω3-fatty acids; or combinations of two or more thereof, for example ezetimibe/simvastatin (VYTORIN or INEGY). In other embodiments, the subject is suffering from, or is at risk of suffering from diabetes, insulin resistance, or metabolic syndrome. In some embodiments, the subject is a primate, particularly a human. In some embodiments of the invention, the triglyceride level of the subject is reduced by at least about 10%. In others, the triglyceride level of the subject is reduced by at least about 20%.

[0067] In yet another aspect of the invention, there are provided methods of decreasing the fasting glucose-level in a subject. The methods comprise administering to a subject, such as a subject in need thereof, an amount of a compound as described herein, or a stereoisomer, tautomer, solvate, prodrug, or pharmaceutically acceptable salt thereof, effective to decrease the fasting glucose-level in a subject relative to the level prior to the administration of the compound. In some embodiments, the glucose level prior to the administration is above about 130 mg/dl. In others, the glucose level is decreased by about 5%, about 10%, about 20% or about 30%. In certain embodiments, the subject suffers from, or is at risk for, a cytokine mediated disorder as described herein. In others, the subject suffers from, or is at risk of suffering from diabetes, insulin resistance, or metabolic syndrome. In some embodiments, the method further comprises administration of tolbutamide, acetohexamide, tolazamide, chlorpropamide, glipizide, glyburide, glimepiride,
gliclazide, repaglinide, nateglinide, metformin, miglitol, acarbose, exendin, pramlintide, insulin, or combinations of two or more thereof. In some embodiments of the invention, the subject is at risk of a vascular event, for example, one or more of thrombotic disorder, myocardial infarction, angina, stroke, transient ischemic attack, thrombotic re-occlusion subsequent to a coronary intervention procedure and/or a disorder in which at least one major coronary artery exhibits greater than 50% stenosis. In some such embodiments, the vascular event is a cardiovascular event or a cerebrovascular event. In some embodiments, a reduction of the occurrence or severity of the vascular event occurs, relative to a subject who is at risk of a vascular event who has not been administered the compound as described herein.

[0068] In another aspect of the invention, there are provided methods of decreasing the HbA1c value in a subject. The methods comprise administering to a subject, such as a subject in need thereof, an amount of a compound as described herein, or a stereoisomer, tautomer, solvate, prodrug, or pharmaceutically acceptable salt thereof, effective to decrease the HbA1c value in the subject relative to the level prior to the administration of the compound. In some such embodiments, the subject has a HbA1c value above about 8%, above about 7.5%, or above about 7%. In others, the HbA1c level is decreased to between about 4% and about 6.5%. In certain embodiments, the subject suffers from, or is at risk for, a cytokine mediated disorder as described herein. In other embodiments, the subject suffers from, or is at risk of suffering from, or is at risk for, diabetes, insulin resistance or metabolic syndrome. In some embodiments, the method further comprises administration of tolbutamide, acetohexamide, tolazamide, chlorpropamide, glipizide, glyburide, glimepiride, gliclazide, repaglinide, nateglinide, metformin, miglitol, acarbose, exendin, pramlintide, insulin, or combinations of two or more thereof. In some embodiments of the invention, the subject is at risk of a vascular event, for example, one or more of thrombotic disorder, myocardial infarction, angina, stroke, transient ischemic attack, thrombotic re-occlusion subsequent to a coronary intervention procedure and/or a disorder in which at least one major coronary artery exhibits greater than 50% stenosis. In some such embodiments, the vascular event is a cardiovascular event or a cerebrovascular event. In some embodiments, a reduction of the occurrence or severity of the vascular event occurs, relative to a subject who is at risk of a vascular event who has not been administered the compound as described herein.
In yet another aspect of the invention, there are provided methods for decreasing the insulin level in a subject. The methods comprise administering to a subject, such as a subject in need thereof, an amount of a compound as described herein, or a stereoisomer, tautomer, solvate, prodrug, or pharmaceutically acceptable salt thereof, effective to decrease the insulin-level in the subject relative to the level prior to the administration of the compound. In some such embodiments, the subject has a fasting insulin level prior to administration of above about 100 pmol/l, above about 150 pmol/l, above about 200 pmol/l, above about 250 pmol/l, above about 300 pmol/l, above about 350 pmol/l, above about 400 pmol/l, or above about 500 pmol/l. In others, the subject has a postprandial insulin level of about 400 pmol/l, above about 500 pmol/l, above about 600 pmol/l, above about 700 pmol/l, or above about 800 pmol/l. In some embodiments, the insulin level is reduced by about 10%, about 20%, about 30%, or about 40%. In certain embodiments, the subject suffers from or is at risk for a cytokine mediated disorder as described herein. In yet other embodiments, the subject suffers from, or is at risk of suffering from diabetes, insulin resistance or metabolic syndrome. In some embodiments of the invention, the method further comprises administration of tolbutamide, acetohexamide, tolazamide, chlorpropamide, glipizide, glyburide, glimepiride, gliclazide, repaglinide, nateglinide, metformin, miglitol, acarbose, exendin, pramlintide, insulin, or a combination of two or more thereof. In some embodiments of the invention, the subject is at risk of a vascular event, for example, one or more of thrombotic disorder, myocardial infarction, angina, stroke, transient ischemic attack, thrombotic re-occlusion subsequent to a coronary intervention procedure and/or a disorder in which at least one major coronary artery exhibits greater than 50% stenosis. In some such embodiments, the vascular event is a cardiovascular event or a cerebrovascular event. In some embodiments, a reduction of the occurrence or severity of the vascular event occurs, relative to a subject who is at risk of a vascular event who has not been administered the compound as described herein.

In another aspect of the invention, there are provided methods for decreasing the HOMA Insulin Resistance Index in a subject. The methods comprise administering to a subject, such as a subject in need thereof, an amount of a compound as described herein, or a stereoisomer, tautomer, solvate, prodrug, or pharmaceutically acceptable salt thereof, effective to decrease the HOMA Insulin Resistance Index in the subject relative to the Index prior to the administration of the compound. In some such embodiments, the insulin


Resistance Index is reduced to below about 2.5, below about 2.0, or below about 1.8. In some embodiments, the Insulin Resistance Index is reduced by about 10%, about 20%, or about 30%. In certain embodiments, the subject is in need of a decreased HOMA Insulin Resistance Index because, e.g., the subject suffers from, or is at risk for, a cytokine mediated disorder as described herein. In others, the subject suffers from, or is at risk of suffering from diabetes, insulin resistance or metabolic syndrome. In some embodiments of the invention, the method further comprises administration of tolbutamide, acetohexamide, tolazamide, chlorpropamide, glipizide, glyburide, gliclazide, repaglinide, nateglinide, metformin, migliitol, acarbose, exendin, pramlintide, insulin, or a combination of two or more thereof. In some embodiments of the invention, the subject is at risk of a vascular event, for example, one or more of thrombotic disorder, myocardial infarction, angina, stroke, transient ischemic attack, thrombotic re-occlusion subsequent to a coronary intervention procedure and/or a disorder in which at least one major coronary artery exhibits greater than 50% stenosis. In some such embodiments, the vascular event is a cardiovascular event or a cerebrovascular event. In some embodiments, a reduction of the occurrence or severity of the vascular event occurs, relative to a subject who is at risk of a vascular event who has not been administered the compound as described herein.

[0071] In yet another aspect of the invention, there are provided methods of increasing the indirect bilirubin-level in a subject. The methods comprise administering to a subject, such as a subject in need thereof, an amount of a compound as described herein, or a stereoisomer, tautomer, solvate, prodrug, or pharmaceutically acceptable salt thereof, effective to increase the indirect bilirubin level in the subject relative to the level prior to the administration of the compound. In some embodiments, the indirect bilirubin level is increased to about 0.4 mg/dl, to about 0.5 mg/dl, to about 0.6 mg/dl, or to about 0.7 mg/dl. In others, the indirect bilirubin level is increased by about 10%, about 20%, or about 30%. In other embodiments, the bilirubin level is increased without causing jaundice. In certain embodiments, the subject is in need of increased indirect bilirubin level because, e.g., the subject suffers from, or is at risk for, a cytokine mediated disorder as described herein. In some embodiments of this aspect of the invention, the subject is at risk of a vascular event, for example, the vascular event is one or more of thrombotic disorder, myocardial infarction, angina, stroke, transient ischemic attack, thrombotic re-occlusion subsequent to a coronary intervention procedure and a disorder in which at least one major coronary artery exhibits
greater than 50% stenosis. In other embodiments, the vascular event is a cardiovascular event or a cerebrovascular event. In some embodiments, a reduction of the occurrence or severity of the vascular event occurs, relative to a subject who is at risk of a vascular event who has not been administered the compound as described herein.

[0072] In some embodiments, compounds as described herein possess inhibitory effects on the procoagulant and profibrinolytic responses during human endotoxemia. In another aspect, the invention therefore also provides a method of anticoagulant and fibrinolytic therapy for a disease or condition relating to blood coagulation or fibrinolysis, comprising administering to a subject in need thereof a pharmaceutically effective amount of the compound as described herein. This administration may be of benefit given either prophylactically to subjects at risk or therapeutically to subjects who have developed complications related to these pathways.

[0073] Compounds disclosed herein may be used in combination therapy with one or more other anticoagulant or fibrinolytic agents. These include recombinant tissue plasminogen activator (rtPA), streptokinase (SK), urokinase (UK), proUK, heparin, enoxoparin, dalteparin, coumarin anticoagulants, aspirin, dipyrimidamole, aggrenox, ticlopidine, clopidogrel (Plavix), abciximab, RheoPro, integrilin, aggrestat, and the like. Particular dosages, formulations and methods of administration of the anticoagulant and fibrinolytic agents are known in the art. In view of the present disclosure it is within the skill in the art to determine appropriate dosages, formulations and methods of administration for the combinations of the compounds of the invention and the anti-coagulant or fibrinolytic agents for particular applications.

[0074] In another aspect of the invention, there is provided a method comprising administering to a subject a combination of a compound as described herein and one or more ingredients A, in an amount effective to control, treat or prevent obesity or obesity-related conditions or disorders in a subject in need thereof, wherein ingredient A is selected from agents useful in the treatment of obesity or an obesity-related condition or disorder. In some such embodiments, the obesity-related disorder is selected from overeating, binge eating, bulimia, diabetes, elevated plasma insulin concentrations, insulin resistance, metabolic syndrome, dyslipidemias, hyperlipidemia, lipodystrophy, osteoarthritis, arthritis deformans,
lumbodynia, emmeniopathy, obstructive sleep apnea, cholelithiasis, gallstones, nonalcoholic steatohepatitis, heart disease, abnormal heart rhythms and abnormal heart arrhythmias, myocardial infarction, congestive heart failure, coronary heart disease, coronary artery disease, angina pectoris, hypertension, sudden death, stroke, cerebral infarction, cerebral thrombosis, transient ischemic attack, polycystic ovary disease, craniopharyngioma, Pickwickian syndrome, fatty liver, Prader-Willi Syndrome, Frohlich's syndrome, GH-deficiency, normal variant short stature, Turner's syndrome, pediatric acute lymphoblastic leukemia, infertility, hypogonadism in males, hirsutism in females, gastrointestinal motility disorders, respiratory disorders, cardiovascular disorders, inflammation, arteriosclerosis, hypercholesterolemia, hyperuricaemia, lower back pain, gallbladder disease, gout, endometrial cancer, breast cancer, prostate cancer, colon cancer or kidney cancer. In other embodiments of the invention, the subject desires to lose body weight relative to the subject's body weight prior to administration of the combination. In some embodiments, the method additionally comprises treatment of the subject with lipoplasty, gastric bypass, laparoscopic adjustable gastric binding, biliopancreatic diversion or vertical banded gastroplasty.

In some embodiments, both the compound as described herein and ingredient A are administered orally. In others, both the compound as described herein and ingredient A are administered intravenously, subcutaneously or by inhalation. In still others, the compound as described herein is administered orally and the ingredient A is administered intravenously, subcutaneously, or by inhalation. Alternatively, the cytokine inhibitor may be administered intravenously, subcutaneously, or by inhalation and the ingredient(s) A may be administered orally.

Examples of agents useful in the treatment of obesity or an obesity-related condition or disorder as ingredients A include an insulin sensitizer, an insulin or insulin mimetic, a sulfonylurea, an α-glucosidase inhibitor, a cholesterol lowering agent, a PPARδ agonist, a CB receptor ligand, a serotonergic agent, an adrenocceptor agonist, a pancreatic lipase inhibitor, an ApoB/MTP inhibitor, a MCH receptor antagonist, an amylin and/or calcitonin receptor agonist, an NPY antagonist, an orexin antagonist, a GLP-1 agonist, an MC agonist, a ghrelin antagonist, a leptin agonist, a CCK agonist, a PYY agonist, a CNTF, a GIH secretagogue, a GH secretagogue receptor modulator, a DP-IV inhibitor, a H3 antagonist or
inverse agonist, a 5HT agonist, a serotonin transport or reuptake inhibitor, a dopamine agonist, a NE transport inhibitor, a DAG inhibitor, a glucose transporter inhibitor, a β-HSD-1 inhibitor, a CETP inhibitor, a squalene synthase inhibitor, a glucocorticoid antagonist, a PDE inhibitor, an anti-platelet agent, an ACE inhibitor, an All receptor antagonist, a UCP-1, -2, or -3 activator, a thyroid hormone β agonist, a COX-2 inhibitor, a monoamine reuptake inhibitor, a mGlu5 receptor antagonist, an acyl-estrogen, a FAS inhibitor, an ACC2 inhibitor, a corticotropin-releasing hormone agonist, a galanin antagonist, a BRS3 agonist, a PTP-1B inhibitor, a fatty acid transporter inhibitor, a dicarboxylate transporter inhibitor, a phosphate transporter inhibitor, a urocortin binding protein antagonist, a urocortin ligand, a human agouti-related protein, a neuromedin U receptor agonist, topiramate, oxyntomodulin, tagatose, CP741952, zonisamide, ID1101, BDC03, S2367, AOD9604, fluasterone, GT389255, QC8172, MK0916, MK0493, MK0364, PD6735, c2735, adiponectin, or a combination of two or more thereof. In some such embodiments, ingredient A is an insulin sensitizer, an insulin or insulin mimetic, a sulfonylurea, an α-glucosidase inhibitor, or a glucose transporter inhibitor. In others, ingredient A is a cholesterol lowering agent, or a PPARδ agonist. In still others, ingredient A is a CB receptor ligand, a serotonergic agent, an adrenoceptor agonist, a pancreatic lipase inhibitor, an ApoB/MTP inhibitor, a DP-IV inhibitor, a H3 antagonist or inverse agonist, a 5HT agonist, a serotonin transport or reuptake inhibitor, a dopamine agonist, a NE transport inhibitor, a CETP inhibitor, a squalene synthase inhibitor, a PDE inhibitor, or an acyl-estrogen. In other embodiments, ingredient A is a MCH receptor antagonist, an NPY antagonist, an orexin antagonist, a GLP-1 agonist, an MC agonist, a ghrelin antagonist, a leptin agonist, a CCK agonist, a PYY agonist, a CNTF, a GH secretagogue, or a GH secretagogue receptor modulator. In some embodiments, ingredient A is rimonabant, sibutramine, fluoxetine, phentermine, bupropion, radafaxine, orlistat, cetilistat, oxyntomodulin, or oloxyestrone.

[0077] Typical examples of ingredients A, and combinations of any two or more thereof, that may be combined with the compounds as described herein, for the treatment or prevention of obesity, diabetes and/or obesity-related disorders, either administered separately or in the same pharmaceutical compositions, include, but are not limited to:

[0078] (i) insulin sensitizers including (i) peroxisome proliferator activated receptors (PPAR) γ agonists, such as glitazones (e.g. isaglitzone; pioglitazone; rosiglitazone;
rivoglitazone, netoglitazone), naveglitazar, farglitazar, metaglidasen, GW6779542, CS038, MBX2044, AZD6610, PLX204, LBM642, AMG131, AVE0847, AVE5376, ONO5129, TAK654, CLX0921, and the like; (ii) biguanides such as metformin and phenformin;

[0079] (b) insulin or insulin mimetics, such as insulin aspart, insulin glulisine, insulin glargine, insulin lispro, insulin detemir, NN5401, NN9101, NN344, AT1391, DTY001, betaRx, insulin zinc suspension (lente and ultralente); insulintropin (by "insulin" is meant a polypeptide or its equivalent useful in regulation of blood glucose levels. A general description of such insulins is provided in Goodman and Gilman’s The Pharmacological Basis of Therapeutics, 8th Ed., Pergamon Press (1990). Such insulins can be fast acting, intermediate acting, or long acting. Various derivatives of insulin exist and are useful in this invention. Such compositions can be administered by any standard route, including oral, nasal, pulmonary, or transdermal administration.);

[0080] (c) sulfonylureas, such as acetohexamide; chlorpropamide; glibenclamide; glipizide; glyburide; glimepiride; gliclazide; glipentide; gliquidone; glisomamide; tolazamide; and tolbutamide;

[0081] (d) α-glucosidase inhibitors, such as alglucosidase alfa, voglibose, celgosivir, miglitol, acarbose, and the like;

[0082] (e) cholesterol lowering agents such as (i) 3-hydroxy-3-methylglutaryl-Coenzyme A (HMG-CoA) reductase inhibitors (atorvastatin, pitavastatin, fluvastatin, rosuvastatin, pravastatin, simvastatin, lovastatin and other statins); (ii) bile acid absorbers/sequestrants, such as colesevelam, colestipol, cholestyramine, dialkylaminocarbonyl derivatives of a cross-linked dextran, and the like; (ii) nicotinyl alcohol, nicotinic acid or a salt thereof; (iii) PPARα agonists such as fenofibric acid derivatives (ciprofibrate, gemfibrozil, clofibrate, fenofibrate and benzafibrate), GW677954, CS038, ABT335, LY674, GFT14, PLX204, K111, naveglitazar, LBM642, GW590735, NS220, AVE5376, AVE8134, DRF10945, ONO5129, KRP101, GW641597, and DRF4832; (iv) inhibitors of cholesterol absorption such as stanol esters, beta-sitosterol, sterol glycosides such as tiqueside; and azetidinones such as ezetimibe, and the like, and acyl CoA cholesterol acyltransferase (ACAT) inhibitors such as SMP797, K604, and SR-45023A, (v) anti-oxidants, such as probucol, (vi) vitamin E, and (vii) thyromimetics;
[0083] (f) PPARδ agonists, such as GW677954, CS068, RWJ800025, GW501516, and CKD501; and

[0084] (g) other therapeutic agents, including anti-obesity and anti-diabetic agents, such as


[0086] (2) anti-obesity serotoninergic agents, such as fenfluramine, dexfenfluramine, phentermine, DOV102677, zimeldine, and sibutramine;

[0087] (3) adrenoceptor agonists, including β3-adrenoceptor agonists, such as solabregon, YM178, amibregon, tesofensine, fenfluramine, amphetamine, phenmetrazine, phentermine, and N5984;

[0088] (4) pancreatic lipase inhibitors, such as orlistat, cetilistat, and GT389255;

[0089] (5) apolipoprotein-B secretion/microsomal triglyceride transfer protein (apo-B/MTP) inhibitors, such as ISIS301012, ISIS301012, JTT130, and SLx4090;


(8) peptide YY (PYY) agonists, such as PYY, PYY 3-36, peptide YY analogs, and PYY agonists, for example, AC162352, N-Acetyl [Leu(28,31)]NPY 24-36, and PYY(3-36)NH2, cyclo-(28/32)-Ac-[Lys28- Glu32]-(25-36)-pNPY, TASP-V, pancreatic peptide (PP), 122U91, and those disclosed in U.S. Pat. Publication No. 2002/0141985 and PCT Application Publication No. WO 2005/077094, WO 03/026591, WO 03/057235, and WO 03/027637;

(9) orexin antagonists, such as orexin-1 receptor antagonists, for example SB334867-A, and those disclosed in PCT Application Nos. WO 01/96302, WO 01/68609, WO 02/51232, and WO 02/51838;

(10) glucagon-like peptide (GLP)-1 agonists, including GLP-1, GLP-1 analogs and derivatives, such as exenatide, exenatide-LAR, liraglutide, CJCl134PC, LY548806, 716155, and AVE0010;

(11) melanocortin (MC) agonists, including MC4 agonists and MC4R agonists, such as Melanotan II, PT15, BL3020, AP1030, or those described in PCT Application Nos. WO 99/64002, WO 00/74679, WO 01/991752, WO 01/74844, WO 02/12166, WO 02/11715, WO 02/12178, WO 03/007949, WO 02/068388,
[0096] (12) ghrelin receptor antagonists, such as NOXB11, CYT09GhrQb, TZP300, EP01492, and those disclosed in PCT Application Nos. WO 01/87335, and WO 02/08250;


[0098] (14) cholecystokinin (CCK) agonists, such as ARR15849, GI181771, JMV180, A71378, A71623, SR146131, UCL2000, and A71378, and those described in U.S. Pat. No. 5,739,106;

[0099] (15) ciliary neurotrophic factors (CNTF), including CNTF, CNTF modulators, and CNTF derivatives, such as Axokine and NT501, and those disclosed in U.S. Pat. Nos. 6,680,291 and 6,767,894 and in PCT Application Nos. WO 94/09134, WO 98/22128, and WO 99/43813;

[00100] (16) growth hormone (GH) secretagogues, growth hormone secretagogue receptor modulators, such as SUN11031, RC1291, tesamorelin, scormorelin, examorelin, NN703, hexarelin, MK677, SM-130686, CP-424,391, L-692,429 and L-163,255;

[00101] (17) dipeptidyl peptidase IV (DP-IV or DPP-IV) inhibitors, such as denagliptin, sitagliptin, SYR322, RO0730699, TS021, ALS20426, vildagliptin, GRC8200, MP513, PHX149, PSN9301, TA6666, saxagliptin, SSR162369, R1438, KRP104, 825964, and the compounds disclosed in PCT Application Nos. WO 03/004498; WO 03/004496; EP 1 258 476; WO 02/083128; WO 02/062764; WO 03/000250; WO 03/002530; WO 03/002531; WO 03/002553; WO 03/002593; WO 03/000180; and WO 03/000181;
(18) histamine receptor-3 (H3) antagonists/inverse agonists, such as GSK189254A, A331440, ABT239, ABT834, BP294, thioperamide, 3-(1H-imidazol-4-yl)propyl N-(4-pentenyl)carbamate, clobenpropit, iodophenpropit, imiproxifan, GT2394, and those described and disclosed in PCT Application Nos. WO 02/15905;

(19) 5-hydroxytryptamine (5HT) agonists, for example 5HT2C (serotonin receptor 2C) agonists, such as lorcaserin, vabicaserin, APD356, and those disclosed in U.S. Pat. No. 3,914,250, and PCT Application Nos. WO 02/36596, WO 02/48124, WO 02/10169, WO 01/66548, WO 02/44152, WO 02/51844, WO 02/40456, and WO 02/40457; and 5HT6 agonists, such as PRX07034;

(20) serotonin transport or serotonin reuptake inhibitors such as nefazodone, citalopram, dapoxetine, duloxetine, desvenlafaxine, fluvoxamine, escitalopram, sibutramine, venlafaxine, vilazodone, DOV21947, LUAA21004, BGC201259, NS2359, UK416244, DOV102677, SEP225289, OPC14523, SLV314, WL1011, WL1017, zimeldine, fluoxetine, paroxetine, fenfluramine, imipramine and sertraline, and those disclosed in U.S. Pat. No. 6,365,633, and PCT Application Nos. WO 01/27060 and WO 01/162341;

(21) dopamine agonists, for example dopamine D2 agonists, such as, ropinirole, bifeprunox, aripiprazole, pergolide, talipexole, ACP104, quinagolide, nolomirole, NH001, SLV308, piribedil, lisuride, bromocriptine, aplindore, tesofensine, and preclamol;

(22) norepinephrine (NE) transport inhibitors, such as lisdexamfetamine, atomoxetine, duloxetine, SLE381, desvenlafaxine, amfbutamone, sibutramine, venlafaxine, DOC21947, radafaxine, bupropion, DOV216303, reboxetine, AD337, NS2359, DOV102677, SEP225289, Xen2174, indeloxazine, protriptyline, and S33005;

(23) diacylglycerol acyltransferase (DAG) inhibitors, such as BAY744113;

(24) glucose transporter inhibitors, for example, sodium glucose cotransporter (SGL.T) inhibitors, such as, KGT1251, 189075, AVE2268, and SGL0010;

(25) 11β-hydroxy steroid dehydrogenase-1 (β-HSD-1) inhibitors, such as INCB13739, and AMG221;
[00110] (26) cholesterol ester transfer protein (CETP) inhibitors, such as torcetrapib, CETi1, JTT705, BAY605521, and JTT302;

[00111] (27) squalene synthase inhibitors, for example, lapaqu sostat;

[00112] (28) glucocorticoid antagonists, for example, mifepristone, Org34517, and Org34850;

[00113] (29) phosphodiesterase (PDE) inhibitors, including phosphodiesterase-3B (PDE3B) inhibitors, for example, tetomilast, tadalaflit, atopik, vardenafil, tipelikast, HT0712, QAD171A, SK3530, ogemilast, acanafil, cilostazol, roflumilast, parogrelil, udenafil, EHT0202, dasantalfil, MEM1414, SLx2101, CC10004, 256066, cilomilast, vimpocetine, ibudilast, pimobendan, ND7001, LAS37779, K123, UK357903, ND1251, tofimilast, UK169903, senazodon, trapidil, arofylline, theophylline, doxofylline, olprinone, pentoxifylline, zaprinast, sildenafil, amrinone, milrinone, cilostamide, rolipram, and cilomilast;

[00114] (30) antiplatelet agents, such as, limaprost, clopidogrel, felbinac, eptifibatide, NCX4016, ticagrelor, tirofiban, abciximab, sarpogrelade, DA697B, argatroban, SCH530348, cilostazol, YSPSL, parogrelil, asasartin, DG041, prasugrel, ramatroban, caogrelor, epoprostenol, beraprost, aspirin, K134, triflusal, YY280, xemilofiban, ozagrel, alprostadil alfadex, TP9201, procainamide, AT1015, Z335, BGC728, glyrofam, EF5077, SH529, and ME3229;

[00115] (31) angiotensin converting enzyme (ACE) inhibitors, such as peridopril, enalapril, ramipril, fosinopril, quinapril, lisinopril, imidapril, benazepril, ilepatril, captopril, trandolapril, temcapi, cilazapril, MC4232, CHF1521, omapatrilat, spirapril, moexipril, zofenopril, delapril, alacepril, S5590, and fasidotril;

[00116] (32) angiotensin II (AII) receptor antagonists, for example, losartan, candesartan, temisartan, couprovel, imidapril, azilsartan, valsartan, irbesartan, olmesartan, CYT006AngQb, TAK491, eprosartan, VNP489, CGP63170, fimesartan, pratosartan, and saralasin;
(33) uncoupling protein (UCP)-1, 2, or 3 activators, such as phytanic acid, 4-((E)-2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-1-propenyl]benzoic acid (TTNPB), retinoic acid, and those disclosed in PCT Patent Application No. WO 99/00123;

(34) thyroid hormone β agonists, such as thyroid hormone, levothyroxine, KB2115, 3,5-diiodothyropropionic acid, liothryronine, methimazole, and those disclosed in PCT Patent Application No. WO 02/15845, and Japanese Patent Application No. JP 2000256190;

(35) cyclooxygenase (COX)-2 inhibitors such as etoricoxib, GW406381, meloxicam, lumiracoxib, diclofenac, valdecoxib, parecoxib, PMI001, 6444784, SVT2016, nimesulide, CS706, cimicoxib, LR3001, LAS34475, P54, rofecoxib, celecoxib, and arecoxia;

(36) monoamine reuptake inhibitors, such as those disclosed in PCT Application No. WO 01/27068, and WO 01/62341;


(38) acyl-estrogens, such as oleoyl-estrone, disclosed in del Mar-Grasa, M. et al., Obesity Research, 9:202-9 (2001);

(39) fatty acid synthase (FAS) inhibitors, such as Cerulenin, and C75;

(40) acetyl-CoA carboxylase-2 (ACC2) inhibitors;

(41) corticotropin-releasing hormone agonists;

(42) galanin antagonists;

(43) bombesin receptor subtype 3 (BRS3) agonists;

(44) protein tyrosine phosphatase-1B (PTP-1B) inhibitors;
[00129] (45) fatty acid transporter inhibitors;

[00130] (46) dicarboxylate transporter inhibitors;

[00131] (47) phosphate transporter inhibitors;

[00132] (48) urocortin binding protein antagonists and urocortin ligands, such as urocortin II;

[00133] (49) human agouti-related proteins (AGRP);

[00134] (50) neuromedin U receptor agonists;

[00135] (51) topiramate, oxyntomodulin, tagatose, CP741952, zonisamide, ID1101, BDC03, S2367, AOD9604, fluasterone, GT389255, QCBT16, MK0916, MK0493, MK0364, PD6735, c2735, and adiponectin.


[00137] Obesity and weight loss treatments also include surgery. Typically the weight loss surgical procedure is liposuction or lipoplasty. Surgical obesity treatments include gastric bypass, laparoscopic adjustable gastric binding, biliopancreatic diversion or vertical banded gastroplasty.

[00138] In another aspect, there is provided a method comprising administering a compound as described herein, or is a mixture of any two or more thereof and/or a stereoisomer, tautomer, solvate, prodrug, or pharmaceutically acceptable salt thereof, and one or more ingredients A to a subject in need thereof, in an amount effective to increase or enhance the effectiveness of the ingredient A when used alone, wherein ingredient A is
selected from agents useful in the treatment of obesity or an obesity-related condition or disorder. In some embodiments, the effectiveness enhancement is obtained by allowing administration of lower dosages of one or more of the ingredient A used in combination as relative to the use of either agent alone.

[00139] In another aspect of the invention, there is provided a method comprising administering to a subject a compound as described herein or a stereoisomer, tautomer, solvate, prodrug, or pharmaceutically acceptable salt thereof, and an ingredient A, in an amount effective to reduce the risk of metabolic disorders in a subject in need thereof relative to the subject’s risk prior to administration of the compound and ingredient A, wherein ingredient A is selected from agents useful in the treatment of obesity or an obesity-related condition or disorder. In some embodiments, the reduction in risk of metabolic disorders is obtained by reducing the body weight of the subject, relative to the subject’s body weight prior to administration of the combination of the compound as described herein and ingredient(s) A.

[00140] For therapeutic use, the pharmaceutical combinations of ingredient A and the compound(s) as described herein may be administered in any conventional dosage form in any conventional manner, including any of the routes described herein. Accordingly, routes of administration include, but are not limited to, intravenous, intramuscular, subcutaneous, intrasynovial, by infusion, sublingual, transdermal, oral, topical and by inhalation. Typical modes of administration are oral, topical or intravenous.

[00141] The pharmaceutical combinations of ingredient A and the compound(s) as described herein may be administered separately, or in a combination formulation with other ingredients or adjuvants that enhance stability of the inhibitors, facilitate administration of pharmaceutical compositions containing them, provide increased dissolution or dispersion, increase inhibitory activity, provide adjunct therapy, or provide like advantages. Such combination therapies typically utilize lower dosages of the conventional therapeutics, and avoid the possible toxicity and adverse side effects incurred when those agents are used as monotherapies. Pharmaceutical combinations of ingredient A and the compound as described herein may therefore be physically combined with the conventional therapeutics or other adjuvants into a single pharmaceutical composition. The ingredient A and/or the compound
as described herein may be used in the combination as a salt, solvate, tautomer or prodrug and as a single stereoisomer or mixtures of stereoisomers, including racemates.

[00142] The proportions in which the two components, ingredient A and the compound as described herein, may be used in the combinations according to the invention are variable. Ingredient A and the compound as described herein are optionally present in the form of their solvates or hydrates. Depending on the choice of the ingredient A and the compound of the invention, the weight ratios which may be used within the scope of the present invention vary on the basis of the different molecular weights of the various compounds and their different potencies. Determination of ratios by weight is dependent on the particular ingredient A and the compound as described herein, and are within the skill in the art.

[00143] In yet another aspect of the invention, there is provided a method of treating a cancer, which comprises administering to a subject in need of such treatment a composition comprising a therapeutically effective amount of a compound as described herein, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

[00144] In some embodiments of the invention, the method of treating cancer further comprises treating the subject with surgery, radiation, cryotherapy, or one or more antiproliferative agents or a combination thereof. In some such embodiments, the antiproliferative agent is an alkylating agent, platinum agent, antimitabolite, topoisomerase inhibitor, antitumor antibiotic, antimitotic agent, aromatase inhibitor, thymidylate synthase inhibitor, DNA antagonist, farnesyltransferase inhibitor, pump inhibitor, histone acetyltransferase inhibitor, metalloprotease inhibitor, ribonucleoside reductase inhibitor, endothelin A receptor antagonist, retinoic acid receptor agonist, immunomodulator, hormonal or antihormonal agent, photodynamic agent, angiogenesis inhibitor, or a tyrosine kinase inhibitor. In some of these embodiments, the alkylating agent is busulfan, procarbazine, ifosfamide, altretamine, hexamethylmelamine, estramustine phosphate, thiopeta, mechlorethamine, dacarbazine, streptozocin, lomustine, temozolomide, cyclophosphamide, semustine, or chlorambucil. Examples of platinum agents include spiroplatin, lobaplatin (Aeterna), tetraplatin, satraplatin (Johnson Matthey), ormaplatin, iproplatin, miriplatin (Sumitomo), nexaplatin (AnorMED), polymer platinate (Access), oxaliplatin, or carboplatin.
In some embodiments, the antimetabolite is azacytidine, trimetrexate, floxuridine, deoxycoformycin, 2-chlorodeoxyadenosine, pentostatin, 6-mercaptopurine, hydroxyurea, 6-thioguanine, decitabine (SuperGen), cytarabine, clofarabine (Bioenvision), 2-fluorodeoxy cytidine, irofulven (MGI Pharma), methotrexate, tomodex, ethynylecytidine (Taiho), fludarabine, gemcitabine, raltitrexed, or capecitabine. In others, the topoisomerase inhibitor is amsacrine, exatecan mesylate (Daichi), epirubicin, quinamed (ChemGenex), etoposide, gimatecan (Sigma-Tau), teniposide, mitoxantrone, diplomotecan (Beaufour-Ipsen), 7-ethyl-10-hydroxy-camptothecin, dexrazoxanet (TopoTarget), elsamitrucin (Spectrum), pixontrone (Novuspharma), edotecarin (Merck & Co), becatecarin (Exelixis), karenitecin (BioNumerik), BBR-3576 (Novuspharma), belotecan (Chong Kun Dang), rubitecan (SuperGen), irinotecan (CPT-11), or topotecan. In yet others, the antitumor antibiotic is dactinomycin (actinomycin D), azonafide, valrubicin, anthrapyrazole, daunorubicin (daunomycin), oxantrazole, therarubicin, losoxantrone, idarubicin, bleomycinic acid, rubidazone, sarabubicin (Menarini), plicamycin, 13-deoxydorubicin hydrochloride (Gem Pharmaceuticals), portifomycin, epirubicin, mitoxantrone (novantrone) or amonafide. Examples of antimitic agents are colchicines, ABT-751 (Abbott), vinblastine, xyotax (Cell Therapeutics), vindesine, IDN 5109 (Bayer), dolastatin 10 (NCI), A 105972 (Abbott), rhizoxin (Fujisawa), A 204197 (Abbott), mivobulin (Warner-Lambert), synthadotin (BASF), cemadotin (BASF), indibulin (ASTAMedica), RPR 109881A (Aventis), TXD 258 (Aventis), combretastatin A4 (BMS), epothilone B (Novartis), isohomohalichondrin-B (PharmaMar), T 900607 (Tularik), ZD 6126 (AstraZeneca), batabulin(Tularik), cryptophycin 52 (Eli Lilly), vinflunine (Fabre), hydravin (Prescient NeuroPharma), auristatin PE (Teikoku Hormone), azaepothilone B (BMS), ixabepilone (BMS), tavaccept (BioNumerik), BMS 184476 (BMS), combrestatin A4 disodium phosphate (OXiGENE), BMS 188797 (BMS), dolastatin-10 (NIH), taxoprexin (Protarga), cantuzumab mertansine (GlaxoSmithKline), docetaxel, vinorelbine, or vincristine. In some embodiments, the aromatase inhibitor is aminoglutethimide, atamestane (BioMedicines), formestane, fadrozole, letrozole, exemestane, or anastrazole. In others, the thymidylate synthase inhibitor is pemetrexed (Eli Lilly), nolatrexed (Eximias), ZD-9331 (BTG), doxifluridine (Nippon Roche), or 5,10-methylenetetrahydrofolate (BioKeys). In yet others, the DNA antagonist is trabectedin (PharmaMar), edotretide (Novartis), glufosfamide (Baxter International), mafosfamide (Baxter International), apaziquone (Spectrum Pharmaceuticals), or thymectacin (NewBiotics). In still others, the farnesyltransferase
inhibitor is arglabin (NuOncology Labs), tipifarnib (Johnson & Johnson), lonafarnib (Schering-Plough), perillyl alcohol (DOR BioPharma), or sorafenib (Bayer). Examples of pump inhibitors are zosuquidar trihydrochloride (Eli Lilly), tariquidar (Xenova), biricodar dicitrate (Vertex), or MS-209 (Schering AG). Examples of histone acetyltransferase inhibitors include tadacipetine (Pfizer), pivaloyloxymethyl butyrate (Titan), AP-CANC-03 and AP-CANC-04 (Aton Pharma), depsipeptide (Fujisawa), or MS-275 (Schering AG). In some embodiments, the metalloproteinase inhibitor is neovastat (Aeterna Laboratories), metastat (CollaGenex), or marimastat (British Biotech). In others, the ribonucleoside reductase inhibitor is gallium maltolate (Titan), tezacitabine (Aventis), triapine (Vion), or didox (Molecules for Health). In yet others, the endothelin A receptor antagonist is atrasentan (Abbott), bosentan (Roche), ambrisentan (BASF), sitaxsentan (Encysive), clazosentan (Roche), darusentan (Knoll), and ZD-4054 (AstraZeneca). In still others, the retinoic acid receptor agonist is fenretinide (Johnson & Johnson), altretinoin (Ligand), tazarotene (Allergan), tetrinoin (Roche), isotretinoin (Roche), 13-cis-retinoic acid (UCSD), or LGD-1550 (Ligand). In some embodiments, the immuno-modulator is interferon, Roferon-A (Roche), dexamethasone (Anosys), oncostage (Antigenics), pentix (Australian Cancer Technology), GMK vaccine (Progenics), CD154 cell therapy (Tragen), adenocarcinoma vaccine (Biomira), transvax (Intercell), avicine (AVI BioPharma), norelin (Biostar), IRX-2 (Immunorx), BLP-25 liposome vaccine (Biomira), PEP-005 (Peplin Biotech), multiganglioside vaccine (Progenics), synchrovax vaccine (CTL Immuno), β-alethine (Dovetail), melanoma vaccine (CTL Immuno), vasocare (Vasogen), rituximab (Genentech/Biogen Idec), or p21 RAS vaccine (GemVax). In others, the hormonal agent is an estrogen, dexamethasone, a conjugated estrogen, prednisone, ethinyl estradiol, methylprednisolone, chlortrianisene, prednisolone, idenestrol, aminoglutethimide, hydroxyprogesterone caproate, leuprolide, medroxyprogesterone, octreotide, testosterone, mitotane, testosterone propionate, fluoxymesterone, methyltestosterone, 2-methoxyestradiol (EntreMed), diethylstilbestrol, arzoxifene (Eli Lilly), megestrol, tamoxifen, bicalutamide, toremofine, flutamide, goserelin, nilutamide, or leuporelin. In yet others, the photodynamic agent is talaporfin (Light Sciences), Pd-bacteriophorphoride (Yeda), theralux (Theratechnologies), lutetium texaphyrin (Pharmacyclics), motexafin, gadolinium (Pharmacyclics), or hypericin. In still others, the angiogenesis inhibitor is neovastat (Aeterna Zentaris), ATN-224 (Attenuon), sorafenib (Bayer), thalidomide, bevacizumab (Genentech),
ranibizumab (Genentech), benefin (Lane Labs), L-651582 (Merck & Co), vatalanib (Novartis), or sertenu (Pfizer). Examples of tyrosine kinase inhibitors include imatinib (Novartis), leflunomide (Aventis), kahalide F (PharmaMar) ireessa (AstraZeneca), lestaurtinib (Cephalon), erlotinib (Oncogene Science), canertinib (Pfizer), tandutinib (Millenium), squalamine (Genaera), midostaurin (Novartis), phenoxodiol, SU6668 (Pharmacia), cetuximab (ImClone), rhu-Mab (Genentech), ZD6474 (AstraZeneca), MDX-H210 (Mclarcx), vatalanib (Novartis), omnitarg (Genentech), lapatinib (GlaxoSmithKline), panitumumab (Abgenix), IMC-1C11 (ImClone), soraðenib (Bayer) or trastuzumab (Genentech). In some embodiments, the anti-proliferative agent is melphalan, carmustine, cisplatin, 5-fluorouracil, mitomycin C, adriamycin (doxorubicin), bleomycin, or paclitaxel (Taxol®).

[00145] In some embodiments of the invention, the cancer is osteosarcoma, Kaposi’s sarcoma, colorectal cancer, brain cancer, epithelial cell-derived neoplasia (epithelial carcinoma), basal cell carcinoma, adenocarcinoma, gastrointestinal cancer, lip cancer, mouth cancer, esophageal cancer, small bowel cancer, stomach cancer, gastric cancer, colon cancer, liver cancer, bladder cancer, pancreas cancer, ovarian cancer, cervical cancer, lung cancer, breast cancer, skin cancer, squamous cell cancer, basal cell cancer, prostate cancer, renal cell carcinoma; leukemia, lymphoma, erythroblastoma, glioblastoma, glioma, meningioma, astrocytoma, myoblastoma, multiple myeloma, acute myelogenous leukemia, myelodysplastic syndrome, non-Hodgkins lymphoma, or follicular lymphoma. In some such embodiments, the cancer is acral lentiginous melanoma, actinic keratoses, adenocarcinoma, adenoid cystic carcinoma, adenomas, adenosarcoma, adenosquamous carcinoma, astrocytic tumors, Bartholin gland carcinoma, basal cell carcinoma, bronchial gland carcinomas, capillary carcinoids, carcinoma, carcinomasarcoma, cavernous, cholangiocarcinoma, chondrosarcoma, choriod plexus papilloma/carcinoma, clear cell carcinoma, cystadenoma, endodermal sinus tumor, endometrial hyperplasia, endometrial stromal sarcoma, endometrioid adenocarcinoma, ependymal, epitheloid, Ewing’s sarcoma, fibrolamellar, local nodular hyperplasia, gastrinoma, germ cell tumors, glioblastoma, glucagonoma, hemangiblastomas, hemangioendothelioma, hemangiomas, hepatic adenoma, hepatic adenomatosis, hepatocellular carcinoma, insulinoma, intaepithelial neoplasia, interpithelial squamous cell neoplasia, invasive squamous cell carcinoma, large cell carcinoma, leiomyosarcoma, lentigo maligna melanomas, malignant melanoma, malignant mesothelial tumors, medulloblastoma, medullopithelioma, melanoma, meningial, mesothelial,
metastatic carcinoma, mucoepidermoid carcinoma, neuroblastoma, neuroepithelial adenocarcinoma nodular melanoma, oat cell carcinoma, oligodendroglial, osteosarcoma, pancreatic polypeptide, papillary serous adenocarcinoma, pineal cell, pituitary tumor, plasmacytoma, pseudosarcoma, pulmonary blastoma, renal cell carcinoma, retinoblastoma, rhabdomyosarcoma, sarcoma, serous carcinoma, small cell carcinoma, soft tissue carcinomas, somatostatin-secreting tumor, squamous carcinoma, squamous cell carcinoma, submesothelial, superficial spreading melanoma, undifferentiated carcinoma, uveal melanoma, verrucous carcinoma, vipoma, well differentiated carcinoma, or Wilm's tumor.

[00146] In some embodiments, the cancer is leukemia, erythroleukemia, multiple myeloma, acute myelogenous leukemia, myelodysplastic syndrome, non-hodgkin's lymphoma or follicular lymphoma. In some embodiments, the cancer is follicular lymphoma, acute myelogenous leukemia, multiple myeloma or non-hodgkin's lymphoma.

[00147] In other embodiments, the cancer is brain cancer, glioblastoma, meningioma, astrocytoma, medulloblastoma, neuroblastoma or retinoblastoma. In some such embodiments, the cancer is glioma or glioblastoma.

[00148] In yet other embodiments, the cancer is osteosarcoma, Kaposi's sarcoma, chondrosarcoma, Ewing's sarcoma or myoblastoma. In some such embodiments, the cancer is osteosarcoma bone cancer.

[00149] In some embodiments, the cancer is breast, lung, kidney or prostate cancer metastasis. In some such embodiments, the neoplasm is bone metastasis.

[00150] In yet another aspect of the invention, there is provided a method of treating, modifying or managing pain, which comprises administering to a patient in need of such treatment, modification or management, a composition comprising a therapeutically effective amount of a compound as described herein, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof. In some embodiments, the composition further comprises an antidepressant, antihypertensive, anxiolytic, calcium channel blocker, α-adrenergic receptor agonist, α-adrenergic receptor antagonist, ketamine, anesthetic, muscle relaxant, non-narcotic analgesic, opioid analgesic, NSAID, immunomodulatory agent, immunosuppressive agent, corticosteroid, anticonvulsant, hyperbaric oxygen, α2δ ligand, NMDA receptor antagonist, or
a combination of any two or more thereof. In some such embodiments, the antidepressant is nortriptyline, amitriptyline, imipramine, doxepin, clomipramine, fluoxetine, sertraline, nefazodone, venlafaxine, trazodone, or bupropion. In others, the anti-hypertensive is nifedipine, terazosin, prazosin, losartan, verapamil, telmisartan, fosinopril, bosentan, or olmesartan. In yet others, the anxiolytic is fluoxetine, paroxetine, sertraline, or venlafaxine. Examples of calcium channel blockers include nifedipine, verapamil and clonidine. In other embodiments, the α-adrenergic receptor agonist is clonidine or midodrine. In yet others, the α-adrenergic receptor antagonist is terazosin, prazosin, or doxasozin. In some embodiments, the anesthetic is procaine, lidocaine, mepivacaine, articaine, prilocaine, etidocaine, bupivacaine, or ropivacaine. Examples of opioid analgesic include hydromorphone, oxycodone, morphine sulfate, meperidine, and fentanyl transdermal patch. In some embodiments, the NSAID is a COX-2 inhibitor, salicylic acid acetate, ibuprofen, ketoprofen, naproxen sodium, ketorolac, diclofenac, indometacin, or acetylsalicylic. In some such embodiments, the COX-2 inhibitor is rofecoxib, celecoxib, or valdecoxib. In yet others, the corticosteroid is prednisone, dexamethasone or hydrocortisone. In others, the anticonvulsant is carbamazepine, oxcarbazepine, gabapentin, pregabalin, phenytoin, sodium valproate, clonazepam, topiramate, lamotrigine, zonisamide, tiagabine, famotidine, phenobarbital, diphenylhydantoin, mephenytoin, ethosuximide, primidone, ethosuximide, methsuximide, phenelzine, trimethadione, benzodiazepine, phenacetin, acetazolamide, progabide, divalproex sodium, magnesium sulfate injection, metharbital, paramethadione, clobazam, sulthiame, dilantin, diphenylamin, or L-5-hydroxytryptophan. In some embodiments, the NMDA receptor antagonist is dextromethorphan, dextrophan, ketamine, memantine, amantadine, agmatine, apigenin, gavestinel, selfotel, 7-chlorokynurate, remacemide, rituximab, pyrroloquinoline quinone or cis-4-(phosphonomethyl)-2-piperidinecarboxylic acid. In others, the α2δ ligand is gabapentin, pregabalin, [(1R,5R,6S)-6-(Aminomethyl)bicyclo[3.2.0]hept-6-yl]acetic acid, 3-(1-Aminomethyl-cyclohexylmethyl)-4H-[1,2,4]oxadiazol-5-one and C-[(1H-Tetrazol-5-ylmethyl)-cycloheptyl]-methylamine. (3S,4S)-(1-Aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid, (1α,3α,5α)(3-amino-methyl-bicyclo[3.2.0]hept-3-yl)-acetic acid, (3S,5R)-3-Aminomethyl-5-methyl-octanoic acid, (3S,5R)-3-amino-5-methyl-heptanoic acid, (3S,5R)-3-amino-5-methyl-nonanoic acid and (3S,5R)-3-Amino-5-methyl-octanoic acid. In yet other embodiments, the composition further comprises acetylsalicylic acid, diclofenac, ibuprofen, indometacin, flufenamic acid, mefenamic acid, morphine,
pethidine, methadone, fentanyl, buprenorphine, tramadol, gabapentin, pregabalin, carbamazepine, lamotrigine, topiramate, phenyloin, levitiracetam, procaine, lidocaine, mepivacaine, articaine, prilocaine, etidocaine, bupivacaine, ropivacaine, amitryptiline, paroxetine, citalopram, bupropione, duxoetine, ketamine, memantine, 2,3-benzodiazepines, or a combination of any two or more thereof.

[00151] In some embodiments of the invention, the pain is acute pain, chronic pain, pain resulting from soft tissue and peripheral damage from acute trauma; neuropathic pain; post-stroke pain; postherpetic neuralgia, occipital neuralgia, trigeminal neuralgia, segmental or intercostal neuralgia and other neuralgias; pain associated with osteoarthritis and rheumatoid arthritis; musculo-skeletal pain; spinal pain, central nervous system pain; lower back pain, sciatica, dental pain, myofascial pain syndromes, episiotomy pain, gout pain, and pain resulting from burns; deep and visceral pain; muscle pain, eye pain, inflammatory pain, orofacial pain; abdominal pain, and gynecological pain; somatogenic pain; pain associated with nerve and root damage; pain associated with limb amputation, tic douloureux, neuroma, or vasculitis; diabetic neuropathy, chemotherapy-induced-neuropathy, acute herpetic and postherpetic neuralgia; atypical facial pain, neuropathic lower back pain, and arachnoiditis, trigeminal neuralgia, segmental or intercostal neuralgia, HIV related neuralgias, AIDS related neuralgias and other neuralgias; allodynia, hyperalgiesia, burn pain, idiopathic pain, pain caused by chemotheraphy; occipital neuralgia, psychogenic pain, brachial plexus avulsion, pain associated with restless leg syndrome; pain associated with gallstones; pain caused by chronic alcoholism or hypothyroidism or uremia or vitamin deficiencies; neuropathic and non-neuropathic pain associated with carcinoma, cancer pain, phantom limb pain, functional abdominal pain; headache; temperomandibular pain and maxillary sinus pain; pain resulting from ankylosing spondylitis; pain caused by increased bladder contractions; complex regional pain syndrome, sympathetic maintained pain syndrome, reflex sympathetic dystrophy, reflex neurovascular dystrophy, reflex dystrophy, Sudeck atrophy of bone, algoneurodystrophy, shoulder hand syndrome, post-traumatic dystrophy, chronic fatigue syndrome, radiculopathy, luetic neuropathy; or painful neuropathic condition induced from a drug post operative pain, scar pain, or chronic non-neuropathic pain.

[00152] In some such embodiments, the musculo-skeletal pain is pain associated with strains, sprains or broken bones. In others, the central nervous system pain is pain due to
spinal cord or brain stem damage. In yet others, the deep and visceral pain is heart pain. In others, the orofacial pain is odontalgia. In some embodiments, the gynecological pain is dysmenorrhoea, labour pain and pain associated with endometriosis. In others, the pain associated with nerve and root damage, is pain associated with peripheral nerve disorders. In some such embodiments, the peripheral nerve disorder is nerve entrapment or brachial plexus avulsions. In some other embodiments, the headache is migraine with aura, migraine without aura, vascular headaches, acute or chronic tension headache, sinus headache or cluster headache. In yet other embodiments, the chronic non-neuropathic pain is pain associated with HIV, antralgia, vasculitis or fibromyalgia. In some embodiments, the complex regional pain syndrome is type I or type II.

[00153] In some other embodiments, the pain is nociceptive pain or neuropathic pain. In some such embodiments, the nociceptive pain is associated with chemical or thermal burn, cut of the skin, contusion of the skin, osteoarthritis, rheumatoid arthritis, systemic lupus erythematosis (SLE), tendonitis, or myofascial pain. In others, the neuropathic pain is diabetic neuropathy, post herpetic neuralgia, trigeminal neuralgia, post-stroke pain, complex regional pain syndrome, sympathetic maintained pain syndrome, reflex sympathetic dystrophy, reflex neurovascular dystrophy, reflex dystrophy, spinal cord injury pain, Sudeck atrophy of bone, algoneurodystrophy, shoulder hand syndrome, post-traumatic dystrophy, pain related to cancer or metastases, phantom limb pain, fibromyalgia, chronic fatigue syndrome, radiculopathy, luetic neuropathy, or painful neuropathic condition induced by a drug. In embodiments where the pain is related to cancer or metastases, the cancer is osteosarcoma, colorectal cancer, brain cancer, epithelial cell-derived neoplasia (epithelial carcinoma), basal cell carcinoma, adeno carcinoma, gastrointestinal cancer, lip cancer, mouth cancer, esophageal cancer, small bowel cancer, stomach cancer, colon cancer, liver cancer, bladder cancer, pancreas cancer, ovarian cancer, cervical cancer, lung cancer, breast cancer, skin cancer, squamous cell and/or basal cell cancers, prostate cancer, renal cell carcinoma, and other known cancers that affect epithelial cells throughout the body; leukemia; lymphoma; or angiogenesis including neoplasia. In other embodiments, the metastases are breast, lung, kidney or prostate cancer metastases.

[00154] In yet another aspect of the invention, there is provided a method of treating pemphigus, which comprises administering to a subject in need of such treatment a
composition comprising a therapeutically effective amount of a compound as described herein, or a stereoisomer, tautomer, solvate, prodrug, or pharmaceutically acceptable salt thereof. In some embodiments of methods of treating pemphigus, the pemphigus is pemphigus vulgaris, pemphigus vegetans, pemphigus foliaceus, pemphigus erythematosus, bullous pemphigoid, paraneoplastic pemphigus, cicatricial pemphigoid, bullous impetigo, or staphylococcal scalded-skin syndrome.

[00155] In another aspect, there are provided methods comprising administering to a subject in need thereof a combination of (i) an effective amount of a compound of the invention and (ii) an effective amount of one or more therapeutic Ingredients A useful in the treatment of pemphigus as described herein, wherein the effective amount of Ingredients A is less than the effective amount of Ingredient A when used alone.

[00156] Also provided are methods comprising administering to a subject exhibiting one or more clinical indicia of pemphigus an amount of a compound as described herein effective to reduce the number and/or severity of clinical indicia of pemphigus relative to those present in the subject prior to the administration of the compound as described herein, wherein the clinical indicia of pemphigus include the percentage of total body surface area (BSA) affected by pemphigus, pemphigus lesion thickness, the number of new pemphigus lesions, the number of active pemphigus lesions (including blisters and erosions), the healing time of active lesions (for example, time to 80% healing), serum anti-desmoglein-1 (DSG1) antibody levels, serum anti-DSG3 antibody levels, serum TNFa-levels, serum IL6 levels, skin TNFa-mRNA levels, skin IL6 mRNA levels, or any two or more thereof. In some embodiments of the invention, the methods additionally comprise administering to the subject an effective amount of one or more Ingredients A, useful in the treatment of pemphigus, as described herein. In some such embodiments, the effective amount of Ingredients A is less than the effective amount of Ingredient A when used alone.

[00157] In some embodiments of the methods of the invention, the methods further comprise administering to the subject an Ingredient A, wherein the Ingredient A is an anti-inflammatory agent, an immunosuppressant, an anti-infective, an antibiotic, a gold salt, an alkylating agent, an immunoglobulin, or a combination of two or more thereof.
In some embodiments in which Ingredient A is an anti-inflammatory agent, the anti-inflammatory may be a corticosteroid, a COX-2 inhibitor, a non-steroidal anti-inflammatory drug (NSAID), a TNFα antagonist, or an IL-1 antagonist. For example, the corticosteroid can be prednisone, prednisolone, or methylprednisolone. Corticosteroids such as these may also be administered with either chlorambusil or mycophenylate mofetil. In some embodiments, the TNFα antagonist is infliximab, etanercept, or adalimumab. In others, the IL-1 antagonist is anakinra.

In other embodiments, the immunosuppressant is mycophenylate mofetil, cyclosporin, azathioprine, methotrexate, alefacept, rituximab, anti-interferon gamma, or cyclophosphamide. In some other embodiments, the anti-infective is dapsone, or hydroxychloroquine. In some embodiments, the gold salt is myochrysine, or solganal. In some embodiments, the alkylating agent is lukeran. In some embodiments, the antibiotic is tetracycline, minocycline, or doxycycline. In some such embodiments, the method further comprises administration of nicotinamide, or niacinamide. In other embodiments of the methods of the invention, the methods of the invention further comprise administering plasmapheresis therapy or photopheresis therapy to the subject.

In some embodiments of the methods of the invention, the dosage of Ingredient A is reduced by from about 10% to about 90% in comparison to the dosage used to achieve the same therapeutic effect with Ingredient A alone. In some embodiments, the dosage is reduced by at least about 10%, about 20%, about 30%, about 40%, about 50%, or about 60%. In some embodiments, Ingredient A is a corticosteroid, for example, prednisone or prednisolone. In some other embodiments, Ingredient A comprises a corticosteroid and either chlorambusil or mycophenylate mofetil. In some embodiments, the dosage of prednisone is reduced to less than about 70 mg/day, less than about 50 mg/day, less than about 30 mg/day, less than about 20 mg/day, less than about 15 mg/day, or less than about 10 mg/day.

In yet other embodiments, the compound as described herein is administered orally or topically. In some embodiments, Ingredient A is a corticosteroid or antibiotic and is administered orally, topically, in a mouthwash or in a mouth spray.
DETAILED DESCRIPTION OF THE INVENTION

[00162] The following terms are used throughout as defined below.

[00163] Generally, reference to a certain element such as hydrogen or H is meant to include all isotopes of that element. For example, if an R group is defined to include hydrogen or H, it also includes deuterium and tritium. Hence, isotopically labeled compounds are within the scope of the invention.

[00164] In general, “substituted” refers to an organic group as defined below (e.g., an alkyl group) in which one or more bonds to a hydrogen atom contained therein are replaced by a bond to atoms other than hydrogen or unsubstituted carbon. Substituted groups also include groups in which one or more bonds to a carbon(s) or hydrogen(s) atom are replaced by one or more bonds, including double or triple bonds, to a heteroatom. Thus, a substituted group will be substituted with one or more substituents, unless otherwise specified. In some embodiments, a substituted group is substituted with 1, 2, 3, 4, 5, or 6 substituents. Examples of substituent groups include halogens (i.e., F, Cl, Br, and I); hydroxyls; alkoxy, alkenoxy, alkyloxy, aralkyloxy, heterocyclyloxy, and heterocyclylalkoxy groups; carbonyls (oxo); carboxyls; esters; urethanes; oximes; hydroxylamines; alkoxyamines; aralkoxyamines; thiols; sulfides; sulfoxides; sulfones; sulfonyls; sulfonamides; amines; N-oxides; hydrazines; hydrazides; hydrazones; azides; amidases; ureas; amidines; guanidines; enamines; imides; isocyanates; isothiocyanates; cyanates; thiocy anates; imines; nitriles (i.e. CN); and the like.

[00165] Substituted ring groups such as substituted cycloalkyl, aryl, heterocyclyl and heteroaryl groups also include rings and fused ring systems in which a bond to a hydrogen atom is replaced with a bond to a carbon atom. Therefore, substituted cycloalkyl, aryl, heterocyclyl and heteroaryl groups may also be substituted with substituted or unsubstituted alkyl, alkenyl, and alkynyl groups as defined below.

[00166] Alkyl groups include straight chain and branched alkyl groups having from 1 to about 20 carbon atoms, and typically from 1 to 12 carbons or, in some embodiments, from 1 to 8, 1 to 6, or 1 to 4 carbon atoms. Alkyl groups further include cycloalkyl groups as defined below. Examples of straight chain alkyl groups include those with from 1 to 8 carbon atoms such as methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, n-heptyl, and n-octyl groups. Examples of branched alkyl groups include, but are not limited to, isopropyl,
iso-butyl, sec-butyl, tert-butyl, neopentyl, isopentyl, and 2,2-dimethylpropyl groups. Representative substituted alkyl groups may be substituted one or more times with substituents such as those listed above.

[00167] Cycloalkyl groups are cyclic alkyl groups such as, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl groups. In some embodiments, the cycloalkyl group has 3 to 10 or 3 to 8 ring members, whereas in other embodiments the number of ring carbon atoms range from 3 to 5, 3 to 6, or 3 to 7. Cycloalkyl groups further include mono-, bicyclic and polycyclic ring systems, such as, for example bridged cycloalkyl groups as described below, and fused rings, such as, but not limited to, decalinyl, and the like. In some embodiments, polycyclic cycloalkyl groups have three rings. Substituted cycloalkyl groups may be substituted one or more times with non-hydrogen and non-carbon groups as defined above. However, substituted cycloalkyl groups also include rings that are substituted with straight or branched chain alkyl, alkenyl or alkynyl groups as defined above. Representative substituted cycloalkyl groups may be mono-substituted or substituted more than once, such as, but not limited to, 2,2-, 2,3-, 2,4-, 2,5- or 2,6-disubstituted cyclohexyl groups, which may be substituted with substituents such as those listed above.

[00168] Bridged cycloalkyl groups are cycloalkyl groups in which two or more hydrogen atoms are replaced by an alkylene bridge, wherein the bridge can contain 2 to 6 carbon atoms if two hydrogen atoms are located on the same carbon atom, or 1 to 5 carbon atoms if the two hydrogen atoms are located on adjacent carbon atoms, or 2 to 4 carbon atoms if the two hydrogen atoms are located on carbon atoms separated by 1 or 2 carbon atoms. Bridged cycloalkyl groups can be bicyclic, such as, for example bicyclo[2.1.1]hexane, or tricyclic, such as, for example, adamantyl. Representative bridged cycloalkyl groups include bicyclo[2.1.1]hexyl, bicyclo[2.2.1]heptyl, bicyclo[3.2.1]octyl, bicyclo[2.2.2]octyl, bicyclo[3.2.2]nonyl, bicyclo[3.3.1]nonyl, bicyclo[3.3.2]decanyl, adamantyl, noradamantyl, bornyl, or norbornyl groups. Substituted bridged cycloalkyl groups may be substituted one or more times with substituents as defined above, including straight or branched chain alkyl, alkenyl, or alkynyl groups. Representative substituted bridged cycloalkyl groups may be mono-substituted or substituted more than once, such as, but not
limited to, mono-, di- or tri-substituted adamantyl groups, which may be substituted with substituents such as those listed above.

[00169] Cycloalkylalkyl groups are alkyl groups as defined above in which a hydrogen or carbon bond of an alkyl group is replaced with a bond to a cycloalkyl group as defined above. In some embodiments, cycloalkylalkyl groups have from 4 to 20 carbon atoms, 4 to 16 carbon atoms, and typically 4 to 10 carbon atoms. Substituted cycloalkylalkyl groups may be substituted at the alkyl, the cycloalkyl or both the alkyl and cycloalkyl portions of the group. Representative substituted cycloalkylalkyl groups may be mono-substituted or substituted more than once, such as, but not limited to, mono-, di- or tri-substituted with substituents such as those listed above.

[00170] Alkenyl groups include straight and branched chain and cycloalkyl groups as defined above, except that at least one double bond exists between two carbon atoms. Thus, alkenyl groups have from 2 to about 20 carbon atoms, and typically from 2 to 12 carbons or, in some embodiments, from 2 to 8, 2 to 6, or 2 to 4 carbon atoms. In some embodiments, alkenyl groups include cycloalkenyl groups having from 4 to 20 carbon atoms, 5 to 20 carbon atoms, 5 to 10 carbon atoms, or even 5, 6, 7 or 8 carbon atoms. Examples include, but are not limited to vinyl, allyl, -CH=CH(CH₃), -CH=C(CH₃)₂, -C(CH₃)=CH₂, -C(CH₃)=CH(CH₃), -C(CH₃(CH₃))=CH₂, cyclohexenyl, cyclopentenyl, cyclohexadienyl, butadienyl, pentadienyl, and hexadienyl, among others. Representative substituted alkenyl groups may be mono-substituted or substituted more than once, such as, but not limited to, mono-, di- or tri-substituted with substituents such as those listed above.

[00171] Cycloalkenylalkyl groups are alkyl groups as defined above in which a hydrogen or carbon bond of the alkyl group is replaced with a bond to a cycloalkenyl group as defined above. Substituted cycloalkenylalkyl groups may be substituted at the alkyl, the cycloalkenyl or both the alkyl and cycloalkenyl portions of the group. Representative substituted cycloalkenylalkyl groups may be substituted one or more times with substituents such as those listed above.

[00172] Alkynyl groups include straight and branched chain alkyl groups, except that at least one triple bond exists between two carbon atoms. Thus, alkynyl groups have from 2 to about 20 carbon atoms, and typically from 2 to 12 carbons or, in some embodiments,
from 2 to 8, 2 to 6, or 2 to 4 carbon atoms. Examples include, but are not limited to -C=CH, 
-C=C(CH₃), -C=C(CH₂CH₃), -CH₂C=CH, -CH₂C=C(CH₃), and -CH₂C=C(CH₂CH₃), among 
others. Representative substituted alkylnyl groups may be mono-substituted or substituted 
more than once, such as, but not limited to, mono-, di- or tri-substituted with substituents 
such as those listed above.

[00173] Aryl groups are cyclic aromatic hydrocarbons that do not contain heteroatoms. 
Aryl groups include monocyclic, bicyclic and polycyclic ring systems. Thus, aryl groups 
include, but are not limited to, phenyl, azulenyl, heptalenyl, biphenylenyl, indacenyl, 
fluorenyl, phenanthrenyl, triphenylenyl, pyrenyl, naphthacenyl, chrysene, biphenyl, 
anthracenyl, indenyl, indanyl, pentalenyl, and naphthyl groups. In some embodiments, aryl 
groups contain 6-14 carbons, and in others from 6 to 12 or even 6 to 10 carbon atoms in the 
ing ring portions of the groups. Although the phrase “aryl groups” includes groups containing 
fused rings, such as fused aromatic-aliphatic ring systems (e.g., indanyl, tetrahydro 
naphthyl, and the like), it does not include aryl groups that have other groups, such as alkyl or halo 
groups, bonded to one of the ring members. Rather, groups such as tolyl are referred to as 
substituted aryl groups. Representative substituted aryl groups may be mono-substituted or 
substituted more than once. For example, monosubstituted aryl groups include, but are not 
limited to, 2-, 3-, 4-, 5-, or 6-substituted phenyl or naphthyl groups, which may be substituted 
with substituents such as those listed above.

[00174] Aralkyl groups are alkyl groups as defined above in which a hydrogen or 
carbon bond of an alkyl group is replaced with a bond to an aryl group as defined above. In 
some embodiments, aralkyl groups contain 7 to 20 carbon atoms, 7 to 14 carbon atoms or 7 to 
10 carbon atoms. Substituted aralkyl groups may be substituted at the alkyl, the aryl, or both 
the alkyl and the aryl portions of the group. Representative aralkyl groups include but are not 
limited to benzyl and phenethyl groups and fused (cycloalkylaryl)alkyl groups such as 
4-ethyl-indanyl. Representative substituted aralkyl groups may be substituted one or more 
times with substituents such as those listed above.

[00175] Heterocyclyl groups include aromatic (also referred to as heteroaryl) and non- 
aromatic ring compounds containing 3 or more ring members, of which one or more is a 
heteroatom such as, but not limited to, N, O, and S. In some embodiments, heterocyclyl
groups include 3 to 20 ring members, whereas other such groups have 3 to 6, 3 to 10, 3 to 12, or 3 to 15 ring members. Heterocyclyl groups encompass unsaturated, partially saturated and saturated ring systems, such as, for example, imidazolyl, imidazolinyl and imidazolidinyl groups. The phrase “heterocyclyl group” includes fused ring species including those comprising fused aromatic and non-aromatic groups, such as, for example, benzotriazolyl, 2,3-dihydrobenzo[1,4]dioxinyl, and benzo[1,3]dioxolyl. The phrase also includes bridged polycyclic ring systems containing a heteroatom such as, but not limited to, quinclidyl. However, the phrase does not include heterocyclyl groups that have other groups, such as alkyl, oxo or halo groups, bonded to one of the ring members. Rather, these are referred to as “substituted heterocyclyl groups”. Heterocyclyl groups include, but are not limited to, aziridinyl, azetidinyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, thiazolidinyl, tetrahydrothiophenyl, tetrahydrofuranyl, dioxolyl, furanyl, thiophenyl, pyrrolyl, pyrrolinyl, imidazolyl, imidazolinyl, pyrazolyl, pyrazolinyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, thiazolyl, thiazolinyl, isothiazolyl, thiadiazolyl, oxadiazolyl, piperidyl, piperazinyl, morpholinyl, thiomorpholinyl, tetrahydropyranyl, tetrahydrothiopyranyl, oxathiane, dioxyl, dithianyl, pyranyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, dihydropyridyl, dihydrodithiinyl, dihydrodithionyl, homopiperazinyl, quinclidyl, indolyl, indolinyll, isoindolyl, azaindolyl (pyrrolopyridyl), indazolyl, indolizinyll, benzotriazolyl, benzimidazolyl, benzo[1,3]dioxolyl, pyrazolopyridyl, imidazopyridyl (azabenzimidazolyl), triazolopyridyl, isoazolopyridyl, purinyl, xanthinyl, adeninyl, guaninyl, quinolinyll, isoquinolinyll, quinolinyl, quinoxalinyl, quinazolinyl, cinnolinyl, phthalazinyl, naphthyridinyl, pteridinyl, thianaphthalenyl, dihydrobenzothiazinyl, dihydrobenzofuranyl, dihydroindolyl, dihydrobenzoxinyl, tetrahydroindolyl, tetrahydroindazolyl, tetrahydrobenzimidazolyl, tetrahydrobenzotriazolyl, tetrahydropyrrolopyridyl, tetrahydropyrazolopyridyl, tetrahydroimidazopyridyl, tetrahydrotriazolopyridyl, and tetrahydroquinolinyl groups. Representative substituted heterocyclyl groups may be mono-substituted or substituted more than once, such as, but not limited to, pyridyl or morpholinyl groups, which are 2-, 3-, 4-, 5-, or 6-substituted, or disubstituted with various substituents such as those listed above.
[00176] Heteroaryl groups are aromatic ring compounds containing 5 or more ring members, of which, one or more is a heteroatom such as, but not limited to, N, O, and S. Heteroaryl groups include, but are not limited to, groups such as pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, thiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiophenyl, benzothiophenyl, furanyl, benzofuranyl, indolyl, azaindolyl (pyrrolopyridyl), indazolyl, benzimidazolyl, imidazopyridyl (azabenimidazolyl), pyrazolopyridyl, triazolopyridyl, benzotriazolyl, benzoxazolyl, benzothiazolyl, benzothiadiazolyl, imidazopyridyl, isoxazolopyridyl, thianaphthalenyl, purinyl, xanthinyl, adeninyl, guaninyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, quinoxalinyl, and quinazolinyl groups. Although the phrase “heteroaryl groups” includes fused ring compounds such as indolyl and 2,3-dihydro indolyl, the phrase does not include heteroaryl groups that have other groups bonded to one of the ring members, such as alkyl groups. Rather, heteroaryl groups with such substitution are referred to as “substituted heteroaryl groups”. Representative substituted heteroaryl groups may be substituted one or more times with various substituents such as those listed above.

[00177] Heterocyclylalkyl groups are alkyl groups as defined above in which a hydrogen or carbon bond of an alkyl group is replaced with a bond to a heterocyclyl group as defined above. Substituted heterocyclylalkyl groups may be substituted at the alkyl, the heterocyclyl or both the alkyl and heterocyclyl portions of the group. Representative heterocyclyl alkyl groups include, but are not limited to, 4-ethyl-morpholinyl, 4-propylmorpholinyl, furan-2-yl methyl, furan-3-yl methyl, pyridine-3-yl methyl, tetrahydrofuran-2-yl ethyl, and indol-2-yl propyl. Representative substituted heterocyclylalkyl groups may be substituted one or more times with substituents such as those listed above.

[00178] Heteroaralkyl groups are alkyl groups as defined above in which a hydrogen or carbon bond of an alkyl group is replaced with a bond to a heteroaryl group as defined above. Substituted heteroaralkyl groups may be substituted at the alkyl, the heteroaryl, or both the alkyl and heteroaryl portions of the group. Representative substituted heteroaralkyl groups may be substituted one or more times with substituents such as those listed above.
Alkoxy groups are hydroxyl groups (–OH) in which the bond to the hydrogen atom is replaced by a bond to a carbon atom of a substituted or unsubstituted alkyl group as defined above. Examples of linear alkoxy groups include but are not limited to methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, and the like. Examples of branched alkoxy groups include but are not limited to isoproxy, sec-butoxy, tert-butoxy, isopentoxy, isohexoxy, and the like. Examples of cycloalkoxy groups include but are not limited to cyclopropoxy, cyclobutyoxy, cyclopentoxy, cyclohexoxy, and the like. Representative substituted alkoxy groups may be substituted one or more times with substituents such as those listed above.

The terms "aryloxy" and "arylalkoxy" refer to, respectively, a substituted or unsubstituted aryl group bonded to an oxygen atom and a substituted or unsubstituted aralkyl group bonded to the oxygen atom at the alkyl. Examples include but are not limited to phenoxy, naphthoxy, and benzyloxy. Representative substituted arloxy and arylalkoxy groups may be substituted one or more times with substituents such as those listed above.

Alkyl, alkenyl, and alkynyl groups may be divalent as well as monovalent. The valency of an alkyl, alkenyl, or alkynyl group will be readily apparent from the context to those of skill in the art. For example, the alkyl group in an aralkyl group is divalent. In some embodiments, divalency is expressly indicated by appending the suffix "ene" or "ylene" to terms defined herein. Thus, for example, "alkylene" refers to divalent alkyl groups and alkenylene refers to divalent alkenyl groups.

The term "carboxylate" as used herein refers to a -COOH group.

The term "carboxylic ester" as used herein refers to –COOR groups. R is a substituted or unsubstituted alkyl, cycloalkyl, alkenyl, alkynyl, aryl, aralkyl, heterocyclylalkyl or heterocyclyl group as defined herein.

The term "amide" (or "amido") includes C- and N-amide groups, i.e., -C(NR)R, and –NR-C(O)R groups, respectively. R and R are independently hydrogen, or a substituted or unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heterocyclylalkyl or heterocyclyl group as defined herein. Amido groups therefore include but are not limited to carbamoyl groups (-C(O)NH2) and formamide groups (-NHC(O)H).
Urethane groups include N- and O-urethane groups, i.e., -NR₃³C(O)OR₃⁴ and -OC(O)NR₃³R₃⁴ groups, respectively. R₃³ and R₃⁴ are independently hydrogen, or a substituted or unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heterocyclylalkyl, or heterocyclyl group as defined herein.

The term “amine” (or “amino”) as used herein refers to -NHR₃⁵ and -NR₃⁶R₃⁷ groups, wherein R₃⁵, R₃⁶ and R₃⁷ are independently hydrogen, or a substituted or unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heterocyclylalkyl or heterocyclyl group as defined herein. In some embodiments, the amine is NH₂, methylamino, dimethylamino, ethylamino, diethylamino, propylamino, isopropylamino, phenylamino, or benzylamino.

The term “sulfonamido” includes S- and N-sulfonamide groups, i.e., -SO₂NR₃⁸R₃⁹ and -NR₃⁸SO₂R₃⁹ groups, respectively. R₃⁸ and R₃⁹ are independently hydrogen, or a substituted or unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heterocyclylalkyl, or heterocyclyl group as defined herein. Sulfonamido groups therefore include but are not limited to sulfamoyl groups (-SO₂NH₂).

The term “thiol” refers to -SH groups, while sulfides include -SR₄⁰ groups, sulfoxides include -S(O)R₄¹ groups, sulfones include -SO₂R₄² groups, and sulfonyls include -SO₂OR₄³. R₄⁰, R₄¹, R₄², and R₄³ are each independently a substituted or unsubstituted alkyl, cycloalkyl, alkenyl, alkynyl, aryl aralkyl, heterocyclyl or heterocyclylalkyl group as defined herein.

The term “urea” refers to -NR₄⁴C(O)-NR₄⁵R₄⁶ groups. R₄⁴, R₄⁵, and R₄⁶ groups are independently hydrogen, or a substituted or unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heterocyclyl, or heterocyclylalkyl group as defined herein.

The term “amidine” refers to -C(NR₄⁷)NR₄⁸R₄⁹ and -NR₄⁷C(NR₄⁸)R₄⁹, wherein R₄⁷, R₄⁸, and R₄⁹ are each independently hydrogen, or a substituted or unsubstituted alkyl, cycloalkyl, alkenyl, alkynyl, aryl aralkyl, heterocyclyl or heterocyclylalkyl group as defined herein.
[00191] The term “guanidine” refers to \(-\text{NR}^{50}\text{C}(\text{NR}^{51})\text{NR}^{52}\text{R}^{53}\), wherein \(\text{R}^{50}, \text{R}^{51}, \text{R}^{52}\)
and \(\text{R}^{53}\) are each independently hydrogen, or a substituted or unsubstituted alkyl, cycloalkyl, alkenyl, alkynyl, aryl aralkyl, heterocycyl or heterocyclylalkyl group as defined herein.

[00192] The term “enamine” refers to \(-\text{C}(\text{R}^{54})=\text{C}(\text{R}^{55})\text{NR}^{56}\text{R}^{57}\) and
\(-\text{NR}^{54}\text{C}(\text{R}^{55})=\text{C}(\text{R}^{56})\text{R}^{57}\), wherein \(\text{R}^{54}, \text{R}^{55}, \text{R}^{56}\) and \(\text{R}^{57}\) are each independently hydrogen, a
substituted or unsubstituted alkyl, cycloalkyl, alkenyl, alkynyl, aryl aralkyl, heterocycyl or
heterocyclylalkyl group as defined herein.

[00193] The term “imide” refers to \(-\text{C}(\text{O})\text{NR}^{58}\text{C}(\text{O})\text{R}^{59}\), wherein \(\text{R}^{58}\) and \(\text{R}^{59}\) are each
independently hydrogen, or a substituted or unsubstituted alkyl, cycloalkyl, alkenyl, alkynyl,
aryl aralkyl, heterocycyl or heterocyclylalkyl group as defined herein.

[00194] The term “imine” refers to \(-\text{CR}^{60}(\text{NR}^{61})\) and \(-\text{N}(\text{CR}^{60})\text{R}^{61}\) groups, wherein \(\text{R}^{60}\)
and \(\text{R}^{61}\) are each independently hydrogen or a substituted or unsubstituted alkyl, cycloalkyl,
alkenyl, alkynyl, aryl aralkyl, heterocycyl or heterocyclylalkyl group as defined herein, with
the proviso that \(\text{R}^{60}\) and \(\text{R}^{61}\) are not both simultaneously hydrogen.

[00195] The term “protected” with respect to hydroxyl groups, amine groups, carboxy
groups, and sulfhydryl groups refers to forms of these functionalities which are protected
from undesirable reaction by means of protecting groups. Protecting groups are known to
those skilled in the art and can be added or removed using well-known procedures, such as
those set forth in Protective Groups in Organic Synthesis, Greene, T. W.; Wuts, P. G. M.,
groups include, but are not limited to, silyl ethers such as those obtained by reaction of a
hydroxyl group with a reagent such as, but not limited to, t-butyldimethyl-chlorosilane,
trimethylchlorosilane, trisopropylchlorosilane, triethylchlorosilane; substituted methyl and
ethyl ethers such as, but not limited to methoxymethyl ether, methyliothemethyl ether,
benzyloxymethyl ether, t-butoxymethyl ether, 2-methoxyethoxymethyl ether,
tetrahydropranyl ethers, 1-ethoxyethyl ether, allyl ether, benzyl ether; esters such as, but not
limited to, benzoylformate, formate, acetate, trichloroacetate, and trifluoroacetate.

[00196] N-Protecting groups comprise acyl groups such as formyl, acetyl, propionyl,
pivaloyl, t-butyacetlyl, 2-chloroacetlyl, 2-bromoacetlyl, trifluoroacetlyl, trichloroacetlyl,
phthalyd, o-nitrophenoxyacetyl, a-chlorobutyryl, benzoyl, 4-chlorobenzoyl, 4-bromobenzoyl, 
4-nitrobenzoyl, and the like; sulfonyl groups such as benzenesulfonyl, p-toluenesulfonyl, and 
the like; carbamate forming groups such as benzylxoycarbonyl, p-chlorobenzylxoycarbonyl, 
p-methoxybenzylxoycarbonyl, p-nitrobenzylxoycarbonyl, 2--nitrobenzylxoycarbonyl, 
p-bromobenzylxoycarbonyl, 3,4-dimethoxybenzylxoycarbonyl, 
3,5-dimethoxybenzylxoycarbonyl, 2,4-dimethoxybenzylxoycarbonyl, 
4-methoxybenzylxoycarbonyl, 2-nitro-4,5-dimethoxybenzylxoycarbonyl, 
3,4,5-trimethoxybenzylxoycarbonyl, 1-(p-biphenyl)-1-methylethoxycarbonyl, 
α,α-dimethyl-3,5-dimethoxybenzylxoycarbonyl, benzhydryloxycarbonyl, t-butyloxycarbonyl, 
diisopropylmethoxycarbonyl, isopropylxoycarbonyl, ethoxycarbonyl, methoxycarbonyl, 
allyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, phenoxyxoycarbonyl, 4-nitrophenoxyxoycarbonyl, 
fluorenyl-9-methoxycarbonyl, cyclopentyloxycarbonyl, adamantoxycarbonyl, 
cyclohexyloxycarbonyl, phenylthiocarbonyl, and the like; alkyl groups such as benzyl, 
triphenylmethyl, benzoxymethyl, and the like; and silyl groups such as trimethysilyl, and 
the like. Typical N-protecting groups are formyl, acetyl, benzoyl, pivaloyl, t-butyrlacetyl, 
phenylsulfonyl, benzyl, 9-fluorenylmethoxycarbonyl (Fmoc), t-butyloxycarbonyl (Boc) and 
benzyloxycarbonyl (Cbz).

[00197] Examples of protected sulfhydryl groups include, but are not limited to, 
thioethers such as S-benzyl thioether, S-t-butylthioether, and S-4-picolyl thioether; 
substituted S-methyl derivatives such as hemithio, dithio and aminothio acetals; and others.

[00198] Representative carboxy protecting groups are C1 to C8 alkyl (e.g., methyl, 
ethyl or tertiary butyl and the like); haloalkyl; alkenyl; cycloalkyl and substituted derivatives 
thereof such as cyclohexyl, cyclopentyl, and the like; cycloalkylalkyl and substituted 
derivatives thereof such as cyclohexylmethyl, cyclopentylmethyl, and the like; arylalkyl, for 
example, phenethyl or benzyl and substituted derivatives thereof such as alkoxynitrobenzyl or 
nitrobenzyl groups, and the like; arylalkenyl, for example, phenylethenyl and the like; aryl 
and substituted derivatives thereof, for example, 5-indanyl and the like; dialkylaminoalkyl 
(e.g., dimethylaminoethyl, and the like); alkanoyloxyalkyl groups such as acetoxyethyl, 
butyroxyethyl, valernyloxyethyl, isobutyroxyethyl, isovaleryloxyethyl, 
1-(propionyloxy)-1-ethyl, 1-(pivaloyloxy)-1-ethyl, 1-methyl-1-(propionyloxy)-1-ethyl, 
pivaloyloxyethyl, propionyloxyethyl, and the like; cycloalkanoyloxyalkyl groups such as
cyclopropylcarbonyloxymethyl, cyclobutylcarbonyloxymethyl,
cyclopentylcarbonyloxymethyl, cyclohexylcarbonyloxymethyl, and the like; aroyloxyalkyl,
such as benzoyloxymethyl, benzoxyethyl, and the like; arylalkylcarbonyloxalkyl, such as
benzylcarbonyloxymethyl, 2-benzylcarbonyloxethyl, and the like; alkoxy carbonylalkyl,
such as methoxycarbonylmethyl, cyclohexyloxycarbonylmethyl, 1-methoxycarbonyl-1-ethyl,
and the like; alkoxy carbonyloxalkyl, such as methoxycarbonyloxymethyl,
t-butyloxycarbonyloxymethyl, 1-ethoxycarbonyloxy-1-ethyl, 1-cyclohexyloxycarbonyloxy-1-
ethyl, and the like; alkoxy carbonylaminooalkyl, such as t-butyloxycarbonylaminomethyl, and
the like; alkylaminocarbonylaminooalkyl, such as methylaminocarbonylaminomethyl, and
the like; alkanoylaminooalkyl, such as acetylaminomethyl, and the like;
heterocyclic carbonyloxalkyl, such as 4-methylpiperazinylcarbonyloxymethyl, and the like;
dialkylaminocarbonylalkyl, such as dimethylaminocarbonylmethyl,
diethylaminocarbonylmethyl, and the like; (5-alkyl)-2-oxo-1,3-dioxolen-4-yl)alkyl, such as
(5-t-butyl-2-oxo-1,3-dioxolen-4-yl)methyl, and the like; and (5-phenyl-2-oxo-1,3-dioxolen-4-
yl)alkyl, such as (5-phenyl-2-oxo-1,3-dioxolen-4-yl)methyl, and the like.

[00199] Those of skill in the art will appreciate that compounds of the invention may
exhibit the phenomena of tautomerism, conformational isomerism, geometric isomerism
and/or optical isomerism. As the formula drawings within the specification and claims can
represent only one of the possible tautomeric, conformational isomeric, optical isomeric or
gonometric isomeric forms, it should be understood that the invention encompasses any
tautomeric, conformational isomeric, optical isomeric and/or geometric isomeric forms of the
compounds having one or more of the utilities described herein, as well as mixtures of these
various different forms.

[00200] "Tautomers" refers to isomeric forms of a compound that are in equilibrium
with each other. The concentrations of the isomeric forms will depend on the environment
the compound is found in and may be different depending upon, for example, whether the
compound is a solid or is in an organic or aqueous solution. For example, in aqueous
solution, triazoles may exhibit the following isomeric forms, which are referred to as
tautomers of each other:
As readily understood by one skilled in the art, a wide variety of functional groups and other structures may exhibit tautomerism, and all tautomers of compounds as described herein are within the scope of the present invention.

Stereoisomers of compounds (also known as optical isomers) include all chiral, diastereomeric, and racemic forms of a structure, unless the specific stereochemistry is expressly indicated. Thus, compounds used in the present invention include enriched or resolved optical isomers at any or all asymmetric atoms as are apparent from the depictions. Both racemic and diastereomeric mixtures, as well as the individual optical isomers can be isolated or synthesized so as to be substantially free of their enantiomeric or diastereomeric partners, and these are all within the scope of the invention.

As used herein, a solvate is an aggregation of a molecule and one or more molecules of solvent. Some compounds have a tendency to trap a fixed molar ratio of solvent molecules in the solid state. The solvent molecules may interact with the non-solvent molecule by dipole-dipole interactions, ion-dipole interactions, coordinate bonds, and the like. When the solvent is water, the solvate is a hydrate. Many organic solvents can also form solvates, including, e.g., ethers, such as diethyl ether and tetrahydrofuran, alcohols, such as methanol and ethanol ketones such as acetone, DMF, DMSO and others. Solvates may be identified by various methods known in the art. For example, solvates in which the solvent molecules contain hydrogen may be observable by $^1$H NMR. Additional methods useful in identifying solvates include thermogravimetric analysis, differential scanning calorimetry, X-ray analysis and elemental analysis. Solvates are readily formed simply by dissolving a compound in a solvent and removing the untrapped solvent by evaporation, freeze-drying or crystallization techniques. It is therefore well within the skill in the art to produce such solvates. Indeed, it is often the case that careful drying of a compound is necessary to remove the residual solvent that is part of a solvate. Compounds described herein may form solvates and all such solvates are within the scope of the invention.

Pharmaceutically acceptable salts of the invention compounds are considered within the scope of the present invention. When the compound of the invention has a basic group, such as, for example, an amino group, pharmaceutically acceptable salts can be formed with inorganic acids (such as hydrochloric acid, hydroboric acid, nitric acid, sulfuric acid, and phosphoric acid), organic acids (e.g., formic acid, acetic acid, trfluoroacetic acid, fumaric acid, oxalic acid, tartaric acid, lactic acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, and p-toluenesulfonic acid) or acidic amino acids (such as aspartic acid and glutamic acid). When the compound of the invention has an acidic group, such as for example, a carboxylic acid group, it can form salts with metals, such as alkali and earth alkali metals (e.g., Na⁺, Li⁺, K⁺, Ca²⁺, Mg²⁺, Zn²⁺), ammonia, organic amines (e.g., trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine), or basic amino acids (e.g., arginine, lysine and ornithine).

Compounds of the invention may be readily synthesized by techniques well known to those of skill in the art. Examples of synthesis approaches can be found in, for example, U.S. Application No.10/939,324 and International Application No. PCT/US2006/006682.

C-reactive protein (CRP) is a plasma protein, and an acute phase protein produced by the liver. CRP is a member of the class of acute phase reactants as its levels rise
dramatically during inflammatory processes occurring in the body. CRP is used mainly as a marker of inflammation. Measuring and charting C-reactive protein values can prove useful in determining disease progress or the effectiveness of treatments. Blood, usually collected in a serum-separating tube, is analyzed in a medical laboratory or at the point of testing. Various analytical methods are available for CRP determination, such as ELISA, immunoturbidimetry, rapid immunodiffusion and visual agglutination. Research suggests that patients with elevated basal levels of CRP are at an increased risk for diabetes, hypertension and cardiovascular disease. It is thought that CRP levels <1mg/l represent low cardiovascular risk, while levels >3mg/l represent high risk.

[00208] Lipoproteins are complexes which contain both a lipid and protein. Most of the lipids in plasma are present as lipoproteins and are transported as such. Lipoproteins are characterized by their flotation constants (e.g., densities). Various classes of lipoproteins exist and include high density lipoproteins (HDL) and low density lipoproteins (LDL). The HDL fraction comprises two major fractions, namely HDL₂ (large, buoyant HDL, density 1.063 - 1.125 g/ml) and HDL₃ (small, dense HDL, density 1.125-1.21 g/ml). LDLs are particularly rich in cholesterol esters. Traditionally, high levels of LDL and/or low levels of HDL are associated with coronary artery disease. Epidemiological studies have shown that high concentrations of HDL (over 60 mg/dl) have protective value against cardiovascular diseases. Low concentrations of HDL (below 40 mg/dl for men, below 50 mg/dl for women) are a positive risk factor for atherosclerotic diseases. A near optimal level of LDL is considered to be between 100 to 129 mg/dl, with levels below 100 mg/dl considered optimal, while very high LDL levels (above 190 mg/dl) correspond to the highest increased risk of heart disease.

[00209] Assessment of these levels is associated with assessing the risk of cardiovascular and/or cerebrovascular disease. Lipoprotein levels and triglyceride levels are measured and assessed using routine methods known in the art. Commercially available kits and assays may be used to evaluate the level of HDL-C, LDL-C and the level of triglycerides in a subject. Typically, cholesterol analysis is performed by two methods, namely an NMR based method and an ultracentrifugation method. The first method is based on NMR analysis of the lipid environment to determine the size classes and utilizes deconvolution to determine the number of particles in each class. The second method, based on density gradient ultracentrifugation, measures the amount of cholesterol across a range of densities and
utilizes deconvolution to determine the amount of cholesterol in each fraction (HDL, including HDL₂ and HDL₃, LDL, IDL, VLDL).

[00210] Apolipoprotein A-I (ApoA-I) is the major protein component of HDL in plasma. The protein promotes cholesterol efflux from tissues to the liver for excretion and helps to clear cholesterol from arteries.

[00211] Glucose, or "blood sugar", is normally present in humans at concentrations of about 80-120 mg/dl and is the principal source of carbohydrate energy for man and many other organisms. Excess glucose is stored in the body (especially in the liver and muscles) as glycogen, a starch-like substance which is, essentially, polymerized glucose. Glycogen is metabolized into glucose as needed to meet bodily requirements.

[00212] Glucose normally stimulates both the secretion and biosynthesis of insulin. In addition to this glucose-stimulated insulin secretion, however, there exists a basal insulin secretion, namely the biological process by which insulin is released into the circulation in the absence of stimulation by levels of glucose, or other agents that promote insulin secretion, that are elevated above their "fasting" or non-fasted levels. The values for fasting and post-prandial (after a meal) insulin are about 14 to 145 pmol/l, and 100 to 300 pmol/l respectively in healthy people, with perhaps 3-to 4-fold higher levels in insulin-resistant people.

[00213] Glycosylated (or glycated) hemoglobin (hemoglobin A₁c, Hb1c, HbA₁c or HgA₁c) is a form of hemoglobin used primarily to identify the plasma glucose concentration over time. The normal range (that found in healthy subjects) is 4% to 5.9%. People with diabetes mellitus often have higher levels of HbA₁c. While diabetic subject treatment goals vary, many include a target range of HbA₁c values. A diabetic with good glucose control has a HbA₁c level that is close to or within the reference range. The International Diabetes Federation and American College of Endocrinology recommends HbA₁c values below 6.5%, while the range recommended by the American Diabetes Association extends to 7%. A very high HbA₁c represents poor glucose control.

[00214] Insulin resistance is the condition in which normal amounts of insulin are inadequate to produce a normal insulin response from fat, muscle and liver cells. Insulin resistance in fat cells results in hydrolysis of stored triglycerides, which elevates free fatty
acids in the blood plasma. Insulin resistance in muscle reduces glucose uptake whereas
insulin resistance in liver reduces glucose storage, with both effects serving to elevate blood
glucose. High plasma levels of insulin and glucose due to insulin resistance often leads to
metabolic syndrome and type 2 diabetes. Metabolic syndrome, also known as Syndrome X,
metabolic syndrome X, insulin resistance syndrome, is a combination of medical disorders,
having at least three of the following symptoms and features: fasting hyperglycemia
(including diabetes mellitus type 2 or impaired fasting glucose, impaired glucose tolerance or
insulin resistance), high blood pressure, central obesity (also known as visceral adiposity),
decreased HDL cholesterol, and elevated triglycerides.

[00215] Insulin resistance can be detected by the following indications: as an increased
level of blood insulin, increased blood level of glucose in response to oral glucose tolerance
test (OGTT), decreased level of phosphorylated protein kinase B (AKT) in response to
insulin administration, and the like. Insulin resistance may be caused by decreased sensitivity
of the insulin receptor-related signaling system in cells and/or by loss of beta cells in the
pancreas through apoptosis. There is also evidence that insulin resistance can be
characterized as having an underlying inflammatory component.

[00216] Bilirubin is formed when red blood cells die and their hemoglobin is broken
down within the macrophages to heme and globins. The heme is further degraded to Fe^{2+},
carbon monoxide and bilirubin via the intermediate compound biliverdin. Since bilirubin is
poorly soluble in water, it is carried to the liver and bound to albumin. Bilirubin is made
water-soluble in the liver by conjugation with glucuronic acid. Conjugated bilirubin, or
bilirubinglucuronide, moves into the bile canaliculi of the liver and then to the gall bladder.
Bilirubin is found in blood either in the conjugated form (also called direct bilirubin), or in
the unconjugated form (also called indirect bilirubin). The reference range for total bilirubin
is 0.3 - 1.0 mg/dl. For direct bilirubin, it is 0.1 - 0.3 mg/dl, while for indirect bilirubin it is
0.2 - 0.7 mg/dl. In diseases where too much hemoglobin is broken down or the removal of
bilirubin does not function properly, the accumulating bilirubin in the body causes jaundice.
Usually the concentration of total bilirubin in the blood must exceed 2–3 mg/dl for the
coloration to be easily visible.
A "cytokine inhibitor" within the context of this invention is a compound which at a concentration of 10 μM inhibits induced cytokine release from a cell by about 50% or greater than 50%. For example, induction of TNFα release can be achieved by, but not limited to, treatment of a cell or cell line with lipopolysaccharide (LPS) or IL-1β and is inhibited by compounds described herein.

The association of disorders with imbalances in specific cytokine levels is well known in the art, as documented by the references in List II.

**LIST II. References describing cytokine-mediated processes and disorders.**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Reference</th>
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[00219] "Treating" within the context of the instant invention, means an alleviation, in whole or in part, of symptoms associated with a disorder or disease, or slowing, or halting of further progression or worsening of those symptoms, or prevention or prophylaxis of the disease or disorder in a subject at risk for developing the disease or disorder. As used herein, a “therapeutically effective amount” of a compound of the invention refers to an amount of the compound that alleviates, in whole or in part, symptoms associated with a disorder or disease, or slows or halts further progression or worsening of those symptoms, or prevents or provides prophylaxis for the disease or disorder in a subject at risk for developing the disease or disorder. As will be apparent to those of skill in the art, it is to be expected that the therapeutically effective amount of a compound disclosed herein may vary depending on the indication being treated, e.g., the therapeutically effective amount of a compound described herein would likely be different for treating subjects suffering from, or at risk for, cytokine-mediated disorders relative to the therapeutically effective amount of the compound for treating subjects suffering from, or at risk of, a different disorder, e.g., vascular event(s), diabetes, insulin resistance, or metabolic syndrome. Similarly, it is also to be expected that, for example, the therapeutically effective amount of a compound for decreasing CRP-levels in a subject would likely be different from the therapeutically effective amount for raising HDL-levels in a subject. However, determining a therapeutically effective amount of a
compound described herein for treating a particular disorder or disease is well within the skill in the art in view of the present disclosure.

[00220] A subject is any animal that can benefit from the administration of a compound as described herein. In some embodiments, the subject is a mammal, for example, a human, a primate, a dog, a cat, a horse, a cow, a pig, a rodent, such as for example a rat or mouse. Typically, the subject is a human.

[00221] Subjects who are at risk for a cardiovascular and/or cerebrovascular event are also subjects who manifest at least one symptom indicative of a vascular disorder/event. Symptoms that are indicative of a coronary-related vascular event, for example, include chest pain, abnormal electrocardiograms, elevated levels of ischemic markers, necrosis markers, or thrombin/fibrin generation markers. Such markers include, but are not limited to, Creatine Kinase with Muscle and/or Brain subunits (CKMB), D-Dimer, F1.2, thrombin anti-thrombin (TAT), soluble fibrin monomer (SFM), fibrin peptide A (FPA), myoglobin, thrombin precursor protein (TPP), platelet monocyte aggregate (PMA) and troponin (c’l’n). Subjects who are at risk also include subjects having a history of a thrombotic event (e.g., disorder), including coronary heart disease (CHD), stroke, or transient ischemic attacks (TIA). A history of CHD can include, for example, a history of MI, coronary revascularization procedure, angina with ischemic changes, or a positive coronary angiogram (e.g., showing greater than about 50% stenosis of at least one major coronary artery).

[00222] The term “cancer” refers to any of various malignant neoplasms characterized by the proliferation of cells that can invade surrounding tissue and metastasize to new body sites. Both benign and malignant tumors are classified according to the type of tissue in which they are found. For example, fibromas are neoplasms of fibrous connective tissue, and melanomas are abnormal growths of pigment (melanin) cells. Malignant tumors originating from epithelial tissue, e.g., in skin, bronchi, and stomach, are termed carcinomas. Malignancies of epithelial glandular tissue such as are found in the breast, prostate, and colon, are known as adenocarcinomas. Malignant growths of connective tissue, e.g., muscle, cartilage, lymph tissue, and bone, are called sarcomas. Lymphomas and leukemias are malignancies arising among the white blood cells.
[00223] In the context of neoplasia, cancer, tumor growth or tumor cell growth, inhibition may be assessed by delayed appearance of primary or secondary tumors, slowed development of primary or secondary tumors, decreased occurrence of primary or secondary tumors, slowed or decreased severity of secondary effects of disease, arrested tumor growth and regression of tumors, among others. In the extreme, complete inhibition, is referred to herein as prevention or chemoprevention. In this context, the term "prevention" includes either preventing the onset of clinically evident neoplasia altogether or preventing the onset of a preclinically evident stage of neoplasia in individuals at risk. Also intended to be encompassed by this definition is the prevention of transformation into malignant cells or to arrest or reverse the progression of premalignant cells to malignant cells. This includes prophylactic treatment of those at risk of developing the neoplasia.

[00224] The term "nociceptive pain" includes, but is not limited to, pain associated with chemical or thermal burns, cuts of the skin, contusions of the skin, osteoarthritis, rheumatoid arthritis, tendinitis, and myofascial pain.

[00225] The term "neuropathic pain" includes, but is not limited to, CRPS (Complex Regional Pain Syndrome) type I, CRPS type II, reflex sympathetic dystrophy (RSD), reflex neurovascular dystrophy, reflex sympathetic dystrophy, reflex neurovascular dystrophy, reflex dystrophy, sympathetically maintained pain syndrome, causalgia, Sudeck atrophy of bone, algoneurodystrophy, shoulder hand syndrome, post-traumatic dystrophy, trigeminal neuralgia, post herpetic neuralgia, cancer and metastases related pain, phantom limb pain, fibromyalgia, chronic fatigue syndrome, spinal cord injury pain, central post-stroke pain, radiculopathy, diabetic neuropathy, post-stroke pain, luetic neuropathy, and other painful neuropathic conditions such as those induced by drugs such as vincristine, velcade and thalidomide. The neuropathic pain can result from a mononeuropathy, polyneuropathy, complex regional pain syndromes or deafferentation.

[00226] The term “neuropathy” includes, but is not limited to, a functional disturbance or pathological change in the nervous system, especially in the peripheral nervous system, and is characterized clinically by sensory or motor neuron abnormalities. The term mononeuropathy indicates that a single nerve is affected, while the term polyneuropathy indicates that several nerves are affected. Deafferentation indicates a loss of
the sensory input from a portion of the body, and can be caused by interruption of either
peripheral sensory fibers or nerves from the central nervous system. The etiology of a
neuropathy can be known or unknown. Known etiologies include complications of a disease
or toxic state such as diabetes, which is the most common metabolic disorder causing
neuropathy, or irradiation, ischemia or vasculitis. It is understood that the methods of the
invention can be used to treat chronic pain of these or other chronic neuropathies of known or
unknown etiology.

[00227] A therapeutically effective amount of a compound as described herein used in
the present invention may vary depending upon the route of administration and dosage form.
Effective amounts of invention compounds typically fall in the range of about 0.001 up to
100 mg/kg/day, and more typically in the range of about 0.05 up to 10 mg/kg/day. Typically,
the compound or compounds used in the instant invention are selected to provide a
formulation that exhibits a high therapeutic index. The therapeutic index is the dose ratio
between toxic and therapeutic effects which can be expressed as the ratio between LD50 and
ED50. The LD50 is the dose lethal to 50% of the population and the ED50 is the dose
therapeutically effective in 50% of the population. The LD50 and ED50 are determined by
standard pharmaceutical procedures in animal cell cultures or experimental animals.

[00228] Treatment may also include administering the compounds or pharmaceutical
formulations of the present invention in combination with other therapies. Combinations of
the invention may be administered simultaneously, separately or sequentially. For example,
the compounds and pharmaceutical formulations of the present invention may be
administered before, during, or after surgical procedure and/or radiation therapy.
Alternatively, the compounds of the invention can also be administered in conjunction with
other anti-inflammatory agents, anticancer agents and other agents described herein. In the
context of inflammation, many types of immunomodulatory, immunosuppressive or
cytostatic drugs, as described herein, can be used in combination with the compounds as
described herein.

[00229] The specific amount of the additional active agent will depend on the specific
agent used, the type of condition being treated or managed, the severity and stage of the
condition, and the amount(s) of compounds and any optional additional active agents concurrently administered to the subject.

[00230] In some embodiments of the invention, one or more compounds of the invention and an additional active agent are administered to a subject, more typically a human, in a sequence and within a time interval such that the compound can act together with the other agent to provide an enhanced benefit relative to the benefits obtained if they were administered otherwise. For example, the additional active agents can be coadministered by coformulation, administered at the same time or administered sequentially in any order at different points in time; however, if not administered at the same time, they should be administered sufficiently close in time so as to provide the desired therapeutic or prophylactic effect. In some embodiments, the compound and the additional active agents exert their effects at times which overlap. Each additional active agent can be administered separately, in any appropriate form and by any suitable route. In other embodiments, the compound is administered before, concurrently or after administration of the additional active agents.

[00231] In various examples, the compound and the additional active agents are administered less than about 1 hour apart, at about 1 hour apart, at about 1 hour to about 2 hours apart, at about 2 hours to about 3 hours apart, at about 3 hours to about 4 hours apart, at about 4 hours to about 5 hours apart, at about 5 hours to about 6 hours apart, at about 6 hours to about 7 hours apart, at about 7 hours to about 8 hours apart, at about 8 hours to about 9 hours apart, at about 9 hours to about 10 hours apart, at about 10 hours to about 11 hours apart, at about 11 hours to about 12 hours apart, no more than 24 hours apart or no more than 48 hours apart. In other examples, the compound and the additional active agents are administered concurrently. In yet other examples, the compound and the additional active agents are administered concurrently by coformulation.

[00232] In other examples, the compound and the additional active agents are administered at about 2 to 4 days apart, at about 4 to 6 days apart, at about 1 week apart, at about 1 to 2 weeks apart, or more than 2 weeks apart.

[00233] In certain examples, the inventive compound and optionally the additional active agents are cyclically administered to a subject. Cycling therapy involves the administration of a first agent for a period of time, followed by the administration of a second
agent and/or third agent for a period of time and repeating this sequential administration. Cycling therapy can provide a variety of benefits, e.g., reduce the development of resistance to one or more of the therapies, avoid or reduce the side effects of one or more of the therapies, and/or improve the efficacy of the treatment.

[00234] In other examples, the inventive compound and optionally the additional active agent are administered in a cycle of less than about 3 weeks, about once every two weeks, about once every 10 days or about once every week. One cycle can comprise the administration of an inventive compound and optionally the second active agent by infusion over about 90 minutes every cycle, about 1 hour every cycle, about 45 minutes every cycle, about 30 minutes every cycle or about 15 minutes every cycle. Each cycle can comprise at least 1 week of rest, at least 2 weeks of rest, at least 3 weeks of rest. The number of cycles administered is from about 1 to about 12 cycles, more typically from about 2 to about 10 cycles, and more typically from about 2 to about 8 cycles.

[00235] Courses of treatment can be administered concurrently to a subject, i.e., individual doses of the additional active agents are administered separately yet within a time interval such that the inventive compound can work together with the additional active agents. For example, one component can be administered once per week in combination with the other components that can be administered once every two weeks or once every three weeks. In other words, the dosing regimens are carried out concurrently even if the therapeutics are not administered simultaneously or during the same day.

[00236] The additional active agents can act additively or, more typically, synergistically with the inventive compound. In one example, the inventive compound is administered concurrently with one or more second active agents in the same pharmaceutical composition. In another example, the inventive compound is administered concurrently with one or more second active agents in separate pharmaceutical compositions. In still another example, the inventive compound is administered prior to or subsequent to administration of a second active agent. The invention contemplates administration of an inventive compound and a second active agent by the same or different routes of administration, e.g., oral and parenteral. In certain embodiments, when the inventive compound is administered concurrently with a second active agent that potentially produces adverse side effects
including, but not limited to, toxicity, the second active agent can advantageously be administered at a dose that falls below the threshold that the adverse side effect is elicited.

[00237] The instant invention also provides for pharmaceutical compositions and medicaments which may be prepared by mixing one or more compounds of the invention, prodrugs thereof, pharmaceutically acceptable salts thereof, stereoisomers thereof, tautomers thereof, or solvates thereof, with pharmaceutically acceptable carriers, excipients, binders, diluents or the like to prevent and treat disorders associated with excess cytokine production. The compounds and compositions of the invention may be used to prepare formulations and medicaments that prevent or treat a variety of disorders associated with excess cytokine production as disclosed herein, e.g., diseases and pathological conditions involving inflammation, pain, cancer, etc. Such compositions can be in the form of, for example, granules, powders, tablets, capsules, syrup, suppositories, injections, emulsions, elixirs, suspensions or solutions. The instant compositions can be formulated for various routes of administration, for example, by oral, parenteral, topical, rectal, nasal, vaginal administration, or via implanted reservoir. Parenteral or systemic administration includes, but is not limited to, subcutaneous, intravenous, intraperitoneally, intramuscular, intra-articular, intrasynovial, intrasternal, intrathecal, intralesional and intracranial injections. The following dosage forms are given by way of example and should not be construed as limiting the instant invention.

[00238] For oral, buccal, and sublingual administration, powders, suspensions, granules, tablets, pills, capsules, gelcaps, and caplets are acceptable as solid dosage forms. These can be prepared, for example, by mixing one or more compounds of the instant invention, or pharmaceutically acceptable salts or tautomers thereof, with at least one additive such as a starch or other additive. Suitable additives are sucrose, lactose, cellulose sugar, mannitol, maltitol, dextran, starch, agar, alginites, chitins, chitosans, pectins, tragacanth gum, gum arabic, gelatins, collagens, casein, albumin, synthetic or semi-synthetic polymers or glycerides. Optionally, oral dosage forms can contain other ingredients to aid in administration, such as an inactive diluent, or lubricants such as magnesium stearate, or preservatives such as paraben or sorbic acid, or anti-oxidants such as ascorbic acid, tocopherol or cysteine, a disintegrating agent, binders, thickeners, buffers, sweeteners, flavoring agents or perfuming agents. Tablets and pills may be further treated with suitable coating materials known in the art.
[00239] Liquid dosage forms for oral administration may be in the form of pharmaceutically acceptable emulsions, syrups, elixirs, suspensions, and solutions, which may contain an inactive diluent, such as water. Pharmaceutical formulations and medicaments may be prepared as liquid suspensions or solutions using a sterile liquid, such as, but not limited to, an oil, water, an alcohol, and combinations of these. Pharmaceutically suitable surfactants, suspending agents, emulsifying agents, may be added for oral or parenteral administration.

[00240] As noted above, suspensions may include oils. Such oils include, but are not limited to, peanut oil, sesame oil, cottonseed oil, corn oil and olive oil. Suspension preparation may also contain esters of fatty acids such as ethyl oleate, isopropyl myristate, fatty acid glycerides and acetylated fatty acid glycerides. Suspension formulations may include alcohols, such as, but not limited to, ethanol, isopropyl alcohol, hexadecyl alcohol, glycerol and propylene glycol. Ethers, such as but not limited to, poly(ethylene glycol), petroleum hydrocarbons such as mineral oil and petrolatum; and water may also be used in suspension formulations.

[00241] Injectable dosage forms generally include aqueous suspensions or oil suspensions which may be prepared using a suitable dispersant or wetting agent and a suspending agent. Injectable forms may be in solution phase or in the form of a suspension, which is prepared with a solvent or diluent. Acceptable solvents or vehicles include sterilized water, Ringer's solution, or an isotonic aqueous saline solution. Alternatively, sterile oils may be employed as solvents or suspending agents. Typically, the oil or fatty acid is non-volatile, including natural or synthetic oils, fatty acids, mono-, di- or tri-glycerides.

[00242] For injection, the pharmaceutical formulation and/or medicament may be a powder suitable for reconstitution with an appropriate solution as described above. Examples of these include, but are not limited to, freeze dried, rotary dried or spray dried powders, amorphous powders, granules, precipitates, or particulates. For injection, the formulations may optionally contain stabilizers, pH modifiers, surfactants, bioavailability modifiers and combinations of these.

[00243] For rectal administration, the pharmaceutical formulations and medicaments may be in the form of a suppository, an ointment, an enema, a tablet or a cream for release of
compound in the intestines, sigmoid flexure and/or rectum. Rectal suppositories are prepared by mixing one or more compounds of the instant invention, or pharmaceutically acceptable salts or tautomers of the compound, with acceptable vehicles, for example, cocoa butter or polyethylene glycol, which is present in a solid phase at normal storing temperatures, and present in a liquid phase at those temperatures suitable to release a drug inside the body, such as in the rectum. Oils may also be employed in the preparation of formulations of the soft gelatin type and suppositories. Water, saline, aqueous dextrose and related sugar solutions, and glycerols may be employed in the preparation of suspension formulations which may also contain suspending agents such as pectins, caromers, methyl cellulose, hydroxypropyl cellulose or carboxymethyl cellulose, as well as buffers and preservatives.

[00244] Compounds of the invention may be administered to the lungs by inhalation through the nose or mouth. Suitable pharmaceutical formulations for inhalation include solutions, sprays, dry powders, or aerosols containing any appropriate solvents and optionally other compounds such as, but not limited to, stabilizers, antimicrobial agents, antioxidants, pH modifiers, surfactants, bioavailability modifiers and combinations of these. Formulations for inhalation administration contain as excipients, for example, lactose, polyoxyethylene-9-lauryl ether, glycocholate and deoxycholate. Aqueous and nonaqueous aerosols are typically used for delivery of inventive compounds by inhalation.

[00245] Ordinarily, an aqueous aerosol is made by formulating an aqueous solution or suspension of the compound together with conventional pharmaceutically acceptable carriers and stabilizers. The carriers and stabilizers vary with the requirements of the particular compound, but typically include nonionic surfactants (Tweens, Pluronics, or polyethylene glycol), innocuous proteins like serum albumin, sorbitan esters, oleic acid, lecithin, amino acids such as glycine, buffers, salts, sugars or sugar alcohols. Aerosols generally are prepared from isotonic solutions. A nonaqueous suspension (e.g., in a fluorocarbon propellant) can also be used to deliver compounds of the invention.

[00246] Aerosols containing compounds for use according to the present invention are conveniently delivered using an inhaler, atomizer, pressurized pack or a nebulizer and a suitable propellant, e.g., without limitation, pressurized dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, nitrogen, air, or carbon dioxide. In the
case of a pressurized aerosol, the dosage unit may be controlled by providing a valve to deliver a metered amount. Capsules and cartridges of, for example, gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch. Delivery of aerosols of the present invention using sonic nebulizers is advantageous because nebulizers minimize exposure of the agent to shear, which can result in degradation of the compound.

[00247] For nasal administration, the pharmaceutical formulations and medicaments may be a spray, nasal drops or aerosol containing an appropriate solvent(s) and optionally other compounds such as, but not limited to, stabilizers, antimicrobial agents, antioxidants, pH modifiers, surfactants, bioavailability modifiers and combinations of these. For administration in the form of nasal drops, the compounds may be formulated in oily solutions or as a gel. For administration of nasal aerosol, any suitable propellant may be used including compressed air, nitrogen, carbon dioxide, or a hydrocarbon based low boiling solvent.

[00248] Dosage forms for the topical (including buccal and sublingual) or transdermal administration of compounds of the invention include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, and patches. The active component may be mixed under sterile conditions with a pharmaceutically-acceptable carrier or excipient, and with any preservatives, or buffers, which may be required. Powders and sprays can be prepared, for example, with excipients such as lactose, tare, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. The ointments, pastes, creams and gels may also contain excipients such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, tare and zinc oxide, or mixtures thereof.

[00249] Transdermal patches have the added advantage of providing controlled delivery of a compound of the invention to the body. Such dosage forms can be made by dissolving or dispersing the agent in the proper medium. Absorption enhancers can also be used to increase the flux of the inventive compound across the skin. The rate of such flux can be controlled by either providing a rate controlling membrane or dispersing the compound in a polymer matrix or gel.
[00250] Ophthalmic formulations, eye ointments, powders, solutions and the like, are also contemplated as being within the scope of this invention. The compounds of this invention can be incorporated into various types of ophthalmic formulations for delivery to the eye (e.g., topically, intracamerally, or via an implant). The compounds are typically incorporated into topical ophthalmic formulations for delivery to the eye. The compounds may be combined with one or more ophthalmologically acceptable preservatives, viscosity enhancers, penetration enhancers, buffers, sodium chloride, and water to form an aqueous, sterile ophthalmic suspension or solution. Ophthalmic solution formulations may be prepared by dissolving a compound in a physiologically acceptable isotonic aqueous buffer. Further, the ophthalmic solution may include an ophthalmologically acceptable surfactant to assist in dissolving the compound. Furthermore, the ophthalmic solution may contain an agent to increase viscosity, such as hydroxyethylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose, methylcellulose, polyvinylpyrrolidone, or the like, to improve the retention of the formulation in the conjunctival sac. Gelling agents can also be used, including, but not limited to, gellan and xanthan gum. In order to prepare sterile ophthalmic ointment formulations, the compound of the invention is combined with a preservative in an appropriate vehicle, such as, mineral oil, liquid lanolin, or white petrolatum. Sterile ophthalmic gel formulations may be prepared by suspending the invention compound in a hydrophilic base prepared from the combination of, for example, carbopol-974, or the like, according to the published formulations for analogous ophthalmic preparations. Preservatives and tonicity agents can be optionally incorporated.

[00251] Intrathecal administration, via bolus dosage or constant infusion, allows the local administration of a compound to a region of the spinal cord, such as the dorsal horn regions, delivering the compound directly to the subarachnoid space containing the CSF (cerebrospinal fluid).

[00252] Central delivery to the spinal cord regions can also be performed by epidural injection to a region of the spinal cord exterior to the arachnoid membrane. Enhancing permeation of the active compound through meningeal membranes may be achieved by using hypertonic dosing solutions that increase permeability of meningeal membranes, or by addition of permeation enhancers, such as, but not limited to, liposomal encapsulation, surfactants, or ion-pairing agents.
Besides those representative dosage forms described above, pharmaceutically acceptable excipients and carriers are generally known to those skilled in the art and are thus included in the instant invention. Such excipients and carriers are described, for example, in "Remington’s Pharmaceutical Sciences" Mack Pub. Co., New Jersey (1991), which is incorporated herein by reference.

The formulations of the invention may be designed to be short-acting, fast-releasing, long-acting, and sustained-releasing as described below. Thus, the pharmaceutical formulations may also be formulated for controlled release or for slow release.

The instant compositions may also comprise, for example, micelles or liposomes, or some other encapsulated form, or may be administered in an extended release form to provide a prolonged storage and/or delivery effect. Therefore, the pharmaceutical formulations and medicaments may be compressed into pellets or cylinders and implanted intramuscularly or subcutaneously as depot injections or as implants such as stents. Such implants may employ known inert materials such as silicones and biodegradable polymers.

The present disclosure also provides medical devices incorporating the compounds as described herein. A representative device includes a vascular stent coated or impregnated with the compounds as described herein. The device can be configured to be inserted into a blood vessel where it can release the compounds as described herein to help reduce or prevent vascular inflammation, for example vascular inflammation.

Other embodiments disclose medical devices that include compounds as described herein, or a combination of the compounds with additional ingredients A, as described herein. The compounds as described herein can be coated on the surface of the medical device or the device can be saturated with the compounds such that the compounds are released from the device, for example over a period of time. Exemplary medical devices including the compounds as disclosed herein include, but are not limited to, vascular medical devices such as vascular stents.

Stents and methods for making and using stents coated or impregnated with therapeutic agents are well-known in the art: see, e.g., U.S. Application No. US20050181977 and U.S. Application No. US20050129729.
Specific dosages may be adjusted depending on conditions of disease, the age, body weight, general health conditions, sex, and diet of the subject. Dose intervals, administration routes, excretion rate, and combinations of drugs. Any of the above dosage forms containing effective amounts are well within the bounds of routine experimentation and therefore, well within the scope of the instant invention.

A therapeutically effective amount of a compound of the present invention may vary depending upon the route of administration and dosage form. Effective amounts of invention compounds typically fall in the range of about 0.001 up to 100 mg/kg/day, and more typically in the range of about 0.05 up to 10 mg/kg/day. Typically, the compound or compounds of the instant invention are selected to provide a formulation that exhibits a high therapeutic index. The therapeutic index is the dose ratio between toxic and therapeutic effects which can be expressed as the ratio between LD$_{50}$ and ED$_{50}$. The LD$_{50}$ is the dose lethal to 50% of the population and the ED$_{50}$ is the dose therapeutically effective in 50% of the population. The LD$_{50}$ and ED$_{50}$ are determined by standard pharmaceutical procedures in animal cell cultures or experimental animals.

In the context of cancer, the compounds as described herein can be used in the methods and compositions of the invention either alone or together with additional treatments or active ingredients or a combination thereof. Additional treatments comprise treatment by surgery, radiation, or cryotherapy, while treatment with additional active ingredients comprises the use of anti-proliferative agents. Combinations of drugs are administered in an attempt to obtain a synergistic cytotoxic effect on most cancers, e.g., carcinomas, melanomas, lymphomas and sarcomas, and to reduce or eliminate emergence of drug-resistant cells and to reduce side effects to each drug. The specific amount of the additional active agent will depend on the specific agent used, the type of cancer being treated or managed, the severity and stage of the cancer, and the amount(s) of compounds as described herein and any optional additional active agents concurrently administered to the subject. Typically, the additional active ingredients that can be used in combination with the compounds as described herein are used at dosages well known in the art.
[00262] In general, surgery and radiation therapy are employed as potentially curative therapies for humans under 70 years of age who present with clinically localized disease and are expected to live at least 10 years.

[00263] The phrase "antiproliferative agents" includes agents that prevent the development, maturation, or spread of cells, by acting directly on the cell, e.g., by cytostatic or cytocidal effects, and not indirectly through mechanisms such as biological response modification. There are large numbers of antiproliferative agents available in commercial use, in clinical evaluation and in pre-clinical development, which could be included in the present invention for treatment of cancer by combination drug chemotherapy.

[00264] Typical antiproliferative agents can be categorized as alkylating agents, platinum agents, antimitabolites, topoisomerase inhibitors, antitumor antibiotics, antimitotic agents, aromatase inhibitors, thymidylate synthase inhibitors, DNA antagonists, farnesyltransferase inhibitors, pump inhibitors, histone acetyltransferase inhibitors, metalloproteinase inhibitors, ribonucleoside reductase inhibitors, endothelin A receptor antagonists, retinoic acid receptor agonists, immunomodulators, hormonal or antihormonal agents, photodynamic agents, angiogenesis inhibitors, tyrosine kinase inhibitors, and the like. Some antiproliferative agents operate through multiple or unknown mechanisms and can thus be classified into more than one category.

[00265] A family of antiproliferative agents which may be used in combination with the present invention includes alkylating-type agents. The alkylating agents are believed to act by alkylating and cross-linking guanine and possibly other bases in DNA, arresting cell division. Typical alkylating agents include nitrogen mustards, ethyleneimine compounds, alkyl sulfates, cisplatin, and various nitrosoureas. A disadvantage with these compounds is that they not only attack malignant cells, but also other cells which are naturally dividing, such as those of bone marrow, skin, gastro-intestinal mucosa, and fetal tissue. Suitable alkylating-type agents that may be used in the present invention include, but are not limited to, busulfan, procarbazine, ifosfamide, altretamine, hexamethylmelamine, estramustine phosphate, thiopeta, mechlorethamine, dacarbazine, streptozocin, lomustine, temozolomide, cyclophosphamide, semustine, and chlorambucil.
A family of antiproliferative agents which may be used in combination with the present invention includes platinum agents. Suitable platinum agents that may be used in the present invention include, but are not limited to spiroplatin, lobaplatin (Acterna), tetraplatin, satraplatin (Johnson Matthey), ormaplatin, iproplatin, mriplatin (Sumitomo), nexplatin (AnorMED), polymer platinate (Access), oxaliplatin, or carboplatin.

An additional family of antiproliferative agents which may be used in combination with the present invention includes antimetabolite-type agents. Antimetabolites are typically reversible or irreversible enzyme inhibitors, or compounds that otherwise interfere with the replication, translation or transcription of nucleic acids. Suitable antimetabolite agents that may be used in the present invention include, but are not limited to azacytidine, trimetrexate, floxuridine, deoxycoformycin, 2-chlorodeoxyadenosine, pentostatin, 6-mercaptopurine, hydroxyurea, 6-thioguanine, decitabine (SuperGen), cytarabine, clofarabine (Beevision), 2-fluorodeoxy cytidine, irofulven (MGI Pharma), methotrexate, tomudex, ethynylycytidine (Taiho), fludarabine, gemcitabine, raltitrexed, or capecitabine.

Another family of antiproliferative agents which may be used in combination with the present invention includes topoisomerase inhibitors. Suitable topoisomerase agents that may be used in the present invention include, but are not limited to amsacrine, exatecan mesylate (Daiichi), epirubicin, quinamed (ChemGenex), etoposide, gimatecan (Sigma-Tau), teniposide, mitoxantrone, diplomotecan (Bcaour-lpsen), 7-ethyl-10-hydroxy-camptothecin, dexrazoxanet (TopoTarget), elsamitracin (Spectrum), pixintrone (Novuspharma), edotecarin (Merck & Co), becatecarin (Exelixis), karenitecin (BioNumerik), BBR-3576 (Novuspharma), belotecan (Chong Kun Dang), rubitecan (SuperGen), irinotecan (CPT-11), or topotecan.

Another family of antiproliferative agents which may be used in combination with the present invention includes antibiotic-type antiproliferative agents. Suitable antibiotic-type antiproliferative agents that may be used in the present invention include, but are not limited to dactinomycin (actinomycin D), azonafide, valubicin, anthrapyrazole, daunorubicin (daunomycin), oxantrazole, therarubicin, losoxantrone, idarubicin, bleomycinic acid, rubidazonc, sabarubicin (Menarini), plicamycin, 13-deoxydorubicin hydrochloride (Gem Pharmaceuticals), porfieromycin, epirubicin, mitoxantrone (novantrone) or aminofide.
[00270] Another family of antiproliferative agents which may be used in combination with the present invention includes antimitotic agents. Suitable antimitotic antiproliferative agents that may be used in the present invention include, but are not limited to, colchicines, ABT-751 (Abbot), vinblastine, xyotax (Cell Therapeutics), vindesine, IDN 5109 (Bayer), dolastatin 10 (NCI), A 105972 (Abbot), rhizinex (Fusisawa), A 204197 (Abbot), mivobulin (Warner-Lambert), synthadotin (BASF), cemadotin (BASF), indribulin (ASTAMedica), RPR 109881A (Aventis), TXD 258 (Aventis), combretastatin A4 (BMS), epothilone B (Novartis), isohomochalichondrin-B (PharmaMar), T 900607 (Tularik), ZD 6126 (AstraZeneca), batabulin (Tularik), cryptophycin 52 (Eli Lilly), vinflunine (Fabre), hydravin (Prescient NeuroPharma), auristatin PE (Teikoku Hormone), azap苞thilone B (BMS), ixabepilone (BMS), tavasept (BioNumerik), BMS 184476 (BMS), combretatin A4 disodium phosphate (OXiGENE), BMS 188797 (BMS), dolastatin-10 (NIH), taxoprexin (Protarga), cantuzumab mertansine (GlaxoSmithKline), docetaxel, vinorelbine, or vincristine.

[00271] Another family of antiproliferative agents which may be used in combination with the present invention includes aromatase inhibitors. Suitable aromatase inhibitors that may be used in the present invention include, but are not limited to, aminogluthethimide, atamestane (BioMedicines), formestane, fadrozole, letrozole, exemestane, or anastrozole.

[00272] An additional family of antiproliferative agents which may be used in combination with the present invention includes the thymidylate synthase inhibitors. Suitable thymidylate synthase inhibitors that may be used in the present invention include, but are not limited to, pemetrexed (Eli Lilly), nalatrexed (Eximias), ZD-9331 (BTG), doxifluridine (Nippon Roche), or 5,10-methylene tetrahydrofolate (BioKeys).

[00273] Yet another family of antiproliferative agents which may be used in combination with the present invention includes DNA antagonists. Suitable DNA antagonists that may be used in the present invention include, but are not limited to, trabectedin (PharmaMar), edotrolotide (Novartis), glufosfamide (Baxter International), mafosfamide (Baxter International), apaziquone (Spectrum Pharmaceuticals), or thymectacin (NewBiotics).

[00274] Another family of antiproliferative agents which may be used in combination with the present invention includes farnesyltransferase inhibitors. Suitable
farnesyltransferase inhibitors that may be used in the present invention include, but are not limited to arglabin (NuOncology Labs), tipifarnib (Johnson & Johnson), lonafarnib (Schering-Plough), perillyl alcohol (DOR BioPharma), or sorafenib (Bayer).

[00275] An additional family of antiproliferative agents which may be used in combination with the present invention includes pump inhibitors. Suitable pump inhibitors that may be used in the present invention include, but are not limited to zosuquidar trihydrochloride (Eli Lilly), tariquidar (Xenova), biricodar dicitrate (Vertex), or MS-209 (Schering AG).

[00276] An alternative family of antiproliferative agents which may be used in combination with the present invention includes histone acetyltransferase inhibitors. Suitable histone acetyltransferase inhibitors that may be used in the present invention include, but are not limited to tacedinaline (Pfizer), pivaloyloxymethyl butyrate (Titan), AP-CANC-03 and AP-CANC-04 (Aton Pharma), depsipeptide (Fujisawa), or MS-275 (Schering AG).

[00277] Another family of antiproliferative agents which may be used in combination with the present invention includes metalloproteinase inhibitors. Suitable metalloproteinase inhibitors that may be used in the present invention include, but are not limited to neovastat (Aeterna Laboratories), metastat (CollaGenex), or marimastat (British Biotech).

[00278] Also, the family of antiproliferative agents which may be used in combination with the present invention includes ribonucleoside reductase inhibitors. Suitable the DNA antagonists that may be used in the present invention include, but are not limited to gallium maltolate (Titan), tezacitabine (Aventis), triapine (Vion), or didox (Molecules for Health).

[00279] Another family of antiproliferative agents which may be used in combination with the present invention includes endothelin A receptor antagonists. Suitable endothelin A receptor antagonists that may be used in the present invention include, but are not limited to atrasentan (Abbott), bosentan (Roche), ambrisentan (BASF), sitaxsentan (Encysive), elazosentan (Roche), darusentan (Knoll), and ZD-4054 (AstraZeneca).

[00280] Yet another family of antiproliferative agents which may be used in combination with the present invention includes retinoic acid receptor agonists. The family
of retinoic acid receptor agonists includes compounds which are natural and synthetic analogues of retinol (Vitamin A). The retinoids bind to one or more retinoic acid receptors to initiate diverse processes such as reproduction, development, bone formation, cellular proliferation and differentiation, apoptosis, hematopoiesis, immune function and vision. Retinoids are required to maintain normal differentiation and proliferation of almost all cells and have been shown to reverse/suppress carcinogenesis in a variety of in vitro and in vivo experimental models of cancer, see (Moon et al., Ch. 14 Retinoids and cancer. In: The Retinoids, Vol. 2. Academic Press, Inc. 1984). Suitable retinoic acid receptor agonists that may be used in the present invention include, but are not limited to fenretinide (Johnson & Johnson), alitretinoin (Ligand), tazarotene (Allergan), tretinoin (Roche), isotretinoin (Roche), 13-cis-retinoic acid (UCSD), or LGD-1550 (Ligand).

[00281] Another family of antiproliferative agents which may be used in combination with the present invention includes immunomodulators. Suitable immunomodulators that may be used in the present invention include, but are not limited to interferon, Roferon-A (Roche), dexamethasone therapy (Anosys), oncophage (Antigenics), pentax (Australian Cancer Technology), GMK vaccine (Progenics), CD154 cell therapy (Tragen), adenocarcinoma vaccine (Biomira), transvax (Intercell), avicene (AVI BioPharma), norelin (Biostar), IRX-2 (Immuno-Rx), BLP-25 liposome vaccine (Biomira), PEP-005 (Peplin Biotech), multiganglioside vaccine (Progenics), synchrovax vaccine (CTL Immuno), β-alethine (Dovetail), melanoma vaccine (CTL Immuno), vasocare (Vasogen), rituximab (Genentech/Biogen Idec), or p21 RAS vaccine (GemVax).

[00282] An additional family of antiproliferative agents which may be used in combination with the present invention includes hormonal agents. Suitable hormonal agents that may be used in the present invention include, but are not limited to an estrogen, dexamethasone, a conjugated estrogen, prednisone, ethinyl estradiol, methylprednisolone, chlorrtrianisen, prednisolone, idenestrol, aminoglutethimide, hydroxyprogesterone caproate, leuprolide, medroxyprogesterone, OCTotide, testosterone, mitotane, testosterone propionate, fluoxymesterone, methyltestosterone, 2-methoxyestradiol (EntreMed), diethylstilbestrol, arzoxifene (Eli Lilly), megestrol, tamoxifen, bicalutamide, toremofine, flutamide, goserelin, nilutamide, or leuporelin.
Yet another family of antiproliferative agents which may be used in combination with the present invention includes photodynamic agents. Suitable photodynamic agents that may be used in the present invention include, but are not limited to talaporfin (Light Sciences), Pd-bacteriopheophorbide (Yeda), theralux (Theratechnologies), lutetium texaphyrin (Pharmacyclics), motexafin, gadolinium (Pharmacyclics), or hypericin.

Yet another family of antiproliferative agents which may be used in combination with the present invention includes angiogenesis inhibitors. Suitable angiogenesis inhibitors that may be used in the present invention include, but are not limited to neovastat (AELeta Zentaris), ATN-224 (Attenuon), sorafenib (Bayer), thalidomide, bevacizumab (Genentech), ramizumab (Genentech), benefin (Lane Labs), L-651582 (Merek & Co), vatalanib (Novartis), or sutent (Pfizer).

Another family of antiproliferative agents which may be used in combination with the present invention includes Tyrosine Kinase Inhibitors. Suitable Tyrosine Kinase Inhibitors that may be used in the present invention include, but are not limited to imatinib (Novartis), leflunomide (Aventis), kahalide F (PharmaMar) irressa (AstraZeneca), lestauretinib (Cephalon), erlotinib (Oncogene Science), canertinib (Pfizer), tandutinib (Millenium), squalamine (Genaera), midostaurin (Novartis), phenoxodiol, SU6668 (Pharmacia), cetuximab (ImClone), rhu-Mab (Genentech), ZD6474 (AstraZeneca), MDX-H210 (Medarex), vatalanib (Novartis), omnitarg (Genentech), lapatinib (GlaxoSmithKline), panitumumab (Abgenix), IMC-1C11 (ImClone), sorafenib (Bayer) or trastuzumab (Genentech).

Additional anti-proliferative agents which may be used in combination with the present invention include melphalan, carmustine, cisplatin, 5-fluorouracil, mitomycin C, adriamycin (doxorubicin), bleomycin, paclitaxel (Taxol®), and the like.

In the context of pain treatment, the compounds of the invention can be used in methods and compositions together with additional active ingredients or agents. Typically, the additional active agents are capable of relieving pain, inhibiting inflammatory reactions, providing a sedative effect or an antineuropathic effect, or ensuring patient comfort. Examples of the additional active agents include, but are not limited to, opioid analgesics, non-narcotic analgesics, anti-inflammatory, COX-2 inhibitors, α-adrenergic receptor agonists or antagonists, ketamine, anesthetic agents, NMDA antagonists, α2δ ligands,
immunomodulatory agents, immunosuppressive agents, antidepressants, anticonvulsants, antihypertensives, anxiolytics, calcium channel blockers, muscle relaxants, corticosteroids, hyperbaric oxygen, other therapeutics known to relieve pain, and pharmaceutically acceptable salts, solvates, hydrates, stereoisomers, prodrugs and pharmacologically active metabolites thereof.

[00288] Opioids can be used to treat severe pain. Examples of opioid analgesics include, but are not limited to, oxycodone (OxyContin™), morphine sulfate (MS Contin™, Duramorph™, Astramorph™), meperidine (Demerol™), and fentanyl transdermal patch (Duragesic™) and other known conventional medications [See, e.g., Physicians' Desk Reference, 594-595, 2851 and 2991 (57th ed., 2003)]. Oxycodone (OxyContin™) is a long-acting form of an opioid and may be used usually in initial and later stages of CRPS. Morphine sulfate may be used for analgesia due to reliable and predictable effects, safety profile, and ease of reversibility with naloxone. Morphine sulfate is sold in the United States under the trade name MS Contin™, Duramorph™, or Astramorph™ [See, e.g., Physicians' Desk Reference, 594-595 (57th ed., 2003)]. Fentanyl transdermal patch (Duragesic™) is a potent narcotic analgesic with much shorter half-life than morphine sulfate. Meperidine (Demerol™) and hydromorphone (Dilaudid™) may also be used for pain management [See, e.g., Physicians' Desk Reference, 2991 (57th ed., 2003)].

[00289] Non-narcotic analgesics and anti-inflammatories are preferably used for treatment of pain during pregnancy and breastfeeding. Anti-inflammatories such as non-steroidal anti-inflammatory drugs (NSAIDs) and cox-2 inhibitors typically inhibit inflammatory reactions and pain by decreasing the activity of cyclo-oxygenase, which is responsible for prostaglandin synthesis. NSAIDs may provide pain relief in the early stage of pain syndrome. Examples of anti-inflammatory drugs include, but are not limited to, salicylic acid acetate (Aspirin™), ibuprofen (Motrin™, Advil™), ketoprofen (Oxynorm™), rofecoxib (Vioxx™), naproxen sodium (Anaprox™, Naprelan™, Naprosyn™), ketorolac (Acular™), and other known conventional medications. A specific cox-2 inhibitor is celecoxib (Celebrex™) [See, e.g., Physicians' Desk Reference, 1990, 1910-1914 and 2891 (57th ed., 2003); Physicians' Desk Reference for Nonprescription Drugs and Dietary Supplements, 511, 667 and 773 (23rd ed., 2002)].
Antidepressants increase the synaptic concentration of serotonin and/or norepinephrine in the CNS by inhibiting their reuptake by presynaptic neuronal membrane. Some antidepressants also have sodium channel blocking ability to reduce the firing rate of injured peripheral afferent fibers. Examples of antidepressants include, but are not limited to, nortriptyline (Pamelor\textsuperscript{TM}), amitriptyline (Elavil\textsuperscript{TM}), imipramine (Tofranil\textsuperscript{TM}), doxepin (Sinequan\textsuperscript{TM}), clomipramine (Anafranil\textsuperscript{TM}), fluoxetine (Prozac\textsuperscript{TM}), sertraline (Zoloft\textsuperscript{TM}), nefazodone (Serzone\textsuperscript{TM}), venlafaxine (Effexor\textsuperscript{TM}), trazodone (Desyrel\textsuperscript{TM}), bupropion (Wellbutrin\textsuperscript{TM}) and other known conventional medications [See, e.g., Physicians' Desk Reference, 329, 1417, 1831 and 3270 (57\textsuperscript{th} ed., 2003)].

Anticonvulsant drugs may also be used in embodiments of the invention. Examples of anticonvulsants include, but are not limited to, carbamazepine, oxcarbazepine, gabapentin (Neurontin\textsuperscript{TM}), phenytoin, sodium valproate, clonazepam, topiramate, lamotrigine, zonisamide, and tiagabine [See, e.g., Physicians' Desk Reference, 2563 (57\textsuperscript{th} ed., 2003)].

Corticosteroids (e.g., prednisone, dexamethasone or hydrocortisone), orally active class Ib anti-arrhythmic agents (e.g., mexiletine), calcium channel blockers (e.g., nifedipine), beta-blockers (e.g., propranolol), \(\alpha\)-blockers (e.g., phenoxybenzamine), and \(\alpha_{2}\)-adrenergic agonists (e.g., clonidine) can also be used in combination with a compound as described herein [See, e.g., Physicians' Desk Reference, 1979, 2006 and 2190 (57\textsuperscript{th} ed., 2003)].

The specific amount of the additional active agent will depend on the specific agent used, the type of pain being treated or managed, the severity and stage of pain, and the amount(s) of compounds as described herein and any optional additional active agents concurrently administered to the patient.

Hydromorphone (Dilaudid\textsuperscript{TM}) is typically administered in an initial dose of about 2 mg orally, or about 1 mg intravenously to manage moderate to severe pain [See, e.g., Physicians' Desk Reference, 2991 (57\textsuperscript{th} ed., 2003)]. Morphine sulfate (Duramorph\textsuperscript{TM}, Astramorph\textsuperscript{TM}, MS Contin\textsuperscript{TM}) is typically administered in an initial dose of about 2 mg IV/SC/IM, depending on whether a patient has already taken narcotic analgesics [See, e.g., Physicians' Desk Reference, 594-595 (57\textsuperscript{th} ed., 2003)]. No intrinsic limit to the amount that
can be given exists, as long as a patient is observed for signs of adverse effects, especially respiratory depression. Various IV doses may be used, commonly titrated until a desired effect is obtained. For patients not using long-term agents, as little as 2 mg IV/SC may be sufficient. Larger doses are typically required for patients taking long-term narcotic analgesics. Morphine sulfate is also available in oral form in immediate-release and timed-release preparations. The long-acting oral form may be administered twice per day. An immediate-release form may be needed for periods of pain break-through, with the dose dependent on previous use. Oxycodone (OxyContin™) is a long-acting form of an opioid and may be used in initial and later stages of pain syndrome. Oxycodone (OxyContin™) is usually administered in an amount of about 10-160 mg twice a day [See, e.g., Physicians' Desk Reference, 2851 (57th ed., 2003)]. Meperidine (Demerol™) is typically administered in an amount of about 50-150 mg PO/IV/IM/SC every 3-4 hours. A typical pediatric dose of meperidine (Demerol™) is 1-1.8 mg/kg (0.5-0.8 mg/lb) PO/IV/IM/SC every 3-4 hours [See, e.g., Physicians' Desk Reference, 2991 (57th ed., 2003)]. Fentanyl transdermal patch (Duragesic™) is available as a transdermal dosage form. Most patients are administered the drug in 72-hour dosing intervals; however, some patients may require dosing intervals of about 48 hours. A typical adult dose is about 25 mcg/h (10 cm²), 50 mcg/h (20 cm²), 75 mcg/h (75 cm²), or 100 mcg/h (100 cm²) [See, e.g., Physicians' Desk Reference, 1775 (57th ed., 2003)].

[00295] Non-narcotic analgesics and anti-inflammatories such as NSAIDs and cox-2 inhibitors may be used to treat patients suffering from mild to moderate pain. Ibuprofen (Motrin™, Advil™) is orally administered in an amount of 400-800 mg three times a day [See, e.g., Physicians' Desk Reference, 1900-1904 (57th ed., 2003); Physicians' Desk Reference for Nonprescription Drugs and Dietary Supplements, 511, 667 and 773 (23rd ed., 2002)]. Naproxen sodium (Anaprox™, Naprelan™, Naprosyn™) may also be used for relief of mild to moderate pain in an amount of about 275 mg thrice a day or about 550 mg twice a day [See, e.g., Physicians' Desk Reference, 1417, 2193 and 2891 (57th ed., 2003)].

[00296] Antidepressants, e.g., nortriptyline (Pamelor™), may also be used in the invention to treat patients suffering from chronic and/or neuropathic pain. The oral adult dose is typically in an amount of about 25-100 mg, and usually does not exceed 200 mg/d. A typical pediatric dose is about 0.1 mg/kg PO as initial dose, increasing, as tolerated, up to
about 0.5-2 mg/d. Amitriptyline (Etrafon\textsuperscript{TM}) is typically used for neuropathic pain in an adult dose of about 25-100 mg PO [See, e.g., Physicians' Desk Reference, 1417 and 2193 (57\textsuperscript{th} ed., 2003)].

[00297] Anticonvulsants such as gabapentin (Neurontin\textsuperscript{TM}) may also be used to treat patients suffering from chronic and neuropathic pain. Typically, gabapentin is orally administered in an amount of about 100-1,200 mg three times a day [See, e.g., Physicians' Desk Reference, 2563 (57\textsuperscript{th} ed., 2003)]. Carbamazepine (Tegretol\textsuperscript{TM}) is used to treat pain associated with true trigeminal neuralgia. The oral adult dose is typically in an amount of about 100 mg twice a day as initial dose, increasing, as tolerated, up to about 2,400 mg/d [See, e.g., Physicians' Desk Reference, 2323-25 (57\textsuperscript{th} ed., 2003)].

[00298] For the treatment of pemphigus, other agents which may be used in combination with the novel compounds of the invention include, but are not limited to, anti-inflammatory agents, immunosuppressants, anti-infectives, antibiotics, gold salts, alkylating agents, immunoglobulins, or a combination of two or more thereof. Examples of anti-inflammatory agents include corticosteroids, COX-2 inhibitors, non-steroidal anti-inflammatory drugs (NSAID), TNF\textalpha antagonists, and IL-1 antagonists. For example, the corticosteroid can be prednisone, prednisolone, or methylprednisolone. Corticosteroids such as these may also be administered with either chlorambusil or mycophenylate mofetil. Examples of TNF\textalpha antagonists are infliximab, etanercept, and adalimumab. An example of an IL-1 antagonist is anakinra. Examples of immunosuppressants are mycophenylate mofetil, cyclosporin, azathioprine, methotrexate, alefacept, rituximab, anti-interferon gamma, and cyclophosphamide, while anti-infectives include dapsone and hydroxychloroquine. In some instances, the gold salt can be myochrysine, or solganal. An example of an alkylating agent is lukcran. Antibiotics useful in combinations are tetracycline, minocycline, and doxycycline, sometimes in combination with nicotinamide, or niacinamide.

[00299] Treatment of pemphigus can also include plasmapheresis therapy or photopheresis therapy to the subject.

[00300] The present invention, thus generally described, will be understood more readily by reference to the following examples, which are provided by way of illustration and are not intended to be limiting of the present invention.
EXAMPLES

[00301] The following abbreviations are used throughout the application with respect to chemical terminology:

AcN: Acetonitrile
AcOH or HOAc: Acetic acid
aq.: Aqueous
Bu: Butyl
BINAP: 2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
Boc: N-tert-Butoxycarbonyl
BOP: (Benzotriazol-1-yl oxy)tris-
(dimethylamino)phosphonium hexafluorophosphate
dba: Dibenzylideneacetone
DIEA: N,N-Diisopropylethylamine
DCM: Dichloromethane
DME: Dimethoxyethane
DMF: N,N-Dimethylformamide
DMSO: Dimethylsulfoxide
DPPA: Diphenyl phosphorazidate
EDC or EDCI: 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
eq.: Equivalent
EtOAc: Ethyl acetate
EtOH: Ethanol
Hex: Hexanes
HPLC: High Pressure Liquid Chromatography
hr: Hour
IC<sub>50</sub> value: The concentration of an inhibitor that causes a 50 % reduction in a measured activity.
LC-MS: Liquid chromatography- mass spectroscopy
MeOH: Methanol
min.: Minute(s)
Compounds are named using the automatic naming application Autonom 2000 (MDL Information Systems, San Leandro, CA), or the automatic name generating tool provided in Chemdraw Ultra (CambridgeSoft, Cambridge, MA), which generates systematic names for chemical structures according to IUPAC rules, with support for the Cahn-Ingold-Prelog rules for stereochemistry.

**Synthesis of aniline-intermediates.**

![Synthesis reaction diagram]

**Intermediate A. 3-Amino-5-tert-butylbenzonitrile. Step 1. tert-Butyl 3-tert-butyl-5-cyanophenylcarbamate.** To a solution of 3-tert-butyl-5-cyanobenzoic acid (1.0 g, 4.9 mmol, prepared as in U.S. application No. 60/842,051) in t-BuOH, DPPA (1.4 ml, 6.4 mmol) and NMM (slight excess) were added. The mixture was stirred at reflux overnight, extracted with DCM, the organic layer was washed with brine, dried (MgSO₄) and evaporated. The residue was purified by chromatography on silica gel (gradient: 5 to 100% EtOAc in Hex). (Calculated mass: 274.4, observed mass: 275.1).
Step 2. To a solution of the compound obtained above in DCM (10 ml), TFA (1.5 ml) was added and the mixture was stirred at r.t. overnight. The solvent was evaporated and the residue used in the next step without further purification. (Calculated mass: 174.2, observed mass: 215.8 (M+AcN)\(^+\)).

Intermediate B. 3-Amino-5-morpholinobenzonitrile. 3-Fluoro-5-nitrobenzonitrile (350 mg, 2.11 mmol) was treated with morpholine (1 ml) in a 40 ml vial. The reaction was capped and stirred at 70°C overnight. The solvent was evaporated and the residue triturated twice with MeOH. The residue was suspended in DMF (0.5 ml), treated with tin chloride dihydrate (2.38 g, 10.5 mmol) and heated at 75°C for 40 min. The reaction was quenched with saturated Na₂CO₃ (7 ml) and solid Na₂CO₃ (3 g). The organic layer was diluted with DCM, filtered, washed with saturated Na₂CO₃ and dried over solid anhydrous Na₂SO₄. The solvents were removed and the residue was purified on silica gel to afford the target compound (282 mg, 65%). \(^1\)H NMR (acetone-d₆) \(\delta\) (ppm) 6.53 (s, 1H), 6.52 (s, 1H), 6.45 (s, 1H), 3.75 (t, \(J = 5.0\) Hz, 4H), 3.123 (t, \(J = 5.0\) Hz, 4H), 2.73 (s, 2H).

Intermediate C. 3-Amino-5-(piperidin-1-yl)benzonitrile was prepared under the same conditions as above, using piperidine as the amine component. \(^1\)H NMR (10% CD₃OD/CDCl₃) \(\delta\) (ppm) 6.47 (dd, \(J = 2.5\) and 1.0 Hz, 1H), 6.34 (t, \(J = 2.0\) Hz, 1H), 6.30 (t, \(J = 1.5\) Hz, 1H), 3.40 (bs, 2H), 3.05 (t, \(J = 11\) Hz, 4H), 1.58 (q, \(J = 6.0\) Hz, 4H), 1.50 (m, 2H).

Intermediate D. 3-Amino-5-(pyrrolidin-1-yl)benzamide. The same conditions as above starting from pyrrolidine as the amine component resulted in formation of the corresponding pyrrolidine benzamide derivative. \(^1\)H NMR (CD₃OD/CDCl₃) \(\delta\) (ppm) 6.37 (t, \(J = 1.5\) Hz, 1H), 6.34 (t, \(J = 1.5\) Hz, 1H), 3.5 (bs, 4H), 3.19 (q, \(J = 3.5\) Hz, 4H), 1.91 (q, \(J = 3.5\) Hz, 4H).
[00308] **Intermediate E. 3-amino-5-tert-butyl-2-methoxy-N-(oxazol-2-yl)benzamide. Step 1. 5-tert-Butyl-2-methoxy-3-nitro-N-(oxazol-2-ylmethyl)benzamide.**

To a solution of 5-tert-butyl-2-methoxybenzoic acid (253 mg, 1 mmol, prepared as in WO2005023761) in DCM/DMF (5 ml, 1:1), oxazol-2-ylmethanamine hydrochloride (135 mg, 1 mmol), PyBOP (1.04 g, 2 mmol) and DIEA (0.87 ml, 5 mmol) were added. The resulting mixture was stirred at r.t. overnight. The DCM was evaporated and the resulting DMF solution was subjected to RP-HPLC (gradient: 40 to 99% AcN in H₂O) to give the TFA-salt of the title compound (78 mg, 17%) as a yellow solid. (Calculated mass: 333.3, observed mass: 334.1).

[00309] **Step 2.** To a solution of the compound obtained above (75 mg, 0.17 mmol) in MeOH (2 ml), a spatula of Raney nickel was added and the suspension was stirred at r.t. under H₂ atmosphere for 4 hr. The mixture was filtered (celite), the solid was washed with MeOH and the filtrate was evaporated to give the target compound (65 mg, 95% yield, >95% pure by LC-MS) as a yellow oil, which was used in the next step without further purification. (Calculated mass: 303.4, observed mass: 304.1).

[00310] **Intermediate F. 3-Amino-5-tert-butyl-2-methoxy-N-((5-methylfuran-2-yl)methyl)benzamide. Step 1. 5-tert-Butyl-2-methoxy-N-((5-methylfuran-2-yl)methyl)-3-nitrobenzamide.** The intermediate compound was prepared as above from 5-methylfuran-2-ylmethanamine (111 mg, 1 mmol). The target compound (224 mg, 65%) was obtained after RP-HPLC (gradient: 40 to 99% AcN in H₂O) as a brown thick oil that solidified upon standing. (Calculated mass: 346.4, observed mass: 347.2).

[00311] **Step 2.** The target compound was prepared as above the compound obtained above (220 mg, 0.64 mmol). The target compound (181 mg, 90% yield, >90% pure by LC-MS) was obtained as a thick yellow oil, which was used in the next step without further purification. (Calculated mass: 316.4, observed mass: 317.1).
Intermediate G. 3-Morpholino-5-(trifluoromethyl)aniline. **Step 1. tert-Butyl 3-morpholino-5-(trifluoromethyl)phenylcarbamate.** To a 2 dram vial containing 3-morpholino-5-(trifluoromethyl)benzoic acid (100 mg, 360 µmol) (prepared as in International Application No. PCT/US06/042679) was added a 1.3 M solution diphenylphosphorylazide in DMF (360 µl, 468 µmol), and a 2.6 M solution of NMM in tert-butanol (360 µl, 0.94 mmol). Additional tert-butanol (1 ml) was added and the reaction was capped and heated at 70°C for 16 hr. The solvent was removed and the residue was purified on silica gel, eluting with 0-40% EtOAc/Hex to afford 61 mg (49% yield) of the tert-butyl 3-morpholino-5-(trifluoromethyl)phenylcarbamate. $^1$H NMR (CDCl$_3$) δ (ppm) 7.316 (s, 1H), 6.953 (s, 1H), 6.775 (s, 1H), 6.593 (s, 1H), 3.848 (t, J=4.5 Hz, 4H), 3.199 (t, J=4.5 Hz, 4H), 1.517 (s, 9H).

**Step 2.** The compound obtained above (61 mg, 176 µmol), was treated with 1:1 TFA/DCM for 30 min. The solvent was removed and the residue was treated with solid Na$_2$CO$_3$ in DCM. Removal of the solvent afforded 46 mg (106% yield) of 3-morpholino-5-(trifluoromethyl)aniline, which was used without further characterization.

Intermediate H. 3-Piperidino-5-(trifluoromethyl)aniline. **Step 1. tert-Butyl 3-(piperidin-1-yl)-5-(trifluoromethyl)phenylcarbamate.** Using the same procedure as above, starting from 3-piperidino-5-(trifluoromethyl)benzoic acid (100 mg, 360 µmol) afforded 42 mg (34%) of the target compound. $^1$H NMR (CDCl$_3$) δ (ppm) 7.203 (s, 1H), 6.955 (s, 1H), 6.802 (s, 1H), 6.511 (s, 1H), 3.200 (t, J=5.5 Hz, 4H), 1.691 (q, J=5.0 Hz, 4H), 1.589 (m, 2H), 1.516 (s, 9H).

**Step 2.** Using the same procedure as above, starting from tert-butyl 3-piperidino-5-(trifluoromethyl)phenylcarbamate (42 mg, 122 µmol) afforded 36 mg (120% yield) of 3-piperidino-5-(trifluoromethyl)aniline.

Intermediate I. Pyrrolidino-5-(trifluoromethyl)aniline. **Step 1. tert-Butyl 3-(pyrrolidin-1-yl)-5-(trifluoromethyl)phenylcarbamate.** Using the same procedure as above, starting from 3-pyrrolidino-5-(trifluoromethyl)benzoic acid (94 mg, 360 µmol)
afforded 52 mg (44%) of tert-butyl 3-pyrrolidino-5-(trifluoromethyl)phenylcarbamate. $^1$H NMR (CDCl$_3$) δ (ppm) 6.824 (s, 2H), 6.526 (s, 1H), 6.432 (s, 1H), 3.295 (t, J=6.5Hz, 4H), 2.005 (q, J=3.5Hz, 4H), 1.519 (s, 9H).

[00317] **Step 2.** Using the same procedure as above, starting from tert-butyl 3-pyrrolidino-5-(trifluoromethyl)phenyl-carbamate (52 mg, 157 μmol), afforded 36 mg (105% yield) of 3-pyrrolidino-5-(trifluoromethyl)aniline.

[00318] **Intermediate J. 5-tert-Butyl-2-methoxy-3-cyanobenzoic acid. Step 1. 3-Bromo-5-tert-butyl-2-methoxybenzoic acid.** NBS (1.71 g, 9.6 mmol) was added to a solution of 5-tert-butyl-2-methoxybenzoic acid (1.0 g, 4.8 mmol) in glacial acetic acid (15 ml) and the mixture was heated to 100°C for 16 hr. The reaction was allowed to cool and was diluted with 10 ml water and then extracted with DCM. The combined organic layers were washed with water, dried over MgSO$_4$ and concentrated to give 5-tert-butyl-2-methoxy-3-bromobenzoic acid (1.2 g, 87%) as a pale yellow solid in > 90% purity. $^1$H-NMR (CDCl$_3$) δ (ppm) 8.01 (s, 1H), 7.78 (s, 1H), 4.00 (s, 3H), 1.33 (s, 9H).

[00319] **Step 2. Methyl 3-bromo-5-tert-butyl-2-methoxybenzoate.** To a solution of the compound obtained above (0.63 g, 2.2 mmol) in DCM (18 ml), oxaly chloride (1.0 ml, 11.5 mmol) and six drops of DMF were added. The mixture was stirred at r.t. for 1 hr, concentrated, the residue was dissolved in MeOH (10 ml) and further stirred at r.t. for 15 minutes. The solvent was evaporated to give a viscous yellow oil (quantitative) in >90% purity. $^1$H-NMR (CDCl$_3$) δ (ppm) 7.75 (s, 1H), 7.73 (s, 1H), 3.95 (s, 3H), 3.92 (s, 3H), 1.33 (s, 9H).

[00320] **Step 3. Methyl 5-tert-butyl-3-cyano-2-methoxybenzoate.** To a solution of 5-tert-butyl-2-methoxy-3-bromobenzoic acid methyl ester (0.15 g, 0.5 mmol) in a 1:1 DMF/dioxane (5 ml) mixture, KCN (65 mg, 1 mmol), Pd(OAc)$_2$ (12 mg, 10 mol%), CsCO$_3$ (0.49 g, 1.5 mmol) and BINAP (62 mg, 20 mol%) were added. The mixture was stirred at 150°C for 40 min. in the microwave, filtered over Celite, and the solids were washed with
DCM. The filtrate was concentrated and the residue purified on reverse phase using 50-99% AcN in water to give the intermediate cyano ester (49 mg, 40%) as a pale yellow solid. \[^1\]H-NMR (CDCl\(_3\)) \(\delta\) (ppm) 8.00 (s, 1H), 7.72 (s, 1H), 4.04 (s, 3H), 3.94 (s, 3H), 1.32 (s, 9H).

**Step 4.** To a solution of 5-tert-butyl-2-methoxy-3-cyanobenzoic acid methyl ester (40 mg, 0.16 mmol) in 1:1 THF/MeOH (1 ml) mixture, 2N NaOH (0.35 ml) was added. The mixture was stirred at room temperature for 1 hr, neutralized with 1N HCl and extracted with approx. 20 ml of EtOAc. The organic layer was dried over MgSO\(_4\) and concentrated to give intermediate J (quantitative) as a white solid which was used in the next step without further purification. \[^1\]H-NMR (CDCl\(_3\)) \(\delta\) (ppm) 7.81 (d, \(J = 2.43\) Hz, 1H), 7.64 (d, \(J = 2.44\) Hz, 1H), 7.02 (br s, 1H), 3.97 (s, 3H), 3.89 (s, 3H), 3.03 (s, 3H), 1.35 (s, 9H).

Intermediate K. 3-tert-Butyl-5-((4-methylpiperazin-1-yl)methyl)aniline.

**Step 1.** Methyl 3-tert-butyl-5-formylbenzoate. Methyl 3-tert-butyl-5-(hydroxymethyl)benzoate (444 mg, 2 mmol), dissolved in DCM (4 ml), was treated with pyridinium chlorochromate (1.72 g, 8 mmol) at r.t. for 2.5 hr. Completion of the reaction was monitored by TLC. Upon completion, the mixture was filtered through silica gel, using DCM as the eluent. Concentration of the filtrate afforded 440 mg of the target compound as a colorless oil, which was used in the next step without purification.

**Step 2.** Methyl 3-tert-butyl-5-((4-methylpiperazin-1-yl)methyl)benzoate. The compound obtained in the previous reaction (ca. 1 mmol) and 1-methylpiperazine (200 mg, 2 mmol) were dissolved in DCM (5 ml) and AcOH (0.5 ml). The reaction mixture was
stirred at r.t. for 1 hr, followed by addition of NaBH(OAc)$_3$ (633 mg, 31 mmol). The resulting mixture was stirred overnight at r.t., diluted with DCM and washed with aq. NaHCO$_3$. The DCM layer was dried over Na$_2$SO$_4$ and concentrated to give the target compound as a yellow oil in 268 mg yield.

[00324] **Step 3.** 3-tert-Butyl-5-((4-methylpiperazin-1-yl)methyl)benzoic acid. The compound obtained above (268 mg, ca. 0.88 mmol) was dissolved in EtOH (2 ml), THF (1.6 ml), and water (0.4 ml), and was treated with 2 N NaOH (1.6 ml) at r.t. for 2 hr and 50°C for 30 min. The reaction mixture was neutralized with aq. HCl, evaporated to dryness and used as such in the next step.

[00325] **Step 4.** tert-Butyl 3-tert-butyl-5-((4-methylpiperazin-1-yl)methyl)phenylcarbamate. The compound obtained above was dissolved in t-BuOH (10 ml) and DPPA (379 μl, 1.8 mmol) and NMM (143 μl, 1.8 mmol) were added. The mixture was stirred at 80°C overnight. The reaction mixture was diluted with EtOAc, and the organic layer was washed with aq. NaHCO$_3$, dried over Na$_2$SO$_4$, filtered and concentrated. The residue was purified by HPLC to afforded 258 mg of a orange oil. (Calculated mass: 362, observed mass: 3262.1).

[00326] **Step 5.** The compound obtained above was treated with TFA/DCM/H$_2$O (6/3/1, 5 ml) for 2 hr at r.t. The solvents were evaporated and the residue was used as such in the next step.

[00327] **Intermediate L.** 3-Amino-5-tert-butyl-2-methoxy-N,N-dimethylbenzenesulfonamide. **Step 1.** 5-tert-Butyl-2-methoxybenzene-1-sulfonyl chloride. 1-tert-Butyl-4-methoxybenzene (3.79 g, 23.08 mmol) was dissolved in DCM (70 ml) and was cooled to 0°C. Chlorosulphonic acid (5 ml, 75.22 mmol) in DCM (40 ml) was added dropwise over 10 min and the reaction was stirred at 0°C for 35 min., after which it was allowed to warm to r.t. over 10 min. The reaction mixture was poured into a mixture of ice (150 ml) and water (150 ml) and the DCM layer was separated. The DCM layer was
washed with aq. saturated NaHCO₃, dried over MgSO₄, filtered and evaporated. ¹H NMR (CDCl₃) δ (ppm) 7.94 (d, 1H), 7.70 (dd, 1H), 7.07 (d, 1H), 4.05 (s, 3H), 1.34 (s, 9H).

[00328] **Step 2. 5-tert-Butyl-2-methoxy-3-nitrobenzene-1-sulfonyl chloride.** The compound obtained above (21.45 g, 82 mmol) was dissolved in nitric acid (85 ml, 1.34 mol). Sulfuric acid (50 ml, 0.9 mol) was added dropwise over 40 min to control the exothermic reaction. The reaction mixture was heated to 90 - 110°C for 85 min, then stirred overnight at r.t. The yellow precipitate was filtered, washed with water and dried in vacuo, yielding 19.3 g of the target product. ¹H NMR (CDCl₃) δ (ppm) 8.21 (d, 1H), 8.20 (d, 1H), 4.12 (s, 3H), 1.41 (s, 9H).

[00329] **Step 3. 5-tert-Butyl-2-methoxy-N,N-dimethyl-3-nitrobenzenesulfonamide.** The compound obtained above (296 mg, 0.962 mmol) was dissolved in 2 M dimethylamine/THF solution (5 ml, 10 mmol). The solution was evaporated and the resulting residue was taken up in diethyl ether. The organic solution was washed with aq. NaHCO₃, water and dried over MgSO₄. After filtration, the solvent was evaporated to yield the target compound in 296 mg yield. ¹H NMR (CDCl₃) δ (ppm) 8.18 (d, 1H), 8.02 (d, 1H), 4.04 (s, 3H), 2.87 (s, 6H), 1.38 (s, 9H).

[00330] **Step 4.** The compound obtained above (0.96 mmol) was dissolved in MeOH and Raney nickel (catalytic amount) was added. The reaction was stirred under hydrogen atmosphere for 17 hr at r.t.. The catalyst was removed by filtration and the solvent was evaporated. The residue was obtained in 257 mg yield and was used as such in the next reaction. ¹H NMR (DMSO-d₆) δ (ppm) 7.03 (d, 1H), 6.85 (d, 1H), 5.26 (s, 2H), 3.68 (s, 3H), 2.66 (s, 6H), 1.23 (s, 9H). (Calculated mass: 286, observed mass: 287).

[00331] **Intermediate M. N-(3-Amino-5-tert-butyl-2-methoxyphenyl)-4-methylpiperazine-1-sulfonamide. Step 1. Sodium 5-tert-butyl-2-methoxy-3-nitrophenylsulfamate.** In a 250 ml round-bottomed flask containing pyridine (20 ml) and pyridine-sulfur trioxide (4.09 g, 25.7 mmol) was added 5-tert-butyl-2-methoxy-3-nitroaniline (1.15 g, 5.13 mmol) in pyridine (5 ml). The vial containing the aniline was rinsed with 5 ml
pyridine twice and the suspension was heated at 50°C for 4 hr. The solvent was evaporated and the residue was dried in high vacuum. The residue was treated with saturated aq. Na₂CO₃ until a basic pH was maintained. The solution was concentrated, diluted to ~20 ml with water, filtered and evaporated to afford 2.73 g of sodium 5-tert-butyl-2-methoxy-3-nitrophenylsulfamate (containing Na₂CO₃) as a yellow powder. ¹H NMR (500 MHz, DMSO-d₆) δ ppm 7.89 (d, J = 2.36 Hz, 1H), 7.21 (d, J = 2.36 Hz, 1H), 6.85 (s, 1H), 3.72 (s, 3H), 1.24 (s, 9H).

**Step 2.** N-(5-tert-Butyl-2-methoxy-3-nitrophenyl)-4-methylpiperazine-1-sulfonamide. The compound obtained above (114 mg, 213 μmol) was place in a 50 ml round-bottomed flask and suspended in DCM (5 ml). To this mixture was added PCl₅ (222 mg, 1.07 mmol) and the flask was fitted with a condenser and a CaSO₄ drying tube and heated at reflux for 3hr. The reaction was treated with 1 drop of brine and the solution was stirred for 15 min. The suspension was diluted with DCM and filtered. The solvent was evaporated to afford 82 mg of 5-tert-butyl-2-methoxy-3-nitrophenylsulfonyl chloride which was used without further purification. This compound was placed in a 50 ml round-bottomed flask and diluted with DCM (5 ml). To this stirred mixture in an ice bath was added 1-methylpiperazine (32 mg, 0.32 mmol) in DCM (2 ml), followed by TEA (29 μl, 0.21 mmol). After 1 hr the solvent was evaporated and the residue was purified on silica gel, eluting with 0 - 20% MeOH/DCM to afford 22 mg (27% yield) of the target compound. ¹H NMR (500 MHz, CDCl₃) δ ppm 7.74 (d, J = 2.15 Hz, 1H), 7.62 (d, J = 2.34 Hz, 1H), 3.93 (s, 3H), 3.65-3.51 (bs, 4H), 2.95-2.65 (bs, 4H), 2.54 (bs, 3H), 1.32 (s, 9H).

**Step 3.** The compound obtained above (22 mg, 57 μmol) was dissolved in MeOH (5 ml) in a 50 ml round-bottomed flask. Raney nickel (50 mg) was added and the solution was stirred under hydrogen atmosphere for 2.5 hr, after which time the mixture was filtered and the solvent evaporated. Intermediate M was used as such in the next step.
Intermediate N. Methyl 3-amino-5-tert-butyl-2-methoxybenzoate. In a 100 ml round-bottomed flask were placed 5-tert-butyl-2-methoxy-3-nitrobenzoic acid (594 mg, 2.35 mmol) (prepared as described in WO2005/023761), DCM (20 ml) and DMF (2 drops). Oxalyl chloride (0.41 ml, 4.69 mmol) was added and the reaction was stirred for 1.5 hr. The solvent was evaporated and the residue was treated with MeOH (10 ml) and evaporated. The residue was diluted with MeOH (20 ml), Raney nickel (200 mg) was added and the resulting mixture was stirred under hydrogen atmosphere overnight. The reaction was filtered and the solvent evaporated to afford 551 mg (99% yield) of Intermediate N. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) (ppm) 7.23 (d, \(J = 2.14\) Hz, 1H), 6.99 (d, \(J = 2.12\) Hz, 1H), 3.84 (s, 3H), 1.28 (s, 9H).

Intermediate O. 5-tert-Butyl-3-(1H-imidazol-1-yl)-2-methoxyaniline. In a 50 ml round-bottomed flask were placed tert-butyl 3-amino-5-tert-butyl-2-methoxyphenylcarbamate (264 mg, 0.90 mmol) (prepared from 5-tert-butyl-2-methoxybenzene-1,3-diamine via standard Boc protection), glyoxal (40% w/w in water, 280 \(\mu\)l, 1.79 mmol), formaldehyde (37% w/w in water, 146 \(\mu\)l, 1.79 mmol) and ammonium hydroxide (28% w/w in water, 109 \(\mu\)l, 1.79 mmol). The flask was capped and heated at 60°C overnight. Glyoxal (560 \(\mu\)l), formaldehyde (290 \(\mu\)l) and ammonium hydroxide (600 \(\mu\)l) were added and the reaction was heated for 1 hr. The solvents were evaporated and the residue was purified on silica gel, eluting with 0 – 100% EtOAc/Hex. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) (ppm) 8.24 (s, 1H), 7.91 (s, 1H), 7.28-7.26 (m, 2H), 7.12 (s, 1H), 6.93 (d, 1H), 3.80 (s, 3H), 1.56 (s, 9H), 1.35(s, 9H).

The Boc group was removed using TFA/DCM and the product was partitioned between DCM and aq. Na\(_2\)CO\(_3\) solution. The DCM layer was dried over Na\(_2\)SO\(_4\), filtered and evaporated to afford the target compound, which was used as such in the next step.
Intermediate P. N-(3-Amino-5-tert-butylphenyl)methanesulfonamide.

**Step 1. 4-tert-Butyl-2,6-dinitrophenol.** 4-tert-Butylphenol (30 g, 0.2 mol) in glacial acetic acid (50 ml) was added dropwise to a stirred solution of 90% nitric acid (48 ml) and glacial acetic acid (100 ml) at -15°C to -10°C over one hr. After the addition was complete, the mixture was stirred at r.t. for 1 hr and then poured into cracked ice. The mixture was diluted with water, cooled and extracted with DCM. The combined organic layers were dried and concentrated. The residue was purified by column chromatography (PE:EtOAc = 50:1) to give the target compound (28 g, 58% yield). $^1$H NMR (300MHz, CDCl$_3$) δ (ppm) 11.3 (s, 1H), 8.3 (s, 2H), 1.38 (s, 9H).

**Step 2. 5-tert-Butyl-2-chloro-1,3-dinitrobenzene.** The compound obtained above (15 g, 62.5 mmol) was added to a mixture of thionyl chloride (22.3 g, 187 mmol), DMF (8.6 g) and dry toluene (200 ml). The mixture was stirred under reflux for 8 hr. The mixture was evaporated under vacuum and the residue was purified by column chromatography (PE:EtOAc = 10:1) to provide the target compound (12.6 g, 78% yield). $^1$H NMR (300MHz, CDCl$_3$) δ (ppm) 7.9 (s, 2H), 1.38 (s, 9H).

**Step 3. 5-tert-Butylbenzene-1,3-diamine.** The compound obtained above (3 g, 11.6 mmol), methanol (300 ml) and 10% Pd/C (1 g) were placed in an autoclave. The mixture was hydrogenated under 3 MPa for 1 hr. Solid K$_2$CO$_3$ (4 g, 29 mmol) and 10% Pd/C (1 g) were added to the above reactor. The mixture was again hydrogenated under 1.5 MPa overnight, filtered and evaporated to provide the target compound (1.5 g, 79% yield). $^1$H NMR (300 MHz, CDCl$_3$) δ (ppm) 6.2 (m, 2H), 5.9 (d, 1H), 3.5 (s, 4H), 1.2 (s, 9H).

**Step 4.** To a solution of the compound above (2 g, 12.2 mmol) in DCM (20 ml) was added TEA (2.5 ml) and methylsulfonyl chloride (1.6 g, 14.6 mmol) dropwise at 0°C. After the addition was complete, the mixture was stirred at r.t. overnight, and washed with saturated brine. The aqueous phase was extracted with DCM and the combined organic layers were dried and evaporated. The residue was purified by column chromatography.
Intermediate Q. **5-tert-butyl-2-methoxy-3-(methylsulfinyl)aniline. Step 1.**

**5-tert-Butyl-2-methoxy-3-nitrobenzenesulfonic acid.** A solution of Na₂SO₃ (580 mg, 6.6 mmol) and NaHCO₃ (420 mg, 5.0 mmol) in water (2.5 ml) was heated at 80°C. Solid 5-tert-butyl-2-methoxy-3-nitrobenzene-1-sulfonyl chloride (539 mg, 1.751 mmol) (obtained as described above) was added over 2 min, with evolution of gas. After 30 min, the solution was allowed to cool to r.t. and stirring was continued overnight, resulting in a very viscous mixture.

**Step 2.** **5-tert-Butyl-2-methoxy-1-(methylsulfinyl)-3-nitrobenzene.** To this reaction mixture was added NaHCO₃ (400 mg, 4.76 mmol) and water (2.5 ml) and the mixture was heated to 80°C. Dimethylsulfate (0.5 ml, 5.3 mmol) was added, resulting in gas evolution. More dimethylsulfate was added in 2 portions (0.2 ml) each at 3 and 4 hr. After 6 hr, the reaction was allowed to cool to r.t. and stirred overnight. The crystalline product was filtered, washed with water and dried. ¹H NMR (500 MHz, CDCl₃) δ (ppm) 8.25 (d, 1H), 8.14 (d, 1H), 4.08 (s, 3H), 3.31 (s, 3H), 1.40 (s, 1H).

**Step 3.** The compound obtained above (155 mg, 0.539 mmol) was dissolved in 12M HCl (1.5 ml) and treated with SnCl₂·2H₂O (400 mg, 1.77 mmol) for 40 min. The precipitated was filtered, washed with 1M aq. HCl and dried. The residue was triturated with DCM and the solution was evaporated. The combined HCl washes were neutralized with 45% NaOH and the product was extracted into DCM. The organic layer was dried over MgSO₄, filtered, and evaporated to yield the target compound. ¹H NMR (500 MHz, CDCl₃) δ (ppm) 7.82 (bs, 1H), 7.68 (bs, 1H), 4.14 (s, 3H), 3.25 (s, 3H), 1.35 (s, 9H).
Synthesis of heteroaryl amine intermediates.

[00344] **Intermediates I - V. Intermediates IA and IB.** A mixture of 2-chloropyrimidin-4-amine and 4-chloropyrimidin-2-amine (100 mg, 0.77 mmol, prepared as in WO2005023761) was derivatized with 2,2,6,6-tetramethylmorpholine hydrochloride (277 mg, 1.54 mmol, prepared as in WO2006066174), by the procedure described in WO2005023761. Briefly, the aminopyrimidine mixture was dissolved in THF (5 ml) and treated with 2 eq. of the amine component in the presence of 3 eq. of DIEA. The mixture was stirred at 80°C overnight, after which the solvent was evaporated. The residue was taken up in EtOAc, the solution was filtered and chromatographed on silica gel (gradient: 0 to 50% EtOAc in Hex) to give the product(s) (59.7 mg, 33%) as a pale yellow solid. (Calculated mass: 236.3, observed mass: 236.0).

[00345] Regioisomers were separated at this stage or after subsequent reactions. The following intermediates were obtained.

[00346] **Intermediate I-A: 2-(2,2,6,6-Tetramethylmorpholino)pyrimidin-4-amine.** (Calculated mass: 236.3, observed mass: 236.0).

[00347] **Intermediate II-A. 2-(8-Oxa-3-azabicyclo[3.2.1]octan-3-yl)pyrimidin-4-amine.** The same procedure as above was carried out with 8-oxa-3-azabicyclo[3.2.1]octane hydrochloride (prepared as in WO200409589) (23.4 mg, 15%). (Calculated mass: 206.3, observed mass: 206.1).

[00348] **Intermediate III-A. 2-(4-Methylpiperazin-1-yl)pyrimidin-4-amine** was similarly prepared from N-methylpiperazine. (Calculated mass: 193.1, observed mass: 193.3). (See also JP50058082).
[00349] Intermediate IV-A and IV-B. tert-Butyl 4-(4-aminopyrimidin-2-yl)piperazine-1-carboxylate (IV-A) was prepared as above from tert-butyl piperazine-1-carboxylate. (Calculated mass: 279.2, observed mass: 279.9).

[00350] Intermediate IV-B. tert-Butyl 4-(2-aminopyrimidin-4-yl)piperazine-1-carboxylate (Calculated mass: 279.2, observed mass: 279.9). (See also WO9825617)

[00351] Intermediates V-A and V-B. 2-(3,5-Dimethylpiperazin-1-yl)pyrimidin-4-amine (V-B) was prepared as above from 2,6-dimethylpiperazine. (Calculated mass: 207.2, observed mass: 207.2).

[00352] Intermediate V-B. 4-(3,5-Dimethylpiperazin-1-yl)pyrimidin-2-amine (Calculated mass: 207.2, observed mass: 207.2).

[00353] Intermediate VI. \(\text{N}^2-(3,3\text{-dimethylbutyl})\text{pyridine-2,4-diamine}\) was prepared using the procedure described in WO2006091862. 2-Chloro-4-nitropyridine 1-oxide was dissolved in EtOH and treated with the amine component (2.2 eq) at 80°C overnight. After evaporation of the EtOH, the residue was dissolved in DCM and purified. Purification of the intermediate 2-(3,3-dimethylbutylamino)-4-nitropyridine 1-oxide was carried out using silica gel (gradient: 0 to 100% (EtOAc/DCM 1:1) in DCM). (Calculated mass: 241.2, observed mass: 281.0 (M+AcN)\(^+\)). \(^1\)H-NMR (500 MHz, CDCl\(_3\)) \(\delta\) (ppm) 8.30 (d, 1H), 7.42 (d, 1H), 7.40 (s, 1H), 6.92 (bs, 1H), 3.38 (m, 2H), 1.66 (t, 2H), 1.02 (s, 9H). Subsequent reduction with Raney nickel and 1 atm hydrogen in MeOH, at r.t. for 3 hr provided the title compound which was used in the next step without further purification.

[00354] Intermediate VII. \(\text{N}^2-(2,6\text{-dimethylpiperidin-1-yl}ethyl)\text{pyridin-2,4-diamine}\) was prepared using a similar procedure to above. Purification of the intermediate 2-(2-(2,6-dimethylpiperidin-1-yl)ethylamino)-4-nitropyridine 1-oxide was carried out using silica gel (gradient: 0 to 100% (MeOH/DCM 1:9) in DCM). \(^1\)H-NMR (500 MHz, DMSO-d\(_6\)) \(\delta\) (ppm) 8.34 (d, 1H), 7.70 (bt, 1H), 7.56 (s, 1H), 6.38 (d, 1H), 3.34 (m, 2H), 2.74 (t, 2H), 2.42 (bs, 2H), 1.58 (d, 1H), 1.46 (d, 2H), 1.25 (m, 1H), 1.12 (m, 2H), 1.06 (s, 6H).
Subsequent reduction as above again provided the title compound which was used in the next step without further purification.

[00355] Intermediate VIII. N-Methyl-5-(tributylstannyl)pyridin-2-amine. Step 1. 5-Bromo-N-methylpyridin-2-amine. Intermediate VIII was prepared using similar methods described in WO2005/023761. 2,5-Dibromopyridine (2.5 g, 10.6 mmol) was treated with a 33% MeNH₂/EtOH (13.2 ml, 106 mmol) at 80°C for several days. The solvent was evaporated, the residue was dissolved in 1 M HCl and the aqueous solution was washed with DCM. The acidic layer was basified with 1 M NaOH to pH ~11 and the milky suspension was extracted with DCM. The organic layer was dried over MgSO₄ and evaporated to give the target product as a brown solid in quantitative yield. (Calculated mass: 187.0, observed mass: 188.3).

[00356] Step 2. To a solution of the compound obtained above (561 mg, 3 mmol) in heptane/THF (30 ml) cooled to -78°C under N₂ atmosphere, a solution of t-BuLi 1.7 M (3.4 ml, 6.6 mmol) was added. After 30 minutes ClSnBu₃ (1.8 g, 6.6 mmol) in THF (3 ml) was added and the reaction mixture was stirred for 2 hr at -78°C. Then a solution of 5% AcOH/THF (20 ml) was added and the mixture was allowed to warm up to room temperature. The solvents were evaporated and the residue was dissolved in EtOAc/H₂O. The compound was extracted into EtOAc and the organic layer was washed with aq. NaHCO₃ and dried over Na₂SO₄. After filtration the solvent was evaporated and the residue was purified by silica gel chromatography, using a gradient of 0-100% 50%EtOAc/Hex, to give the target compound in 380 mg yield. (Calculated mass = 397.2, observed mass = 399.0).

Synthesis of naphthalenyl intermediates.
[00357] **Intermediate a.** 2-(4-(3-Cyanopropoxy)naphthalen-1-yl)-2-oxoacetic acid. \(X = \text{CH}_2\text{CN}\). **Step 1.** 4-(Naphthalen-1-yl oxy)butanenitrile. A mixture of 1-naphthol (144 mg, 1 mmol), t-BuOK (224 mg, 2 mmol) and 4-chlorobutyronitrile (0.13 ml, 1.5 mmol) in DMF was stirred at 60°C overnight. The mixture was filtered and the solvent was removed under vacuum. The residue was taken up in DCM, the organic layer was washed with saturated aq. NaHCO₃, dried (MgSO₄), and evaporated. The residue was purified by chromatography on silica gel using Hex/EtOAc as eluents.

[00358] **Step 2.** Methyl 2-(4-(3-cyanopropoxy)naphthalen-1-yl)-2-oxoacetate. The title compound was prepared from the compound above (106 mg, 0.5 mmol) using the procedure described in WO2005023761. Briefly, AlCl₃ (1.5 eq.) was mixed with methyl 2-chloro-2-oxoacetate (1.4 eq. an stirred for 5 min, and then added to the starting material, which was suspended in DCM and cooled. The mixture was stirred for 2 hr and then quenched with H₂O. The organic layer was washed with NaHCO₃, dried and evaporated. The residue was purified over silica gel using EtOAc/Hex.

[00359] **Step 3.** Intermediate a was prepared from the compound obtained in the previous step, using the procedure described in WO2005023761, by suspending the material in THF, and treating with LiOH (3-4 eq.) for 2 hr. The compound was extracted into DCM, which was dried, evaporated and used as such in the next step.

[00360] **Intermediate b.** 2-(4-(2-(2-Methoxyethoxy)ethoxy)naphthalen-1-yl)-2-oxoacetic acid \(X = \text{O} (\text{CH}_2)_2\text{OMe}\) was similarly prepared.

[00361] **Intermediate c.** 2-Oxo-2-(4-(2,2,6,6-tetramethylmorpholino)ethoxy)naphthalen-1-yl)acetic acid. **Step 1.** 2,2,6,6-Tetramethyl-4-(2-(naphthalen-1-yl oxy)ethyl)morpholine. To a solution of 1-(2-chloroethoxy)naphthalene (200 mg, 0.97 mmol, see J. Med. Chem. 2004, 47, 3823) in DMF (5 ml), was added 2,2,6,6-tetramethylmorpholine hydrochloride (172 mg, 0.96 mmol, prepared as in
WO2006066174) and K₂CO₃ (664 mg, 4.80 mmol) and the suspension was stirred at 100°C overnight. The mixture was filtered and the DMF solution subjected to RP-HPLC (gradient: 10 to 95% AcN in H₂O) to give the TFA-salt of the product (173 mg, 42%) as a brown crystalline solid. (Calculated mass: 313.4, observed mass: 314.2).

[00362] **Step 2.** Methyl 2-oxo-2-(4-(2,2,6,6-tetramethylmorpholinoo)ethoxy)naphthalen-1-ylacetate. Methyl 2-oxo-2-(4-(2,2,6,6-tetramethylmorpholinoo)ethoxy)naphthalen-1-ylacetate was prepared from the compound obtained above using a similar procedure to that described to above and in WO2005023761. The crude yellow oil (69 mg, 87% yield, >95% pure by LC-MS) was of sufficient purity to be used in the next step. (Calculated mass: 399.5, observed mass: 400.3).

[00363] **Step 3.** The target compound was prepared from the compound obtained above using a similar procedure to described in WO2005023761. Specifically, a solution of the compound obtained above was dissolved in THF/MeOH (1/1, 2 ml) and 2 N NaOH (2 eq.) was added. The reaction mixture was stirred at r.t. for 30 min, neutralized with 1 N HCl, and evaporated. The pale brown solid obtained was used in next step without further purification. (Calculated mass: 385.5, observed mass: 386.2).

[00364] **Intermediate d.** 2-(4-(2-(8-Oxa-3-azabicyclo[3.2.1]octan-3-yl)ethoxy)naphthalen-1-yl)-2-oxoacetic acid. **Step 1.** 3-(2-(Naphthalen-1-yloxy)ethyl)-8-oxa-3-azabicyclo[3.2.1]octane. The compound was obtained using the same procedure as above with 8-oxa-3-azabicyclo[3.2.1]octane hydrochloride (72 mg, 0.48 mmol, prepared as in WO2000409898), to afford the TFA-salt of the target product (66 mg, 34%) as a pale yellow solid. (Calculated mass: 283.4, observed mass: 284.0).

[00365] **Step 2.** Methyl 2-(4-(2-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)ethoxy)naphthalen-1-yl)-2-oxoacetate. Methyl 2-(4-(2-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)ethoxy)naphthalen-1-yl)-2-oxoacetate, prepared as above from 3-(2-(naphthalen-1-yloxy)ethyl)-8-oxa-3-azabicyclo[3.2.1]octane, was obtained as a yellow oil (44 mg, 72% yield, >95% pure by LC-MS). (Calculated mass: 369.4, observed mass: 370.2).

[00366] **Step 3.** The target compound was prepared as above from methyl 2-(4-(2-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)ethoxy)naphthalen-1-yl)-2-oxoacetate and was obtained as a pale brown solid, which was used in next step without further purification. (Calculated mass: 355.4, observed mass: 356.1).
**Intermediate e** was similarly prepared using 10-Oxa-4-aza-tricyclo[5.2.1.01,6]decane (see WO2004009589).

**Intermediate f. 4-(2,2,6,6-Tetramethylmorpholino)ethoxy)naphthalen-1-amine.** **Step 1.** tert-Butyl 4-(2,2,6,6-tetramethylmorpholino)ethoxy)naphthalen-1-ylcarbamate. To a solution of tert-butyl 4-(2-chloroethoxy)naphthalen-1-ylcarbamate (50 mg, 0.16 mmol, prepared as in WO2006010082) in DMF (2 ml), was added 2,2,6,6-tetramethylmorpholine hydrochloride (29 mg, 0.16 mmol, prepared as in WO2006066174) and K$_2$CO$_3$ (107 mg, 0.78 mmol), and the suspension was stirred at 100°C overnight. The mixture was filtered and the DMF solution was subjected to RP-HPLC (gradient: 25 to 80% AcN in H$_2$O) to give the TFA-salt of the product (≤70% pure by LC-MS). (Calculated mass: 428.6, observed mass: 429.4).

**Step 2.** The title compound was prepared by treating the compound obtained above with a 1:1 mixture of DCM:TFA and was used in the next step without further purification.

**Intermediate g. 4-(2-(8-Oxa-3-azabicyclo[3.2.1]octan-3-yl)ethoxy)naphthalen-1-amine.** **Step 1.** tert-Butyl 4-(2-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)ethoxy)naphthalen-1-ylcarbamate. The same procedure as above was used, starting with 8-oxa-3-azabicyclo[3.2.1]octane hydrochloride (24 mg, 0.16 mmol, prepared as in WO2004009589), yielding the TFA-salt of the above product (≤70% pure by LC-MS) after RP-HPLC (gradient: 10-95% AcN in H$_2$O). (Calculated mass: 398.5, observed mass: 399.3).

**Step 2.** The target compound was prepared as above, from tert-butyl 4-(2-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)ethoxy)naphthalen-1-ylcarbamate, and was used in the next step without further purification.

The intermediates are used in the reactions exemplified in the following examples.
Example 1: Formation of target compounds via coupling reaction with naphthalenyl oxoacetic acid compounds.

[00373] **Method A. PyBOP Coupling. N-((5-tert-butyl-2-methoxy-3-(methylsulfonylamido)phenyl)-2-((4-(3-cyanoproxy)naphthalen-1-yl))-2-oxoacetamide (X=CH₃CN, R=Me).** To a solution of 2-((4-(3-cyanoproxy)naphthalen-1-yl))-2-oxoacetic acid (Intermediate a) in DCM, N-((3-amino-5-tert-butyl-2-methoxyphenyl)methanesulfonamide (1.1 eq., prepared as in WO2005023761). PyBOP (2 eq.) and DIEA (5 eq.) were added. The resulting mixture was stirred at r.t. overnight, concentrated and purified via preparative LC-MS to yield 8 mg of target product. (Calculated mass: 537.6, observed mass: 560.5 (M + Na⁺)).

[00374] **N-((5-tert-butyl-2-methoxy-3-(propylsulfonylamido)phenyl)-2-((4-(3-cyanoproxy)naphthalen-1-yl))-2-oxoacetamide (X=CH₃CN, R=Pr).** Prepared as above from N-((3-amino-5-tert-butyl-2-methoxyphenyl)propane-1-sulfonamide (prepared as in WO2005023761). (Calculated mass: 565.7, observed mass: 566.6 (M + H)⁺, 588.6 (M + Na⁺)).

[00375] **N-((5-tert-Butyl-2-methoxy-3-(methylsulfonylamido)phenyl)-2-((4-(2-(2-methoxyethoxy)naphthalen-1-yl))-2-oxoacetamide (X=O(CH₃)₂OMe, R=Me).** To a solution of 2-((4-(2-(2-methoxyethoxy)ethoxy)naphthalen-1-yl))-2-oxoacetic acid (Intermediate b) in DMF, N-((3-amino-5-tert-butyl-2-methoxyphenyl)methanesulfonamide (1.1 eq., prepared as in WO2005023761). PyBOP (1.5 eq.) and DIEA (5 eq.) were added. The resulting mixture was stirred at r.t. overnight, concentrated and purified via LC-MS to yield 3 mg of target product. (Calculated mass: 572.7, observed mass: 595.6 (M + Na⁺)).

[00376] **N-((5-tert-Butyl-2-methoxy-3-(propylsulfonylamido)phenyl)-2-((4-(2-(2-methoxyethoxy)naphthalen-1-yl))-2-oxoacetamide (X=O(CH₃)₂OMe, R=Pr).** Prepared as above from N-((3-amino-5-tert-butyl-2-methoxyphenyl)propane-1-sulfonamide (prepared as in WO2005023761). (Calculated mass: 600.7, observed mass: 623.7 (M + Na⁺)).
[00377] **Method B. EDC coupling.** N-(3-Cyano-5-morpholinophenyl)-2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamide (R¹= morpholinyl, R²= CN, R³= H).

In an 18 mm test tube containing 2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetic acid (255 mg, 0.70 mmol, Y=OH, prepared as in WO2005023761) and 3-amino-5-morpholinobenzonitrile (150 mg, 0.74 mmol) was added DMF (1 ml) followed by EDC (170 mg, 0.89 mmol) dissolved in DCM (2 ml). NMM (81 μl, 0.74 mmol) was added followed by DCM (1 ml) and the reaction was allowed to sit at r.t. for 40 min after which time the solvent was removed. The residue was purified on silica gel, eluting with 0-50% EtOAc/Hex to afford the title compound (250 mg, 70%) as a pale yellow solid. (Calculated mass: 514.2, observed mass: 515.6).

[00378] **N-(3-tert-Butyl-5-cyanophenyl)-2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamide (R¹= t-Bu, R²= CN, R³= H).** The procedure above with 3-amino-5-tert-butylbenzonitrile (Intermediate A) (21 mg, 0.12 mmol) gave the target compound (19.0 mg, 31%) after preparative LC-MS as the TFA-salt. (Calculated mass: 485.2, observed mass: 486.5).

[00379] **N-(3-Fluoro-5-morpholinophenyl)-2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamide (R¹= morpholinyl, R²= F, R³= H).** Using the procedure above with 3-fluoro-5-morpholinoaniline (24 mg, 0.12 mmol, prepared as in WO200300909) gave the target compound (25 mg, 34%) after preparative LC-MS as the bis-TFA-salt. (Calculated mass: 507.2, observed mass: 508.5).

[00380] **N-(5-tert-Butyl-3-cyano-2-methoxyphenyl)-2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamide (R¹= t-Bu, R²= CN, R³= OMe).**

Using a similar procedure to above with 3-amino-5-tert-butyl-2-methoxybenzonitrile (21 mg, 0.12 mmol, prepared as in International Application No. PCT/US06/042679) gave the target compound.
compound (6.6 mg, 10%) after preparative LC-MS as the TFA-salt. (Calculated mass: 515.2, observed mass: 516.5).

[00381] N-(3-Morpholino-5-((trifluoromethyl)phenyl)-2-(4-(2-morpholinoethoxy)naphthalen-1-y1)-2-oxoacetamide (R¹= morpholiny1, R²= CF₃, R³= H). The procedure above with 3-morpholino-5-((trifluoromethyl)aniline (24 mg, 0.12 mmol, see WO200405281) afforded the target compound (22.8 mg, 82%) after chromatography on silica gel eluting with 0-100% EtOAc/Hex followed by 0-100% (20% MeOH/DCM)/EtOAc, as the bis-TFA-salt. (Calculated mass: 557.2, observed mass: 558.6).

[00382] 2-(4-(2-Morpholinoethoxy)naphthalen-1-y1)-2-oxo-N-(3-(piperidin-1-yl)-5-(trifluoromethyl)phenyl)acetamide (R¹= piperidinyl, R²= CF₃, R³= H). Using the procedure above with 3-(piperidin-1-yl)-5-(trifluoromethyl)aniline (12 mg, 0.05 mmol) (prepared as in International Application No. PCT/US06/042679) gave the target compound (9.3 mg, 33%) after chromatography on silica gel eluting with 0-100% EtOAc/Hex followed by 0-100% (20% MeOH/DCM)/EtOAc. (Calculated mass: 555.2, observed mass: 556.6).

[00383] 2-(4-(2-Morpholinoethoxy)naphthalen-1-y1)-2-oxo-N-(3-(pyrrolidin-1-yl)-5-(trifluoromethyl)phenyl)acetamide (R¹= pyrrolidinyl, R²= CF₃, R³= H). Using a similar procedure to above with 3-(pyrrolidin-1-yl)-5-(trifluoromethyl)aniline (12 mg, 0.05 mmol, see WO2001051456) gave the target compound (8.8 mg, 33%) after chromatography on silica gel eluting with 0-100% EtOAc/Hex followed 0-100% (20% MeOH/DCM)/EtOAc. (Calculated mass: 541.2, observed mass: 542.6).

[00384] N-(3-Bromo-5-tert-butyl-2-methoxyphenyl)-2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamide (R¹= t-Bu, R²= Br, R³= OMe). Using a similar procedure to above with 3-bromo-5-tert-butyl-2-methoxyaniline (0.23 mmol, prepared as in International Application No. PCT/US06/042679) gave the target compound (28.9 mg, 76%) after chromatography on silica gel eluting with 0-100% EtOAc/Hex followed 0-100% (20% MeOH/DCM)/EtOAc. (Calculated mass: 568.2, observed mass: 569.5).

[00385] N-(5-tert-Butyl-2-methoxy-3-(4-methylpiperazine-1-sulfonamido)phenyl)-2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamide (R¹= t-Bu, R²= NH₄SO₂-4-methylpiperazinyl, R³= OMe). Using a similar procedure to above with Intermediate M (57 μmol) afforded the target compound (22 mg, 60%) after preparative HPLC, eluting with 10-70% AcN/water. (Calculated mass: 667.3, observed mass: 668.0). ¹H NMR (500 MHz,
CDCl₃/CD₂OD, 9:1 δ (ppm) 8.78 (d, J = 8.52 Hz, 1H), 8.45 (d, J = 8.32 Hz, 1H), 8.20 (d, J = 8.48, 1H), 8.14 (d, J = 2.26, 1H), 7.64 (ddd, J = 1.5, 7.0, 8.5, 1H), 7.53 (dd, J = 1.0, 7.0, 8.0, 1H), 7.23 (d, J = 2.26, 1H), 6.88 (d, J = 8.43, 1H), 4.65 (t, J = 4.0, 2H), 3.96-3.93 (m, 4H), 3.83 (s, 3H), 3.66 (t, J = 4.5, 2H), 3.54 (bs, 8H), 2.74 (s, 3H), 1.26 (s, 9H).

[00386] **Method C. Acid Chloride coupling.** 5-tert-Butyl-2-methoxy-3-(2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamido)-N-(oxazol-2-ylmethyl)benzamide (R¹= t-Bu, R²= CONHCH₂-oxazolyl, R³= OMe). The target compound was prepared from 2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetyl chloride (Y = Cl) (66 mg, 0.19 mmol, prepared as in WO2005023761) and Intermediate E (65 mg, TFA-salt, 0.15 mmol) using a similar procedure to that described in WO2005023761. Briefly, to a suspension of 2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetic acid (0.19 mmol) in DCM (3 ml) containing a few drops of DMF, was added oxalyl chloride (5 eq.). The mixture was stirred at r.t. for 1 hr, after which the solvent was evaporated. The residue was dissolved in DCM (3 ml) and the amine (1 eq.) and DIEA (5 eq.) were added. The resulting mixture was stirred at r.t. overnight and then washed with H₂O, dried, and evaporated. The residue was purified by RP-HPLC (gradient: 10 to 95% AcN in H₂O), followed by chromatography over silica gel with EtOAc as eluent, to yield the final product (7.8 mg, 8.5%) as a thick yellow oil. (Calculated mass: 614.7, observed mass: 615.7).

[00387] **5-tert-Butyl-2-methoxy-N-((5-methylfuran-2-yl)methyl)-3-(2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamido)benzamide (R¹= t-Bu, R²= CONHCH₂-5-methylfuryl, R³= OMe).** The target compound was prepared as above from Intermediate F (175 mg, 0.55 mmol). The TFA-salt of the final product (58 mg, 14%) was obtained after RP-HPLC (gradient: 10 to 95% AcN in H₂O), followed by a second RP-HPLC purification (gradient: 40 to 99% AcN in H₂O) as a thick brown oil. (Calculated mass: 627.7, observed mass: 628.7).

[00388] **N-(3-Cyano-5-piperidinophenyl)-2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamide (R¹= piperidinyl, R²= CN, R³= H).** Using a similar procedure to above with Intermediate C (35 mg, 0.14 mmol) the target compound (7.3 mg, 20%) was obtained, after chromatography on silica gel, eluting with 0-100% EtOAc/Hex followed by 0-100% (20% MeOH/DCM)EtOAc, as a pale yellow solid. (Calculated mass: 512.2, observed mass: 513.6).
N-(3-Cyano-5-(pyrrolidin-1-yl)phenyl)-2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamide (R₁= pyrrolidinyl, R²= CN, R³= H).

**Step 1.** Using the procedure above with Intermediate D (35 mg, 0.14 mmol) yielded 3-(2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamido)-5-(pyrrolidin-1-yl)benzamide (15.9 mg, 44%) after chromatography on silica gel, eluting with 0-100% EtOAc/Hex followed by 0-100% (20% MeOH/DCM)/EtOAc, as a pale yellow solid. (Calculated mass: 516.2, observed mass: 517.6).

**Step 2.** To a solution of this compound in DCM (3 ml), TEA (22 μl, 154 μmol) was added, followed by triflic anhydride (26 μl, 154 μmol). The resulting mixture was stirred at r.t. overnight after which additional TEA (75 μl, 0.47 mmol) and triflic anhydride (75 μl, 0.46 mmol) were added. After stirring for 1 hr, the reaction was diluted with DCM and quenched with water. The organic layer was dried over Na₂SO₄ and the solvent was removed in vacuo. The residue was purified on silica gel, eluting with 0-100% EtOAc/Hex followed by 0-100% (20% MeOH/DCM)/EtOAc to afford the title compound (3.2 mg) which contained triethylamine hydrochloride. The residue was triturated with water and the solid was dried to afford 2.8 mg (18% yield) of the pure product. (Calculated mass: 498.2, observed mass: 499.6).

Methyl 5-tert-butyl-2-methoxy-3-(2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamido)benzoate (R₁= t-Bu, R²= COOMe, R³= OMe). Using the acid chloride procedure above with Intermediate N (551 mg, 2.32 mmol) the target compound was obtained in 859 mg (67% yield) after purification on silica gel, eluting with 0 - 100% EtOAc/Hex. ¹H NMR (500 MHz, CDCl₃) δ (ppm) 9.81 (s, 1H), 8.85 (d, J = 8.47 Hz, 1H), 8.82 (d, J = 2.48 Hz, 1H), 8.64 (d, J = 8.36 Hz, 1H), 8.34 (d, J = 7.98 Hz, 1H), 7.69 (ddd, J = 8.46, 6.86, 1.41 Hz, 1H), 7.65 (d, J = 2.47 Hz, 1H), 7.57 (ddd, J = 8.16, 6.85, 1.13 Hz, 1H), 6.89 (d, J = 8.44 Hz, 1H), 4.46 (s, 2H), 3.97 (s, 3H), 3.96 (s, 3H), 3.79 (bs, 4H), 3.07 (bs, 2H), 2.74 (bs, 4H), 1.37 (s, 9H).

N-(5-tert-Butyl-3-(1H-imidazol-1-yl)-2-methoxyphenyl)-2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamide (R₁= t-Bu, R²= 1H-imidazol-1-yl, R³= OMe). Intermediate O (60 mg, 0.25 mmol) was coupled using the acid chloride method to afford 7.4 mg (5% yield) of the target molecule. (Calculated mass: 556.3, observed mass: 557.1).
[00393] N-(5-tert-Butyl-2-methoxy-3-(4-methyl-1H-imidazol-1-yl)phenyl)-2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamide (R^1= t-Bu, R^2= 4-methyl-1H-imidazol-1-yl, R^3= OMe). Using essentially the same acid chloride method starting from 5-tert-butyl-2-methoxy-3-(4-methyl-1H-imidazol-1-yl)aniline (9 mg, 0.03 mmol) (prepared as described for Intermediate O), the target compound was obtained (17 mg, 71% yield). (Calculated mass: 570.3, observed mass: 571.1).

[00394] tert-Butyl 5-tert-butyl-2-methoxy-3-(2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamido)phenylcarbamate oxoacetamide (R^1= t-Bu, R^2= NH-Boc, R^3= OMe). Using essentially the same method starting from tert-butyl 3-amino-5-tert-butyl-2-methoxyphenylcarbamate (217 mg, 0.74 mmol) (prepared from 5-tert-butyl-2-methoxybenzene-1,3-diamine via standard Boc protection), the target compound was obtained (232 mg, 57% yield). ^1H NMR CDCl_3 δ (ppm) 9.52 (s, 1H), 8.82 (d, J = 8.5 Hz, 1H), 8.64 (d, J = 8.0 Hz, 1H), 8.27 (bs, 1H), 8.21 (d, J = 2.5 Hz, 1H), 7.95 (bs, 1H), 7.70 (td, J = 7.0, 1.5 Hz, 1H), 7.59 (td, J = 7.0, 1.0 Hz, 1H), 7.93 (d, J = 8.5 Hz, 1H), 6.89 (bs, 1H), 4.84 (bs, 2H), 3.96 (bs, 4H), 3.87 (s, 3H), 3.54 (bs, 4H), 3.09 (bs, 2H), 1.56 (s, 9H), 1.36 (s, 9H).

[00395] N-(5-tert-Butyl-3-cyano-2-methoxyphenyl)-2-oxo-2-(4-(2,2,6,6-tetramethylmorpholinoo)ethoxy)naphthalen-1-yl)acetamide (R^1= CN, R= 2,2,6,6-tetramethylmorpholine). The title compound was prepared from Intermediate e and 3-amino-5-tert-butyl-2-methoxybenzonitrile (prepared as in International application No. PCT/US06/042679) using the acid chloride procedure described above (see also WO2005023761). The TFA-salt of the product (28.3 mg, 46%) was obtained as a yellow solid after RP-HPLC (gradient: 35 to 80% AcN in H_2O). (Calculated mass: 571.7, observed mass: 572.7).

[00396] 2-(4-(2-(8-Oxa-3-azabicyclo[3.2.1]octan-3-yl)ethoxy)naphthalen-1-yl)-N-(5-tert-butyl-2-methoxy-3-(methylsulfonamido)phenyl)-2-oxoacetamide (R^1= NHSO_2Me,
R= 8-oxa-3-azabicyclo[3.2.1]octanyl. The target compound was prepared using the acid chloride method above from Intermediate d and N-(3-amino-5-tert-butyl-2-methoxyphenyl)methanesulfonamide (prepared as in WO2005023761). The TFA-salt of the product (6.0 mg, 14%) was obtained as a yellow solid after RP-HPLC (gradient: 10 to 70% AcN in H₂O). (Calculated mass: 609.7, observed mass: 610.7).

[00397] 2-(4-(2-(8-Oxa-3-azabicyclo[3.2.1]octan-3-yl)ethoxy)naphthalen-1-yl)-N-(5-tert-butyl-3-cyano-2-methoxyphenyl)-2-oxoacetamide (R¹= CN, R= 8-oxa-3-azabicyclo[3.2.1]octanyl). The target compound was prepared as above from Intermediate d and 3-amino-5-tert-butyl-2-methoxybenzonitrile (prepared as in International Application No. PCT/US06/042679). The TFA-salt of the product (15.1 mg, 38%) was obtained as a yellow solid after RP-HPLC (gradient: 10 to 65% AcN in H₂O). (Calculated mass: 541.7, observed mass: 542.5).

Example 2: Formation of target compounds via crosscoupling reaction with bromonaphthalenyl compounds.

[00398] Step 1. 2-(4-Bromonaphthalen-1-yl)-N-(3-tert-butyl-5-cyanophenyl)-2-oxoacetamide (R¹= t-Bu, R²= CN, R³= H). The intermediate product was prepared from 2-(4-bromonaphthalen-1-yl)-2-oxoacetyl chloride (41 mg, 0.14 mmol, prepared as in WO2006091862) and Intermediate A (24 mg, 0.14 mmol) via an acid chloride coupling reaction similar to described above, using TEA as a base. The residue was purified by chromatography over silica gel (gradient: 0-100% EtOAc/Hex) to give the final product (4.8 mg, 7.9%) as a pale yellow solid. ¹H-NMR (500 MHz, CDCl₃) δ (ppm) 9.22 (br s, 1H), 8.58 (m, 1H), 8.43 (m, 1H), 8.25 (d, J = 7.91 Hz, 1H), 8.07 (m, 1H), 7.96 (d, J = 7.89 Hz, 1H), 7.90 (t, J = 1.91 Hz, 1H), 7.73 (m, 2H), 7.55 (t, J = 1.55 Hz, 1H), 1.39 (s, 9H).

[00399] 2-(4-Bromonaphthalen-1-yl)-N-(3-fluoro-5-morpholinophenyl)-2-oxoacetamide (R¹= morpholino, R²= F, R³= H). Prepared using the acid chloride procedure described above using 3-fluoro-5-morpholinoaniline (prepared as in WO20030909).
2-(4-Bromonaphthalen-1-yl)-N-(5-tert-butyl-3-cyano-2-methoxyphenyl)-2-oxoacetamide (R¹=t-Bu, R²= CN, R³= OMe). The acid chloride procedure described above was used with 3-amino-5-tert-butyl-2-methoxybenzonitrile (prepared as in International Application No. PCT/US06/042679) to afford the title compound (72.5 mg, 11%) after RP-HPLC (gradient: 25 to 100% AcN in H₂O) as a pale yellow solid. ¹H-NMR (500 MHz, CDCl₃) δ (ppm) 9.73 (br s, 1H), 8.85 (d, J = 2.38 Hz, 1H), 8.58-8.56 (m, 1H), 8.41-8.39 (m, 1H), 8.22 (d, J = 7.91 Hz, 1H), 7.93 (d, J = 7.88 Hz, 1H), 7.72-7.70 (m, 2H), 7.38 (d, J = 2.37 Hz, 1H), 4.24 (s, 3H), 1.35 (s, 9H).

Step 2. N-(5-tert-Butyl-5-cyanophenyl)-2-oxo-2-(4-(2-(pyrrolidin-1-yl)pyrimidin-4-ylamino)naphthalen-1-yl)acetamide (R¹=t-Bu, R²= CN, R³= H, NR²= pyrrolidinyl). The title compound was prepared from 2-(4-bromonaphthalen-1-yl)-N-(3-tert-butyl-5-cyanophenyl)-2-oxoacetamide (73 mg, 0.17 mmol) (as obtained in step 1 above) and 2-(pyrrolidin-1-yl)pyrimidin-4-amino (30 mg, 0.19 mmol, prepared as in WO200609186) using the procedure described in WO200609186. Briefly, the compound obtained above was dissolved in toluene/dioxane 1/1 and BINAP (0.2 eq.), Cs₂CO₃ (2 eq.) and Pd(II)OAc₂ (0.1 eq.) were added. The reaction was heated to 80°C overnight. The residue was purified by RP-HPLC (gradient: 5 to 90% AcN in H₂O) to yield the TFA-salt of the final product (43 mg, 40%) as a yellow solid. (Calculated mass: 518.6, observed mass: 519.5).

N-(3-Fluoro-5-morpholinophenyl)-2-oxo-2-(4-(2-(pyrrolidin-1-yl)pyrimidin-4-ylamino)naphthalen-1-yl)acetamide (R¹= morpholinyl, R²= F, R³= H, NR²= pyrrolidinyl). The title compound was prepared using the palladium-mediated coupling described above using 2-(4-bromonaphthalen-1-yl)-N-(3-fluoro-5-morpholinophenyl)-2-oxoacetamide. (Calculated mass: 540.6, observed mass: 541.6).

N-(5-tert-Butyl-2-methoxyphenyl)-2-oxo-2-(4-(2-(pyrrolidin-1-yl)pyrimidin-4-ylamino)naphthalen-1-yl)acetamide (R¹=t-Bu, R²= H, R³= OMe, NR²= pyrrolidinyl). The target compound was similarly prepared using 2-(4-bromonaphthalen-1-yl)-N-(5-tert-butyl-2-methoxyphenyl)-2-oxoacetamide and 2-(pyrrolidin-1-yl)pyrimidin-4-amine (prepared as in WO2006091862). (Calculated mass: 523.6, observed mass: 524.6).
[00404] N-(5-tert-butyl-2-methoxy-3-(methylsulfonamido)phenyl)-2-oxo-2-(4-(2,2,6,6-tetramethylmorpholino)pyrimidin-4-ylamino)naphthalen-1-yl)acetamide (R¹= t-Bu, R²= NH₂SO₂Me, R³= OMe, NR₂= 2,2,6,6-tetramethylmorpholino). The target compound was prepared via the palladium-mediated coupling above using 2-(4-bromonaphthalen-1-yl)-N-(5-tert-butyl-2-methoxy-3-(methylsulfonamido)phenyl)-2-oxoacetamide (23.3 mg, 44 µmol, see WO2006091862) and Intermediate I-A (11.3 mg, 48 44 µmol). The TFA-salt of the title compound (2.4 mg, 7%) was obtained after RP-HPLC (gradient: 10 to 95% AcN in H₂O) as a yellow solid. (Calculated mass: 688.8, observed mass: 689.1).

[00405] N-(5-tert-Butyl-3-cyano-2-methoxyphenyl)-2-oxo-2-(4-(2,2,6,6-tetramethylmorpholino)pyrimidin-4-ylamino)naphthalen-1-yl)acetamide (R¹= t-Bu, R²= CN, R³= OMe, NR₂= 2,2,6,6-tetramethylmorpholino). The compound was prepared similarly using 2-(4-bromonaphthalen-1-yl)-N-(5-tert-butyl-3-cyano-2-methoxyphenyl)-2-oxoacetamide and Intermediate I-A. The TFA-salt of the title compound (10.1 mg, 24%) was obtained after RP-HPLC (gradient: 10 to 95% AcN in H₂O) as a yellow solid. (Calculated mass: 620.7, observed mass: 621.1).

[00406] 2-(4-(2-(8-Oxa-3-azabicyclo[3.2.1]octan-3-yl)pyrimidin-4-ylamino)naphthalen-1-yl)-N-(5-tert-butyl-3-cyano-2-methoxyphenyl)-2-oxoacetamide (R¹= t-Bu, R²= CN, R³= OMe, NR₂= 8-oxa-3-azabicyclo[3.2.1]octan-3-yl). The title compound was similarly prepared from Intermediate II-A. The TFA-salt of the title compound (16.4 mg, 37%) was obtained after RP-HPLC (gradient: 10 to 100% AcN in H₂O) as a yellow solid. (Calculated mass: 590.7, observed mass: 591.1).

[00407] N-(5-tert-butyl-2-methoxy-3-(methylsulfonamido)phenyl)-2-(4-(2-(4-methylpiperazin-1-yl)pyrimidin-4-ylamino)naphthalen-1-yl)-2-oxoacetamide (R¹= t-Bu, R²= NH₂SO₂Me, R³= OMe, NR₂= 4-methylpiperazinyl). Prepared using the palladium-mediated coupling described above from 2-(4-bromonaphthalen-1-yl)-N-(5-tert-butyl-2-methoxy-3-(methylsulfonamido)phenyl)-2-oxoacetamide (26 mg, 49 µmol, see WO2006091862 A2) and Intermediate III-A (49 µmol). The pure compound (8.1 mg, 25%) was obtained after RP-HPLC and silica gel purification. (Calculated mass: 645.3, observed mass: 646.3).
00408]  N-(5-tert-Butyl-2-methoxy-3-(methylsulfonamido)phenyl)-2-oxo-2-(4-(2-piperazin-1-yl)pyrimidin-4-ylamino)naphthalen-1-yl)acetamide (R^1= t-Bu, R^2= NHSO_2Me, R^3= OMe, NR^2= piperazinyl). The compound was prepared similarly using Intermediate IV-A and subsequent deprotection by treatment with 95% TFA/H_2O (3 ml). (Calculated mass: 631.3, observed mass: 632.1).

00409]  N-(5-tert-Butyl-2-methoxy-3-(methylsulfonamido)phenyl)-2-(4-(2-(3,5-dimethylpiperazin-1-yl)pyrimidin-4-ylamino)naphthalen-1-yl)-2-oxoacetamide (R^1= t-Bu, R^2= NHSO_2Me, R^3= OMe, NR^2= 3,5-dimethylpiperazinyl). The compound was prepared as above using Intermediate V-A. (Calculated mass: 659.3, observed mass: 660.1).

00410]  N-(5-tert-butyl-2-methoxy-3-(methylsulfonamido)phenyl)-2-oxo-2-(4-(4-(piperazin-1-yl)pyrimidin-2-ylamino)naphthalen-1-yl)acetamide (NR^2= piperazinyl). The target compound was prepared using 2-(4-bromonaphthalen-1-yl)-N-(5-tert-butyl-2-methoxy-3-(methylsulfonamido)phenyl)-2-oxoacetamide (prepared as in WO2006091862) and Intermediate IV-B using a similar procedure to that described in WO2006091862, followed by Boc-deprotection as above. (Calculated mass: 631.3, observed mass: 632.1).

00411]  N-(5-tert-butyl-2-methoxy-3-(methylsulfonamido)phenyl)-2-(4-(4-(3,5-dimethylpiperazin-1-yl)pyrimidin-2-ylamino)naphthalen-1-yl)-2-oxoacetamide (NR^2= 3,5-dimethylpiperazinyl). The target compound was prepared using the palladium mediated coupling described above using Intermediate V-B. (Calculated mass: 659.3, observed mass: 660.1).
[00412] N-(5-tert-Butyl-3-cyano-2-methoxyphenyl)-2-(4(2-(3,3-dimethylbutylamino)pyridine-4-ylamino)naphthalene-1-yl)-2-oxoacetamide (R=NH(CH₂)₂-t-Bu). The target compound was prepared from Intermediate VI (0.1 mmol) and 2-(4-bromonaphthalen-1-yl)-N-(5-tert-butyl-3-cyano-2-methoxyphenyl)-2-oxoacetamide (32 mg, 0.07 mmol), using a palladium-mediated coupling procedure similar to above (see also WO2006091862). The TFA-salt of the title compound (25.5 mg, 53%) was obtained after preparative LC-MS (gradient: 40 to 100% AcN in H₂O) as an orange-red solid. (Calculated mass: 577.7, observed mass: 578.2).

[00413] N-(5-tert-Butyl-3-cyano-2-methoxyphenyl)-2-(4-(2-(2,6-dimethylpiperidin-1-yl)ethylamino)pyridine-4-ylamino)naphthalene-1-yl)-2-oxoacetamide (R=2-(2,6-dimethylpiperidin-1-yl)ethylamino) was prepared using a similar palladium-mediated-coupling procedure as above, using Intermediate IX. (Calculated mass: 632.8, observed mass: 633.2).

[00414] N-(5-tert-Butyl-3-cyano-2-methoxyphenyl)-2-oxo-2-(4-pyridin-4-ylamino)naphthalene-1-yl)acetamide (R=H) was prepared using a similar procedure as above, using pyridin-4-amine. (Calculated mass: 478.5, observed mass: 479.1).

[00415] N-(5-tert-buty1-3-cyano-2-methoxyphenyl)-2-(4-(6-(methy lamino)pyridin-3-yl)naphthalen-1-yl)-2-oxoacetamide. 2-(4-Bromonaphthalen-1-yl)-N-(5-tert-butyl-3-cyano-2-methoxyphenyl)-2-oxoacetamide (28 mg, 0.06 mmol), prepared using a procedure similar to above (see also WO2006091862), and Intermediate VIII (26 mg, 0.06 mmol) were dissolved in toluene (0.5 ml) and dioxane (1 ml). The reaction mixture was placed under a nitrogen atmosphere and Pd₂(dba)₃.CHCl₃ (9.3 mg, 15 mol%) was added. The reaction was stirred at 30°C for 3 hr. After removal of the solvents, the residue was dissolved in DCM and purified by silica gel chromatography (gradient: 0 to 100% 50% EtOAc/Hex). The target compound was obtained as an orange-red solid. (Calculated mass: 492.6, observed mass: 493.0).
N-(3-tert-Butyl-5-((4-methylpiperazin-1-yl)methyl)phenyl)-2-oxo-2-(4-pyridin-3-yl)naphthalen-1-yl)acetamide. 2-(4-Bromonaphthalen-1-yl)-N-(3-tert-butyl-5-((4-methylpiperazin-1-yl)methyl)phenyl)-2-oxoacetamide (52 mg, 0.1 mmol) (prepared using a procedure similar to above) and pyridin-3-ylboronic acid (24 mg, 0.2 mmol) were dissolved in DME (1.3 ml) and (PPh₃)₂PdCl₂ (7 mg, 10 mol%), Pd₂dba₃CHCl₃ (10 mg, 10 mol%) and Cs₂CO₃ (97 mg, 0.3 mmol) were added. The reaction was placed under N₂ atmosphere and was heated to 100°C for 3 hr. The mixture was filtered through a silica gel column, which was washed with DMF. The resulting solution was purified via preparative LC-MS (gradient: 10-60% AcN/H₂O over 8.5 min), yielding the target product in 17.1 mg yield. (Calculated mass: 520.7, observed mass: 521.1).

Step 1. 2-(4-Bromonaphthalen-1-yl)-N-(3-tert-butyl-1-p-tolyl-1H-pyrazol-5-yl)-2-oxoacetamide (R= p-Me). The target compound was prepared from 2-(4-bromonaphthalen-1-yl)-2-oxoacetyl chloride (112 mg, 0.38 mmol, prepared as in WO2006091862) and 3-tert-butyl-1-p-tolyl-1H-pyrazol-5-amine (87 mg, 0.38 mmol, prepared as in WO2005023761) using the acid chloride procedure described above (see also WO2006091862). The residue was chromatographed over silica gel (gradient: 0 to 50% EtOAc/Hex) to give the final product (72 mg, 39%). ¹H-NMR (500 MHz, CDCl₃) δ (ppm) 9.45 (br s, 1H), 8.55 (m, 1H), 8.38 (m, 1H), 8.26 (d, J = 7.95 Hz, 1H), 7.90 (d, J = 7.94 Hz, 1H), 7.68 (m, 2H), 7.44 (d, J = 8.39 Hz, 2H), 7.38 (d, J = 7.09 Hz, 2H), 6.85 (s, 1H), 2.45 (s, 3H), 1.41 (s, 9H).
2-(4-Bromonaphthalen-1-yl)-N-(3-tert-butyl-1-m-tolyl-1H-pyrazol-5-yl)-2-oxoacetamide (R= m-Me) was similarly prepared using 3-tert-butyl-1-m-tolyl-1H-pyrazol-5-amine (87 mg, 0.38 mmol, prepared as in WO2005023761).

**Step 2.** N-(3-tert-Butyl-1-p-tolyl-1H-pyrazol-5-yl)-2-oxo-2-(4-(2-(pyrrolidin-1-yl)pyrimidin-4-ylamino)naphthalen-1-yl)acetamide (R= p-Me). The title compound was prepared from 2-(4-bromonaphthalen-1-yl)-N-(3-tert-butyl-1-p-tolyl-1H-pyrazol-5-yl)-2-oxoacetamide (72 mg, 0.15 mmol) and 2-(pyrrolidin-1-yl)pyrimidin-4-amine (25 mg, 0.15 mmol, prepared as in WO2006091862), using a palladium-mediated coupling procedure similar to the one described above and in WO2006091862. The residue was purified over silica gel (gradient: 0 to 100% EtOAc/Hex, then 10% MeOH/Hex) to yield the final product (8.2 mg, 9.5%) as an orange solid. (Calculated mass: 573.7, observed mass: 574.7).

N-(3-tert-Butyl-1-m-tolyl-1H-pyrazol-5-yl)-2-oxo-2-(4-(2-(pyrrolidin-1-yl)pyrimidin-4-ylamino)naphthalen-1-yl)acetamide (R= m-Me). The compound was prepared similarly, starting from 2-(4-bromonaphthalen-1-yl)-N-(3-tert-butyl-1-m-tolyl-1H-pyrazol-5-yl)-2-oxoacetamide (36 mg, 0.073 mmol). The residue was purified over silica gel (gradient: 0 to 100% EtOAc/Hex, then 10% MeOH/Hex) followed by RP-HPLC (gradient: 35 to 70% AcN in H2O) to yield the TFA-salt of the final product (4.0 mg, 8.0%) as a yellow solid. (Calculated mass: 573.7, observed mass: 574.6).

**Example 3:** Formation of N-(naphthalen-1-yl)-2-oxo-2-(1H-pyrazol-5-yl)acetamide compounds.

![Diagram](image)

2-(3-tert-Butyl-1-methyl-1H-pyrazol-5-yl)-2-oxo-N-(4-(2,2,6,6-tetramethylmorpholinol)ethoxy)naphthalen-1-yl)acetamide (R= 2,2,6,6-tetramethylmorpholinol). To a solution of the TFA-salt of Intermediate f (8.8 mg, 0.02 mmol) in DCM (2 ml), was added 2-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-2-oxoacetic acid (X = OH) (4.6 mg, 0.022 mmol, prepared as in WO2005023761 or US20050107399),
BOP (excess) and DIEA (excess). The mixture was stirred at r.t. overnight, evaporated and the residue was subjected to RP-HPLC (gradient: 20 to 80% AcN in H2O) to give the TFA-salt of the final product (2.8 mg, 22%) as a yellow solid. (Calculated mass: 520.7, observed mass: 521.3).

[00422] N-(4-(2-(8-Oxa-3-azabicyclo[3.2.1]octan-3-yl)ethoxy)naphthalen-1-yl)-2-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-2-oxoacetamide (R= 8-Oxa-3-azabicyclo[3.2.1]octan-3-yl). Using the same procedure as above, starting with the TFA-salt of intermediate g (20.6 mg, 0.05 mmol) gave the TFA-salt of the final product (3.0 mg, 9.9%) as a yellow solid after repeated RP-HPLC (gradient: 20 to 80%, followed by 10 to 60% AcN in H2O). (Calculated mass: 490.6, observed mass: 491.2).

Example 4: Additional derivatization reactions.

[00423] N-(5-tert-Butyl-2-methoxy-3-(methylsulfonamido)phenyl)-2-(hydroxyimino)-2-(4-(2-(pyrrolidin-1-yl)pyrimidin-4-ylamino)naphthalen-1-yl)acetamide. The title compound was prepared from N-(5-tert-butyl-2-methoxy-3-(methylsulfonamido)phenyl)-2-oxo-2-(4-(2-(pyrrolidin-1-yl)pyrimidin-4-ylamino)naphthalen-1-yl)acetamide (prepared as in WO2006091862) using the procedure described in WO2005023761, namely the starting material was treated with hydroxylamine hydrochloride in EtOH containing catalytic pyridine. (Calculated mass: 631.7, observed mass: 632.6).

[00424] N-(4-(2-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)ethoxy)naphthalen-1-yl)-2-(5-tert-butyl-2-methylfuran-3-yl)-2-(hydroxyimino)acetamide. The title compound was prepared from N-(4-(2-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)ethoxy)naphthalen-1-yl)-2-(5-
tert-butyl-2-methylfuran-3-yl)-2-oxoacetamide (itself prepared from 2-(5-tert-butyl-2-methylfuran-3-yl)-2-oxoacetic acid, synthesized as described in WO2006091862, and intermediate g via BOP coupling as described above) using the procedure described in WO2005023761: namely the starting material was treated with hydroxylamine hydrochloride in EtOH containing catalytic pyridine. The two oxime isomers were separated by RP-HPLC, affording 10.6 mg of the E-isomer and 5.0 mg of the Z-isomer. E-isomer: 1H-NMR (500 MHz, MeOD) δ (ppm) 8.34 - 8.32 (m, 1H), 8.24 - 8.22 (m, 1H), 7.60 - 7.58 (m, 2H), 7.55 (d, J = 8.16 Hz, 1H), 7.01 (d, J = 8.23 Hz, 1H), 6.24 (s, 1H), 4.62 - 4.61 (m, 2H), 4.56 (m, 2H), 3.78 - 3.77 (m, 2H), 3.58 - 3.55 (m, 2H), 3.50 - 3.47 (m, 2H), 2.45 (s, 3H), 2.17 - 2.08 (m, 4H), 1.30 (s, 9H); Z-isomer: 1H-NMR (500 MHz, MeOD) δ (ppm) 8.34 (d, J = 8.0 Hz, 1H), 7.98 (d, J = 8.21 Hz, 1H), 7.63 - 7.58 (m, 3H), 7.01 (d, J = 8.17 Hz, 1H), 6.26 (s, 1H), 4.62-4.60 (m, 2H), 4.57 - 4.56 (m, 2H), 3.78 - 3.77 (m, 2H), 3.57 - 3.55 (m, 2H), 3.50 - 3.47 (m, 2H), 2.30 (s, 1H), 2.19 - 2.07 (m, 4H), 1.29 (s, 9H).

N-(5-tert-Butyl-2-methoxy-3-(methylsulfonamido)phenyl)-2-hydroxy-2-(4-(2-(pyrrolidin-1-yl)pyrimidin-4-ylamino)naphthalen-1-yl)acetamide. To a solution of N-(5-tert-butyl-2-methoxy-3-(methylsulfonamido)phenyl)-2-oxo-2-(4-(2-(pyrrolidin-1-yl)pyrimidin-4-ylamino)naphthalen-1-yl)acetamide (prepared as in WO2006091862) in DCM/MeOH, NaBH₄ (excess) was added and the mixture was stirred at r.t. overnight, to afford 18 mg of product. (Calculated mass: 618.7, observed mass: 619.5).

4-(2-(4-(2-(5-tert-Butyl-2-methoxy-3-(methylsulfonamido)phenylamino)-2-oxoacetyl)naphthalen-1-yl oxy)ethy)morpholine 4-oxide. To a solution of N-(5-tert-butyl-2-methoxy-3-(methylsulfonamido)phenyl)-2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamide (100 mg, 0.17 mmol) (obtained as described in WO2005/023761) in
MeOH/AcN (3 ml, 2:1), H₂O₂ (1 ml, 30% aq. solution) was added and the mixture was stirred at r.t. for several days. The solvent was evaporated and the residue was subjected to RP-HPLC (gradient of 10-90% AcN in H₂O) to give the product as a brown film (14.0 mg, 14%). (Calculated mass: 599.7, observed mass: 599.9).

[00427] 5-tert-Butyl-2-methoxy-3-(2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamido)-N-(2-(pyrrolidin-1-yl)ethyl)benzamide. In a 50 ml round-bottomed flask were placed MeOH (3 ml), THF (2 ml), methyl 5-tert-butyl-2-methoxy-3-(2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamido)benzoate (795 mg, 1.45 mmol) (prepared as described above) and NaOH (182 mg, 4.55 mmol). The reaction was heated overnight, then evaporated. The residue was suspended in THF (10 ml), treated with 2N HCl (2.27 ml, 4.55 mmol) and evaporated. The residue was lyophilized from dioxane. The compound obtained (50 mg, 0.094 mmol) was suspended in DCM (3 ml), treated with DMF (1 drop) followed by oxalyl chloride (110 µl, 0.54 mmol). After 0.5 hr the solvent was evaporated and the residue was stripped from THF. To half of this residue was added 2-(pyrrolidin-1-yl)ethanamine (24 µl, 0.19 mmol). The reaction mixture was loaded onto silica gel, eluting with 0 - 10% MeOH/DCM to afford 2.2 mg of the target compound. Calculated mass: 630.3, observed mass: 631.1.

[00428] N-(5-tert-Butyl-2-methoxy-3-(1H-tetrazol-5-yl)phenyl)-2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamide. To a solution of N-(5-tert-butyl-3-cyano-2-methoxyphenyl)-2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamide (51 mg, 91 µmol) in DMF (0.5 ml), triethylamine hydrochloride (25 mg, 180 µmol) and sodium azide (14 mg, 215 µmol) were added. The mixture was stirred at 80°C overnight,
after which the mixture was purified via preparative LC-MS to afford the target compound (35.2 mg, 57%) as the TFA-salt. (Calculated 558.2, observed 559.4).

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\text{N-(3-amino-5-tert-butyl-2-methoxyphenyl)-2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamide.} \quad \text{tert-Butyl 5-tert-butyl-2-methoxy-3-(2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamido)phenylcarbamate (232 mg, 0.38 mmol) was dissolved in DCM (5 ml) and treated with TFA (5 ml). After 5 min the solvent was evaporated and the residue (245 mg, 100% yield) was used as the TFA salt without further purification.}
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\text{N-(3-Azido-5-tert-butyl-2-methoxyphenyl)-2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamide.} \quad \text{In a 250 ml round-bottomed flask containing the compound obtained above (245 mg, 0.38 mmol), dissolved in 10% H}_2\text{SO}_4 \text{ (10 ml) in an ice bath, was added sodium nitrite (35 mg, 0.51 mmol). After 10 min stirring, sodium nitrite (50 mg, 0.76 mmol) was added and the reaction was allowed to warm to r.t. The reaction was quenched with solid Na}_2\text{CO}_3 \text{ and extracted with DCM and dried over Na}_2\text{SO}_4 \text{. The solvent was removed to afford 188 mg (103% yield) of the target compound. (Calculated mass: 531.2, observed mass: 532.1).}
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\text{N-(5-tert-Butyl-2-methoxy-3-(1H-1,2,3-triazol-1-yl)phenyl)-2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamide.} \quad \text{To the compound obtained above (24 mg, 0.038 mmol) in AcN (4 ml) and water (400 µl) was added TMS-acetylene (700 µl) }
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and copper wire. After heating at 50°C for seven days, the solvent was evaporated and the reaction was treated with 2M HCl in dioxane (4 ml) and THF (2 ml) for 2 days. The solvents were evaporated and the residue was purified on preparative HPLC to afford N-(5-tert-butyl-2-methoxy-3-(1H-1,2,3-triazol-1-yl)phenyl)-2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamide (7.8 mg, 31% yield) (Calculated mass: 557.3, observed mass: 558.1), and N-(5-tert-butyl-2-methoxy-3-(4-(trimethylsilyl)-1H-1,2,3-triazol-1-yl)phenyl)-2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamide (8.7 mg, 31% yield) (Calculated mass: 629.3, observed mass: 630.1).

[00432] N-(5-tert-Butyl-3-(4-(hydroxymethyl)-1H-1,2,3-triazol-1-yl)-2-methoxyphenyl)-2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamide. The target compound was prepared using an analogous procedure (11 mg, 41% yield) starting from propargyl alcohol (26 mg, 0.45 mmol) and the compound obtained above (24 mg, 0.038 mmol), heating at 100°C overnight. (Calculated mass: 587.3, observed mass: 588.1).

Biological Testing.

Example 5: Inhibition of TNFa production in THP cells

[00433] The inhibition of cytokine production can be observed by measuring inhibition of TNFa in lipopolysaccharide-stimulated THP-1 cells (see Prichett et al. J. Inflammation, 1995, 45, 97). THP-1 cells (ATCC TIB 202, American Type Culture Collection, Rockville, MD) were maintained at 37°C, 5% CO2 in RPMI 1640 media with 10% fetal bovine serum, 10 mM Hepes, 1 mM sodium pyruvate, 4.5 g/l glucose and 0.05 mM 2-mercaptoethanol as suggested by ATCC. For the assay, the cells and compounds were diluted in the media above except with 1% fetal bovine serum (assay media). Test compound stocks in DMSO were diluted into assay media to 6x the final assay concentration, with a final DMSO concentration of less than 0.3% in the assay. THP-1 cells were plated at 1x10⁵/well in 96 well tissue culture plates. Diluted compounds (or DMSO control) were added and allowed to preincubate with the cells at 37°C, 5% CO2 for 30 minutes prior to the addition of LPS (Sigma) to a final concentration of 1 μg/ml. Cells were then incubated 18-20 hours at 37°C/5% CO2. The assay
was terminated by centrifuging the plates for 10 min at r.t. Supernatants were removed to clean culture plates and aliquots were removed for analysis for TNFα by a commercially available ELISA kit (R&D Systems #DY210, Minneapolis, MN). Data was analyzed by non-linear regression using PRISM 4 software from Graphpad Software (San Diego, CA). The calculated IC₅₀ is the concentration of the test compound that caused a 50% decrease in the maximal TNFα production.

[00434] Each of the compounds in List 1 was tested in the TNFα ELISA assay and was found to have activity therein, with most compounds having IC₅₀ below 10 μM in this assay.

Example 6: Inflammation models

[00435] Methods for the testing of systemic lupus erythematosus (SLE) in susceptible mice are known in the art (Knight et al., J. Exp. Med., 1978, 147, 1653; Reinersten et al., New Eng. J. Med., 1978, 299, 515). Myasthenia Gravis (MG) is tested in SJL/J female mice by inducing the disease with soluble AchR protein from another species (Lindstrom et al., Adv. Immunol., 1988, 42, 233). Arthritis is induced in a susceptible strain of mice by injection of Type II collagen (Stuart et al., Ann. Rev. Immunol., 1984, 42, 233). A model by which adjuvant arthritis is induced in susceptible rats by injection of mycobacterial heat shock protein has been described (Van Eden et al., Nature, 1988, 331, 171). Thyroiditis is induced in mice by administration of thyroglobulin as described (Maron et al., J. Exp. Med., 1980, 152, 1115). Insulin dependent diabetes mellitus (IDDM) occurs naturally or can be induced in certain strains of mice such as those described by Kanasawa et al., Diabetologia, 1984, 27, 113. Experimental autoimmune encephalomyelitis (EAE) in mouse and rat serves as a model for MS in human. In this model, the demyelinating disease is induced by administration of myelin basic protein (see Paterson, Textbook of Immunopathology, Mischer et al., eds., Grune and Stratton, New York, 1986, pp. 179-213; McFarlin et al., Science, 1973, 179, 478; and Satoh et al., J. Immunol., 1987, 138, 179). Examples are described in more detail below.

[00436] Collagen Induced Arthritis model in mice. Immunization of for example, DBA/1 mice with murine type II collagen induces a chronic relapsing polyarthritis that provides a strong model for human autoimmune arthritis. The model is described, for example, by Courtenay et al., Nature, 1980, 282, 666; Kato et al., Ann. Rheum. Dis., 1996, 55, 535; and Myers et al., Life Sci., 1997, 61, 1861-1878, each of which is incorporated
herein by reference. Briefly, mice are quarantined for at least three days. On day 0, the mice are weighed and separated into treatment groups. The non-diseased control group animals receive no adjuvant (10 mice), in contrast to diseased mice (20 mice/treatment group). The mice are anesthetized, shaved at the base of tail, and injected (id) with adjuvant (50 μl/mouse; 100 μg/mouse collagen; 100μg/mouse M. tuberculosis H37Ra), using a 1 ml syringe fitted with a 26 G needle. On day 21, the adjuvant is prepared by emulsifying (in an homogenizer) a 1:1 combination of collagen and M. tuberculosis H37Ra. The adjuvant is injected (id) (50 μl/mouse; 100 μg/mouse collagen; 100μg/mouse M. tuberculosis H37Ra) using 1 ml syringe fitted with a 26 G needle. On days 22-27 the macroscopic signs of arthritis are scored daily. Each paw receives a score: 0 = no visible effects of arthritis; 1 = edema and/or erythema of one digit; 2 = edema and/or erythema of two joints; 3 = edema and/or erythema of more than two joints; or 4 = severe arthritis of the entire paw and digits. The Arthritic Index is calculated by addition of all the individual paw scores, and recorded (maximum arthritic index = 16). On day 28 the mouse weights are recorded and the macroscopic signs of arthritis are scored. The mice are sorted into treatment groups (10 mice/group) based upon their arthritic index. Each treatment group is designed to have a similar average Arthritic Index and a similar range of arthritic indices. The dosing regimen by oral route is initiated. On day 29-42 the mice are dosed and any adverse effects of test agent administration are recorded. The macroscopic signs of arthritis for each paw are scored daily. On day 43 the macroscopic signs of arthritis are scored, the mice are exsanguinated and their blood is collected in heparinized tubes. The hindlimbs and/or forelimbs are removed and immersed in four volumes of 10% buffered formalin. The paws are evaluated for decalcification and histology. Livers are removed and their weights are recorded.

[00437] Collagen Induced Arthritis model in rats. Female Lewis rats, (Charles River ref #7218419), weighing 125-150 g on arrival (8/group for arthritis, 4/group for normal control), are housed 4/cage, and are acclimated for 4-8 days after arrival. Acclimated animals are anesthetized with Isoflurane and given collagen injections (D0). On day 6 they are anesthetized again for the second collagen injection. Collagen is prepared by making a 4 mg/ml solution in 0.01 N acetic acid. Equal volumes of collagen and Freund’s incomplete adjuvant are emulsified by hand mixing until a bead of this material holds its form when placed in water. Each animal receives 300 μl of the mixture each time spread over 3 subcutaneous sites on its back. Caliper measurements of normal (pre-disease) right and left
ankle joints are collected on day 9. On days 10-11, the onset of arthritis occurs and the rats are randomized into treatment groups. Animals to be given vehicle or compound doses are enrolled and qd (24 hr. intervals) dosing is initiated for days 1-6 using a volume of 5 ml/kg for oral solutions. The rats are weighed on days 1-7 of arthritis; caliper measurements of ankles are taken every day. The final body weights are collected on day 7 of arthritis. On day 7, the animals are anesthetized for whole blood draw to exsanguinate (serum can be used for clinical chemistry) and then euthanized. Both hind paws and knees are removed, the hind paws are weighed and then (with knees) placed in formalin and processed for microscopy. Following 1-2 days in fixative and 4-5 days in decalcifier, the ankle joints are cut in half longitudinally, the knees are cut in half in the frontal plane, processed, embedded, sectioned and stained with toluidine blue. The arthritic ankles and knees are given scores of 0 (normal) -5 (severe effects) for inflammation, pannus formation and bone resorption. Percent inhibition of paw weight and AUC is calculated using the following formula:

\[
\% \text{ Inhibition} = \frac{A - B}{A} \times 100
\]

with $A = (\text{Mean Disease Control} - \text{Mean Normal})$ and $B = (\text{Mean Treated} - \text{Mean Normal})$.

[00438] **Inflammatory Bowel and Crohn's Disease Models.** To evaluate the effectiveness of test compounds in Crohn's disease, the TNF$^{\Delta A R E}$ transgenic mouse model of Crohn's disease (originally described by Kontoyiannis et al., Immunity, 1999, 10, 387) is used (the DSS (dextran sodium sulfate) model can also be used in a similar fashion). The animals develop an IBD phenotype with similarity to Crohn's disease starting between 4 and 8 weeks of age. Test compounds are administered at either 3 weeks of age (to test prevention of disease) or 6 weeks of age (to test stabilization, prevention of progression or reversal of disease symptoms), and animals are scored by weight and histologically as described herein. Test compositions are administered either weekly or twice weekly, or can be administered continuously, for example, using an osmotic pump. Alternatively, oral delivery formulations can also be applied. The studies are continued for up to 7 weeks or more once initiated. Animals can be monitored for bowel disease according to a standard scale as described in Kontoyiannis et al., 2002, supra. Paraffin-embedded intestinal tissue sections of ileum are histologically evaluated in a blinded fashion according to the following scale: Acute and chronic inflammation are assessed separately in a minimum of 8 high power fields (hpf) as
follows -- acute inflammatory score: 0 = (0-1) polymorphonuclear (PMN) cells per hpf (PMN/hpf); 1 = (2-10) PMN/hpf within mucosa; 2 = (11-20) PMN/hpf within mucosa; 3 = (21-30) PMN/hpf within mucosa or (11-20) PMN/hpf with extension below muscularis mucosae; and 4 = > 30 PMN/hpf within mucosa or > 20 PMN/hpf with extension below muscularis mucosae. Chronic inflammatory score: 0 = (0-10) mononuclear leukocytes (ML) per hpf (ML/hpf) within mucosa; 1 = (11-20) ML/hpf within mucosa; 2 = (21-30) ML/hpf within mucosa or (11-20) ML/hpf with extension below muscularis mucosae; 3 = (31-40) ML/hpf within mucosa or (21-30) ML/hpf with extension below muscularis mucosae or follicular hyperplasia; and 4 = > 40 ML/hpf within mucosa or > 30 ML/hpf with extension below muscularis mucosae or follicular hyperplasia. Total disease score per mouse is calculated by summation of the acute inflammatory or chronic inflammatory scores for each mouse.

[00439] Efficacy in the TNF$\Delta^{AARE}$ model of Crohn's disease is shown by any of: i) a failure to develop disease symptoms when administered to animals beginning at 3 weeks of age; ii) lessened severity of disease symptoms appearing when administered starting at 3 weeks of age, relative to control animals; iii) failure to progress to more severe disease or progression at a lower rate relative to control animals when administered beginning at 6 weeks of age; iv) reversal of symptoms at any of 7, 8, 9, 10, 11, 12, or 14 weeks when administered to an animal beginning at 6 weeks of age. In particular, treatment is considered effective if the average histopathological disease score is lower in treated animals (by a statistically significant amount) than that of a vehicle control group. Treatment is also considered effective if the average histopathological score is lower by at least 0.5 units, at least 1.0 units, at least 1.5 units, at least 2.0 units, at least 2.5 units, at least 3.0 units, or by at least 3.5 units relative to the vehicle-only control group. Alternatively, the treatment is effective if the average histopathological score remains at or is lowered to 0 to 0.5 throughout the course of the therapeutic regimen.

[00440] Other models of IBD include, for example, the DSS model of chronic colitis in BALB/c mice. The DSS model was originally described by Okayasu et al., Gastroenterology, 1990, 98, 694 and was modified by Kojouharoff et al., Clin Exp. Immunol. 1997, 107, 353 (see also WO 2004/041862, incorporated herein by reference). BALB/c mice weighing 21-22 g are treated to induce chronic colitis by the administration of DSS in their drinking water at 5% w/v in cycles of 7 days of treatment and 12 days recovery interval without DSS. The 4th recovery period can be extended from 12 to 21 days to represent a chronic
inflammation status, rather than the acute status modeled by shorter recovery. After the last recovery period, treatment with a compound of the invention, optionally with one or more ingredient(s) A, is initiated. Weekly administration is recommended initially, but can be adjusted by one of skill in the art as necessary. At intervals during treatment, animals are killed, the intestine is dissected and histopathological scores are assessed as described herein or as described in Kojouharoff et al., 1997, supra. Other animal models of inflammatory bowel disease include the chronic intestinal inflammation induced by rectal instillation of 2,4,6-Trinitrobenzene sulfonic acid (TNBS; method described by Neurath et al., J. Exp. Med., 1995, 182, 1281; see also U.S. Patent No. 6,764,838, incorporated herein by reference). Histopathological scoring can be performed using the same standard described above.

Example 7: Clinical Inflammatory Disease Assessments

[00441] Ex-vivo LPS challenge endotoxemia model. Ex-vivo treatment of blood from patients treated with anti-inflammatory compounds with endotoxin represents a safe, well-defined model of acute inflammation in humans. It is also an excellent tool to study the mechanisms contributing to inflammatory responses in man in vivo. Given the importance of the balance of inflammatory and anti-inflammatory cytokines and other factors in the etiology of inflammatory diseases such as rheumatoid arthritis and Crohn's disease, evaluation of compounds as described herein in a human LPS model could prove beneficial in elucidating potential effects of anti-inflammatory compounds in human inflammatory processes.

[00442] Compounds described herein are administered orally at different doses to human volunteers. After 1 to 24 hours, blood samples are collected via venepuncture into vacutainer tubes and heparinized. Prior to the stimulation assay, a monocyte count is performed for each individual's undiluted heparinized whole blood sample (Cell Dyn 3500 SL). For this purpose a small volume (100-200 µl) is aspirated directly from the whole blood sample into the analyzer. For each sample and for each subject the following stimulation assays are performed: a. Unstimulated control (only vehicle) and b. Stimulated: 10 ng/ml LPS (final concentration). The stimulation assays are performed within one hour after withdrawal of the whole blood samples. The stimulation assay procedure is as follows.

1. Dilute the whole blood sample 1 + 1 with RPMI-1640 medium; mix gently by inversion.
2. Pipette the diluted whole blood into each of the two separate sterile tubes (one for each condition).

3. Add to each tube 200 µl of the appropriate LPS stock (or blank) to yield the above-listed final LPS concentrations. Mix gently by inversion.

4. From each tube, add gently 0.5 ml per well into multiple (e.g., eight) master block wells.

5. Any empty wells should be filled with 0.5 ml of PBS buffer.

6. Cover the master blocks with their specific covers.

7. Incubate for 24 hours at 37°C and 5% CO₂.

8. At the end of the incubation period, centrifuge the blocks at 1000 x g for 10 minutes at r.t.

9. Collect the supernatants and pool the appropriate wells into their appropriate polypropylene tubes (expected yield at 1:1 whole blood dilution: 40-60% of volume).

10. Mix and aliquot into separate tubes; one for each cytokine to be analyzed (target supernatant volume per aliquot: 0.5 ml).

11. Store samples at -70°C until analysis.

[00443] TNF-α, IL-1β, IL-6 or other cytokines are analyzed using validated ELISA methods.

[00444] Rheumatoid Arthritis disease assessment. Rheumatoid arthritis is clinically scored on the basis of several clinically accepted scales, such as those described in U.S. Patent No. 5,698,195, which is incorporated herein by reference, and Alctaha et al., Clin. Exp. Rheumatol. 2005, 23 (suppl. 39), S 100. Disease activity and change effected with treatment can be evaluated using the disease activity score (DAS) and/or the chronic arthritis systemic index (CASI), see Carotti et al., 2002, Ann. Rheum. Dis. 61:877-882, and Salaffi et al., 2000, Rheumatology 39: 90-96. Briefly, clinical response studies can assess the following parameters: A. Number of tender joints; B. Number of swollen joints (Both tenderness and swelling are evaluated for each joint separately); and C. Visual analog pain scale (0-10 cm). Clinical response is assessed using a subjective reporting system as follows: Without any difficulty, With some difficulty, With much difficulty, or Unable to do. The visual analog scale for pain is a straight line with the left end of the line representing no pain
and the right end of the line representing the worst pain. Patients are asked to mark on the line where they think their pain is.

Additionally, blood chemistry analysis determines levels of CRP, Rheumatoid Factor, cytokines and other biomarkers.


Psoriasis disease assessment. Efficacy of psoriasis treatment can be monitored by changes in clinical signs and symptoms of the disease, including Psoriasis Area and Severity Index (PASI) scores, physician’s global assessment (PGA) of the patient compared with the baseline condition. A decrease in PASI score indicates a therapeutic effect. Psoriatic disease activity can also be determined based on Overall Lesion Severity (OLS) scale, percentage of total body surface area (BSA) affected by psoriasis, and psoriasis plaque thickness. Skin biopsies are studied for the effects of the drug on lymphocytes within psoriatic lesions. Histological analysis of skin biopsies can be performed to look for reduction in epidermal thickness and T-cell infiltration and reversal of pathological epidermal hyperplasia. Immunological activity can be monitored by testing for the effects of treatment on cell-mediated immunity reactions (delayed hypersensitivity), tetanus antibody responses, and lymphocyte subpopulations (flow cytometry).

Example 8: Cardiovascular and metabolic disease models

Lipid determinations. The anti-atherosclerotic activity of compounds may be demonstrated by determining the amount of agent required to alter plasma lipid levels, for example HDL cholesterol levels, LDL cholesterol levels, VLDL cholesterol levels or triglycerides, in the plasma of certain animals, for example marmosets (Crook et al. Arteriosclerosis 10, 625, 1990) or Golden Syrian Hamsters (Goulain et al., J. Lipid Res., 34, 943, 1993), and others, that possess a plasma lipoprotein profile similar to that of humans.
Blood chemistry evaluation in Marmosets. Adult marmosets are assigned to treatment groups so that each group has a similar mean +/-SD for total, HDL, and/or LDL plasma cholesterol concentrations. After group assignment, the marmosets are dosed daily with compound as a dietary admix or by intragastric intubation for from one to eight days. Control marmosets receive only the dosing vehicle. Plasma total, LDL VLDL and HDL cholesterol values may be determined at any point during the study by obtaining blood from an antecubital vein and separating plasma lipoproteins into their individual subclasses by density gradient centrifugation, and by measuring cholesterol concentration as previously described (Crook et al. Arteriosclerosis 10, 625, 1990).

Blood chemistry evaluation in cynomolgous monkeys. Sixteen male and 16 female cynomolgous monkeys are assigned to four dose groups. A compound is formulated in a suitable vehicle at low, medium, and high concentrations. The three dosages of the compound and vehicle alone are administered once daily by oral gavage for 90 consecutive days to all male and female monkeys in the corresponding dose group. Blood samples (4 to 6 ml) are collected from the femoral vein at days 0, 28, and 90. The blood samples are processed for serum, and clinical chemistry values, including, for example, HDL cholesterol, triglyceride and total bilirubin levels, which are determined by standard methods.

Blood chemistry evaluation in Wistar rats. Eighty male and 80 female Wistar rats are assigned to four dose groups. A compound is formulated in a suitable vehicle at low, medium, and high concentrations. The three dosages of the compound and vehicle alone are administered once daily by oral gavage for 90 consecutive days to all male and female rats in the corresponding dose group. Blood samples (2 to 3 ml) are collected via the orbital sinus at days 0, 28, and 90. The blood samples are processed for serum, and clinical chemistry values, including, for example, HDL cholesterol levels, which are determined by standard methods.

Blood chemistry evaluation in Golden Syrian Hamsters. Female Golden Syrian Hamsters (6-8 weeks old) were quarantined for 72 hours and then assigned to treatment groups. A sample bleed was taken by retro-orbital bleed on day 0, prior to dosing, and processed to 1 ml serum in pre-chilled EDTA-treated tubes. Each serum sample was aliquoted to 0.5 ml and 0.3 ml volumes and stored at -20°C until shipment. Subsequently the test compound or vehicle was administered orally (typically 5 ml/kg, for a dose of 30 mg/kg).
Once daily dosing at those doses was continued on days 1-13. On day 2, day 6 or 13, terminal bleeds were taken several hours after the final oral dose, and the sera were processed, aliquoted and stored as before. Lipid analysis and clinical chemistry panel analysis was performed on all blood samples.

**Rabbit Atherosclerosis Assay.** Anti-atherosclerotic effects of the compounds may be determined by the amount of compound required to reduce the lipid deposition in rabbit aorta. Male New Zealand White rabbits are fed a diet containing 0.2% cholesterol and 10% coconut oil for 4 days (meal-fed once per day). Rabbits are bled from the marginal ear vein and total plasma cholesterol values are determined from these samples. The rabbits are then assigned to treatment groups so that each group has a similar mean \( \pm /- \) SD for total plasma cholesterol concentration, HDL cholesterol concentration, triglyceride concentration and/or cholesteryl ester transfer protein activity. After group assignment, rabbits are dosed daily with compound given as a dietary admix or on a small piece of gelatin based confection. Control rabbits receive only the dosing vehicle, be it the food or the gelatin confection. The cholesterol/coconut oil diet is continued along with the compound administration throughout the study. Plasma cholesterol values may be determined at any point during the study by obtaining blood from the marginal ear vein. After 3-5 months, the rabbits are sacrificed and the aortae are removed from the thoracic arch to the branch of the iliac arteries. The aortae are cleaned of adventitia, opened longitudinally and then analyzed unstained or stained with Sudan IV as described by Holman et al. (Lab. Invest. 1958, 7, 42-47). The percent of the lesioned surface area is quantitated by densitometry using an Optimas Image Analyzing System (Image Processing Systems). Reduced lipid deposition is indicated by a reduction in the percent of lesioned surface area in the compound-receiving group in comparison with the control rabbits.

and infiltration of monocytes, followed by a rapid induction of neointima formation, and in
the induction in foam cell accumulation within the cuffed vessel segment.

[00455] Briefly, male ApoE3 Leiden mice (age 12 weeks) are fed a mildly
hypercholesterolemic diet for 3 weeks prior to surgical cuff placement. After 3 weeks mice
are divided in 3 groups, matched for plasma cholesterol levels. The mice either receive daily
(from day-1 on) a control gavage solution or a gavage solution containing test compound
(typically at a concentration of 30 mg/kg). On day 0 surgery is performed, i.e. a non-
constricting cuff (2-3 mm in length) is placed around both the femoral arteries of the mice.
Mice are sacrificed after 2 days for analysis of monocyte adhesion and infiltration, and
additional mice are sacrificed after 2 weeks for histomorphometric analysis to quantify the
(inhibition of) accelerated atherosclerotic lesions and neointima formation.

Example 9: Clinical Cardiovascular and Metabolic Disease Assessments

[00456] Anti-obesity assay. The ability of compounds to cause weight loss may be
assessed in obese human subjects with body mass index (BMI) ≥30 kg/m². Doses of inhibitor
are administered sufficient to result in an increase of ≥15% in HDL cholesterol levels. BMI
and body fat distribution, defined as waist (W) to hip (H) ratio (WHR), are monitored during
the course of the 3-6 month studies, and the results for treatment groups compared to those
receiving placebo.

[00457] Diagnostic methods for glucose and insulin disorders. Oral glucose
tolerance testing (OGTT). During a glucose tolerance test, which may be used to diagnose
diabetes mellitus, a fasted subject takes a 75 gram oral dose of glucose. Blood glucose levels
are then measured over the following 2 hours. Interpretation is based on WHO guidelines,
but glycemia greater than or equal to 11.1mmol/L at 2 hours or greater than or equal to
7.0mmol/L fasting is diagnostic for diabetes mellitus. OGTT can be normal or mildly
abnormal in simple insulin resistance. Often, there are raised glucose levels in the early
measurements, reflecting the loss of a postprandial (after the meal) peak in insulin
production. Extension of the testing (for several more hours) may reveal a hypoglycemic
"dip", which is a result of an overshoot in insulin production after the failure of the
physiologic postprandial insulin response.

[00458] Hyperinsulinemic euglycemic clamp. The standard for investigating and
quantifying insulin resistance is the "hyperinsulinemic euglycemic clamp," so called because
it measures the amount of glucose necessary to compensate for an increased insulin level without causing hypoglycemia. The procedure takes about 2 hours. Through a peripheral vein, insulin is infused at 10-120 mU per m² per minute. In order to compensate for the insulin infusion, glucose 20% is infused to maintain blood sugar levels between 5 and 5.5 mmol/l. The rate of glucose infusion is determined by checking the blood sugar levels every 5-10 minutes. Low dose insulin infusions are more useful for assessing the response of the liver whereas high dose insulin infusions are useful for assessing peripheral (i.e. muscle and fat) insulin action. The rate of glucose infusion during the last 30 minutes of the test determines insulin sensitivity. If high levels (7.5 mg/min or higher) are required, the subject is insulin-sensitive. Very low levels (4.0 mg/min or lower) indicate that the body is resistant to insulin action. Levels between 4.0 and 7.5 mg/min are not definitive and suggest "impaired glucose tolerance," an early sign of insulin resistance.

[00459] Given the complicated nature of the "clamp" technique (and the potential dangers of hypoglycemia in some subjects), alternatives have been sought to simplify the measurement of insulin resistance. The first was the Homeostatic Model Assessment (HOMA) [Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412-9], and a more recent method is QUICKI (quantitative insulin sensitivity check index). Both employ fasting insulin and glucose levels to calculate insulin resistance, and both correlate reasonably with the results of clamping studies.

[00460] Using a fasting blood sample, insulin resistance (IR) is quantified using the following formula:

\[ IR = \frac{Glucose \ (mg/dl) \times Insulin \ (\mu U/ml)}{405} \]

[00461] In this equation, one should use the constant 22.5 instead of 405 if the glucose is reported in mmol/l. This model correlates well with estimates using the euglycemic clamp method.


Example 10: Analysis of biomarkers in clinical samples.

[00463] Patients with low HDL-C and elevated TG levels, with or without concomitant lipid-lowering therapy (e.g., statins, bile acid sequestrants, or cholesterol absorption inhibitors), are treated with a compound as described herein, administered orally once daily for 6 weeks. A fasting lipid panel (total cholesterol, HDL-C, LDL-C, TG), CRP and general laboratory parameters (CBC, general chemistry panel) are assessed at baseline, every two weeks during dosing and 4 weeks after the end of dosing. At Week 1, patients have a general chemistry panel assessed. Weight, and waist and hip circumference are assessed at each visit, other than Week 1. Lipid/metabolic, inflammatory, and prothrombotic biomarkers are assessed at Baseline, Week 2, Week 4, Week 6 and Follow-up. Urinalysis and coagulation parameters are assessed at baseline and at the end of dosing.

Example 11: Cancer models

[00464] Proliferation assay. Human non-small cell lung carcinoma cells A549 (ATCC# CCL-185), are grown at 37°C +/- 0.5°C and 5% CO₂ in DMEM supplemented with 10% FBS, 2 mM glutamine, 1% penicillin, and 1% streptomycin. Anti-proliferation assays are performed in 384-well plates. 6.6 μL of 10x stock compound solutions is added to 40 μL of culture media in assay wells. The tumor cells are liberated from the culture flask using a solution of 0.25% trypsin. Cells are diluted in culture media such that 3000 or 6000 cells are delivered in 20 μL of media into each assay well. Assay plates are incubated for 72-80 hours at 37°C +/-0.5°C with 5% CO₂. Twenty microliters of 20% Alamar Blue warmed to 37°C +/- 0.5°C is added to each assay well following the incubation period. Alamar Blue metabolism is quantified by the amount of fluorescence intensity 3.5-5.0 hours after addition. Quantification, using an LJI Analyst AD reader (LJI Biosystems), is taken in the middle of the well with high attenuation, a 100 msec read time, an excitation filter at 530 nm, and an emission filter at 575 nm. For some experiments, quantification is performed using a Wallac Victor2 reader. Measurements are taken at the top of the well with stabilized energy lamp.
control; a 100 msec read time, an excitation filter at 530 nm, and an emission filter at 590 nm. No significant differences between plate readers are measured.

[00465] The percent inhibition (% I) for each well is calculated using the following formula:

\[ \% \, I = 1 - \frac{([\text{avg. untreated wells}-\text{treated well}])/([\text{avg. untreated wells}])}{x \, 100} \]

[00466] The average untreated well value (avg. untreated wells) is the arithmetic mean of 40 wells from the same assay plate treated with vehicle alone. Negative inhibition values result from local variations in treated wells as compared to untreated wells.

[00467] The anti-cancer effect that can be demonstrated with the tumor cell lines referred to herein can be similarly demonstrated using other cancer cell lines, such as, for example, NSC lung carcinoma, MCF7 mammary adenocarcinoma, PA-1 ovarian teratocarcinoma, HT29 colorectal adenocarcinoma, H1299 large cell carcinoma, U-2 OS osteogenic sarcoma, U-373 MG glioblastoma, U-118 MG glioblastoma, U-138 MG glioblastoma, LN-229 glioma, Hep-3B hepatocellular carcinoma, BT-549 mammary carcinoma, T-24 bladder cancer, C-33A cervical carcinoma, H1-3 metastatic cervical carcinoma, SiHa squamous cervical carcinoma, CaSki epidermoid cervical carcinoma, NCI-H292 mucoepidermoid lung carcinoma, NCI-2030, non small cell lung carcinoma, HeLa, epithelial cervical adenocarcinoma, KB epithelial mouth carcinoma, HT1080 epithelial fibrosarcoma, Saos-2 epithelial osteogenic sarcoma, PC3 epithelial prostate adenocarcinoma, SW480 colorectal carcinoma, CCL-228, MS-751 epidermoid cervical carcinoma, LOX IMVI melanoma, MALME-3M melanoma, M14 melanoma, SK-MEL-2 melanoma, SK-MEL-28 melanoma, SK-MEL-5 melanoma, UACC-257 melanoma, or UACC-62 melanoma cell lines. The specificity can be tested by using cells such as NHLF lung fibroblasts, NHDF dermal fibroblasts, HMEC mammary epithelial cells, PrEC prostate epithelial cells, HRE renal epithelial cells, NHBE bronchial epithelial cells, CoSmC Colon smooth muscle cells, CoEC colon endothelial cells, NHEK epidermal kerinoocytes, and bone marrow cells as control cells.

[00468] As will be recognized by those of skill in the art, many more cancer cell lines, such as those available from American Type Culture Collection (ATCC) (P.O. Box 1549 Manassas, VA 20108, USA), can be used similarly.
Example 12

Table 3 lists compounds of the invention prepared using the methods of Examples 1-5 or methods previously disclosed. Each compound was analyzed by LCMS and displayed the expected molecular ion. Each of the compounds in Table 3 was tested in the TNFa ELISA assay (Example 5) and found to have activity therein, with some compounds having IC$_{50}$s below 10 µM in this assay.

<table>
<thead>
<tr>
<th>No.</th>
<th>Structure</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>N-(5-tert-butyl)-2-methoxy-3-(methylsulfonamido)phenyl)-2-(hydroxyimino)-2-(4-(2-(pyrrolidin-1-yl)pyrimidin-4-ylamino)naphthalen-1-yl)acetamide</td>
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<td>N-(5-tert-butyl)-2-methoxy-3-(methylsulfonamido)phenyl)-2-(4-(3-cyanopropoxy)naphthalen-1-yl)-2-oxoacetamide</td>
</tr>
<tr>
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<tr>
<td>5</td>
<td><img src="image5.png" alt="Structure" /></td>
<td>N-(5-tert-butyl)-2-methoxy-3-(methylsulfonamido)phenyl)-2-(4-(2-(2-methoxyethoxy)ethoxy)naphthalen-1-yl)-2-oxoacetamide</td>
</tr>
<tr>
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<td><img src="image5" alt="Structure" /></td>
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</tr>
<tr>
<td>-----</td>
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</tr>
<tr>
<td>14</td>
<td><img src="image1.png" alt="Structure 14" /></td>
<td>N-(3-tert-butyl-1-m-tolyl-1H-pyrazol-5-yl)-2-oxo-2-(4-(2-(pyrrolidin-1-yl)pyrimidin-4-ylamino)naphthalen-1-yl)acetamide</td>
</tr>
<tr>
<td>15</td>
<td><img src="image2.png" alt="Structure 15" /></td>
<td>N-(3-cyano-5-morpholinophenyl)-2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamide</td>
</tr>
<tr>
<td>16</td>
<td><img src="image3.png" alt="Structure 16" /></td>
<td>N-(3-morpholino-5-(trifluoromethyl)phenyl)-2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamide</td>
</tr>
<tr>
<td>17</td>
<td><img src="image4.png" alt="Structure 17" /></td>
<td>2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxo-N-(3-(piperidin-1-yl)-5-(trifluoromethyl)phenyl)acetamide</td>
</tr>
<tr>
<td>18</td>
<td><img src="image5.png" alt="Structure 18" /></td>
<td>2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxo-N-(3-(pyrrolidin-1-yl)-5-(trifluoromethyl)phenyl)acetamide</td>
</tr>
<tr>
<td>19</td>
<td><img src="image6.png" alt="Structure 19" /></td>
<td>N-(3-bromo-5-tert-butyl-2-methoxyphenyl)-2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamide</td>
</tr>
<tr>
<td>20</td>
<td><img src="image7.png" alt="Structure 20" /></td>
<td>N-(5-tert-butyl-2-methoxyphenyl)-2-oxo-2-(4-(2-(pyrrolidin-1-yl)pyrimidin-4-ylamino)naphthalen-1-yl)acetamide</td>
</tr>
<tr>
<td>No.</td>
<td>Structure</td>
<td>Name</td>
</tr>
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</tr>
<tr>
<td>21</td>
<td><img src="image1.png" alt="Structure 21" /></td>
<td>5-tert-butyl-2-methoxy-3-(2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamido)-N-(oxazol-2-ylmethyl)benzamide</td>
</tr>
<tr>
<td>22</td>
<td><img src="image2.png" alt="Structure 22" /></td>
<td>5-tert-butyl-2-methoxy-N-((5-methylfuran-2-yl)methyl)-3-(2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamido)benzamide</td>
</tr>
<tr>
<td>23</td>
<td><img src="image3.png" alt="Structure 23" /></td>
<td>N-(3-cyano-5-(piperidin-1-yl)phenyl)-2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamide</td>
</tr>
<tr>
<td>24</td>
<td><img src="image4.png" alt="Structure 24" /></td>
<td>N-(3-cyano-5-(pyrrolidin-1-yl)phenyl)-2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamide</td>
</tr>
<tr>
<td>25</td>
<td><img src="image5.png" alt="Structure 25" /></td>
<td>N-(5-tert-butyl-3-cyano-2-methoxyphenyl)-2-oxo-2-(4-(2-(2,2,6,6-tetramethylmorpholino)ethoxy)naphthalen-1-yl)acetamide</td>
</tr>
<tr>
<td>26</td>
<td><img src="image6.png" alt="Structure 26" /></td>
<td>2-(4-(2-(8-oxa-3-aza-bicyclo[3.2.1]octan-3-yl)ethoxy)naphthalen-1-yl)-N-(5-tert-butyl-2-methoxy-3-(methylsulfonamido)phenyl)-2-oxoacetamide</td>
</tr>
<tr>
<td>27</td>
<td><img src="image7.png" alt="Structure 27" /></td>
<td>2-(4-(2-(8-oxa-3-aza-bicyclo[3.2.1]octan-3-yl)ethoxy)naphthalen-1-yl)-N-(5-tert-butyl-3-cyano-2-methoxyphenyl)-2-oxoacetamide</td>
</tr>
<tr>
<td>No.</td>
<td>Structure</td>
<td>Name</td>
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<tr>
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</tr>
<tr>
<td>28</td>
<td><img src="image" alt="Structure 28" /></td>
<td>N-(5-tert-butyl-2-methoxy-3-(1H-tetrazol-5-yl)phenyl)-2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamide</td>
</tr>
<tr>
<td>29</td>
<td><img src="image" alt="Structure 29" /></td>
<td>N-(5-tert-butyl-2-methoxy-3-(methylsulfonamido)phenyl)-2-(4-(2-(4-methylpiperazin-1-yl)pyrimidin-4-ylamino)naphthalen-1-yl)-2-oxoacetamide</td>
</tr>
<tr>
<td>30</td>
<td><img src="image" alt="Structure 30" /></td>
<td>2-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-2-oxo-N-(4-(2,2,6,6-tetramethylmorpholino)ethoxy)naphthalen-1-yl)acetamide</td>
</tr>
<tr>
<td>31</td>
<td><img src="image" alt="Structure 31" /></td>
<td>N-(4-(2-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)ethoxy)naphthalen-1-yl)-2-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-2-oxoacetamide</td>
</tr>
<tr>
<td>32</td>
<td><img src="image" alt="Structure 32" /></td>
<td>N-(5-tert-butyl-2-methoxy-3-(methylsulfonamido)phenyl)-2-oxo-2-(4-(2,2,6,6-tetramethylmorpholino)pyrimidin-4-ylamino)naphthalen-1-yl)acetamide</td>
</tr>
<tr>
<td>33</td>
<td><img src="image" alt="Structure 33" /></td>
<td>N-(5-tert-butyl-2-methoxy-3-(methylsulfonamido)phenyl)-2-oxo-2-(4-(2-(piperazin-1-yl)pyrimidin-4-ylamino)naphthalen-1-yl)acetamide</td>
</tr>
<tr>
<td>34</td>
<td><img src="image" alt="Structure 34" /></td>
<td>N-(5-tert-butyl-2-methoxy-3-(methylsulfonamido)phenyl)-2-oxo-2-(4-(4-(piperazin-1-yl)pyrimidin-2-ylamino)naphthalen-1-yl)acetamide</td>
</tr>
<tr>
<td>35</td>
<td><img src="image" alt="Structure 35" /></td>
<td>N-(5-tert-butyl-3-cyano-2-methoxyphenyl)-2-oxo-2-(4-(2,2,6,6-tetramethylmorpholino)pyrimidin-4-ylamino)naphthalen-1-yl)acetamide</td>
</tr>
<tr>
<td>No.</td>
<td>Structure</td>
<td>Name</td>
</tr>
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</tr>
<tr>
<td>36</td>
<td><img src="image1" alt="Structure" /></td>
<td>2-(4-(2-(8-oxa-3-aza-bicyclo[3.2.1]octan-3-yl)pyrimidin-4-ylamino)naphthalen-1-yl)-N-(5-tert-butyl-3-cyano-2-methoxyphenyl)-2-oxoacetamide</td>
</tr>
<tr>
<td>37</td>
<td><img src="image2" alt="Structure" /></td>
<td>N-(5-tert-butyl-3-cyano-2-methoxyphenyl)-2-(4-(2-(3,3-dimethylbutylamino)pyridin-4-ylamino)naphthalen-1-yl)-2-oxoacetamide</td>
</tr>
<tr>
<td>38</td>
<td><img src="image3" alt="Structure" /></td>
<td>N-(5-tert-butyl-3-cyano-2-methoxyphenyl)-2-(4-(2-(2-(2,6-dimethylpiperidin-1-yl)ethylamino)pyridin-4-ylamino)naphthalen-1-yl)-2-oxoacetamide</td>
</tr>
<tr>
<td>39</td>
<td><img src="image4" alt="Structure" /></td>
<td>N-(5-tert-butyl-3-cyano-2-methoxyphenyl)-2-oxo-2-(4-(pyridin-4-ylamino)naphthalen-1-yl)acetamide</td>
</tr>
<tr>
<td>40</td>
<td><img src="image5" alt="Structure" /></td>
<td>N-(5-tert-butyl-2-methoxy-3-(methylsulfonamido)phenyl)-2-(4-(2-(3,5-dimethylpiperazin-1-yl)pyrimidin-4-ylamino)naphthalen-1-yl)-2-oxoacetamide</td>
</tr>
<tr>
<td>41</td>
<td><img src="image6" alt="Structure" /></td>
<td>N-(5-tert-butyl-2-methoxy-3-(methylsulfonamido)phenyl)-2-(4-(4-(3,5-dimethylpiperazin-1-yl)pyrimidin-2-ylamino)naphthalen-1-yl)-2-oxoacetamide</td>
</tr>
<tr>
<td>42</td>
<td><img src="image7" alt="Structure" /></td>
<td>N-(5-tert-Butyl-3-methanesulfonylamino-2-methoxyphenyl)-2-(4-[2-(10-oxa-4-azatricyclo[5.2.1.0^2,6]dec-4-yl)-ethoxy]-naphthalen-1-yl)-2-oxoacetamide</td>
</tr>
<tr>
<td>No.</td>
<td>Structure</td>
<td>Name</td>
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</tr>
<tr>
<td>43</td>
<td><img src="image" alt="Structure" /></td>
<td>N-(5-tert-Butyl-3-cyano-2-methoxy-phenyl)-2-{4-[2-(10-oxa-4-aza-tricyclo[5.2.1.0^2.6]dec-4-yl)-ethoxy]-naphthalen-1-yl}-2-oxoacetamide</td>
</tr>
<tr>
<td>44</td>
<td><img src="image" alt="Structure" /></td>
<td>N-(5-tert-butyl-2-methoxy-3-(methylsulfonamido)phenyl)-2-(4-(2-(3,3-dimethylbutylamino)pyridin-4-ylamino)naphthalen-1-yl)-2-oxoacetamide</td>
</tr>
<tr>
<td>45</td>
<td><img src="image" alt="Structure" /></td>
<td>2-(4-(2-(3,8-diaza-bicyclo[3.2.1]octan-8-yl)pyrimidin-4-ylamino)naphthalen-1-yl)-N-(5-tert-butyl-2-methoxy-3-(methylsulfonamido)phenyl)-2-oxoacetamide</td>
</tr>
<tr>
<td>46</td>
<td><img src="image" alt="Structure" /></td>
<td>2-(4-(4-(3,8-diaza-bicyclo[3.2.1]octan-8-yl)pyrimidin-2-ylamino)naphthalen-1-yl)-N-(5-tert-butyl-2-methoxy-3-(methylsulfonamido)phenyl)-2-oxoacetamide</td>
</tr>
<tr>
<td>47</td>
<td><img src="image" alt="Structure" /></td>
<td>5-tert-butyl-N-cyclopropyl-2-methoxy-3-(2-oxo-2-(4-(pyridin-4-ylamino)naphthalen-1-yl)acetamido)benzamide</td>
</tr>
<tr>
<td>48</td>
<td><img src="image" alt="Structure" /></td>
<td>5-tert-butyl-2-methoxy-3-(2-oxo-2-(4-(pyridin-4-ylamino)naphthalen-1-yl)acetamido)benzamide</td>
</tr>
<tr>
<td>No.</td>
<td>Structure</td>
<td>Name</td>
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</tr>
<tr>
<td>49</td>
<td><img src="image1" alt="Structure" /></td>
<td>2-(4-(2-(bis(2-hydroxyethyl)amino)ethoxy)-naphthalen-1-yl)-N-(5-tert-butyl-2-methoxy-3-(methylsulfonamido)phenyl)-2-oxoacetamide</td>
</tr>
<tr>
<td>50</td>
<td><img src="image2" alt="Structure" /></td>
<td>4-(2-(4-(2-(5-tert-butyl-2-methoxy-3-(methylsulfonamido)-phenylamino)-2-oxoacetyl)naphthalen-1-yl)oxy)ethyl)morpholine 4-oxide</td>
</tr>
<tr>
<td>51</td>
<td><img src="image3" alt="Structure" /></td>
<td>N-(5-tert-butyl-3-cyano-2-methoxyphenyl)-2-(4-(2-methylpyridin-4-yl)naphthalen-1-yl)-2-oxoacetamide</td>
</tr>
<tr>
<td>52</td>
<td><img src="image4" alt="Structure" /></td>
<td>N-(5-tert-butyl-3-cyano-2-methoxyphenyl)-2-oxo-2-(4-(pyridin-4-yl)naphthalen-1-yl)acetamide</td>
</tr>
<tr>
<td>53</td>
<td><img src="image5" alt="Structure" /></td>
<td>N-(5-tert-butyl-3-cyano-2-methoxyphenyl)-2-oxo-2-(4-(pyridin-3-yl)naphthalen-1-yl)acetamide</td>
</tr>
<tr>
<td>54</td>
<td><img src="image6" alt="Structure" /></td>
<td>N-(5-tert-butyl-3-cyano-2-methoxyphenyl)-2-(4-(6-methoxypyridin-3-yl)naphthalen-1-yl)-2-oxoacetamide</td>
</tr>
<tr>
<td>No.</td>
<td>Structure</td>
<td>Name</td>
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</tr>
<tr>
<td>55</td>
<td><img src="image" alt="Structure 55" /></td>
<td>N-(5-tert-butyl-3-cyano-2-methoxyphenyl)-2-(4-(6-fluoropyridin-3-yl)naphthalen-1-yl)-2-oxoacetamide</td>
</tr>
<tr>
<td>56</td>
<td><img src="image" alt="Structure 56" /></td>
<td>N-(5-tert-butyl-3-cyano-2-methoxyphenyl)-2-(4-(2-(4-methylpiperazin-1-yl)pyridin-4-yl)naphthalen-1-yl)-2-oxoacetamide</td>
</tr>
<tr>
<td>57</td>
<td><img src="image" alt="Structure 57" /></td>
<td>2-(4-(2-(bis(2-methoxyethyl)amino)ethoxy)naphthalen-1-yl)-N-(5-tert-butyl-2-methoxy-3-(methylsulfonamido)phenyl)-2-oxoacetamide</td>
</tr>
<tr>
<td>58</td>
<td><img src="image" alt="Structure 58" /></td>
<td>N-(5-tert-butyl-3-cyano-2-methoxyphenyl)-2-(4-(6-(methylamino)pyridin-3-yl)naphthalen-1-yl)-2-oxoacetamide</td>
</tr>
<tr>
<td>59</td>
<td><img src="image" alt="Structure 59" /></td>
<td>N-(5-tert-butyl-3-cyano-2-methoxyphenyl)-2-(4-(6-(3,3-dimethylbutylamino)pyridin-3-yl)naphthalen-1-yl)-2-oxoacetamide</td>
</tr>
<tr>
<td>60</td>
<td><img src="image" alt="Structure 60" /></td>
<td>N-(5-tert-butyl-2-methoxy-3-(4-methylpiperazine-1-sulfonamido)phenyl)-2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamide</td>
</tr>
<tr>
<td>No.</td>
<td>Structure</td>
<td>Name</td>
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</tr>
<tr>
<td>61</td>
<td><img src="image" alt="Structure 61" /></td>
<td>N-(3-tert-butyl-5-((4-methylpiperazin-1-yl)methyl)phenyl)-2-oxo-2-(4-(pyridin-3-yl)naphthalen-1-yl)acetamide</td>
</tr>
<tr>
<td>62</td>
<td><img src="image" alt="Structure 62" /></td>
<td>N-(5-tert-butyl-3-cyano-2-methoxyphenyl)-2-oxo-2-(4-(2-(pyrrolidin-1-yl)pyrimidin-4-ylamino)naphthalen-1-yl)acetamide</td>
</tr>
<tr>
<td>63</td>
<td><img src="image" alt="Structure 63" /></td>
<td>(Z)-2-(4-(2-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)ethoxy)naphthalen-1-yl)-N-(5-tert-butyl-3-cyano-2-methoxyphenyl)-2-(hydroxyimino)acetamide</td>
</tr>
<tr>
<td>64</td>
<td><img src="image" alt="Structure 64" /></td>
<td>(Z)-2-(4-(2-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)pyrimidin-4-ylamino)naphthalen-1-yl)-N-(5-tert-butyl-3-cyano-2-methoxyphenyl)-2-(hydroxyimino)acetamide</td>
</tr>
<tr>
<td>65</td>
<td><img src="image" alt="Structure 65" /></td>
<td>N-(3-tert-butyl-5-((4-methylpiperazin-1-yl)methyl)phenyl)-2-oxo-2-(4-((methylamino)pyridin-3-yl)naphthalen-1-yl)acetamide</td>
</tr>
<tr>
<td>66</td>
<td><img src="image" alt="Structure 66" /></td>
<td>N-(3-tert-butyl-5-((4-methylpiperazin-1-yl)methyl)phenyl)-2-(4-(2-methylpyridin-4-yl)naphthalen-1-yl)-2-oxoacetamide</td>
</tr>
<tr>
<td>No.</td>
<td>Structure</td>
<td>Name</td>
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</tr>
<tr>
<td>67</td>
<td><img src="image" alt="Structure" /></td>
<td>2-(4-(2-(1,4'-bipiperidin-1'-yl)pyrimidin-4-ylamino)naphthalen-1-yl)-N-(5-tert-butyl-2-methoxy-3-(methylsulfonamido)phenyl)-2-oxoacetamide</td>
</tr>
<tr>
<td>68</td>
<td><img src="image" alt="Structure" /></td>
<td>(S)-N-(5-tert-butyl-2-methoxy-3-(methylsulfonamido)phenyl)-2-oxo-2-(4-(2-(pyrroloidin-1-ylmethyl)pyrroloidin-1-yl)pyrimidin-4-ylamino)naphthalen-1-yl)acetamide</td>
</tr>
<tr>
<td>69</td>
<td><img src="image" alt="Structure" /></td>
<td>(R)-N-(5-tert-butyl-2-methoxy-3-(methylsulfonamido)phenyl)-2-(4-(2-(3-(dimethylamino)pyrroloidin-1-yl)pyrimidin-4-ylamino)naphthalen-1-yl)-2-oxoacetamide</td>
</tr>
<tr>
<td>70</td>
<td><img src="image" alt="Structure" /></td>
<td>N-(5-tert-butyl-2-methoxy-3-(methylsulfonamido)phenyl)-2-(4-(2-(4-isopropylpiperazin-1-yl)pyrimidin-4-ylamino)naphthalen-1-yl)-2-oxoacetamide</td>
</tr>
<tr>
<td>71</td>
<td><img src="image" alt="Structure" /></td>
<td>N-(5-tert-butyl-2-methoxy-3-(methylsulfonamido)phenyl)-2-(4-(2-(4-methyl-1,4-diazezan-1-yl)pyrimidin-4-ylamino)naphthalen-1-yl)-2-oxoacetamide</td>
</tr>
<tr>
<td>72</td>
<td><img src="image" alt="Structure" /></td>
<td>N-(5-tert-butyl-2-methoxy-3-(methylsulfonamido)phenyl)-2-(4-(2-(4-morpholinopiperidin-1-yl)pyrimidin-4-ylamino)naphthalen-1-yl)-2-oxoacetamide</td>
</tr>
<tr>
<td>No.</td>
<td>Structure</td>
<td>Name</td>
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</tr>
<tr>
<td>73</td>
<td><img src="image1" alt="Structure" /></td>
<td>N-(5-tert-butyl-2-methoxy-3-((methylsulfonamido)phenyl)-2-(4-((2-4((cyclopropylmethyl)piperazin-1-yl)pyrimidin-4-ylamino)naphthalen-1-yl)-2-oxoacetamide</td>
</tr>
<tr>
<td>74</td>
<td><img src="image2" alt="Structure" /></td>
<td>N-(5-tert-butyl-3-cyano-2-methoxyphenyl)-2-(4-((2-4((cyclopropylmethyl)piperazin-1-yl)pyrimidin-4-ylamino)naphthalen-1-yl)-2-oxoacetamide</td>
</tr>
<tr>
<td>75</td>
<td><img src="image3" alt="Structure" /></td>
<td>2-(4-((2-4(1,4'-bipiperidin-1'-yl)pyrimidin-4-ylamino)naphthalen-1-yl)-N-(5-tert-butyl-3-cyano-2-methoxyphenyl)-2-oxoacetamide</td>
</tr>
<tr>
<td>76</td>
<td><img src="image4" alt="Structure" /></td>
<td>(S)-N-(5-tert-butyl-3-cyano-2-methoxyphenyl)-2-oxo-2-(4-((2-4(2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl)pyrimidin-4-ylamino)naphthalen-1-yl)acetamide</td>
</tr>
<tr>
<td>77</td>
<td><img src="image5" alt="Structure" /></td>
<td>(R)-N-(5-tert-butyl-3-cyano-2-methoxyphenyl)-2-(4-((2-(3-(dimethylamino)pyrrolidin-1-yl)pyrimidin-4-ylamino)naphthalen-1-yl)-2-oxoacetamide</td>
</tr>
<tr>
<td>78</td>
<td><img src="image6" alt="Structure" /></td>
<td>N-(5-tert-butyl-3-cyano-2-methoxyphenyl)-2-(4-((2-4-isopropylpiperazin-1-yl)pyrimidin-4-ylamino)naphthalen-1-yl)-2-oxoacetamide</td>
</tr>
<tr>
<td>No.</td>
<td>Structure</td>
<td>Name</td>
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</tr>
<tr>
<td>79</td>
<td><img src="image1" alt="Structure" /></td>
<td>N-(5-tert-butyl-3-cyano-2-methoxyphenyl)-2-(4-(2-(4-methyl-1,4-diazepan-1-yl)pyrimidin-4-ylamino)naphthalen-1-yl)-2-oxoacetamide</td>
</tr>
<tr>
<td>80</td>
<td><img src="image2" alt="Structure" /></td>
<td>N-(5-tert-butyl-3-cyano-2-methoxyphenyl)-2-(4-(2-(4-morpholinopiperidin-1-yl)pyrimidin-4-ylamino)naphthalen-1-yl)-2-oxoacetamide</td>
</tr>
<tr>
<td>81</td>
<td><img src="image3" alt="Structure" /></td>
<td>(E)-2-(4-(2-(8-oxa-3-aza-bicyclo[3.2.1]octan-3-yl)ethoxy)naphthalen-1-yl)-N-(5-tert-butyl-3-cyano-2-methoxyphenyl)-2-(hydroxyimino)acetamide</td>
</tr>
<tr>
<td>82</td>
<td><img src="image4" alt="Structure" /></td>
<td>(E)-2-(4-(2-(8-oxa-3-aza-bicyclo[3.2.1]octan-3-yl)pyrimidin-4-ylamino)naphthalen-1-yl)-N-(5-tert-butyl-3-cyano-2-methoxyphenyl)-2-(hydroxyimino)acetamide</td>
</tr>
<tr>
<td>83</td>
<td><img src="image5" alt="Structure" /></td>
<td>N-(5-tert-butyl-2-methoxy-3-(methylsulfonamido)phenyl)-2-oxo-2-(4-(2-(2,2,6,6-tetramethylmorpholinio)ethoxy)naphthalen-1-yl)acetamide</td>
</tr>
<tr>
<td>84</td>
<td><img src="image6" alt="Structure" /></td>
<td>N-(5-tert-butyl-2-methoxyphenyl)-2-(4-(2-(cyclopropylamino)pyridin-4-ylamino)naphthalen-1-yl)-2-oxoacetamide</td>
</tr>
<tr>
<td>No.</td>
<td>Structure</td>
<td>Name</td>
</tr>
<tr>
<td>-----</td>
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<td>------</td>
</tr>
<tr>
<td>85</td>
<td><img src="image1" alt="Structure" /></td>
<td>N-(5-tert-butyl-2-methoxyphenyl)-2-(4-(2-(3,3-dimethylbutylamino)pyridin-4-ylamino)naphthalen-1-yl)-2-oxoacetamide</td>
</tr>
<tr>
<td>86</td>
<td><img src="image2" alt="Structure" /></td>
<td>N-(5-tert-butyl-2-methoxyphenyl)-2-(4-(2-(2,6-dimethylpiperidin-1-yl)ethylamino)pyridin-4-ylamino)naphthalen-1-yl)-2-oxoacetamide</td>
</tr>
<tr>
<td>87</td>
<td><img src="image3" alt="Structure" /></td>
<td>N-(5-tert-butyl-2-methoxyphenyl)-2-(4-(2-methylpyridin-4-ylamino)naphthalen-1-yl)-2-oxoacetamide</td>
</tr>
<tr>
<td>88</td>
<td><img src="image4" alt="Structure" /></td>
<td>N-(5-tert-butyl-3-cyano-2-methoxyphenyl)-2-(4-(2-methylpyridin-4-ylamino)naphthalen-1-yl)-2-oxoacetamide</td>
</tr>
<tr>
<td>89</td>
<td><img src="image5" alt="Structure" /></td>
<td>2-(4-(2-(benzylamino)pyridin-4-ylamino)naphthalen-1-yl)-N-(5-tert-butyl-2-methoxyphenyl)-2-oxoacetamide</td>
</tr>
<tr>
<td>90</td>
<td><img src="image6" alt="Structure" /></td>
<td>(S)-N-(5-tert-butyl-2-methoxyphenyl)-2-oxo-2-(4-(2-(1-phenylethylamino)pyridin-4-ylamino)naphthalen-1-yl)acetamide</td>
</tr>
<tr>
<td>No.</td>
<td>Structure</td>
<td>Name</td>
</tr>
<tr>
<td>-----</td>
<td>-----------</td>
<td>------</td>
</tr>
<tr>
<td>91</td>
<td><img src="91.png" alt="Structure" /></td>
<td>2-(4-(2-(benzylamino)pyridin-4-ylamino)naphthalen-1-yl)-N-(5-tert-buty1-3-cyano-2-methoxyphenyl)-2-oxoacetamide</td>
</tr>
<tr>
<td>92</td>
<td><img src="92.png" alt="Structure" /></td>
<td>(S)-N-(5-tert-butyl-3-cyano-2-methoxyphenyl)-2-oxo-2-(4-(2-(1-phenylethylamino)pyridin-4-ylamino)naphthalen-1-yl)acetamide</td>
</tr>
<tr>
<td>93</td>
<td><img src="93.png" alt="Structure" /></td>
<td>N-(5-tert-butyl-2-methoxy-3-(piperazine-1-carbonyl)phenyl)-2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamide</td>
</tr>
<tr>
<td>94</td>
<td><img src="94.png" alt="Structure" /></td>
<td>N-(5-tert-butyl-2-methoxy-3-(4-methylpiperazine-1-carbonyl)phenyl)-2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamide</td>
</tr>
<tr>
<td>95</td>
<td><img src="95.png" alt="Structure" /></td>
<td>N-(5-tert-butyl-3-(4-isopropylpiperazine-1-carbonyl)-2-methoxyphenyl)-2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamide</td>
</tr>
<tr>
<td>96</td>
<td><img src="96.png" alt="Structure" /></td>
<td>N-(5-tert-butyl-3-(4-(cyclopropylmethyl)piperazine-1-carbonyl)-2-methoxyphenyl)-2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamide</td>
</tr>
<tr>
<td>No.</td>
<td>Structure</td>
<td>Name</td>
</tr>
<tr>
<td>-----</td>
<td>-----------</td>
<td>------</td>
</tr>
<tr>
<td>97</td>
<td><img src="image1.png" alt="Structure Image" /></td>
<td>N-(5-tert-butyl-3-(4-(2-hydroxyethyl)piperazine-1-carbonyl)-2-methoxyphenyl)-2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamide</td>
</tr>
<tr>
<td>98</td>
<td><img src="image2.png" alt="Structure Image" /></td>
<td>N-(5-tert-butyl-2-methoxy-3-(4-methyl-1,4-diazepane-1-carbonyl)phenyl)-2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamide</td>
</tr>
<tr>
<td>99</td>
<td><img src="image3.png" alt="Structure Image" /></td>
<td>(R)-N-(5-tert-butyl-3-(3-(dimethylamino)pyrrolidine-1-carbonyl)-2-methoxyphenyl)-2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamide</td>
</tr>
<tr>
<td>100</td>
<td><img src="image4.png" alt="Structure Image" /></td>
<td>5-tert-butyl-2-methoxy-N-(1-methylpiperidin-4-yl)-3-(2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamido)benzamide</td>
</tr>
<tr>
<td>101</td>
<td><img src="image5.png" alt="Structure Image" /></td>
<td>(S)-N-(5-tert-butyl-3-cyano-2-methoxyphenyl)-2-oxo-2-(4-(2-phenylethylamino)pyrimidin-4-ylamino)naphthalen-1-yl)acetamide</td>
</tr>
<tr>
<td>102</td>
<td><img src="image6.png" alt="Structure Image" /></td>
<td>N-(3-(3,8-diazabicyclo[3.2.1]octane-3-carbonyl)-5-tert-butyl-2-methoxyphenyl)-2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamide</td>
</tr>
<tr>
<td>No.</td>
<td>Structure</td>
<td>Name</td>
</tr>
<tr>
<td>-----</td>
<td>-----------</td>
<td>------</td>
</tr>
<tr>
<td>103</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>N-(5-tert-butyl-3-cyano-2-methoxyphenyl)-2-(4-(2-cyclopropylamino)pyrimidin-4-ylamino)naphthalen-1-yl)-2-oxoacetamide</td>
</tr>
<tr>
<td>104</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>5-tert-butyl-2-methoxy-3-(2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamido)-N-(piperidin-4-yl)benzamide</td>
</tr>
<tr>
<td>105</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>5-tert-butyl-2-methoxy-3-(2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamido)-N-(piperidin-3-yl)benzamide</td>
</tr>
<tr>
<td>106</td>
<td><img src="image4.png" alt="Structure" /></td>
<td>N-(5-tert-butyl-2-methoxyphenyl)-2-(4-(2-cyclopropylamino)pyrimidin-4-ylamino)naphthalen-1-yl)-2-oxoacetamide</td>
</tr>
<tr>
<td>107</td>
<td><img src="image5.png" alt="Structure" /></td>
<td>5-tert-butyl-N-((1-ethylpyrrolidin-2-yl)methyl)-2-methoxy-3-(2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamido)benzamide</td>
</tr>
<tr>
<td>108</td>
<td><img src="image6.png" alt="Structure" /></td>
<td>5-tert-butyl-2-methoxy-N-((1-methylpiperidin-4-yl)methyl)-3-(2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamido)benzamide</td>
</tr>
<tr>
<td>No.</td>
<td>Structure</td>
<td>Name</td>
</tr>
<tr>
<td>-----</td>
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<td>------</td>
</tr>
<tr>
<td>109</td>
<td><img src="image1" alt="Structure" /></td>
<td>(S)-N-(5-tert-butyl-2-methoxy-3-(2-(pyrrolo(1-yl)methyl)pyrroldine-1-carbonyl)phenyl)-2-(4-(2-morpholinoethyl)naphthalen-1-yl)-2-oxoacetamide</td>
</tr>
<tr>
<td>110</td>
<td><img src="image2" alt="Structure" /></td>
<td>N-(5-tert-butyl-3-(2-(((dimethylamino)methyl)piperidine-1-carbonyl)-2-methoxyphenyl)-2-(4-(2-morpholinoethyl)naphthalen-1-yl)-2-oxoacetamide</td>
</tr>
<tr>
<td>111</td>
<td><img src="image3" alt="Structure" /></td>
<td>5-tert-butyl-2-methoxy-3-(2-(4-(2-morpholinoethyl)naphthalen-1-yl)-2-oxoacetamido)-N-(2-(pyrrolo(1-yl)ethyl)benzamido</td>
</tr>
<tr>
<td>112</td>
<td><img src="image4" alt="Structure" /></td>
<td>5-tert-butyl-2-methoxy-N-((1-methylpiperidine-2-yl)methyl)-3-(2-(4-(2-morpholinoethyl)naphthalen-1-yl)-2-oxoacetamido)benzamido</td>
</tr>
<tr>
<td>113</td>
<td><img src="image5" alt="Structure" /></td>
<td>3-tert-butyl-5-(2-(4-(2-morpholinoethyl)naphthalen-1-yl)-2-oxoacetamido)-N-(piperidine-3-yl)benzamido</td>
</tr>
<tr>
<td>114</td>
<td><img src="image6" alt="Structure" /></td>
<td>3-tert-butyl-5-(2-(4-(2-morpholinoethyl)naphthalen-1-yl)-2-oxoacetamido)-N-(2-(pyrrolo(1-yl)ethyl)benzamido</td>
</tr>
<tr>
<td>No.</td>
<td>Structure</td>
<td>Name</td>
</tr>
<tr>
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<td>------</td>
</tr>
<tr>
<td>115</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>3-tert-butyl-N-(2-(methylamino)ethyl)-5-(2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamido)benzamide</td>
</tr>
<tr>
<td>116</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>3-tert-butyl-N-(2-(diethylamino)ethyl)-5-(2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamido)benzamide</td>
</tr>
<tr>
<td>117</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>N-(5-tert-butyl-3-(1H-imidazol-1-yl)-2-methoxyphenyl)-2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamide</td>
</tr>
<tr>
<td>118</td>
<td><img src="image4.png" alt="Structure" /></td>
<td>N-(5-tert-butyl-2-methoxy-3-(4-methyl-1H-imidazol-1-yl)phenyl)-2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamide</td>
</tr>
<tr>
<td>119</td>
<td><img src="image5.png" alt="Structure" /></td>
<td>2-(4-(2-(8-oxa-3-aza-bicyclo[3.2.1]octan-3-yl)pyrimidin-4-ylamino)naphthalen-1-yl)-N-(5-tert-butyl-2-methoxy-3-(methylsulfonamido)phenyl)-2-oxoacetamide</td>
</tr>
<tr>
<td>120</td>
<td><img src="image6.png" alt="Structure" /></td>
<td>N-(3-azido-5-tert-butyl-2-methoxyphenyl)-2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamide</td>
</tr>
<tr>
<td>No.</td>
<td>Structure</td>
<td>Name</td>
</tr>
<tr>
<td>-----</td>
<td>-----------</td>
<td>------</td>
</tr>
<tr>
<td>121</td>
<td><img src="image121.png" alt="Structure 121" /></td>
<td>N-(5-tert-butyl-2-methoxy-3-(1H-1,2,3-triazol-1-yl)phenyl)-2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamide</td>
</tr>
<tr>
<td>122</td>
<td><img src="image122.png" alt="Structure 122" /></td>
<td>N-(5-tert-butyl-3-(4-(hydroxymethyl)-1H-1,2,3-triazol-1-yl)-2-methoxyphenyl)-2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamide</td>
</tr>
<tr>
<td>123</td>
<td><img src="image123.png" alt="Structure 123" /></td>
<td>N-(5-tert-butyl-2-methoxy-3-(4-(trimethylsilyl)-1H-1,2,3-triazol-1-yl)phenyl)-2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamide</td>
</tr>
<tr>
<td>124</td>
<td><img src="image124.png" alt="Structure 124" /></td>
<td>N-(5-tert-butyl-3-(N,N-dimethylsulfamoyl)-2-methoxyphenyl)-2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamide</td>
</tr>
<tr>
<td>125</td>
<td><img src="image125.png" alt="Structure 125" /></td>
<td>N-(3-tert-butyl-5-(methylsulfonylamido)phenyl)-2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamide</td>
</tr>
<tr>
<td>126</td>
<td><img src="image126.png" alt="Structure 126" /></td>
<td>N-(5-tert-butyl-2-methoxy-3-(methylsulfonyl)phenyl)-2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamide</td>
</tr>
<tr>
<td>No.</td>
<td>Structure</td>
<td>Name</td>
</tr>
<tr>
<td>-----</td>
<td>-----------</td>
<td>------</td>
</tr>
<tr>
<td>127</td>
<td><img src="image1" alt="Structure Image" /></td>
<td>N-(4-(2-(8-oxa-3-aza-bicyclo[3.2.1]octan-3-yl)ethoxy)naphthalen-1-yl)-2-(5-tert-butyl-2-methylfuran-3-yl)-2-oxoacetamide</td>
</tr>
<tr>
<td>128</td>
<td><img src="image2" alt="Structure Image" /></td>
<td>(E)-N-(4-(2-(8-oxa-3-aza-bicyclo[3.2.1]octan-3-yl)ethoxy)naphthalen-1-yl)-2-(5-tert-butyl-2-methylfuran-3-yl)-2-(hydroxyimino)acetamide</td>
</tr>
<tr>
<td>129</td>
<td><img src="image3" alt="Structure Image" /></td>
<td>(Z)-N-(4-(2-(8-oxa-3-aza-bicyclo[3.2.1]octan-3-yl)ethoxy)naphthalen-1-yl)-2-(5-tert-butyl-2-methylfuran-3-yl)-2-(hydroxyimino)acetamide</td>
</tr>
<tr>
<td>130</td>
<td><img src="image4" alt="Structure Image" /></td>
<td>(Z)-N-(4-(2-(8-oxa-3-aza-bicyclo[3.2.1]octan-3-yl)ethoxy)naphthalen-1-yl)-2-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-2-(hydroxyimino)acetamide</td>
</tr>
<tr>
<td>131</td>
<td><img src="image5" alt="Structure Image" /></td>
<td>(E)-N-(4-(2-(8-oxa-3-aza-bicyclo[3.2.1]octan-3-yl)ethoxy)naphthalen-1-yl)-2-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-2-(hydroxyimino)acetamide</td>
</tr>
<tr>
<td>132</td>
<td><img src="image6" alt="Structure Image" /></td>
<td>N-(5-tert-butyl-2-methoxy-3-(methylsulfonylamido)phenyl)-2-oxo-2-(4-(2-(piperidin-1-yl)ethoxy)naphthalen-1-yl)acetamide</td>
</tr>
<tr>
<td>No.</td>
<td>Structure</td>
<td>Name</td>
</tr>
<tr>
<td>-----</td>
<td>-----------</td>
<td>------</td>
</tr>
<tr>
<td>133</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>2-((4-(2-morpholinoethoxy)naphthalen-1-yl)-N-(naphthalen-2-yl)-2-oxoacetamide</td>
</tr>
<tr>
<td>134</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>N-(5-isopropyl-2-methoxyphenyl)-2-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamide</td>
</tr>
<tr>
<td>135</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>2-(5-tert-butyl-2-methoxy-3-(methylsulfonamido)phenyl)-N-(4-(2-morpholinoethoxy)naphthalen-1-yl)-2-oxoacetamide</td>
</tr>
</tbody>
</table>

[00470] As will be understood by one skilled in the art, for any and all purposes, particularly in terms of providing a written description, all ranges disclosed herein also encompass any and all possible subranges and combinations of subranges thereof. Any listed range can be easily recognized as sufficiently describing and enabling the same range being broken down into at least equal halves, thirds, quarters, fifths, tenths, etc. As a non-limiting example, each range discussed herein can be readily broken down into a lower third, middle third and upper third, etc. As will also be understood by one skilled in the art all language such as “up to,” “at least,” “greater than,” “less than,” and the like include the number recited and refer to ranges which can be subsequently broken down into subranges as discussed above. Finally, as will be understood by one skilled in the art, a range includes each individual member. Thus, for example, a group having 1-3 atoms refers to groups having 1, 2, or 3 atoms. Similarly, a group having 1-5 atoms refers to groups having 1, 2, 3, 4, or 5 atoms, and so forth.

[00471] All publications, patent applications, issued patents, and other documents referred to in this specification are herein incorporated by reference as if each individual publication, patent application, issued patent, or other document was specifically and
individually indicated to be incorporated by reference in its entirety. Definitions that are contained in text incorporated by reference are excluded to the extent that they contradict definitions in this disclosure.

[00472] While certain embodiments have been illustrated and described, it should be understood that changes and modifications can be made therein in accordance with ordinary skill in the art without departing from the invention in its broader aspects as defined in the following claims.
CLAIMS

What is claimed is:

1. A compound of Formula I:

   \[ \begin{array}{c}
   \text{G} \text{N} \text{X} \text{Ar} \text{L} \text{Q} \\
   \text{H}
   \end{array} \]

   I

   stereoisomers thereof, tautomers thereof, solvates thereof, prodrugs thereof, and pharmaceutically acceptable salts thereof, wherein:

   G is phenyl or pyrazolyl, wherein G is substituted by one or more R¹, R² or R³;

   X is C(O) or C(S);

   Ar is (Y)-naphthyl;

   Y is C(O) or C(NOR);

   L-Q is selected from:

   1) O-(C₁₋₄ alkyl)-Q, wherein Q is CN, O-(C₁₋₄ alkyl)-OR, N(C₁₋₄ alkyl)-OR₂,
   or a heterocyclyl group selected from

   \[ \begin{array}{c}
   \text{N} \text{O} \\
   \text{O}
   \end{array} \]

   \[ \begin{array}{c}
   \text{N} \text{O} \\
   \text{O}
   \end{array} \]

   \[ \begin{array}{c}
   \text{N} \text{O} \\
   \text{O}
   \end{array} \]

   or

   \[ \begin{array}{c}
   \text{N} \text{O} \\
   \text{O}
   \end{array} \]

   2) \[ \begin{array}{c}
   \text{N} \text{H} \\
   \text{R}^₄
   \end{array} \]

   3) \[ \begin{array}{c}
   \text{N} \text{H} \\
   \text{R}^₅
   \end{array} \]

   \[ \begin{array}{c}
   \text{N} \text{H} \\
   \text{R}^₆
   \end{array} \]
4) \[
\begin{array}{c}
\text{R}^6
\end{array}
\]

or

5) \[
\begin{array}{c}
\text{R}^7
\end{array}
\]

each R^1 is independently F, Cl, Br, I, NR_2, CN, or a substituted or unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl or heterocyclalkyl group;

each R^2 is independently F, Cl, Br, I, CN, NO_2, a substituted or unsubstituted alkyl, heterocyclyl, or heterocyclalkyl group, OR', C(O)R'', C(O)OR', C(O)NR'_2, NR'_2, NRC(O)R'', NR'C(O)OR'', NR'SO_2R'', NR'C(O)NR'_2, NR'C(S)NR'_2, S(O)_mR'', or SO_2NR'_2;

each R^3 is independently a substituted or unsubstituted alkyl, alkenyl, or alkynyl group, or an O(C_{1-4} alkyl) group, wherein each alkyl group is optionally partially or fully halogenated;

R^4 is a substituted or unsubstituted C_{1-4} alkyl, NH-(C_{1-8} alkyl), NH-aralkyl, or NH-heterocyclalkyl group;

R^5 is selected from substituted or unsubstituted NH-(C_{1-8} alkyl) group or a substituted or unsubstituted heterocyclyl selected from:

\[
\begin{array}{c}
\text{N} \quad \text{N} \quad \text{N} \quad \text{N} \quad \text{N} \quad \text{N} \quad \text{N} \quad \text{N} \quad \text{N} \\
\text{R} \quad \text{R} \quad \text{R} \quad \text{R} \quad \text{R} \quad \text{R} \quad \text{R} \quad \text{R} \quad \text{R}
\end{array}
\]

R^6 is selected from a substituted or unsubstituted C_{1-4} alkyl, heterocyclyl, NH-(C_{1-4} alkyl), NH-alkylaryl, or NH-heterocyclalkyl group;
$R^7$ is selected from F or Cl, or a substituted or unsubstituted NH-(C$_{3,8}$ alkyl) group;

each R is independently hydrogen or a substituted or unsubstituted C$_{1,6}$ alkyl group;

each $R'$ is independently hydrogen, or a substituted or unsubstituted alkyl, cycloalkyl, cycloalkylalkyl, aryl, heterocyclyl, aralkyl, or heterocyclylalkyl group;

each $R''$ is independently a substituted or unsubstituted alkyl, cycloalkyl, cycloalkylalkyl, aryl, heterocyclyl, aralkyl or heterocyclylalkyl group; and

each m is independently 0, 1 or 2.

2. The compound of claim 1, wherein G is

![Diagram](image)

3. The compound of claim 1, wherein Ar is

![Diagram](image)

4. The compound of claim 1, wherein L-Q is $-$O-(C$_{2,3}$ alkyl)-Q, and Q is $-$N(C$_{2,3}$ alkyl-OR)$_2$.

![Diagram](image)

5. The compound of claim 4, wherein L-Q is

![Diagram](image)
6. The compound of claim 1, wherein L-Q is

\[ \text{Structure A} \]

and R³ is a substituted or unsubstituted C₁₋₄ alkyl or -NH-(C₁₋₅ alkyl) group.

7. The compound of claim 6, wherein R⁴ is

\[ \text{Structure B} \quad \text{or} \quad \text{Structure C} \]

8. The compound of claim 1, wherein L-Q is

\[ \text{Structure D} \]

and R³ is selected from substituted or unsubstituted

\[ \text{Options A through I} \]

9. The compound of claim 1, wherein L-Q is

\[ \text{Structure E} \]

and R⁵ is

\[ \text{Structure F} \quad \text{or} \quad \text{Structure G} \]

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10. The compound of claim 1, wherein L-Q is

\[ \text{R}^7 \]

and \( \text{R}^7 \) is F, or a 3,3-dimethylbutan-1-amine-1-yl group.

11. The compound of claim 1, wherein \( \text{R}^1 \) is a substituted or unsubstituted \( \text{C}_{1-6} \) alkyl, or heterocycyl group.

12. The compound of claim 11, wherein \( \text{R}^1 \) is a substituted or unsubstituted methyl, isopropyl, tert-butyl, isobutyl, sec-butyl, neopentyl, cyclohexyl, pyrrolidinyl, piperidinyl, piperazinyl, oxazepanyl, morpholiny, or thiomorpholiny group.

13. The compound of claim 1, wherein \( \text{R}^2 \) is a substituted or unsubstituted (\( \text{C}_{1-6} \) alkyl), heterocycyl, or heterocyclylalkyl group, \( \text{F}, \text{Br}, \text{CN}, \text{C}(\text{O})\text{NR}^2, \text{C}(\text{O})\text{R}^\prime, \text{S}(\text{O})_m\text{R}^\prime, \text{NR}^\prime\text{SO}_2\text{R}^\prime, \) or \( \text{SO}_2\text{NR}^\prime_2. \)

14. The compound of claim 13, wherein \( \text{R}^2 \) is \( \text{F}, \text{Br}, \text{CN}, \text{CF}_3, \) imidazolyl, triazolyl, tetrazolyl, \( \text{C}(\text{O})\text{NH}_2, \text{C}(\text{O})\text{NH}(\text{C}_{1-6} \text{ alkyl}), \text{C}(\text{O})\text{NH}(\text{C}_{3-6} \text{ cycloalkyl}), \)
\( \text{C}(\text{O})\text{NH}(\text{heterocycyl}), \text{C}(\text{O})\text{NH}(\text{heterocyclylalkyl}), (\text{CH}_2)_{1-3}\text{-heterocycyl}, \)
\( \text{C}(\text{O})\text{-heterocycyl}, \text{NHSO}_2(\text{C}_{1-6} \text{ alkyl}), \text{NHSO}_2(\text{C}_{3-6} \text{ cycloalkyl}), \text{NHSO}_2(\text{heterocycyl}), \)
\( \text{SO}_2\text{NH}(\text{C}_{1-6} \text{ alkyl}), \text{SO}_2\text{N}(\text{C}_{1-6} \text{ alkyl})_2, \) wherein each \( \text{C}_{1-6} \) alkyl, \( \text{C}_{3-6} \) cycloalkyl, heterocycyl, and heterocyclylalkyl group is substituted or unsubstituted.

15. The compound of claim 14, wherein the \( \text{C}_{1-6} \) alkyl or \( \text{C}_{3-6} \) cycloalkyl group is a methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, sec-butyl, isobutyl, neopentyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, wherein the alkyl or cycloalkyl group is optionally substituted by OH or N(\( \text{C}_{1-3} \) alkyl)\(_2\) group.

16. The compound of claim 14, wherein the heterocycyl group is a pyrrolidinyl, piperidinyl, piperazinyl, azepanyl, or 3,8-diazabicyclo[3.2.1]octanyl group.

17. The compound of claim 14, wherein the heterocyclylalkyl group is a (\( \text{CH}_2)_{1-3}\)pyrrolidinyl, (\( \text{CH}_2)_{1-3}\)piperidinyl, (\( \text{CH}_2)_{1-3}\)piperazinyl, (\( \text{CH}_2)_{1-3}\)furanyl, (\( \text{CH}_2)_{1-3}\)oxazolyl, or (\( \text{CH}_2)_{1-3}\)isoxazolyl group.
18. The compound of claim 14, wherein the heterocyclal and heterocyclalkyl group is substituted with methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, sec-butyl, isobutyl, neopentyl, (CH$_2$)$_{0-3}$-cyclopropyl, (CH$_2$)$_{0-3}$-cyclobutyl, (CH$_2$)$_{0-3}$-cyclopentyl, (CH$_2$)$_{0-3}$-cyclohexyl, (CH$_2$)$_{0-3}$-OH, (CH$_2$)$_{0-3}$NH(C$_{1-3}$ alkyl), (CH$_2$)$_{0-3}$N(C$_{1-3}$ alkyl)$_2$, or (CH$_2$)$_{1-3}$-pyrrolidinyl.

19. The compound of claim 1, wherein R$^3$ is a substituted or unsubstituted C$_{1-4}$ alkyl or O(C$_{1-4}$ alkyl) group, or is a partially or fully halogenated O(C$_{1-2}$ alkyl) group.

20. The compound of claim 1, wherein G is phenyl and R$^1$ a substituted or unsubstituted methyl, isopropyl, tert-butyl, isobutyl, sec-butyl, neopentyl, cyclohexyl, pyrrolidinyl, piperidinyl, piperazinyl, oxazepanyl, morpholinyl, or thiomorpholinyl group.

21. The compound of claim 20, wherein R$^2$ is a substituted or unsubstituted (C$_{1-6}$ alkyl) or heterocyclalkyl group, F, Br, CN, C(O)NR$^2$, C(O)R$^2$, S(O)$_n$R$^2$, NR$^2$SO$_2$R$^2$, or SO$_2$NR$^2$.

22. The compound of claim 20, wherein R$^2$ is is F, Br, CN, CF$_3$, imidazolyl, triazolyl, tetrazolyl, C(O)NH$_2$, C(O)NH(C$_{1-6}$ alkyl), C(O)NH(C$_{3-6}$ cycloalkyl), C(O)NH(heterocycl), C(O)NH(heterocyclalkyl), (CH$_2$)$_{1-3}$-heterocycl, C(O)-heterocycl, NH$_2$SO$_2$(C$_{1-6}$ alkyl), NH$_2$SO$_2$(C$_{3-6}$ cycloalkyl), NH$_2$SO$_2$(heterocycl), SO$_2$NH(C$_{1-6}$ alkyl), SO$_2$N(C$_{1-6}$ alkyl)$_2$, wherein each C$_{1-6}$ alkyl, C$_{3-6}$ cycloalkyl, heterocycl, and heterocyclalkyl group is substituted or unsubstituted.

23. The compound of claim 20, wherein R$^3$ is a substituted or unsubstituted C$_{1-4}$ alkyl or O(C$_{1-4}$ alkyl) group, or is a partially or fully halogenated O(C$_{1-2}$ alkyl) group.


25. A method of treating a disorder mediated by cytokines which comprises administering to a subject in need of such treatment a therapeutically effective amount of a compound of any one of claims 1-23.
26. The method according to claim 25, wherein the cytokine-mediated disorder is rheumatoid arthritis, osteoarthritis, Crohn's disease, ulcerative colitis, psoriatic arthritis, traumatic arthritis, rubella arthritis, inflammatory bowel disease, multiple sclerosis, graft versus host disease, systemic lupus erythematosus, toxic shock syndrome, irritable bowel syndrome, muscle degeneration, allograft rejection, pancreatitis, insulinitis, glomerulonephritis, diabetic nephropathy, renal fibrosis, chronic renal failure, gout, leprosy, acute synovitis, Reiter's syndrome, gouty arthritis, Behcet's disease, spondylitis, endometriosis, non-articular inflammatory conditions, acute or chronic pain, stroke, chronic heart failure, endotoxemia, reperfusion injury, ischaemia reperfusion, myocardial ischaemia, restenosis, thrombosis, angiogenesis, coronary heart disease, coronary artery disease, acute coronary syndrome, Takayasu arteritis, cardiac failure, hypercholesteremia, diseases or conditions related to blood coagulation or fibrinolysis, atherosclerosis, allergic conjunctivitis, uveitis, glaucoma, optic neuritis, retinal ischaemia, diabetic retinopathy, laser induced optic damage, surgery or trauma-induced proliferative vitreoretinopathy, allergic rhinitis, asthma, adult respiratory distress syndrome, chronic pulmonary inflammation, chronic obstructive pulmonary disease, obliterative bronchiolitis, emphysema, bronchitis, mucus hypersecretion, silicosis, SARS infection, respiratory tract inflammation, psoriasis, pemphigus, eczema, atopic dermatitis, contact dermatitis, acne, Guillain-Barre syndrome, Parkinson's disease, Huntington's disease, Alzheimer's disease, amyotrophic lateral sclerosis, multiple sclerosis, demyelinating diseases, viral meningitis, bacterial meningitis, CNS trauma, spinal cord injury, seizures, convulsions, olivopontocerebellar atrophy, AIDS dementia complex, MERRF syndrome, MELAS syndrome, Leber's disease, Wernicke's encephalopathy, Rett syndrome, homocystinuria, hyperprolinemia, hyperhomocysteinemia, nonketotic hyperglycinemia, hydroxybutyric aciduria, sulfite oxidase deficiency, combined systems disease, lead encephalopathy, Tourette's syndrome, hepatic encephalopathy, drug addiction, drug tolerance, drug dependency, depression, anxiety, schizophrenia, aneurism, epilepsy, diabetes, systemic cachexia, cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome, obesity, anorexia nervosa, bulimia nervosa, bone resorption diseases, osteopetrosis, osteoporosis, sepsis, HIV infection, HCV infection, malaria, infectious arthritis, leishmaniasis, Lyme disease, cancer, Castleman's disease, or drug resistance.
27. The method of claim 25, wherein the disorder is abnormal bleeding, an abscess, actinic reticuloid syndrome, acute confusional migraine, acute confusional senile dementia, acute hepatocellular injury, acute tubular necrosis, adenohypophyseal diseases, adenovirus infections, adhesions, adhesive capsulitis, adenitis, agammaglobulinemia, allergy, alopecia, fibrosing alveolitis, amyloidosis, angioplasty, angor pectoris, antiphospholipid syndrome, arteriosclerotic dementia, arteritis temporal, arthropod-borne encephalitis, asphyxia, atopic hypersensitivity, beaver fever, biliary cirrhosis, bone loss, bronchiolitis, cancer of endocrine gland, cancer of larynx, candidiasis, small cell lung carcinoma, cardiac hypertrophy, cardiac surgery, cardiomegaly, carditis, carotid angioplasty, carotid endarterectomy, carotid stents, carotid ulcer, celiac disease, cirrhosis, colitis, colitis granulomatous, coronary artery bypass graft, coronary artery bypass surgery, degenerative joint disease, dermatitis, diarrhea, dry eye, dyslipidemia, dyspnea, edema, end-stage renal disease, epstein-barr virus infections, fever, gastroenteritis, heart attack, heart bypass surgery, heart surgery, heart transplantation, hepatitis A, hepatitis B, hepatitis C, chronic hepatitis, insulin resistance, kidney failure, kidney transplantation, adult chronic leukemia, liver cirrhosis, liver transplantation, meningitis, bacterial meningitis, myeloproliferative disorders, myopathies, myositis, neonatal-onset multisystem inflammatory disease, nephritis, neuromuscular disorders, neuropathy, obliterative bronchiolitis, oral cancer, percutaneous coronary intervention, peripheral nerve disorders, neuropathy, peritoneal dialysis, pleural disease, pneumonitis, polymyositis, pulmonary fibrosis, renal cancer, renal dialysis, scleroderma, septic arthritis, sjogren's syndrome, ankylosing spondylitis, Still's disease, toxemia, tuberculosis, urticaria, viral hepatitis, or Wegener's granulomatosis.

28. A method comprising administering to a subject an amount of a compound of any one of claims 1-23 effective to reduce a level of a cytokine relative to the level prior to administration of the compound.

29. A method comprising exposing a cell to an amount of a compound of any one of claims 1-23 effective to reduce the level of cytokine released from the cell in response to a pro-inflammatory stimulus relative to the level of released cytokine prior to contacting the cell with the compound.
30. A method comprising contacting p38 with an amount of a compound of any one of claims 1-23 effective to inhibit p38 activity, the phosphorylation of p38, or both.

31. A method comprising administering to a subject in need thereof, an amount of a compound of any one of claims 1-23 effective to reduce the activity of a pro-inflammatory mediator relative to the activity prior to the administration of the compound.

32. A method comprising administering to a subject an amount of a compound of any one of claims 1-23 effective to reduce the circulating levels of C-Reactive Protein or Rheumatoid Factor, or both, in blood relative to the level prior to the administration of the compound.

33. A method comprising administering to a subject exhibiting one or more indicia of rheumatoid arthritis, an amount of a compound of any one of claims 1-23 effective to reduce at least one of the indicia to a level below that which exists prior to the administration of the compound, wherein the indicia are selected from erythrocyte sedimentation rate (ESR), joint redness, joint pain, joint tenderness, Ritchie articular index, duration of morning stiffness, joint immobility, joint swelling, and/or circulating C-reactive protein level.

34. A method comprising administering to a subject exhibiting one or more clinical signs of psoriasis an amount of a compound of any one of claims 1-23 effective to reduce the number or severity of clinical signs of psoriasis relative to those present in the subject prior to the administration of the compound, wherein the clinical signs of psoriasis are the percentage of total body surface area (BSA) affected by psoriasis, psoriasis plaque thickness, level of lymphocytes within psoriatic lesions, epidermal thickness, T-cell infiltration, pathological epidermal hyperplasia, cell-mediated immunity reactions, tetanus antibody response, lymphocyte subpopulations, or any two or more thereof.

35. A compound of Formula II:
Formula II

wherein X is CN, CF₃, or a halogen; and Pₜ is H, or an amine protecting group.

36. A compound selected from List I.