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Methods and compositions using selective cytokine inhibitory drugs for treatment and management of cancers and other diseases

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(54) Title: METHODS AND COMPOSITIONS USING SELECTIVE CYTOKINE INHIBITORY DRUGS FOR TREATMENT AND MANAGEMENT OF CANCERS AND OTHER DISEASES

(57) Abstract: Methods of treating, preventing and/or managing cancer as well as and diseases and disorders associated with, or characterized by, undesired angiogenesis are disclosed. Specific methods encompass the administration of a selective cytokine inhibitory drug alone or in combination with a second active ingredient. The invention further relates to methods of reducing or avoiding adverse side effects associated with chemotherapy, radiation therapy, hormonal therapy, biological therapy or immunotherapy which comprise the administration of a selective cytokine inhibitory drug. Pharmaceutical compositions, single unit dosage forms, and kits suitable for use in methods of the invention are also disclosed.



WO 03/097040 A1

**METHODS AND COMPOSITIONS USING
SELECTIVE CYTOKINE INHIBITORY DRUGS FOR
TREATMENT AND MANAGEMENT OF CANCERS AND OTHER DISEASES**

This application claims the benefit of U.S. provisional application nos. 60/380,842, filed May 17, 2002, and 60/424,601, filed November 6, 2002, the entireties of which are
5 incorporated herein by reference.

1. FIELD OF THE INVENTION

This invention relates to methods of treating, preventing and/or managing specific cancers, and other diseases including, but not limited to, those associated with, or
10 characterized by, undesired angiogenesis, by the administration of one or more selective cytokine inhibitory drugs alone or in combination with other therapeutics. In particular, the invention encompasses the use of specific combinations, or "cocktails," of drugs and other therapy, *e.g.*, radiation to treat these specific cancers, including those refractory to conventional therapy. The invention also relates to pharmaceutical compositions and
15 dosing regimens.

2. BACKGROUND OF THE INVENTION

2.1 PATHOBIOLOGY OF CANCER AND OTHER DISEASES

Cancer is characterized primarily by an increase in the number of abnormal cells derived from a given normal tissue, invasion of adjacent tissues by these abnormal cells, or
20 lymphatic or blood-borne spread of malignant cells to regional lymph nodes and to distant sites (metastasis). Clinical data and molecular biologic studies indicate that cancer is a multistep process that begins with minor preneoplastic changes, which may under certain conditions progress to neoplasia. The neoplastic lesion may evolve clonally and develop an increasing capacity for invasion, growth, metastasis, and heterogeneity, especially under
25 conditions in which the neoplastic cells escape the host's immune surveillance. Roitt, I., Brostoff, J and Kale, D., *Immunology*, 17.1-17.12 (3rd ed., Mosby, St. Louis, Mo., 1993).

There is an enormous variety of cancers which are described in detail in the medical literature. Examples includes cancer of the lung, colon, rectum, prostate, breast, brain, and intestine. The incidence of cancer continues to climb as the general population ages, as new
30 cancers develop, and as susceptible populations (*e.g.*, people infected with AIDS or

excessively exposed to sunlight) grow. A tremendous demand therefore exists for new methods and compositions that can be used to treat patients with cancer.

Many types of cancers are associated with new blood vessel formation, a process known as angiogenesis. Several of the mechanisms involved in tumor-induced angiogenesis have been elucidated. The most direct of these mechanisms is the secretion by the tumor cells of cytokines with angiogenic properties. Examples of these cytokines include acidic and basic fibroblastic growth factor (a,b-FGF), angiogenin, vascular endothelial growth factor (VEGF), and TNF- α . Alternatively, tumor cells can release angiogenic peptides through the production of proteases and the subsequent breakdown of the extracellular matrix where some cytokines are stored (*e.g.*, b-FGF). Angiogenesis can also be induced indirectly through the recruitment of inflammatory cells (particularly macrophages) and their subsequent release of angiogenic cytokines (*e.g.*, TNF- α , bFGF).

A variety of other diseases and disorders are also associated with, or characterized by, undesired angiogenesis. For example, enhanced or unregulated angiogenesis has been implicated in a number of diseases and medical conditions including, but not limited to, ocular neovascular diseases, choroidal neovascular diseases, retina neovascular diseases, rubeosis (neovascularization of the angle), viral diseases, genetic diseases, inflammatory diseases, allergic diseases, and autoimmune diseases. Examples of such diseases and conditions include, but are not limited to: diabetic retinopathy; retinopathy of prematurity; corneal graft rejection; neovascular glaucoma; retrolental fibroplasia; and proliferative vitreoretinopathy.

Accordingly, compounds that can control angiogenesis or inhibit the production of certain cytokines, including TNF- α , may be useful in the treatment and prevention of various diseases and conditions.

2.2 METHODS OF TREATMENT

Current cancer therapy may involve surgery, chemotherapy, hormonal therapy and/or radiation treatment to eradicate neoplastic cells in a patient (see, for example, Stockdale, 1998, *Medicine*, vol. 3, Rubenstein and Federman, eds., Chapter 12, Section IV). Recently, cancer therapy could also involve biological therapy or immunotherapy. All of these approaches pose significant drawbacks for the patient. Surgery, for example, may be contraindicated due to the health of a patient or may be unacceptable to the patient. Additionally, surgery may not completely remove neoplastic tissue. Radiation therapy is only effective when the neoplastic tissue exhibits a higher sensitivity to radiation than normal tissue. Radiation therapy can also often elicit serious side effects. Hormonal

therapy is rarely given as a single agent. Although hormonal therapy can be effective, it is often used to prevent or delay recurrence of cancer after other treatments have removed the majority of cancer cells. Biological therapies and immunotherapies are limited in number and may produce side effects such as rashes or swellings, flu-like symptoms, including
5 fever, chills and fatigue, digestive tract problems or allergic reactions.

With respect to chemotherapy, there are a variety of chemotherapeutic agents available for treatment of cancer. A majority of cancer chemotherapeutics act by inhibiting DNA synthesis, either directly, or indirectly by inhibiting the biosynthesis of deoxyribonucleotide triphosphate precursors, to prevent DNA replication and concomitant
10 cell division. Gilman et al., *Goodman and Gilman's: The Pharmacological Basis of Therapeutics*, Tenth Ed. (McGraw Hill, New York).

Despite availability of a variety of chemotherapeutic agents, chemotherapy has many drawbacks. Stockdale, *Medicine*, vol. 3, Rubenstein and Federman, eds., ch. 12, sect. 10, 1998. Almost all chemotherapeutic agents are toxic, and chemotherapy causes
15 significant, and often dangerous side effects including severe nausea, bone marrow depression, and immunosuppression. Additionally, even with administration of combinations of chemotherapeutic agents, many tumor cells are resistant or develop resistance to the chemotherapeutic agents. In fact, those cells resistant to the particular chemotherapeutic agents used in the treatment protocol often prove to be resistant to other
20 drugs, even if those agents act by different mechanism from those of the drugs used in the specific treatment. This phenomenon is referred to as pleiotropic drug or multidrug resistance. Because of the drug resistance, many cancers prove refractory to standard chemotherapeutic treatment protocols.

Other diseases or conditions associated with, or characterized by, undesired
25 angiogenesis are also difficult to treat. However, some compounds such as protamine, heparin and steroids have been proposed to be useful in the treatment of certain specific diseases. Taylor et al., *Nature* 297:307 (1982); Folkman et al., *Science* 221:719 (1983); and U.S. Pat. Nos. 5,001,116 and 4,994,443. Thalidomide and certain derivatives of it have also been proposed for the treatment of such diseases and conditions. U.S. patent nos.
30 5,593,990, 5,629,327, 5,712,291, 6,071,948 and 6,114,355 to D'Amato.

Still, there is a significant need for safe and effective methods of treating, preventing and managing cancer and other diseases and conditions, particularly for diseases that are refractory to standard treatments, such as surgery, radiation therapy, chemotherapy and

hormonal therapy, while reducing or avoiding the toxicities and/or side effects associated with the conventional therapies.

2.3 SELECTIVE CYTOKINE INHIBITORY DRUGS

- Compounds referred to as SelCIDs™ (Celgene Corporation) or Selective Cytokine Inhibitory Drugs have been synthesized and tested. These compounds potentially inhibit TNF- α production, but exhibit modest inhibitory effects on LPS induced IL1 β and IL12, and do not inhibit IL6 even at high drug concentrations. In addition, SelCIDs™ tend to produce a modest IL10 stimulation. L.G. Corral, *et al.*, Ann. Rheum. Dis. 58:(Suppl I) 1107-1113 (1999).
- Further characterization of the selective cytokine inhibitory drugs shows that they are potent PDE4 inhibitors. PDE4 is one of the major phosphodiesterase isoenzymes found in human myeloid and lymphoid lineage cells. The enzyme plays a crucial part in regulating cellular activity by degrading the ubiquitous second messenger cAMP and maintaining it at low intracellular levels. *Id.* Inhibition of PDE4 activity results in increased cAMP levels leading to the modulation of LPS induced cytokines including inhibition of TNF- α production in monocytes as well as in lymphocytes.

3. SUMMARY OF THE INVENTION

- This invention encompasses methods of treating and preventing certain types of cancer, including primary and metastatic cancer, as well as cancers that are refractory or resistant to conventional chemotherapy. The methods comprise administering to a patient in need of such treatment or prevention a therapeutically or prophylactically effective amount of a selective cytokine inhibitory drug, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof. The invention also encompasses methods of managing certain cancers (*e.g.*, preventing or prolonging their recurrence, or lengthening the time of remission) which comprise administering to a patient in need of such management a prophylactically effective amount of a selective cytokine inhibitory drug of the invention, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof.

- In particular methods of the invention, a selective cytokine inhibitory drug is administered in combination with a therapy conventionally used to treat, prevent or manage cancer. Examples of such conventional therapies include, but are not limited to, surgery, chemotherapy, radiation therapy, hormonal therapy, biological therapy and immunotherapy.

This invention also encompasses methods of treating, managing or preventing diseases and disorders other than cancer that are associated with, or characterized by, undesired angiogenesis, which comprise administering to a patient in need of such treatment, management or prevention a therapeutically or prophylactically effective amount
5 of a selective cytokine inhibitory drug, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof.

In other methods of the invention, a selective cytokine inhibitory drug is administered in combination with a therapy conventionally used to treat, prevent or manage diseases or disorders associated with, or characterized by, undesired angiogenesis.
10 Examples of such conventional therapies include, but are not limited to, surgery, chemotherapy, radiation therapy, hormonal therapy, biological therapy and immunotherapy.

This invention encompasses pharmaceutical compositions, single unit dosage forms, dosing regimens and kits which comprise a selective cytokine inhibitory drug, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug
15 thereof, and a second, or additional, active agent. Second active agents include specific combinations, or "cocktails," of drugs.

4. DETAILED DESCRIPTION OF THE INVENTION

A first embodiment of the invention encompasses methods of treating, managing, or preventing cancer which comprises administering to a patient in need of such treatment or
20 prevention a therapeutically or prophylactically effective amount of a selective cytokine inhibitory drug of the invention, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof.

In particular methods encompassed by this embodiment, the selective cytokine inhibitory drug is administered in combination with another drug ("second active agent") or
25 method of treating, managing, or preventing cancer. Second active agents include small molecules and large molecules (*e.g.*, proteins and antibodies), examples of which are provided herein, as well as stem cells. Methods, or therapies, that can be used in combination with the administration of the selective cytokine inhibitory drug include, but are not limited to, surgery, blood transfusions, immunotherapy, biological therapy, radiation
30 therapy, and other non-drug based therapies presently used to treat, prevent or manage cancer.

Another embodiment of the invention encompasses methods of treating, managing or preventing diseases and disorders other than cancer that are characterized by undesired angiogenesis. These methods comprise the administration of a therapeutically or

prophylactically effective amount of a selective cytokine inhibitory drug, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof.

5 Examples of diseases and disorders associated with, or characterized by, undesired angiogenesis include, but are not limited to, inflammatory diseases, autoimmune diseases, viral diseases, genetic diseases, allergic diseases, bacterial diseases, ocular neovascular diseases, choroidal neovascular diseases, retina neovascular diseases, and rubeosis (neovascularization of the angle).

10 In particular methods encompassed by this embodiment, the selective cytokine inhibitory drug is administered in combination with a second active agent or method of treating, managing, or preventing the disease or condition. Second active agents include small molecules and large molecules (*e.g.*, proteins and antibodies), examples of which are provided herein, as well as stem cells. Methods, or therapies, that can be used in combination with the administration of the selective cytokine inhibitory drug include, but
15 are not limited to, surgery, blood transfusions, immunotherapy, biological therapy, radiation therapy, and other non-drug based therapies presently used to treat, prevent or manage disease and conditions associated with, or characterized by, undesired angiogenesis.

20 The invention also encompasses pharmaceutical compositions (*e.g.*, single unit dosage forms) that can be used in methods disclosed herein. Particular pharmaceutical compositions comprise a selective cytokine inhibitory drug of the invention, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof, and a second active agent.

4.1 SELECTIVE CYTOKINE INHIBITORY DRUGS

25 Compounds used in the invention include racemic, stereomerically pure or stereomerically enriched selective cytokine inhibitory drugs, stereomerically or enantiomerically pure compounds that have selective cytokine inhibitory activities, and pharmaceutically acceptable salts, solvates, hydrates, stereoisomers, clathrates, and prodrugs thereof. Preferred compounds used in the invention are known Selective Cytokine Inhibitory Drugs (SelCIDs™) of Celgene Corporation.

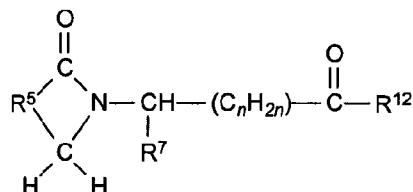
30 As used herein and unless otherwise indicated, the terms “selective cytokine inhibitory drug” and “SelCIDs™” encompass small molecule drugs, *e.g.*, small organic molecules which are not peptides, proteins, nucleic acids, oligosaccharides or other macromolecules. Preferred compounds inhibit TNF- α production. Further, the compounds may also have a modest inhibitory effect on LPS induced IL1 β and IL12. More preferably,

the compounds of the invention are potent PDE4 inhibitors. PDE4 is one of the major phosphodiesterase isoenzymes found in human myeloid and lymphoid lineage cells. The enzyme plays a crucial part in regulating cellular activity by degrading the ubiquitous second messenger cAMP and maintaining it at low intracellular levels. Without being limited by theory, inhibition of PDE4 activity results in increased cAMP levels leading to the modulation of LPS induced cytokines, including inhibition of TNF- α production in monocytes as well as in lymphocytes.

Specific examples of selective cytokine inhibitory drugs include, but are not limited to, the cyclic imides disclosed in U.S. patent no. 5,605,914; the cycloalkyl amides and cycloalkyl nitriles of U.S. patent nos. 5,728,844 and 5,728,845, respectively; the aryl amides (for example, an embodiment being N-benzoyl-3-amino-3-(3',4'-dimethoxyphenyl)-propanamide) of U.S. patent nos. 5,801,195 and 5,736,570; the imide/amide ethers and alcohols (for example, 3-phthalimido-3-(3',4'-dimethoxyphenyl)propan-1-ol) disclosed in U.S. patent no. 5,703,098; the succinimides and maleimides (for example methyl 3-(3',4',5'6'-petrahydrophthalimido)-3-(3'',4''-dimethoxyphenyl)propionate) disclosed in U.S. patent no. 5,658,940; imido and amido substituted alkanohydroxamic acids disclosed in WO 99/06041 and substituted phenethylsulfones disclosed in U.S. patent no. 6,020,358; and aryl amides such as N-benzoyl-3-amino-3-(3',4'-dimethoxyphenyl)propanamide as described in U.S. patent no. 6,046,221. The entireties of each of the patents and patent applications identified herein are incorporated herein by reference.

Additional selective cytokine inhibitory drugs belong to a family of synthesized chemical compounds of which typical embodiments include 3-(1,3-dioxobenzo-[f]isoindol-2-yl)-3-(3-cyclopentyloxy-4-methoxyphenyl)propionamide and 3-(1,3-dioxo-4-azaisoindol-2-yl)-3-(3,4-dimethoxyphenyl)-propionamide.

Other specific selective cytokine inhibitory drugs belong to a class of non-polypeptide cyclic amides disclosed in U.S. patent nos. 5,698,579 and 5,877,200, both of which are incorporated herein. Representative cyclic amides include compounds of the formula:



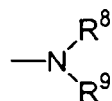
wherein n has a value of 1, 2, or 3;

R⁵ is o-phenylene, unsubstituted or substituted with 1 to 4 substituents each selected independently from the group consisting of nitro, cyano, trifluoromethyl, carboxy,

carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, alkylamino, dialkylamino, acylamino, alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10 carbon atoms, and halo;

- 5 R^7 is (i) phenyl or phenyl substituted with one or more substituents each selected independently of the other from the group consisting of nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10 carbon atoms, and halo, (ii) benzyl unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, 10 acetoxy, carboxy, hydroxy, amino, alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10 carbon atoms, and halo, (iii) naphthyl, and (iv) benzyloxy;

R^{12} is -OH, alkoxy of 1 to 12 carbon atoms, or



R^8 is hydrogen or alkyl of 1 to 10 carbon atoms; and

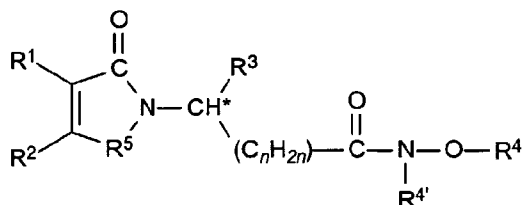
- 15 R^9 is hydrogen, alkyl of 1 to 10 carbon atoms, $-\text{COR}^{10}$, or $-\text{SO}_2\text{R}^{10}$, wherein R^{10} is hydrogen, alkyl of 1 to 10 carbon atoms, or phenyl.

Specific compounds of this class include, but are not limited to:

- 3-phenyl-2-(1-oxoisindolin-2-yl)propionic acid;
3-phenyl-2-(1-oxoisindolin-2-yl)propionamide;
20 3-phenyl-3-(1-oxoisindolin-2-yl)propionic acid;
3-phenyl-3-(1-oxoisindolin-2-yl)propionamide;
3-(4-methoxyphenyl)-3-(1-oxoisindolin-yl)propionic acid;
3-(4-methoxyphenyl)-3-(1-oxoisindolin-yl)propionamide;
3-(3,4-dimethoxyphenyl)-3-(1-oxoisindolin-2-yl)propionic acid;
25 3-(3,4-dimethoxyphenyl)-3-(1-oxo-1,3-dihydroisindol-2-yl)-propionamide;
3-(3,4-dimethoxyphenyl)-3-(1-oxoisindolin-2-yl)propionamide;
3-(3,4-diethoxyphenyl)-3-(1-oxoisindolin-yl)propionic acid;
methyl 3-(1-oxoisindolin-2-yl)-3-(3-ethoxy-4-methoxyphenyl)propionate;
3-(1-oxoisindolin-2-yl)-3-(3-ethoxy-4-methoxyphenyl)propionic acid;
30 3-(1-oxoisindolin-2-yl)-3-(3-propoxy-4-methoxyphenyl)propionic acid;
3-(1-oxoisindolin-2-yl)-3-(3-butoxy-4-methoxyphenyl)propionic acid;
3-(1-oxoisindolin-2-yl)-3-(3-propoxy-4-methoxyphenyl)propionamide;
3-(1-oxoisindolin-2-yl)-3-(3-butoxy-4-methoxyphenyl)propionamide;
methyl 3-(1-oxoisindolin-2-yl)-3-(3-butoxy-4-methoxyphenyl)propionate; and

methyl 3-(1-oxoisoindolin-2-yl)-3-(3-propoxy-4-methoxyphenyl)propionate.

Other specific selective cytokine inhibitory drugs include the imido and amido substituted alkanohydroxamic acids disclosed in WO 99/06041, which is incorporated herein by reference. Examples of such compound include, but are not limited to:



5

wherein each of R¹ and R², when taken independently of each other, is hydrogen, lower alkyl, or R¹ and R², when taken together with the depicted carbon atoms to which each is bound, is *o*-phenylene, *o*-naphthylene, or cyclohexene-1,2-diyl, unsubstituted or substituted with 1 to 4 substituents each selected independently from the group consisting of

10 nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetox, carboxy, hydroxy, amino, alkylamino, dialkylamino, acylamino, alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10 carbon atoms, and halo;

R³ is phenyl substituted with from one to four substituents selected from the group consisting of nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxyl, carboxyl, hydroxyl, amino, alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10 carbon atoms, alkylthio of 1 to 10 carbon atoms, benzyloxy, cycloalkoxy of 3 to 6 carbon atoms, C₄-C₆-cycloalkylidenemethyl, C₃-C₁₀-alkylidenemethyl, indanyloxy, and halo;

R⁴ is hydrogen, alkyl of 1 to 6 carbon atoms, phenyl, or benzyl;

20 R^{4'} is hydrogen or alkyl of 1 to 6 carbon atoms;

R⁵ is -CH₂-, -CH₂-CO-, -SO₂-, -S-, or -NHCO-;

n has a value of 0, 1, or 2; and

the acid addition salts of said compounds which contain a nitrogen atom capable of being protonated.

25 Additional specific selective cytokine inhibitory drugs used in the invention include,
but are not limited to:

3-(3-ethoxy-4-methoxyphenyl)-N-hydroxy-3-(1-oxoisindolinyl)propionamide;

3-(3-ethoxy-4-methoxyphenyl)-N-methoxy-3-(1-oxoisindolinyl)propionamide;

N-benzyloxy-3-(3-ethoxy-4-methoxyphenyl)-3-phthalimidopropionamide:

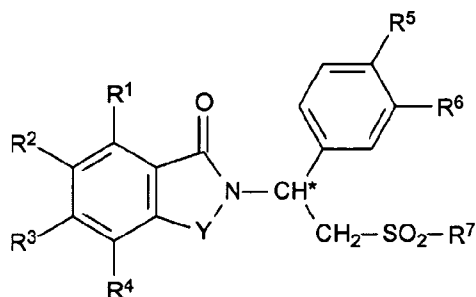
30 N-benzyloxy-3-(3-ethoxy-4-methoxyphenyl)-3-(3-nitrophthalimido)propionamide;

N-benzyloxy-3-(3-ethoxy-4-methoxyphenyl)-3-(1-oxoisindolinyl)propionamide;

3-(3-ethoxy-4-methoxyphenyl)-N-hydroxy-3-phthalimidopropionamide;

- N-hydroxy-3-(3,4-dimethoxyphenyl)-3-phthalimidopropionamide;
 3-(3-ethoxy-4-methoxyphenyl)-N-hydroxy-3-(3-nitrophthalimido)propionamide;
 N-hydroxy-3-(3,4-dimethoxyphenyl)-3-(1-oxoisindolinyl)propionamide;
 3-(3-ethoxy-4-methoxyphenyl)-N-hydroxy-3-(4-methyl-phthalimido)propionamide;
 5 3-(3-cyclopentyloxy-4-methoxyphenyl)-N-hydroxy-3-phthalimidopropionamide;
 3-(3-ethoxy-4-methoxyphenyl)-N-hydroxy-3-(1,3-dioxo-2,3-dihydro-1H-benzo[f]isoindol-2-yl)propionamide;
 N-hydroxy-3-{3-(2-propoxy)-4-methoxyphenyl}-3-phthalimidopropionamide;
 3-(3-ethoxy-4-methoxyphenyl)-3-(3,6-difluorophthalimido)-N-
 10 hydroxypropionamide;
 3-(4-aminophthalimido)-3-(3-ethoxy-4-methoxyphenyl)-N-hydroxypropionamide;
 3-(3-aminophthalimido)-3-(3-ethoxy-4-methoxyphenyl)-N-hydroxypropionamide;
 N-hydroxy-3-(3,4-dimethoxyphenyl)-3-(1-oxoisindolinyl)propionamide;
 3-(3-cyclopentyloxy-4-methoxyphenyl)-N-hydroxy-3-(1-oxoisindolinyl)
 15 propionamide; and
 N-benzyloxy-3-(3-ethoxy-4-methoxyphenyl)-3-(3-nitrophthalimido)propionamide.

Additional selective cytokine inhibitory drugs used in the invention include the substituted phenethylsulfones substituted on the phenyl group with a oxoisindine group. Examples of such compounds include, but are not limited to, those disclosed in U.S. patent
 20 no. 6,020,358, which is incorporated herein, which include the following:



wherein the carbon atom designated * constitutes a center of chirality;

- Y is C=O, CH₂, SO₂, or CH₂C=O; each of R¹, R², R³, and R⁴, independently of the others, is hydrogen, halo, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, nitro,
 25 cyano, hydroxy, or -NR⁸R⁹; or any two of R¹, R², R³, and R⁴ on adjacent carbon atoms, together with the depicted phenylene ring are naphthylidene;

each of R⁵ and R⁶, independently of the other, is hydrogen, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, cyano, or cycloalkoxy of up to 18 carbon atoms;

R⁷ is hydroxy, alkyl of 1 to 8 carbon atoms, phenyl, benzyl, or NR⁸R⁹;

each of R^8 and R^9 taken independently of the other is hydrogen, alkyl of 1 to 8 carbon atoms, phenyl, or benzyl, or one of R^8 and R^9 is hydrogen and the other is $-COR^{10}$ or $-SO_2R^{10}$, or R^8 and R^9 taken together are tetramethylene, pentamethylene, hexamethylene, or $-CH_2CH_2X^1CH_2CH_2-$ in which X^1 is $-O-$, $-S-$ or $-NH-$;

5 each of $R^{8'}$ and $R^{9'}$ taken independently of the other is hydrogen, alkyl of 1 to 8 carbon atoms, phenyl, or benzyl, or one of $R^{8'}$ and $R^{9'}$ is hydrogen and the other is $-COR^{10'}$ or $-SO_2R^{10'}$, or $R^{8'}$ and $R^{9'}$ taken together are tetramethylene, pentamethylene, hexamethylene, or $-CH_2CH_2X^2CH_2CH_2-$ in which X^2 is $-O-$, $-S-$, or $-NH-$;
 R^{10} is hydrogen, alkyl of 1 to 8 carbon atoms or phenyl; and $R^{10'}$ is hydrogen, alkyl of 1
 10 to 8 carbon atoms, or phenyl.

It will be appreciated that while for convenience the above compounds are identified as phenethylsulfones, they include sulfonamides when R^7 is $NR^{8'}R^{9'}$.

Specific groups of such compounds are those in which Y is $C=O$ or CH_2 .

A further specific group of such compounds are those in which each of R^1 , R^2 , R^3 ,
 15 and R^4 independently of the others, is hydrogen, halo, methyl, ethyl, methoxy, ethoxy, nitro, cyano, hydroxy, or $-NR^{8'}R^{9'}$ in which each of R^8 and R^9 taken independently of the other is hydrogen or methyl or one of R^8 and R^9 is hydrogen and the other is $-COCH_3$.

Particular compounds are those in which one of R^1 , R^2 , R^3 , and R^4 is $-NH_2$ and the remaining of R^1 , R^2 , R^3 , and R^4 are hydrogen.

20 Particular compounds are those in which one of R^1 , R^2 , R^3 , and R^4 is $-NHCOCH_3$ and the remaining of R^1 , R^2 , R^3 , and R^4 are hydrogen.

Particular compounds are those in which one of R^1 , R^2 , R^3 , and R^4 is $-N(CH_3)_2$ and the remaining of R^1 , R^2 , R^3 , and R^4 are hydrogen.

A further preferred group of such compounds are those in which one of R^1 , R^2 , R^3 ,
 25 and R^4 is methyl and the remaining of R^1 , R^2 , R^3 , and R^4 are hydrogen.

Particular compounds are those in which one of R^1 , R^2 , R^3 , and R^4 is fluoro and the remaining of R^1 , R^2 , R^3 , and R^4 are hydrogen.

Particular compounds are those in which each of R^5 and R^6 , independently of the other, is hydrogen, methyl, ethyl, propyl, methoxy, ethoxy, propoxy, cyclopentoxy, or
 30 cyclohexoxy.

Particular compounds are those in which R^5 is methoxy and R^6 is monocycloalkoxy, polycycloalkoxy, and benzocycloalkoxy.

Particular compounds are those in which R^5 is methoxy and R^6 is ethoxy.

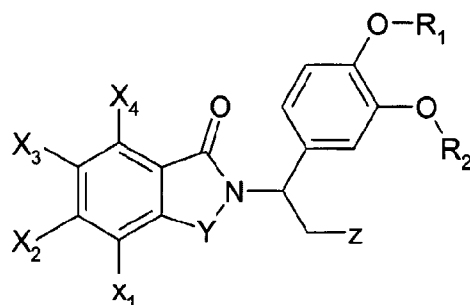
Particular compounds are those in which R^7 is hydroxy, methyl, ethyl, phenyl, benzyl, or $NR^{8'}R^{9'}$ in which each of $R^{8'}$ and $R^{9'}$ taken independently of the other is hydrogen or methyl.

Particular compounds are those in which R^7 is methyl, ethyl, phenyl, benzyl or $NR^{8'}R^{9'}$ in which each of $R^{8'}$ and $R^{9'}$ taken independently of the other is hydrogen or methyl.

Particular compounds are those in which R^7 is methyl.

- 5 Particular compounds are those in which R^7 is $NR^{8'}R^{9'}$ in which each of $R^{8'}$ and $R^{9'}$ taken independently of the other is hydrogen or methyl.

Other specific selective cytokine inhibitory drugs include fluoroalkoxy-substituted 1,3-dihydro-isoindolyl compounds found in United States Provisional Application No. 60/436,975 to G. Muller *et al.*, filed December 30, 2002, which is incorporated herein in its
10 entirety by reference. Representative fluoroalkoxy-substituted 1,3-dihydro-isoindolyl compounds include compounds of the formula:



wherein:

Y is $-C(O)-$, $-CH_2-$, $-CH_2C(O)-$, $-C(O)CH_2-$, or SO_2 ;

- 15 Z is $-H$, $-C(O)R^3$, $-(C_{0-1}\text{-alkyl})-SO_2-(C_{1-4}\text{-alkyl})$, $-C_{1-8}\text{-alkyl}$, $-CH_2OH$, $CH_2(O)(C_{1-8}\text{-alkyl})$ or $-CN$;

R_1 and R_2 are each independently $-CHF_2$, $-C_{1-8}\text{-alkyl}$, $-C_{3-18}\text{-cycloalkyl}$, or $-(C_{1-10}\text{-alkyl})(C_{3-18}\text{-cycloalkyl})$, and at least one of R_1 and R_2 is CHF_2 ;

- 20 R^3 is $-NR^4R^5$, $-alkyl$, $-OH$, $-O-alkyl$, phenyl, benzyl, substituted phenyl, or substituted benzyl;

R^4 and R^5 are each independently $-H$, $-C_{1-8}\text{-alkyl}$, $-OH$, $-OC(O)R^6$;

R^6 is $-C_{1-8}\text{-alkyl}$, $-amino(C_{1-8}\text{-alkyl})$, $-phenyl$, $-benzyl$, or $-aryl$;

- X_1 , X_2 , X_3 , and X_4 are each independent $-H$, $-halogen$, $-nitro$, $-NH_2$, $-CF_3$, $-C_{1-6}\text{-alkyl}$, $-(C_{0-4}\text{-alkyl})-(C_{3-6}\text{-cycloalkyl})$, $(C_{0-4}\text{-alkyl})-NR^7R^8$, $(C_{0-4}\text{-alkyl})-N(H)C(O)-(R^8)$, $(C_{0-4}\text{-alkyl})-N(H)C(O)N(R^7R^8)$, $(C_{0-4}\text{-alkyl})-N(H)C(O)O(R^7R^8)$, $(C_{0-4}\text{-alkyl})-OR^8$, $(C_{0-4}\text{-alkyl})-$
25 imidazolyl, $(C_{0-4}\text{-alkyl})$ -pyrrolyl, $(C_{0-4}\text{-alkyl})$ -oxadiazolyl, or $(C_{0-4}\text{-alkyl})$ -triazolyl, or two of X_1 , X_2 , X_3 , and X_4 may be joined together to form a cycloalkyl or heterocycloalkyl ring, (e.g., X_1 and X_2 , X_2 and X_3 , X_3 and X_4 , X_1 and X_3 , X_2 and X_4 , or X_1 and X_4 may form a 3, 4, 5, 6, or 7 membered ring which may be aromatic, thereby forming a bicyclic system with
30 the isoindolyl ring); and

R⁷ and R⁸ are each independently H, C₁₋₉-alkyl, C₃₋₆-cycloalkyl, (C₁₋₆-alkyl)-(C₃₋₆-cycloalkyl), (C₁₋₆-alkyl)-N(R⁷R⁸), (C₁₋₆-alkyl)-OR⁸, phenyl, benzyl, or aryl;

or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof.

5 Specific compounds include, but are not limited to:

3-(4-Acetylamino-1,3-dioxo-1,3-dihydro-isoindol-2-yl)-3-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-propionic acid;

3-(4-Acetylamino-1,3-dioxo-1,3-dihydro-isoindol-2-yl)-3-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-N,N-dimethyl-propionamide;

10 3-(4-Acetylamino-1,3-dioxo-1,3-dihydro-isoindol-2-yl)-3-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-propionamide;

3-(3-Cyclopropylmethoxy-4-difluoromethoxy-phenyl)-3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-propionic acid;

15 3-(3-Cyclopropylmethoxy-4-difluoromethoxy-phenyl)-3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-N-hydroxy-propionamide;

3-(3-Cyclopropylmethoxy-4-difluoromethoxy-phenyl)-3-(7-nitro-1-oxo-1,3-dihydro-isoindol-2-yl)-propionic acid methyl ester;

3-(3-Cyclopropylmethoxy-4-difluoromethoxy-phenyl)-3-(7-nitro-1-oxo-1,3-dihydro-isoindol-2-yl)-propionic acid;

20 3-(3-Cyclopropylmethoxy-4-difluoromethoxy-phenyl)-3-(7-nitro-1-oxo-1,3-dihydro-isoindol-2-yl)-N,N-dimethyl-propionamide;

3-(7-Amino-1-oxo-1,3-dihydro-isoindol-2-yl)-3-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-N,N-dimethyl-propionamide;

25 3-(4-Difluoromethoxy-3-ethoxy-phenyl)-3-(7-nitro-1-oxo-1,3-dihydro-isoindol-2-yl)-propionic acid methyl ester;

3-(7-Amino-1-oxo-1,3-dihydro-isoindol-2-yl)-3-(4-difluoromethoxy-3-ethoxy-phenyl)-propionic acid methyl ester;

3-[7-(Cyclopropanecarbonyl-amino)-1-oxo-1,3-dihydro-isoindol-2-yl]-3-(4-difluoromethoxy-3-ethoxy-phenyl)-propionic acid methyl ester;

30 3-(7-Acetylamino-1-oxo-1,3-dihydro-isoindol-2-yl)-3-(4-difluoromethoxy-3-ethoxy-phenyl)-propionic acid methyl ester;

3-(7-Acetylamino-1-oxo-1,3-dihydro-isoindol-2-yl)-3-(4-difluoromethoxy-3-ethoxy-phenyl)-propionic acid;

35 3-[7-(Cyclopropanecarbonyl-amino)-1-oxo-1,3-dihydro-isoindol-2-yl]-3-(4-difluoromethoxy-3-ethoxy-phenyl)-propionic acid;

Cyclopropanecarboxylic acid {2-[2-carbamoyl-1-(4-difluoromethoxy-3-ethoxy-phenyl)-ethyl]-3-oxo-2,3-dihydro-1H-isoindol-4-yl}-amide;

Cyclopropanecarboxylic acid {2-[1-(4-difluoromethoxy-3-ethoxy-phenyl)-2-dimethylcarbamoyl-ethyl]-3-oxo-2,3-dihydro-1H-isoindol-4-yl}-;

5 Cyclopropanecarboxylic acid {2-[1-(4-difluoromethoxy-3-ethoxy-phenyl)-2-hydroxycarbamoyl-ethyl]-3-oxo-2,3-dihydro-1H-isoindol-4-yl}-amide;

3-(7-Acetylamino-1-oxo-1,3-dihydro-isoindol-2-yl)-3-(4-difluoromethoxy-3-ethoxy-phenyl)-propionamide;

10 3-(7-Acetylamino-1-oxo-1,3-dihydro-isoindol-2-yl)-3-(4-difluoromethoxy-3-ethoxy-phenyl)-N,N-dimethyl-propionamide;

3-(7-Acetylamino-1-oxo-1,3-dihydro-isoindol-2-yl)-3-(4-difluoromethoxy-3-ethoxy-phenyl)-N-hydroxy-propionamide;

3-(4-Acetylamino-1,3-dioxo-1,3-dihydro-isoindol-2-yl)-3-(4-difluoromethoxy-3-ethoxy-phenyl)-propionic acid;

15 3-(4-Acetylamino-1,3-dioxo-1,3-dihydro-isoindol-2-yl)-3-(4-difluoromethoxy-3-ethoxy-phenyl)-propionamide;

3-(4-Acetylamino-1,3-dioxo-1,3-dihydro-isoindol-2-yl)-3-(4-difluoromethoxy-3-ethoxy-phenyl)-N,N-dimethyl-propionamide;

20 3-(4-Acetylamino-1,3-dioxo-1,3-dihydro-isoindol-2-yl)-3-(4-difluoromethoxy-3-ethoxy-phenyl)-N-hydroxy-propionamide;

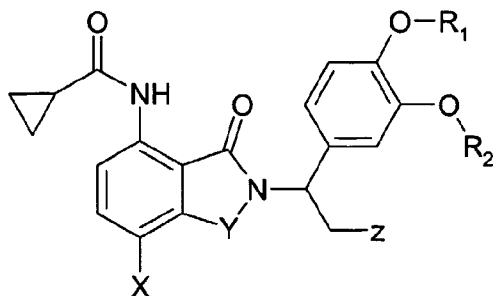
Cyclopropanecarboxylic acid {2-[1-(4-difluoromethoxy-3-ethoxy-phenyl)-2-methanesulfonyl-ethyl]-3-oxo-2,3-dihydro-1H-isoindol-4-yl}-amide;

N-{2-[1-(4-Difluoromethoxy-3-ethoxy-phenyl)-2-methanesulfonyl-ethyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl}-acetamide; and

25 Cyclopropanecarboxylic acid {2-[2-carbamoyl-1-(4-difluoromethoxy-3-ethoxy-phenyl)-ethyl]-7-chloro-3-oxo-2,3-dihydro-1H-isoindol-4-yl}-amide.

Other selective cytokine inhibitory drugs include 7-amido-substituted isoindolyl compounds found in United States Provisional Application No. 60/454,155 to G. Muller *et al.*, filed March 12, 2003, which is incorporated herein in its entirety by reference.

30 Representative 7-amido-substituted isoindolyl compounds include compounds of the formula:



wherein:

Y is -C(O)-, -CH₂-, -CH₂C(O)- or SO₂;

5 X is H;

Z is (C₀₋₄-alkyl)-C(O)R³, C₁₋₄-alkyl, (C₀₋₄-alkyl)-OH, (C₁₋₄-alkyl)-O(C₁₋₄-alkyl), (C₁₋₄-alkyl)-SO₂(C₁₋₄-alkyl), (C₀₋₄-alkyl)-SO(C₁₋₄-alkyl), (C₀₋₄-alkyl)-NH₂, (C₀₋₄-alkyl)-N(C₁₋₈-alkyl)₂, (C₀₋₄-alkyl)-N(H)(OH), CH₂NSO₂(C₁₋₄-alkyl);

R₁ and R₂ are independently C₁₋₈-alkyl, cycloalkyl, or (C₁₋₄-alkyl)cycloalkyl;

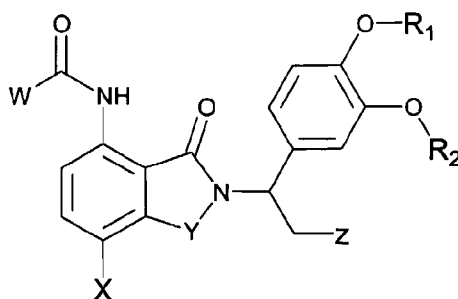
10 R³ is, NR⁴ R⁵, OH, or O-(C₁₋₈-alkyl);

R⁴ is H;

R⁵ is -OH, or -OC(O)R⁶;

R⁶ is C₁₋₈-alkyl, amino-(C₁₋₈-alkyl), (C₁₋₈-alkyl)-(C₃₋₆-cycloalkyl), C₃₋₆-cycloalkyl, phenyl, benzyl, or aryl;

15 or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof; or the formula:

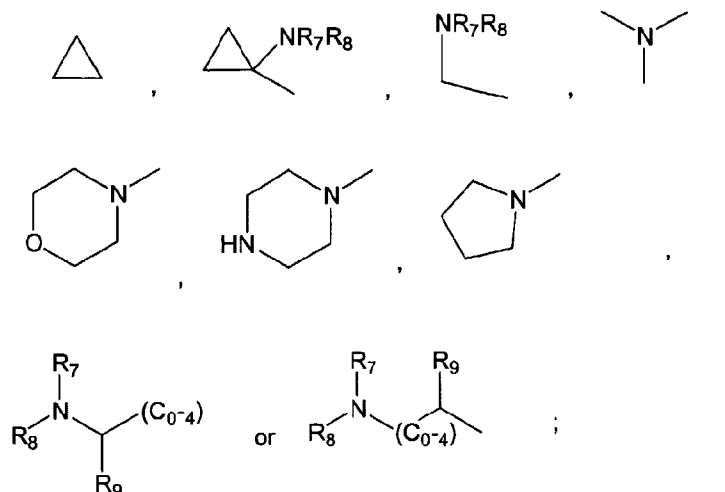


wherein:

Y is -C(O)-, -CH₂-, -CH₂C(O)-, or SO₂;

20 X is halogen, -CN, -NR₇R₈, -NO₂, or -CF₃,

W is



Z is $(\text{C}_{0-4}\text{alkyl})\text{-SO}_2(\text{C}_{1-4}\text{-alkyl})$, $-(\text{C}_{0-4}\text{alkyl})\text{-CN}$, $-(\text{C}_{0-4}\text{alkyl})\text{-C(O)R}^3$, $\text{C}_{1-4}\text{-alkyl}$, $(\text{C}_{0-4}\text{-alkyl})\text{OH}$, $(\text{C}_{0-4}\text{-alkyl})\text{O}(\text{C}_{1-4}\text{-alkyl})$, $(\text{C}_{0-4}\text{-alkyl})\text{SO}(\text{C}_{1-4}\text{-alkyl})$, $(\text{C}_{0-4}\text{-alkyl})\text{NH}_2$, $(\text{C}_{0-4}\text{-alkyl})\text{N}(\text{C}_{1-8}\text{-alkyl})_2$, $(\text{C}_{0-4}\text{-alkyl})\text{N(H)(OH)}$, or $(\text{C}_{0-4}\text{-alkyl})\text{NSO}_2(\text{C}_{1-4}\text{-alkyl})$;

5 W is $-\text{C}_{3-6}\text{-cycloalkyl}$, $-(\text{C}_{1-8}\text{-alkyl})\text{-(C}_{3-6}\text{-cycloalkyl)}$, $-(\text{C}_{0-8}\text{-alkyl})\text{-(C}_{3-6}\text{-cycloalkyl})\text{-NR}_7\text{R}_8$, $(\text{C}_{0-8}\text{-alkyl})\text{-NR}_7\text{R}_8$, $(\text{C}_{0-4}\text{-alkyl})\text{-CHR}_9\text{-(C}_{0-4}\text{-alkyl})\text{-NR}_7\text{R}_8$;

R_1 and R_2 are independently $\text{C}_{1-8}\text{-alkyl}$, cycloalkyl , or $(\text{C}_{1-4}\text{-alkyl})\text{cycloalkyl}$;

R^3 is $\text{C}_{1-8}\text{-alkyl}$, NR^4R^5 , OH , or $\text{O-(C}_{1-8}\text{-alkyl)}$;

R^4 and R^5 are independently H , $\text{C}_{1-8}\text{-alkyl}$, $(\text{C}_{0-8}\text{-alkyl})\text{-(C}_{3-6}\text{-cycloalkyl)}$, OH , or $-\text{OC(O)R}^6$;

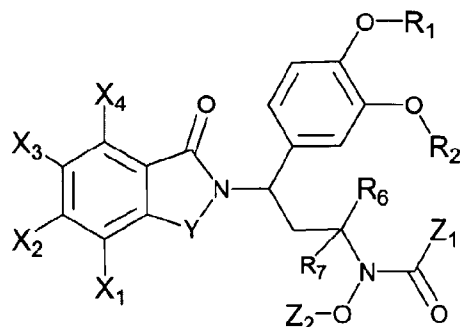
R^6 is $\text{C}_{1-8}\text{-alkyl}$, $(\text{C}_{0-8}\text{-alkyl})\text{-(C}_{3-6}\text{-cycloalkyl)}$, $\text{amino-(C}_{1-8}\text{-alkyl)}$, phenyl , benzyl , or aryl ;

R_7 and R_8 are each independently H , $\text{C}_{1-8}\text{-alkyl}$, $(\text{C}_{0-8}\text{-alkyl})\text{-(C}_{3-6}\text{-cycloalkyl)}$, phenyl , benzyl , aryl , or can be taken together with the atom connecting them to form a 3 to 7 membered heterocycloalkyl or heteroaryl ring;

R_9 is $\text{C}_{1-4}\text{-alkyl}$, $(\text{C}_{0-4}\text{-alkyl})\text{aryl}$, $(\text{C}_{0-4}\text{-alkyl})\text{-(C}_{3-6}\text{-cycloalkyl)}$, $(\text{C}_{0-4}\text{-alkyl})\text{-heterocycle}$;

or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof.

20 Still other selective cytokine inhibitory drugs include N-alkyl-hydroxamic acid-isoindolyl compounds found in United States Provisional Application No. 60/454,149 to G. Muller *et al.*, filed March 12, 2003, which is incorporated herein in its entirety by reference. Representative N-alkyl-hydroxamic acid-isoindolyl compounds include compounds of the formula:



wherein:

Y is -C(O)-, -CH₂, -CH₂C(O)- or SO₂;

R₁ and R₂ are independently C₁₋₈-alkyl, CF₂H, CF₃, CH₂CHF₂, cycloalkyl, or (C₁₋₈-alkyl)cycloalkyl;

Z₁ is H, C₁₋₆-alkyl, -NH₂, -NR₃R₄ or OR₅;

Z₂ is H or C(O)R₅;

X₁, X₂, X₃ and X₄ are each independent H, halogen, NO₂, OR₃, CF₃, C₁₋₆-alkyl, (C₀₋₄-alkyl)-(C₃₋₆-cycloalkyl), (C₀₋₄-alkyl)-N-(R₈R₉), (C₀₋₄-alkyl)-NHC(O)-(R₈), (C₀₋₄-alkyl)-NHC(O)CH(R₈)(R₉), (C₀₋₄-alkyl)-NHC(O)N(R₈R₉), (C₀₋₄-alkyl)-NHC(O)O(R₈), (C₀₋₄-alkyl)-O-R₈, (C₀₋₄-alkyl)-imidazolyl, (C₀₋₄-alkyl)-pyrrolyl, (C₀₋₄-alkyl)-oxadiazolyl, (C₀₋₄-alkyl)-triazolyl or (C₀₋₄-alkyl)-heterocycle;

R₃, R₄, and R₅ are each independently H, C₁₋₆-alkyl, O-C₁₋₆-alkyl, phenyl, benzyl, or aryl;

R₆ and R₇ are independently H or C₁₋₆-alkyl;

R₈ and R₉ are each independently H, C₁₋₉-alkyl, C₃₋₆-cycloalkyl, (C₁₋₆-alkyl)-(C₃₋₆-cycloalkyl), (C₀₋₆-alkyl)-N(R₄R₅), (C₁₋₆-alkyl)-OR₅, phenyl, benzyl, aryl, piperidinyl, piperizinyl, pyrrolidinyl, morpholino, or C₃₋₇-heterocycloalkyl; or

a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof.

Specific selective cytokine inhibitory drugs include, but are not limited to:

2-[1-(3-ethoxy-4-methoxyphenyl)-2-methyl-sulfonyl-ethyl]isoindolin-1-one;

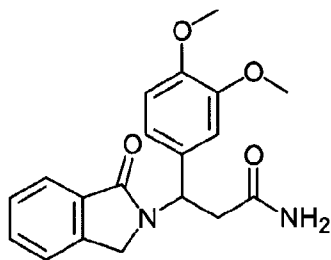
2-[1-(3-ethoxy-4-methoxyphenyl)-2-(N,N-dimethyl-aminosulfonyl)ethyl]isoindolin-1-one;

2-[1-(3-ethoxy-4-methoxyphenyl)-2-methyl-sulfonyl-ethyl]isoindoline-1,3-dione;

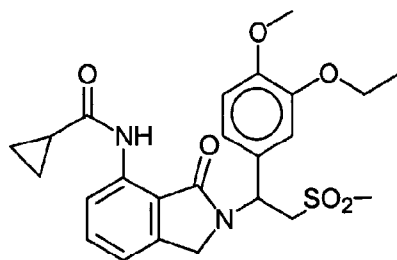
2-[1-(3-ethoxy-4-methoxyphenyl)-2-methyl-sulfonyl-ethyl]-5-nitro-isoindoline-1,3-dione;

2-[1-(3-ethoxy-4-methoxyphenyl)-2-methyl-sulfonyl-ethyl]-4-nitroisoindoline-1,3-dione;

- 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-aminoisoindoline-1,3-dione;
- 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-5-methylisoindoline-1,3-dione;
- 5 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-5-acetamidoisoindoline-1,3-dione;
- 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-dimethylaminoisoindoline-1,3-dione;
- 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-5-
- 10 dimethylaminoisoindoline-1,3-dione;
- 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]benzo[e]isoindoline-1,3-dione;
- 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-methoxyisoindoline-1,3-dione;
- 15 1-(3-cyclopentyloxy-4-methoxyphenyl)-2-methylsulfonylethyl-amine;
- 2-[1-(3-cyclopentyloxy-4-methoxyphenyl)-2-methylsulfonylethyl]isoindoline-1,3-dione; and
- 2-[1-(3-cyclopentyloxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-dimethylaminoisoindoline-1,3-dione.
- 20 Additional selective cytokine inhibitory drugs include the enantiomerically pure compounds disclosed in U.S. provisional patent application nos. 60/366,515 and 60/366,516 to G. Muller *et al.*, both of which were filed March 20, 2002; U.S. provisional patent application nos 60/438, 450 and 60/438,448 to G. Muller *et al.*, both of which were filed on Januray 7, 2003; and U.S. provisional patent application no. 60/452,460 to G. Muller *et al.*
- 25 filed on March 5, 2003, all of which are incorporated herein by reference. Specific compounds include an enantiomer of 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione and an enantiomer of 3-(3,4-dimethoxy-phenyl)-3-(1-oxo-1,3-dihydro-isoindol-2-yl)-propionamide.
- Specific selective cytokine inhibitory drugs used in the invention are 3-(3,4-
- 30 dimethoxy-phenyl)-3-(1-oxo-1,3-dihydro-isoindol-2-yl)-propionamide and cyclopropanecarboxylic acid {2-[1-(3-ethoxy-4-methoxy-phenyl)-2-methanesulfonylethyl]-3-oxo-2,3-dihydro-1 *H*-isoindol-4-yl}-amide, which are available from Celgene Corp., Warren, NJ. 3-(3,4-dimethoxy-phenyl)-3-(1-oxo-1,3-dihydro-isoindol-2-yl)-propionamide has the following chemical structure:



Cyclopropanecarboxylic acid {2-[1-(3-ethoxy-4-methoxy-phenyl)-2-methanesulfonyl-ethyl]-3-oxo-2,3-dihydro-1 *H*-isoindol-4-yl}-amide has the following chemical structure:



Compounds of the invention can either be commercially purchased or prepared according to the methods described in the patents or patent publications disclosed herein. Further, optically pure compounds can be asymmetrically synthesized or resolved using known resolving agents or chiral columns as well as other standard synthetic organic chemistry techniques.

As used herein and unless otherwise indicated, the term "pharmaceutically acceptable salt" encompasses non-toxic acid and base addition salts of the compound to which the term refers. Acceptable non-toxic acid addition salts include those derived from organic and inorganic acids or bases known in the art, which include, for example, hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, methanesulphonic acid, acetic acid, tartaric acid, lactic acid, succinic acid, citric acid, malic acid, maleic acid, sorbic acid, aconitic acid, salicylic acid, phthalic acid, embolic acid, enanthic acid, and the like.

Compounds that are acidic in nature are capable of forming salts with various pharmaceutically acceptable bases. The bases that can be used to prepare pharmaceutically acceptable base addition salts of such acidic compounds are those that form non-toxic base addition salts, *i.e.*, salts containing pharmacologically acceptable cations such as, but not limited to, alkali metal or alkaline earth metal salts and the calcium, magnesium, sodium or potassium salts in particular. Suitable organic bases include, but are not limited to, *N,N*-dibenzylethylenediamine, chlorprocaine, choline, diethanolamine, ethylenediamine, meglumine (*N*-methylglucamine), lysine, and procaine.

As used herein and unless otherwise indicated, the term "prodrug" means a derivative of a compound that can hydrolyze, oxidize, or otherwise react under biological

conditions (*in vitro* or *in vivo*) to provide the compound. Examples of prodrugs include, but are not limited to, derivatives of selective cytokine inhibitory drugs of the invention that comprise biohydrolyzable moieties such as biohydrolyzable amides, biohydrolyzable esters, biohydrolyzable carbamates, biohydrolyzable carbonates, biohydrolyzable ureides, and
5 biohydrolyzable phosphate analogues. Other examples of prodrugs include derivatives of selective cytokine inhibitory drugs of the invention that comprise -NO, -NO₂, -ONO, or -ONO₂ moieties. Prodrugs can typically be prepared using well-known methods, such as those described in 1 *Burger's Medicinal Chemistry and Drug Discovery*, 172-178, 949-982 (Manfred E. Wolff *ed.*, 5th ed. 1995), and *Design of Prodrugs* (H. Bundgaard *ed.*, Elsevier,
10 New York 1985).

As used herein and unless otherwise indicated, the terms "biohydrolyzable amide," "biohydrolyzable ester," "biohydrolyzable carbamate," "biohydrolyzable carbonate," "biohydrolyzable ureide," "biohydrolyzable phosphate" mean an amide, ester, carbamate, carbonate, ureide, or phosphate, respectively, of a compound that either: 1) does not
15 interfere with the biological activity of the compound but can confer upon that compound advantageous properties *in vivo*, such as uptake, duration of action, or onset of action; or 2) is biologically inactive but is converted *in vivo* to the biologically active compound. Examples of biohydrolyzable esters include, but are not limited to, lower alkyl esters, lower acyloxyalkyl esters (such as acetoxymethyl, acetoxylethyl, aminocarbonyloxymethyl,
20 pivaloyloxymethyl, and pivaloyloxyethyl esters), lactonyl esters (such as phthalidyl and thiophthalidyl esters), lower alkoxyacyloxyalkyl esters (such as methoxycarbonyloxymethyl, ethoxycarbonyloxyethyl and isopropoxycarbonyloxyethyl esters), alkoxyalkyl esters, choline esters, and acylamino alkyl esters (such as acetamidomethyl esters). Examples of biohydrolyzable amides include, but are not limited to, lower alkyl amides,
25 α -amino acid amides, alkoxyacyl amides, and alkylaminoalkylcarbonyl amides. Examples of biohydrolyzable carbamates include, but are not limited to, lower alkylamines, substituted ethylenediamines, amino acids, hydroxyalkylamines, heterocyclic and heteroaromatic amines, and polyether amines.

Various selective cytokine inhibitory drugs of the invention contain one or more
30 chiral centers, and can exist as racemic mixtures of enantiomers or mixtures of diastereomers. This invention encompasses the use of stereomerically pure forms of such compounds, as well as the use of mixtures of those forms. For example, mixtures comprising equal or unequal amounts of the enantiomers of a particular selective cytokine inhibitory drugs of the invention may be used in methods and compositions of the
35 invention. These isomers may be asymmetrically synthesized or resolved using standard

techniques such as chiral columns or chiral resolving agents. *See, e.g.,* Jacques, J., *et al.*, *Enantiomers, Racemates and Resolutions* (Wiley-Interscience, New York, 1981); Wilen, S. H., *et al.*, *Tetrahedron* 33:2725 (1977); Eliel, E. L., *Stereochemistry of Carbon Compounds* (McGraw-Hill, NY, 1962); and Wilen, S. H., *Tables of Resolving Agents and Optical Resolutions* p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN, 1972).

As used herein and unless otherwise indicated, the term "stereomerically pure" means a composition that comprises one stereoisomer of a compound and is substantially free of other stereoisomers of that compound. For example, a stereomerically pure composition of a compound having one chiral center will be substantially free of the opposite enantiomer of the compound. A stereomerically pure composition of a compound having two chiral centers will be substantially free of other diastereomers of the compound. A typical stereomerically pure compound comprises greater than about 80% by weight of one stereoisomer of the compound and less than about 20% by weight of other stereoisomers of the compound, more preferably greater than about 90% by weight of one stereoisomer of the compound and less than about 10% by weight of the other stereoisomers of the compound, even more preferably greater than about 95% by weight of one stereoisomer of the compound and less than about 5% by weight of the other stereoisomers of the compound, and most preferably greater than about 97% by weight of one stereoisomer of the compound and less than about 3% by weight of the other stereoisomers of the compound. As used herein and unless otherwise indicated, the term "stereomerically enriched" means a composition that comprises greater than about 60% by weight of one stereoisomer of a compound, preferably greater than about 70% by weight, more preferably greater than about 80% by weight of one stereoisomer of a compound. As used herein and unless otherwise indicated, the term "enantiomerically pure" means a stereomerically pure composition of a compound having one chiral center. Similarly, the term "stereomerically enriched" means a stereomerically enriched composition of a compound having one chiral center.

It should be noted that if there is a discrepancy between a depicted structure and a name given that structure, the depicted structure is to be accorded more weight. In addition, if the stereochemistry of a structure or a portion of a structure is not indicated with, for example, bold or dashed lines, the structure or portion of the structure is to be interpreted as encompassing all stereoisomers of it.

4.2 SECOND ACTIVE AGENTS

Selective cytokine inhibitory drugs can be combined with other pharmacologically active compounds ("second active agents") in methods and compositions of the invention. It is believed that certain combinations work synergistically in the treatment of particular types of cancer and certain diseases and conditions associated with, or characterized by, undesired angiogenesis. Selective cytokine inhibitory drugs can also work to alleviate adverse effects associated with certain second active agents, and some second active agents can be used to alleviate adverse effects associated with selective cytokine inhibitory drugs.

One or more second active ingredients or agents can be used in the methods and compositions of the invention together with a selective cytokine inhibitory drug. Second active agents can be large molecules (*e.g.*, proteins) or small molecules (*e.g.*, synthetic inorganic, organometallic, or organic molecules).

Examples of large molecule active agents include, but are not limited to, hematopoietic growth factors, cytokines, and monoclonal and polyclonal antibodies. Typical large molecule active agents are biological molecules, such as naturally occurring or artificially made proteins. Proteins that are particularly useful in this invention include proteins that stimulate the survival and/or proliferation of hematopoietic precursor cells and immunologically active poietic cells *in vitro* or *in vivo*. Others stimulate the division and differentiation of committed erythroid progenitors in cells *in vitro* or *in vivo*. Particular proteins include, but are not limited to: interleukins, such as IL-2 (including recombinant IL-II ("rIL2") and canarypox IL-2), IL-10, IL-12, and IL-18; interferons, such as interferon alfa-2a, interferon alfa-2b, interferon alfa-n1, interferon alfa-n3, interferon beta-I a, and interferon gamma-I b; GM-CSF and GM-CSF; and EPO.

Particular proteins that can be used in the methods and compositions of the invention include, but are not limited to: filgrastim, which is sold in the United States under the trade name Neupogen® (Amgen, Thousand Oaks, CA); sargramostim, which is sold in the United States under the trade name Leukine® (Immunex, Seattle, WA); and recombinant EPO, which is sold in the United States under the trade name Epogen® (Amgen, Thousand Oaks, CA).

Recombinant and mutated forms of GM-CSF can be prepared as described in U.S. patent nos. 5,391,485; 5,393,870; and 5,229,496; all of which are incorporated herein by reference. Recombinant and mutated forms of G-CSF can be prepared as described in U.S. patent nos. 4,810,643; 4,999,291; 5,528,823; and 5,580,755; all of which are incorporated herein by reference.

This invention encompasses the use of native, naturally occurring, and recombinant proteins. The invention further encompasses mutants and derivatives (*e.g.*, modified forms) of naturally occurring proteins that exhibit, *in vivo*, at least some of the pharmacological activity of the proteins upon which they are based. Examples of mutants include, but are not limited to, proteins that have one or more amino acid residues that differ from the corresponding residues in the naturally occurring forms of the proteins. Also encompassed by the term “mutants” are proteins that lack carbohydrate moieties normally present in their naturally occurring forms (*e.g.*, nonglycosylated forms). Examples of derivatives include, but are not limited to, pegylated derivatives and fusion proteins, such as proteins formed by fusing IgG1 or IgG3 to the protein or active portion of the protein of interest. *See, e.g.*, Penichet, M.L. and Morrison, S.L., *J. Immunol. Methods* 248:91-101 (2001).

Antibodies that can be used in combination with compounds of the invention include monoclonal and polyclonal antibodies. Examples of antibodies include, but are not limited to, trastuzumab (Herceptin[®]), rituximab (Rituxan[®]), bevacizumab (Avastin[™]), pertuzumab (Omnitarg[™]), tositumomab (Bexxar[®]), edrecolomab (Panorex[®]), and G250. Compounds of the invention can also be combined with, or used in combination with, anti-TNF- α antibodies.

Large molecule active agents may be administered in the form of anti-cancer vaccines. For example, vaccines that secrete, or cause the secretion of, cytokines such as IL-2, G-CSF, and GM-CSF can be used in the methods, pharmaceutical compositions, and kits of the invention. *See, e.g.*, Emens, L.A., *et al.*, *Curr. Opinion Mol. Ther.* 3(1):77-84 (2001).

In one embodiment of the invention, the large molecule active agent reduces, eliminates, or prevents an adverse effect associated with the administration of a selective cytokine inhibitory drug. Depending on the particular selective cytokine inhibitory drug and the disease or disorder being treated, adverse effects can include, but are not limited to, drowsiness and somnolence, dizziness and orthostatic hypotension, neutropenia, infections that result from neutropenia, increased HIV-viral load, bradycardia, Stevens-Johnson Syndrome and toxic epidermal necrolysis, and seizures (*e.g.*, grand mal convulsions). A specific adverse effect is neutropenia.

Second active agents that are small molecules can also be used to alleviate adverse effects associated with the administration of a selective cytokine inhibitory drug. However, like some large molecules, many are believed to be capable of providing a synergistic effect when administered with (*e.g.*, before, after or simultaneously) a selective cytokine

inhibitory drug. Examples of small molecule second active agents include, but are not limited to, anti-cancer agents, antibiotics, immunosuppressive agents, and steroids.

Examples of anti-cancer agents include, but are not limited to: acivicin; aclarubicin; acodazole hydrochloride; acronine; adozelesin; aldesleukin; altretamine; ambomycin; 5 ametantrone acetate; amsacrine; anastrozole; anthramycin; asparaginase; asperlin; azacitidine; azetepa; azotomycin; batimastat; benzodepa; bicalutamide; bisantrene hydrochloride; bisnafide dimesylate; bizelesin; bleomycin sulfate; brequinar sodium; bropiramine; busulfan; cactinomycin; calusterone; caracemide; carbetimer; carboplatin; carmustine; carubicin hydrochloride; carzelesin; cedefingol; celecoxib (COX-2 inhibitor); 10 chlorambucil; cirolemycin; cisplatin; cladribine; crisnatol mesylate; cyclophosphamide; cytarabine; dacarbazine; dactinomycin; daunorubicin hydrochloride; decitabine; dexormaplatin; dezaguanine; dezaguanine mesylate; diaziquone; docetaxel; doxorubicin; doxorubicin hydrochloride; droloxifene; droloxifene citrate; dromostanolone propionate; duazomycin; edatrexate; eflornithine hydrochloride; elsamitrucin; enloplatin; enpromate; 15 epiropidine; epirubicin hydrochloride; erbulozole; esorubicin hydrochloride; estramustine; estramustine phosphate sodium; etanidazole; etoposide; etoposide phosphate; etoprine; fadrozole hydrochloride; fazarabine; fenretinide; floxuridine; fludarabine phosphate; fluorouracil; flurocitabine; fosquidone; fostriecin sodium; gemcitabine; gemcitabine hydrochloride; hydroxyurea; idarubicin hydrochloride; ifosfamide; ilmofofosine; iproplatin; 20 irinotecan; irinotecan hydrochloride; lanreotide acetate; letrozole; leuprolide acetate; liarozole hydrochloride; lometrexol sodium; lomustine; losoxantrone hydrochloride; masoprocol; maytansine; mechlorethamine hydrochloride; megestrol acetate; melengestrol acetate; melphalan; menogaril; mercaptopurine; methotrexate; methotrexate sodium; metoprine; meturedopa; mitindomide; mitocarcin; mitocromin; mitogillin; mitomalcin; 25 mitomycin; mitosper; mitotane; mitoxantrone hydrochloride; mycophenolic acid; nocodazole; nogalamycin; ormaplatin; oxisuran; paclitaxel; pegaspargase; peliomycin; pentamustine; peplomycin sulfate; perfosfamide; pipobroman; piposulfan; piroxantrone hydrochloride; plicamycin; plomestane; porfimer sodium; porfiromycin; prednimustine; procarbazine hydrochloride; puromycin; puromycin hydrochloride; pyrazofurin; riboprine; 30 safingol; safingol hydrochloride; semustine; simtrazene; sparfosate sodium; sparsomycin; spirogermanium hydrochloride; spiromustine; spiroplatin; streptonigrin; streptozocin; sulofenur; talisomycin; tecogalan sodium; taxotere; tegafur; teloxantrone hydrochloride; temoporfin; teniposide; teroxirone; testolactone; thiamiprine; thioguanine; thiotepa; tiazofurin; tirapazamine; toremifene citrate; trestolone acetate; tricyclic phosphate;

trimetrexate; trimetrexate glucuronate; triptorelin; tubulozole hydrochloride; uracil mustard; uredepa; vapreotide; verteporfin; vinblastine sulfate; vincristine sulfate; vindesine; vindesine sulfate; vinepidine sulfate; vinglycinat sulfate; vinleurosine sulfate; vinorelbine tartrate; vinrosidine sulfate; vinzolidine sulfate; vorozole; zeniplatin; zinostatin; and
 5 zorubicin hydrochloride.

Other anti-cancer drugs include, but are not limited to: 20-epi-1,25 dihydroxyvitamin D3; 5-ethynyluracil; abiraterone; aclarubicin; acylfulvene; adecypenol; adozelesin; aldesleukin; ALL-TK antagonists; altretamine; ambamustine; amidox; amifostine; aminolevulinic acid; amrubicin; amsacrine; anagrelide; anastrozole;
 10 andrographolide; angiogenesis inhibitors; antagonist D; antagonist G; antarelix; anti-dorsalizing morphogenetic protein-1; antiandrogen, prostatic carcinoma; antiestrogen; antineoplaston; antisense oligonucleotides; aphidicolin glycinate; apoptosis gene modulators; apoptosis regulators; apurinic acid; ara-CDP-DL-PTBA; arginine deaminase; asulacrine; atamestane; atrimustine; axinastatin 1; axinastatin 2; axinastatin 3; azasetron;
 15 azatoxin; azatyrosine; baccatin III derivatives; balanol; batimastat; BCR/ABL antagonists; benzochlorins; benzoylstauosporine; beta lactam derivatives; beta-alethine; betaclamycin B; betulinic acid; bFGF inhibitor; bicalutamide; bisantrene; bisaziridinylspermine; bisnafide; bistratene A; bizelesin; breflate; broprimine; budotitane; buthionine sulfoximine; calcipotriol; calphostin C; camptothecin derivatives; capecitabine;
 20 carboxamide-amino-triazole; carboxyamidotriazole; CaRest M3; CARN 700; cartilage derived inhibitor; carzelesin; casein kinase inhibitors (ICOS); castanospermine; cecropin B; cetorelix; chlorins; chloroquinoxaline sulfonamide; cicaprost; cis-porphyrin; cladribine; clomifene analogues; clotrimazole; collismycin A; collismycin B; combretastatin A4; combretastatin analogue; conagenin; crambescidin 816; crisnatol; cryptophycin 8;
 25 cryptophycin A derivatives; curacin A; cyclopentantraquinones; cycloplatam; cypemycin; cytarabine ocfosfate; cytolytic factor; cytostatin; dacliximab; decitabine; dehydrodidemnin B; deslorelin; dexamethasone; dexifosfamide; dexrazoxane; dexverapamil; diaziquone; didemnin B; didox; diethylnorspermine; dihydro-5-azacytidine; dihydrotaxol, 9-;
 dioxamycin; diphenyl spiromustine; docetaxel; docosanol; dolasetron; doxifluridine;
 30 doxorubicin; droloxifene; dronabinol; duocarmycin SA; ebselen; ecomustine; edelfosine; edrecolomab; eflornithine; elemene; emitefur; epirubicin; epristeride; estramustine analogue; estrogen agonists; estrogen antagonists; etanidazole; etoposide phosphate; exemestane; fadrozole; fazarabine; fenretinide; filgrastim; finasteride; flavopiridol; flezelastine; fluasterone; fludarabine; fluorodaunorubicin hydrochloride; forfenimex;

- formestane; fostriecin; fotemustine; gadolinium texaphyrin; gallium nitrate; galocitabine; ganirelix; gelatinase inhibitors; gemcitabine; glutathione inhibitors; hepsulfam; heregulin; hexamethylene bisacetamide; hypericin; ibandronic acid; idarubicin; idoxifene; idramantone; ilmofofosine; ilomastat; imatinib (*e.g.*, Gleevec[®]), imiquimod; immunostimulant
- 5 peptides; insulin-like growth factor-1 receptor inhibitor; interferon agonists; interferons; interleukins; iobenguane; iododoxorubicin; ipomeanol, 4-; iroplact; irsogladine; isobengazole; isohomohalicondrin B; itasetron; jasplakinolide; kahalalide F; lamellarin-N triacetate; lanreotide; leinamycin; lenograstim; lentinan sulfate; leptolstatin; letrozole; leukemia inhibiting factor; leukocyte alpha interferon; leuprolide+estrogen+progesterone;
- 10 leuprorelin; levamisole; liarozole; linear polyamine analogue; lipophilic disaccharide peptide; lipophilic platinum compounds; lissoclinamide 7; lobaplatin; lombricine; lometrexol; lonidamine; losoxantrone; loxoribine; lurtotecan; lutetium texaphyrin; lysofylline; lytic peptides; maitansine; mannostatin A; marimastat; masoprocol; maspin; matrilysin inhibitors; matrix metalloproteinase inhibitors; menogaril; merbarone; meterelin;
- 15 methioninase; metoclopramide; MIF inhibitor; mifepristone; miltefosine; mirimostim; mitoguazone; mitolactol; mitomycin analogues; mitonafide; mitotoxin fibroblast growth factor-saporin; mitoxantrone; mofarotene; molgramostim; Erbitux, human chorionic gonadotrophin; monophosphoryl lipid A+mycobacterium cell wall sk; mopidamol; mustard anticancer agent; mycaperoxide B; mycobacterial cell wall extract; myriaporone;
- 20 N-acetyldinaline; N-substituted benzamides; nafarelin; nagrestip; naloxone+pentazocine; napavin; naphterpin; nartograstim; nedaplatin; nemorubicin; neridronic acid; nilutamide; nisamycin; nitric oxide modulators; nitroxide antioxidant; nitrullyn; oblimersen (Genasense[®]); O⁶-benzylguanine; octreotide; okicenone; oligonucleotides; onapristone; ondansetron; ondansetron; oracin; oral cytokine inducer; ormaplatin; osaterone; oxaliplatin;
- 25 oxaunomycin; paclitaxel; paclitaxel analogues; paclitaxel derivatives; palauamine; palmitoylrhizoxin; pamidronic acid; panaxytriol; panomifene; parabactin; pazelliptine; pegaspargase; peldesine; pentosan polysulfate sodium; pentostatin; pentrozele; perflubron; perfosfamide; perillyl alcohol; phenazinomycin; phenylacetate; phosphatase inhibitors; picibanil; pilocarpine hydrochloride; pirarubicin; piritrexim; placetin A; placetin B;
- 30 plasminogen activator inhibitor; platinum complex; platinum compounds; platinum-triamine complex; porfimer sodium; porfiromycin; prednisone; propyl bis-acridone; prostaglandin J2; proteasome inhibitors; protein A-based immune modulator; protein kinase C inhibitor; protein kinase C inhibitors, microalgal; protein tyrosine phosphatase inhibitors; purine nucleoside phosphorylase inhibitors; purpurins;

pyrazoloacridine; pyridoxylated hemoglobin polyoxyethylene conjugate; raf antagonists; raltitrexed; ramosetron; ras farnesyl protein transferase inhibitors; ras inhibitors; ras-GAP inhibitor; retelliptine demethylated; rhenium Re 186 etidronate; rhizoxin; ribozymes; RII retinamide; rohitukine; romurtide; roquinimex; rubiginone B1; ruboxyl; safingol; saintopin; 5 SarCNU; sarcophytol A; sargramostim; Sdi 1 mimetics; semustine; senescence derived inhibitor 1; sense oligonucleotides; signal transduction inhibitors; sizofiran; sobuzoxane; sodium borocaptate; sodium phenylacetate; solverol; somatomedin binding protein; sonermin; sparfosic acid; spicamycin D; spiromustine; splenopentin; spongistatin 1; squalamine; stipiamide; stromelysin inhibitors; sulfinosine; superactive vasoactive intestinal 10 peptide antagonist; suradista; suramin; swainsonine; tallimustine; tamoxifen methiodide; tauromustine; tazarotene; tecogalan sodium; tegafur; tellurapyrylium; telomerase inhibitors; temoporfin; teniposide; tetrachlorodecaoxide; tetrazomine; thaliblastine; thiocoraline; thrombopoietin; thrombopoietin mimetic; thymalfasin; thymopoietin receptor agonist; thymotrigan; thyroid stimulating hormone; tin ethyl etiopurpurin; tirapazamine; titanocene 15 bichloride; topsentin; toremifene; translation inhibitors; tretinoin; triacetyluridine; tricinibine; trimetrexate; triptorelin; tropisetron; turosteride; tyrosine kinase inhibitors; tyrphostins; UBC inhibitors; ubenimex; urogenital sinus-derived growth inhibitory factor; urokinase receptor antagonists; vapreotide; variolin B; velaresol; veramine; verdins; verteporfin; vinorelbine; vinxaltine; vitaxin; vorozole; zanoterone; zeniplatin; zilascorb; and 20 zinostatin stimalamer.

Specific second active agents include, but are not limited to, oblimersen (Genasense[®]), remicade, docetaxel, celecoxib, melphalan, dexamethasone (Decadron[®]), steroids, gemcitabine, cisplatin, temozolomide, etoposide, cyclophosphamide, temodar, carboplatin, procarbazine, gliadel, tamoxifen, topotecan, methotrexate, Arisa[®], taxol, 25 taxotere, fluorouracil, leucovorin, irinotecan, xeloda, CPT-11, interferon alpha, pegylated interferon alpha (*e.g.*, PEG INTRON-A), capecitabine, cisplatin, thiotepa, fludarabine, carboplatin, liposomal daunorubicin, cytarabine, doxetaxol, paclitaxel, vinblastine, IL-2, GM-CSF, dacarbazine, vinorelbine, zoledronic acid, palmitronate, biaxin, busulphan, prednisone, bisphosphonate, arsenic trioxide, vincristine, doxorubicin (Doxil[®]), paclitaxel, 30 ganciclovir, adriamycin, estramustine sodium phosphate (Emcy[®]), sulindac, and etoposide.

4.3 METHODS OF TREATMENTS AND PREVENTION

Methods of this invention encompass methods of treating, preventing and/or managing various types of cancer and diseases and disorders associated with, or characterized by, undesired angiogenesis. As used herein, unless otherwise specified, the

term "treating" refers to the administration of a compound of the invention or other additional active agent after the onset of symptoms of the particular disease or disorder. As used herein, unless otherwise specified, the term "preventing" refers to the administration prior to the onset of symptoms, particularly to patients at risk of cancer, and other diseases and disorders associated with, or characterized by, undesired angiogenesis. The term "prevention" includes the inhibition of a symptom of the particular disease or disorder. Patients with familial history of cancer and diseases and disorders associated with, or characterized by, undesired angiogenesis are preferred candidates for preventive regimens. As used herein and unless otherwise indicated, the term "managing" encompasses preventing the recurrence of the particular disease or disorder in a patient who had suffered from it, and/or lengthening the time a patient who had suffered from the disease or disorder remains in remission.

As used herein, the term "cancer" includes, but is not limited to, solid tumors and blood born tumors. The term "cancer" refers to disease of skin tissues, organs, blood, and vessels, including, but not limited to, cancers of the bladder, bone or blood, brain, breast, cervix, chest, colon, endometrium, esophagus, eye, head, kidney, liver, lymph nodes, lung, mouth, neck, ovaries, pancreas, prostate, rectum, stomach, testis, throat, and uterus. Specific cancers include, but are not limited to, advanced malignancy, amyloidosis, neuroblastoma, meningioma, hemangiopericytoma, multiple brain metastase, glioblastoma multiforms, glioblastoma, brain stem glioma, poor prognosis malignant brain tumor, malignant glioma, recurrent malignant glioma, anaplastic astrocytoma, anaplastic oligodendroglioma, neuroendocrine tumor, rectal adenocarcinoma, Dukes C & D colorectal cancer, unresectable colorectal carcinoma, metastatic hepatocellular carcinoma, Kaposi's sarcoma, karotype acute myeloblastic leukemia, Hodgkin's lymphoma, non-Hodgkin's lymphoma, cutaneous T-Cell lymphoma, cutaneous B-Cell lymphoma, diffuse large B-Cell lymphoma, low grade follicular lymphoma, malignant melanoma, malignant mesothelioma, malignant pleural effusion mesothelioma syndrome, peritoneal carcinoma, papillary serous carcinoma, gynecologic sarcoma, soft tissue sarcoma, scleroderma, cutaneous vasculitis, Langerhans cell histiocytosis, leiomyosarcoma, fibrodysplasia ossificans progressive, hormone refractory prostate cancer, resected high-risk soft tissue sarcoma, unresectable hepatocellular carcinoma, Waldenstrom's macroglobulinemia, smoldering myeloma, indolent myeloma, fallopian tube cancer, androgen independent prostate cancer, androgen dependent stage IV non-metastatic prostate cancer, hormone-insensitive prostate cancer, chemotherapy-insensitive prostate cancer, papillary thyroid carcinoma, follicular thyroid

carcinoma, medullary thyroid carcinoma, and leiomyoma. In a specific embodiment, the cancer is metastatic. In another embodiment, the cancer is refractory or resistance to chemotherapy or radiation; in particular, refractory to thalidomide.

As used herein to refer to diseases and conditions other than cancer, the terms
5 “diseases or disorders associated with, or characterized by, undesired angiogenesis,”
“diseases or disorders associated with undesired angiogenesis,” and “diseases or disorders
characterized by undesired angiogenesis” refer to diseases, disorders and conditions that are
caused, mediated or attended by undesired, unwanted or uncontrolled angiogenesis,
including, but not limited to, inflammatory diseases, autoimmune diseases, genetic diseases,
10 allergic diseases, bacterial diseases, ocular neovascular diseases, choroidal neovascular
diseases, and retina neovascular diseases.

Examples of such diseases or disorders associated with undesired angiogenesis
include, but are not limited to, diabetic retinopathy, retinopathy of prematurity, corneal graft
rejection, neovascular glaucoma, retrolental fibroplasia, proliferative vitreoretinopathy,
15 trachoma, myopia, optic pits, epidemic keratoconjunctivitis, atopic keratitis, superior
limbic keratitis, pterygium keratitis sicca, sjogrens, acne rosacea, phlyctenulosis, syphilis,
lipid degeneration, bacterial ulcer, fungal ulcer, Herpes simplex infection, Herpes zoster
infection, protozoan infection, Kaposi sarcoma, Mooren ulcer, Terrien’s marginal
degeneration, marginal keratolysis, rheumatoid arthritis, systemic lupus, polyarteritis,
20 trauma, Wegeners sarcoidosis, Scleritis, Steven’s Johnson disease, periphigoid radial
keratotomy, sickle cell anemia, sarcoid, pseudoxanthoma elasticum, Pagets disease, vein
occlusion, artery occlusion, carotid obstructive disease, chronic uveitis, chronic vitritis,
Lyme’s disease, Eales disease, Bechets disease, retinitis, choroiditis, presumed ocular
histoplasmosis, Bests disease, Stargarts disease, pars planitis, chronic retinal detachment,
25 hyperviscosity syndromes, toxoplasmosis, rubeosis, sarcodiosis, sclerosis, soriatis, psoriasis,
primary sclerosing cholangitis, proctitis, primary biliary srosis, idiopathic pulmonary
fibrosis, and alcoholic hepatitis.

In specific embodiments of the invention, diseases or disorders associated with
undesired angiogenesis do not include congestive heart failure, cardiomyopathy, pulmonary
30 edema, endotoxin-mediated septic shock, acute viral myocarditis, cardiac allograft rejection,
myocardial infarction, HIV, hepatitis, adult respiratory distress syndrome, bone-resorption
disease, chronic obstructive pulmonary diseases, chronic pulmonary inflammatory disease,
dermatitis, cystic fibrosis, septic shock, sepsis, endotoxic shock, hemodynamic shock,
sepsis syndrome, post ischemic reperfusion injury, meningitis, psoriasis, fibrotic disease,

cachexia, graft rejection, rheumatoid spondylitis, osteoporosis, Crohn's disease, ulcerative colitis, inflammatory-bowel disease, multiple sclerosis, systemic lupus erythematosus, erythema nodosum leprosum in leprosy, radiation damage, asthma, hyperoxic alveolar injury, malaria, mycobacterial infection, and opportunistic infections resulting from HIV.

5 This invention encompasses methods of treating patients who have been previously treated for cancer or diseases or disorders associated with, or characterized by, undesired angiogenesis, but are non-responsive to standard therapies, as well as those who have not previously been treated. The invention also encompasses methods of treating patients regardless of patient's age, although some diseases or disorders are more common in certain
10 age groups. The invention further encompasses methods of treating patients who have undergone surgery in an attempt to treat the disease or condition at issue, as well as those who have not. Because patients with cancer and diseases and disorders characterized by undesired angiogenesis have heterogenous clinical manifestations and varying clinical outcomes, the treatment given to a patient may vary, depending on his/her prognosis. The
15 skilled clinician will be able to readily determine without undue experimentation specific secondary agents, types of surgery, and types of non-drug based standard therapy that can be effectively used to treat an individual patient with cancer and other diseases or disorders.

 Methods encompassed by this invention comprise administering one or more selective cytokine inhibitory drug of the invention, or a pharmaceutically acceptable salt,
20 solvate, hydrate, stereoisomer, clathrate, or prodrug thereof, to a patient (*e.g.*, a human) suffering, or likely to suffer, from cancer or a disease or disorder mediated by undesired angiogenesis.

 In one embodiment of the invention, the recommended daily dose range of a selective cytokine inhibitory drug for the conditions described herein lie within the range of
25 from about 1 mg to about 10,000 mg per day, given as a single once-a-day dose, or preferably in divided doses throughout a day. More specifically, the daily dose is administered twice daily in equally divided doses. Specifically, a daily dose range should be from about 1 mg to about 5,000 mg per day, more specifically, between about 10 mg and about 2,500 mg per day, between about 100 mg and about 800 mg per day, between
30 about 100 mg and about 1,200 mg per day, or between about 25 mg and about 2,500 mg per day. In managing the patient, the therapy should be initiated at a lower dose, perhaps about 1 mg to about 2,500 mg, and increased if necessary up to about 200 mg to about 5,000 mg per day as either a single dose or divided doses, depending on the patient's global response. In a particular embodiment, 3-(3,4-dimethoxy-phenyl)-3-(1-oxo-1,3-dihydro-isoindol-2-yl)-

propionamide can be preferably administered in an amount of about 400, 800, 1,200, 2,500, 5,000 or 10,000 mg a day as two divided doses.

In a specific embodiment, 3-(3,4-dimethoxy-phenyl)-3-(1-oxo-1,3-dihydro-isoindol-2-yl)-propionamide may be administered in an amount of about 400, 800, or 1,200
5 mg per day to patients with relapsed multiple myeloma. In a particular embodiment, 3-(3,4-dimethoxy-phenyl)-3-(1-oxo-1,3-dihydro-isoindol-2-yl)-propionamide may be administered initially in an amount of 100 mg/day and the dose can be escalated every week to 200, 400, 800, 1,200, and 2,500 mg/day. In a specific embodiment, the compound can be administered in an amount of up to about 5,000 mg/day to patients with solid tumor. In a
10 particular embodiment, the compound can be administered in an amount of up to about 10,000 mg/day to patients with glioma.

In a specific embodiment, 3-(3,4-dimethoxy-phenyl)-3-(1-oxo-1,3-dihydro-isoindol-2-yl)-propionamide may be administered to patients with Crohn's disease initially in an amount of 400 mg and can be escalated to 800 mg and 1200 mg daily.

15 **4.3.1 Combination Therapy With A Second Active Agent**

Specific methods of the invention comprise administering a selective cytokine inhibitory drug of the invention, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof, in combination with one or more second active agents, and/or in combination with radiation therapy, blood transfusions, or surgery.

20 Examples of selective cytokine inhibitory drugs of the invention are disclosed herein (*see, e.g.,* section 4.1). Examples of second active agents are also disclosed herein (*see, e.g.,* section 4.2).

Administration of the selective cytokine inhibitory drugs and the second active agents to a patient can occur simultaneously or sequentially by the same or different routes
25 of administration. The suitability of a particular route of administration employed for a particular active agent will depend on the active agent itself (*e.g.,* whether it can be administered orally without decomposing prior to entering the blood stream) and the disease being treated. A preferred route of administration for a selective cytokine inhibitory drug of the invention is oral or ophthalmic. Preferred routes of administration for the second active
30 agents or ingredients of the invention are known to those of ordinary skill in the art. *See, e.g., Physicians' Desk Reference*, 1755-1760 (56th ed., 2002).

In one embodiment of the invention, the second active agent is administered intravenously or subcutaneously and once or twice daily in an amount of from about 1 to about 1000 mg, from about 5 to about 500 mg, from about 10 to about 350 mg, or from

about 50 to about 200 mg. The specific amount of the second active agent will depend on the specific agent used, the type of disease being treated or managed, the severity and stage of disease, and the amount(s) of selective cytokine inhibitory drugs of the invention and any optional additional active agents concurrently administered to the patient. In a particular
5 embodiment, the second active agent is oblimersen (Genasense[®]), GM-CSF, G-CSF, EPO, taxotere, irinotecan, dacarbazine, transretinoic acid, topotecan, pentoxifylline, ciprofloxacin, dexamethasone, vincristine, doxorubicin, cox-2 inhibitors, IL2, IL8, IL18, IFN, Ara-C, vinorelbine, or a combination thereof.

In a particular embodiment, GM-CSF, G-CSF or EPO is administered
10 subcutaneously during about five days in a four or six week cycle in an amount of from about 1 to about 750 mg/m²/day, preferably in an amount of from about 25 to about 500 mg/m²/day, more preferably in an amount of from about 50 to about 250 mg/m²/day, and most preferably in an amount of from about 50 to about 200 mg/m²/day. In a certain embodiment, GM-CSF may be administered in an amount of from about 60 to about 500
15 mcg/m² intravenously over 2 hours, or from about 5 to about 12 mcg/m²/day subcutaneously. In a specific embodiment, G-CSF may be administered subcutaneously in an amount of about 1 mcg/kg/day initially and can be adjusted depending on rise of total granulocyte counts. The maintenance dose of G-CSF may be administered in an amount of about 300 (in smaller patients) or 480 mcg subcutaneously. In a certain embodiment, EPO
20 may be administered subcutaneously in an amount of 10,000 Unit 3 times per week.

In another embodiment, 3-(3,4-dimethoxy-phenyl)-3-(1-oxo-1,3-dihydro-isoindol-2-yl)-propionamide in an amount of about 25 mg/d and dacarbazine in an amount of about
from 800 to 1,200 mg/m²/d are administered to patients with metastatic malignant melanoma. In a specific embodiment, 3-(3,4-dimethoxy-phenyl)-3-(1-oxo-1,3-dihydro-
25 isoindol-2-yl)-propionamide is administered in an amount of from about 200 to about 800 mg/d to patients with metastatic malignant melanoma whose disease has progressed on treatment with dacarbazine, IL-2 or IFN. In a specific embodiment, 3-(3,4-dimethoxy-phenyl)-3-(1-oxo-1,3-dihydro-isoindol-2-yl)-propionamide is administered to patients with relapsed or refractory multiple myeloma in an amount of about 400 mg/d twice a day or
30 about 800 mg/d four times a day in a combination with dexamethasone.

In another embodiment, a selective cytokine inhibitory drug is administered with melphalan and dexamethasone to patients with amyloidosis. In a specific embodiment, a selective cytokine inhibitory drug of the invention and steroids can be administered to patients with amyloidosis.

In another embodiment, a selective cytokine inhibitory drug is administered with gemcitabine and cisplatin to patients with locally advanced or metastatic transitional cell bladder cancer.

In another embodiment, a selective cytokine inhibitory drug is administered in
5 combination with a second active ingredient as follows: temozolomide to pediatric patients with relapsed or progressive brain tumors or recurrent neuroblastoma; celecoxib, etoposide and cyclophosphamide for relapsed or progressive CNS cancer; temodar to patients with recurrent or progressive meningioma, malignant meningioma, hemangiopericytoma, multiple brain metastases, relapsed brain tumors, or newly diagnosed glioblastoma
10 multiforms; irinotecan to patients with recurrent glioblastoma; carboplatin to pediatric patients with brain stem glioma; procarbazine to pediatric patients with progressive malignant gliomas; cyclophosphamide to patients with poor prognosis malignant brain tumors, newly diagnosed or recurrent glioblastoma multiforms; Gliadel® for high grade recurrent malignant gliomas; temozolomide and tamoxifen for anaplastic astrocytoma; or
15 topotecan for gliomas, glioblastoma, anaplastic astrocytoma or anaplastic oligodendroglioma.

In another embodiment, a selective cytokine inhibitory drug is administered with methotrexate and cyclophosphamide to patients with metastatic breast cancer.

In another embodiment, a selective cytokine inhibitory drug is administered with
20 temozolomide to patients with neuroendocrine tumors.

In another embodiment, a selective cytokine inhibitory drug is administered with gemcitabine to patients with recurrent or metastatic head or neck cancer. In another embodiment, a selective cytokine inhibitory drug is administered with gemcitabine to patients with pancreatic cancer.

25 In another embodiment, a selective cytokine inhibitory drug is administered to patients with colon cancer in combination with Arisa®, taxol and/or taxotere.

In another embodiment, a selective cytokine inhibitory drug is administered with capecitabine to patients with refractory colorectal cancer or patients who fail first line therapy or have poor performance in colon or rectal adenocarcinoma.

30 In another embodiment, a selective cytokine inhibitory drug is administered in combination with fluorouracil, leucovorin, and irinotecan to patients with Dukes C & D colorectal cancer or to patients who have been previously treated for metastatic colorectal cancer.

In another embodiment, a selective cytokine inhibitory drug is administered to patients with refractory colorectal cancer in combination with capecitabine, xeloda, and/or CPT-11.

5 In another embodiment, a selective cytokine inhibitory drug of the invention is administered with capecitabine and irinotecan to patients with refractory colorectal cancer or to patients with unresectable or metastatic colorectal carcinoma.

In another embodiment, a selective cytokine inhibitory drug is administered alone or in combination with interferon alpha or capecitabine to patients with unresectable or metastatic hepatocellular carcinoma; or with cisplatin and thiotepa to patients with primary
10 or metastatic liver cancer.

In another embodiment, a selective cytokine inhibitory drug is administered in combination with pegylated interferon alpha to patients with Kaposi's sarcoma.

In another embodiment, a selective cytokine inhibitory drug is administered in combination with fludarabine, carboplatin, and/or topotecan to patients with refractory or
15 relapsed or high-risk acuted myelogenous leukemia.

In another embodiment, a selective cytokine inhibitory drug is administered in combination with liposomal daunorubicin, topotecan and/or cytarabine to patients with unfavorable karotype acute myeloblastic leukemia.

In another embodiment, a selective cytokine inhibitory drug is administered in combination with gemcitabine and irinotecan to patients with non-small cell lung cancer. In
20 one embodiment, a selective cytokine inhibitory drug is administered in combination with carboplatin and irinotecan to patients with non-small cell lung cancer. In one embodiment, a selective cytokine inhibitory drug is administered with doxorubicin to patients with non-small cell lung cancer who have been previously treated with carbo/VP 16 and radiotherapy.

25 In another embodiment, a selective cytokine inhibitory drug is administered in combination with carboplatin and/or taxotere, or in combination with carboplatin, paclitaxel and/or thoracic radiotherapy to patients with non-small cell lung cancer. In a specific embodiment, a selective cytokine inhibitory drug is administered in combination with taxotere to patients with stage IIIB or IV non-small cell lung cancer.

30 In another embodiment, a selective cytokine inhibitory drug of the invention is administered in combination with oblimersen (Genasense[®]) to patients with small cell lung cancer.

In another embodiment, a selective cytokine inhibitory drug is administered alone or in combination with a second active ingredient such as vinblastine or fludarabine to patients

with various types of lymphoma, including, but not limited to, Hodgkin's lymphoma, non-Hodgkin's lymphoma, cutaneous T-Cell lymphoma, cutaneous B-Cell lymphoma, diffuse large B-Cell lymphoma or relapsed or refractory low grade follicular lymphoma.

In another embodiment, a selective cytokine inhibitory drug is administered in
5 combination with taxotere, IL-2, IFN, GM-CSF, and/or dacarbazine to patients with various types or stages of melanoma.

In another embodiment, a selective cytokine inhibitory drug is administered alone or in combination with vinorelbine to patients with malignant mesothelioma, or stage IIIB non-small cell lung cancer with pleural implants or malignant pleural effusion
10 mesothelioma syndrome.

In another embodiment, a selective cytokine inhibitory drug is administered to patients with various types or stages of multiple myeloma in combination with dexamethasone, zoledronic acid, palmitronate, GM-CSF, biaxin, vinblastine, melphalan, busulphan, cyclophosphamide, IFN, palmidronate, prednisone, bisphosphonate, celecoxib,
15 arsenic trioxide, PEG INTRON-A, vincristine, doxil, decadron, or a combination thereof.

In another embodiment, a selective cytokine inhibitory drug is administered to patients with relapsed or refractory multiple myeloma in combination with doxorubicin (Doxil[®]), vincristine and/or dexamethasone (Decadron[®]).

In another embodiment, a selective cytokine inhibitory drug is administered to
20 patients with various types or stages of ovarian cancer such as peritoneal carcinoma, papillary serous carcinoma, refractory ovarian cancer or recurrent ovarian cancer, in combination with taxol, carboplatin, doxorubicin, gemcitabine, cisplatin, xeloda, paclitaxel, dexamethasone, or a combination thereof.

In another embodiment, a selective cytokine inhibitory drug is administered to
25 patients with various types or stages of prostate cancer, in combination with xeloda, 5 FU/LV, gemcitabine, irinotecan plus gemcitabine, cyclophosphamide, vincristine, dexamethasone, GM-CSF, celecoxib, taxotere, ganciclovir, paclitaxel, adriamycin, docetaxel, estramustine, Emcyt, or a combination thereof.

In another embodiment, a selective cytokine inhibitory drug is administered to
30 patients with various types or stages of renal cell cancer, in combination with capecitabine, IFN, tamoxifen, IL-2, GM-CSF, Celebrex[®], or a combination thereof.

In another embodiment, a selective cytokine inhibitory drug is administered to patients with various types or stages of gynecologic, uterus or soft tissue sarcoma cancer in combination with IFN, a COX-2 inhibitor such as Celebrex[®], and/or sulindac.

In another embodiment, a selective cytokine inhibitory drug is administered to patients with various types or stages of solid tumors in combination with celebrex, etoposide, cyclophosphamide, docetaxel, apicitabine, IFN, tamoxifen, IL-2, GM-CSF, or a combination thereof.

- 5 In another embodiment, a selective cytokine inhibitory drug is administered to patients with scleroderma or cutaneous vasculitis in combination with celebrex, etoposide, cyclophosphamide, docetaxel, apicitabine, IFN, tamoxifen, IL-2, GM-CSF, or a combination thereof.

- This invention also encompasses a method of increasing the dosage of an anti-cancer
10 drug or agent that can be safely and effectively administered to a patient, which comprises administering to a patient (*e.g.*, a human) a selective cytokine inhibitory drug of the invention, or a pharmaceutically acceptable derivative, salt, solvate, clathrate, hydrate, or prodrug thereof. Patients that can benefit by this method are those likely to suffer from an adverse effect associated with anti-cancer drugs for treating a specific cancer of the skin,
15 subcutaneous tissue, lymph nodes, brain, lung, liver, bone, intestine, colon, heart, pancreas, adrenal, kidney, prostate, breast, colorectal, or combinations thereof. The administration of a selective cytokine inhibitory drug of the invention alleviates or reduces adverse effects which are of such severity that it would otherwise limit the amount of anti-cancer drug.

- In one embodiment, a selective cytokine inhibitory drug of the invention can be
20 administered orally and daily in an amount of from about 1 to about 5,000 mg, from about 10 to about 2,500 mg, from about 25 to about 2,500 mg, from about 100 to about 1,200 mg, or from about 100 to about 800 mg prior to, during, or after the occurrence of the adverse effect associated with the administration of an anti-cancer drug to a patient. In a particular embodiment, a selective cytokine inhibitory drug of the invention is administered in
25 combination with specific agents such as heparin, aspirin, coumadin, or G-CSF to avoid adverse effects that are associated with anti-cancer drugs such as but not limited to neutropenia or thrombocytopenia.

- In one embodiment, a selective cytokine inhibitory drug of the invention can be administered to patients with diseases and disorders associated with, or characterized by,
30 undesired angiogenesis in combination with additional active ingredients including but not limited to anti-cancer drugs, anti-inflammatories, antihistamines, antibiotics, and steroids.

In another embodiment, this invention encompasses a method of treating, preventing and/or managing cancer, which comprises administering a selective cytokine inhibitory drug of the invention, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer,

clathrate, or prodrug thereof, in conjunction with (e.g. before, during, or after) conventional therapy including, but not limited to, surgery, immunotherapy, biological therapy, radiation therapy, or other non-drug based therapy presently used to treat, prevent or manage cancer.

The combined use of the selective cytokine inhibitory drugs of the invention and

5 conventional therapy may provide a unique treatment regimen that is unexpectedly effective in certain patients. Without being limited by theory, it is believed that selective cytokine inhibitory drugs of the invention may provide additive or synergistic effects when given concurrently with conventional therapy.

As discussed elsewhere herein, the invention encompasses a method of reducing,
10 treating and/or preventing adverse or undesired effects associated with conventional therapy including, but not limited to, surgery, chemotherapy, radiation therapy, hormonal therapy, biological therapy and immunotherapy. One or more selective cytokine inhibitory drugs of the invention and other active ingredient can be administered to a patient prior to, during, or after the occurrence of the adverse effect associated with conventional therapy.

15 In one embodiment, a selective cytokine inhibitory drug of the invention can be administered in an amount of from about 1 to about 5,000 mg, from about 10 to about 2,500 mg, from about 25 to about 2,500 mg, from about 100 to about 1,200 mg, or from about 100 to about 800 mg orally and daily alone, or in combination with a second active agent disclosed herein (*see, e.g.*, section 4.2), prior to, during, or after the use of conventional
20 therapy.

In a specific embodiment of this method, a selective cytokine inhibitory drug of the invention and doxorubicin are administered to patients with non-small cell lung cancer who were previously treated with carbo/VP 16 and radiotherapy.

4.3.2 Use With Transplantation Therapy

25 Compounds of the invention can be used to reduce the risk of Graft Versus Host Disease (GVHD). Therefore, the invention encompasses a method of treating, preventing and/or managing cancer, which comprises administering the selective cytokine inhibitory drug of the invention, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof, in conjunction with transplantation therapy.

30 As those of ordinary skill in the art are aware, the treatment of cancer is often based on the stages and mechanism of the disease. For example, as inevitable leukemic transformation develops in certain stages of cancer, transplantation of peripheral blood stem cells, hematopoietic stem cell preparation or bone marrow may be necessary. The combined use of the selective cytokine inhibitory drug of the invention and transplantation

therapy provides a unique and unexpected synergism. In particular, a selective cytokine inhibitory drug of the invention exhibits activity that may provide additive or synergistic effects when given concurrently with transplantation therapy in patients with cancer.

A selective cytokine inhibitory drug of the invention can work in combination with
5 transplantation therapy reducing complications associated with the invasive procedure of transplantation and risk of GVHD. This invention encompasses a method of treating, preventing and/or managing cancer which comprises administering to a patient (*e.g.*, a human) a selective cytokine inhibitory drug of the invention, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof, before, during,
10 or after the transplantation of umbilical cord blood, placental blood, peripheral blood stem cell, hematopoietic stem cell preparation or bone marrow. Examples of stem cells suitable for use in the methods of the invention are disclosed in U.S. provisional patent application no. 60/372,348, filed April 12, 2002 by R. Hariri *et al.*, the entirety of which is incorporated herein by reference.

15 In one embodiment of this method, a selective cytokine inhibitory drug of the invention is administered to patients with multiple myeloma before, during, or after the transplantation of autologous peripheral blood progenitor cell.

In another embodiment, a selective cytokine inhibitory drug is administered to patients with relapsing multiple myeloma after the stem cell transplantation.

20 In another embodiment, a selective cytokine inhibitory drug and prednisone are administered as maintenance therapy to patients with multiple myeloma following the transplantation of autologous stem cell.

In another embodiment, a selective cytokine inhibitory drug and dexamethasone are administered as salvage therapy for low risk post transplantation to patients with multiple
25 myeloma.

In another embodiment, a selective cytokine inhibitory drug and dexamethasone are administered as maintenance therapy to patients with multiple myeloma following the transplantation of autologous bone marrow.

In another embodiment, a selective cytokine inhibitory drug is administered
30 following the administration of high dose of melphalan and the transplantation of autologous stem cell to patients with chemotherapy responsive multiple myeloma.

In another embodiment, a selective cytokine inhibitory drug and PEG INTRO-A are administered as maintenance therapy to patients with multiple myeloma following the transplantation of autologous CD34-selected peripheral stem cell.

In another embodiment, a selective cytokine inhibitory drug is administered with post transplant consolidation chemotherapy to patients with newly diagnosed multiple myeloma to evaluate anti-angiogenesis.

In another embodiment, a selective cytokine inhibitory drug and dexamethasone are administered as maintenance therapy after DCEP consolidation, following the treatment with high dose of melphalan and the transplantation of peripheral blood stem cell to 65 years of age or older patients with multiple myeloma.

4.3.3 Cycling Therapy

In certain embodiments, the prophylactic or therapeutic agents of the invention are cyclically administered to a patient. Cycling therapy involves the administration of an active agent for a period of time, followed by a rest for a period of time, and repeating this sequential administration. Cycling therapy can reduce the development of resistance to one or more of the therapies, avoid or reduce the side effects of one of the therapies, and/or improves the efficacy of the treatment.

Consequently, in one specific embodiment of the invention, a selective cytokine inhibitory drug of the invention is administered daily in a single or divided doses in a four to six week cycle with a rest period of about a week or two weeks. The invention further allows the frequency, number, and length of dosing cycles to be increased. Thus, another specific embodiment of the invention encompasses the administration of a selective cytokine inhibitory drug of the invention for more cycles than are typical when it is administered alone. In yet another specific embodiment of the invention, a selective cytokine inhibitory drug of the invention is administered for a greater number of cycles that would typically cause dose-limiting toxicity in a patient to whom a second active ingredient is not also being administered.

In one embodiment, a selective cytokine inhibitory drug of the invention is administered daily and continuously for three or four weeks at a dose of from about 1 to about 5,000 mg/d followed by a break of one or two weeks. 3-(3,4-Dimethoxy-phenyl)-3-(1-oxo-1,3-dihydro-isoindol-2-yl)-propionamide is preferably administered daily and continuously at an initial dose of 1 to 5 mg/d with dose escalation (every week) by 10 to 100 mg/d to a maximum dose of 5,000 mg/d for as long as therapy is tolerated. In a particular embodiment, the compound is administered in an amount of about 400, 800, or 1,200 mg/day, preferably in an amount of about 800 mg/day for three to four weeks, followed by one week or two weeks of rest in a four or six week cycle.

In one embodiment of the invention, a selective cytokine inhibitory drug of the invention and a second active ingredient are administered orally, with administration of a selective cytokine inhibitory drug of the invention occurring 30 to 60 minutes prior to a second active ingredient, during a cycle of four to six weeks. In another embodiment of the invention, the combination of a selective cytokine inhibitory drug of the invention and a second active ingredient is administered by intravenous infusion over about 90 minutes every cycle. In a specific embodiment, one cycle comprises the administration of from about 400 to about 800 mg/day of 3-(3,4-dimethoxy-phenyl)-3-(1-oxo-1,3-dihydro-isoindol-2-yl)-propionamide and from about 50 to about 200 mg/m²/day of a second active ingredient daily for 3 to 4 weeks and then one or two weeks of rest. In another specific embodiment, each cycle comprises the administration of from about 200 to about 400 mg/day of 3-(3,4-dimethoxy-phenyl)-3-(1-oxo-1,3-dihydro-isoindol-2-yl)-propionamide and from about 50 to about 200 mg/m²/day of a second active ingredient for three to four weeks followed by one or two weeks of rest. Typically, the number of cycles during which the combinatorial treatment is administered to a patient will be from about one to about 24 cycles, more typically from about two to about 16 cycles, and even more typically from about four to about eight cycles.

4.4 PHARMACEUTICAL COMPOSITIONS

Pharmaceutical compositions can be used in the preparation of individual, single unit dosage forms. Pharmaceutical compositions and dosage forms of the invention comprise a selective cytokine inhibitory drug of the invention, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof. Pharmaceutical compositions and dosage forms of the invention can further comprise one or more excipients.

Pharmaceutical compositions and dosage forms of the invention can also comprise one or more additional active ingredients. Consequently, pharmaceutical compositions and dosage forms of the invention comprise the active ingredients disclosed herein (*e.g.*, a selective cytokine inhibitory drug and a second active agent). Examples of optional second, or additional, active ingredients are disclosed herein (*see, e.g.*, section 4.2).

Single unit dosage forms of the invention are suitable for oral, mucosal (*e.g.*, nasal, sublingual, vaginal, buccal, or rectal), parenteral (*e.g.*, subcutaneous, intravenous, bolus injection, intramuscular, or intraarterial), topical (*e.g.*, eye drops or other ophthalmic preparations), transdermal or transcutaneous administration to a patient. Examples of dosage forms include, but are not limited to: tablets; caplets; capsules, such as soft elastic

gelatin capsules; cachets; troches; lozenges; dispersions; suppositories; powders; aerosols (e.g., nasal sprays or inhalers); gels; liquid dosage forms suitable for oral or mucosal administration to a patient, including suspensions (e.g., aqueous or non-aqueous liquid suspensions, oil-in-water emulsions, or a water-in-oil liquid emulsions), solutions, and elixirs; liquid dosage forms suitable for parenteral administration to a patient; eye drops or other ophthalmic preparations suitable for topical administration; and sterile solids (e.g., crystalline or amorphous solids) that can be reconstituted to provide liquid dosage forms suitable for parenteral administration to a patient.

The composition, shape, and type of dosage forms of the invention will typically vary depending on their use. For example, a dosage form used in the acute treatment of a disease may contain larger amounts of one or more of the active ingredients it comprises than a dosage form used in the chronic treatment of the same disease. Similarly, a parenteral dosage form may contain smaller amounts of one or more of the active ingredients it comprises than an oral dosage form used to treat the same disease. These and other ways in which specific dosage forms encompassed by this invention will vary from one another will be readily apparent to those skilled in the art. See, e.g., *Remington's Pharmaceutical Sciences*, 18th ed., Mack Publishing, Easton PA (1990).

Typical pharmaceutical compositions and dosage forms comprise one or more excipients. Suitable excipients are well known to those skilled in the art of pharmacy, and non-limiting examples of suitable excipients are provided herein. Whether a particular excipient is suitable for incorporation into a pharmaceutical composition or dosage form depends on a variety of factors well known in the art including, but not limited to, the way in which the dosage form will be administered to a patient. For example, oral dosage forms such as tablets may contain excipients not suited for use in parenteral dosage forms. The suitability of a particular excipient may also depend on the specific active ingredients in the dosage form. For example, the decomposition of some active ingredients may be accelerated by some excipients such as lactose, or when exposed to water. Active ingredients that comprise primary or secondary amines are particularly susceptible to such accelerated decomposition. Consequently, this invention encompasses pharmaceutical compositions and dosage forms that contain little, if any, lactose or other mono- or disaccharides. As used herein, the term "lactose-free" means that the amount of lactose present, if any, is insufficient to substantially increase the degradation rate of an active ingredient.

Lactose-free compositions of the invention can comprise excipients that are well known in the art and are listed, for example, in the *U.S. Pharmacopeia* (USP) 25-NF20 (2002). In general, lactose-free compositions comprise active ingredients, a binder/filler, and a lubricant in pharmaceutically compatible and pharmaceutically acceptable amounts.

- 5 Preferred lactose-free dosage forms comprise active ingredients, microcrystalline cellulose, pre-gelatinized starch, and magnesium stearate.

This invention further encompasses anhydrous pharmaceutical compositions and dosage forms comprising active ingredients, since water can facilitate the degradation of some compounds. For example, the addition of water (*e.g.*, 5%) is widely accepted in the pharmaceutical arts as a means of simulating long-term storage in order to determine characteristics such as shelf-life or the stability of formulations over time. *See, e.g.*, Jens T. Carstensen, *Drug Stability: Principles & Practice*, 2d. Ed., Marcel Dekker, NY, NY, 1995, pp. 379-80. In effect, water and heat accelerate the decomposition of some compounds. Thus, the effect of water on a formulation can be of great significance since moisture and/or humidity are commonly encountered during manufacture, handling, packaging, storage, shipment, and use of formulations.

Anhydrous pharmaceutical compositions and dosage forms of the invention can be prepared using anhydrous or low moisture containing ingredients and low moisture or low humidity conditions. Pharmaceutical compositions and dosage forms that comprise lactose and at least one active ingredient that comprises a primary or secondary amine are preferably anhydrous if substantial contact with moisture and/or humidity during manufacturing, packaging, and/or storage is expected.

An anhydrous pharmaceutical composition should be prepared and stored such that its anhydrous nature is maintained. Accordingly, anhydrous compositions are preferably packaged using materials known to prevent exposure to water such that they can be included in suitable formulary kits. Examples of suitable packaging include, but are not limited to, hermetically sealed foils, plastics, unit dose containers (*e.g.*, vials), blister packs, and strip packs.

The invention further encompasses pharmaceutical compositions and dosage forms that comprise one or more compounds that reduce the rate by which an active ingredient will decompose. Such compounds, which are referred to herein as "stabilizers," include, but are not limited to, antioxidants such as ascorbic acid, pH buffers, or salt buffers.

Like the amounts and types of excipients, the amounts and specific types of active ingredients in a dosage form may differ depending on factors such as, but not limited to, the

route by which it is to be administered to patients. However, typical dosage forms of the invention comprise a selective cytokine inhibitory drug of the invention or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof in an amount of from about 0.10 to about 150 mg. Typical dosage forms comprise a selective cytokine inhibitory drug of the invention or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof in an amount of about 0.1, 1, 2, 5, 7.5, 10, 12.5, 15, 17.5, 20, 25, 50, 100, 150 or 200 mg. In a particular embodiment, a preferred dosage form comprises 4-(amino)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3-dione (ActimidTM) in an amount of about 1, 2, 5, 10, 25 or 50mg. In a specific embodiment, a preferred dosage form comprises 3-(3,4-dimethoxy-phenyl)-3-(1-oxo-1,3-dihydro-isoindol-2-yl)-propionamide in an amount of about 5, 10, 25 or 50mg. Typical dosage forms comprise the second active ingredient in an amount of 1 to about 1000 mg, from about 5 to about 500 mg, from about 10 to about 350 mg, or from about 50 to about 200 mg. Of course, the specific amount of the anti-cancer drug will depend on the specific agent used, the type of cancer being treated or managed, and the amount(s) of a selective cytokine inhibitory drug of the invention and any optional additional active agents concurrently administered to the patient.

4.4.1 Oral Dosage Forms

Pharmaceutical compositions of the invention that are suitable for oral administration can be presented as discrete dosage forms, such as, but are not limited to, tablets (*e.g.*, chewable tablets), caplets, capsules, and liquids (*e.g.*, flavored syrups). Such dosage forms contain predetermined amounts of active ingredients, and may be prepared by methods of pharmacy well known to those skilled in the art. *See generally, Remington's Pharmaceutical Sciences*, 18th ed., Mack Publishing, Easton PA (1990).

Typical oral dosage forms of the invention are prepared by combining the active ingredients in an intimate admixture with at least one excipient according to conventional pharmaceutical compounding techniques. Excipients can take a wide variety of forms depending on the form of preparation desired for administration. For example, excipients suitable for use in oral liquid or aerosol dosage forms include, but are not limited to, water, glycols, oils, alcohols, flavoring agents, preservatives, and coloring agents. Examples of excipients suitable for use in solid oral dosage forms (*e.g.*, powders, tablets, capsules, and caplets) include, but are not limited to, starches, sugars, micro-crystalline cellulose, diluents, granulating agents, lubricants, binders, and disintegrating agents.

Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit forms, in which case solid excipients are employed. If desired, tablets can be coated by standard aqueous or nonaqueous techniques. Such dosage forms can be prepared by any of the methods of pharmacy. In general, pharmaceutical compositions and dosage forms are prepared by uniformly and intimately admixing the active ingredients with liquid carriers, finely divided solid carriers, or both, and then shaping the product into the desired presentation if necessary.

For example, a tablet can be prepared by compression or molding. Compressed tablets can be prepared by compressing in a suitable machine the active ingredients in a free-flowing form such as powder or granules, optionally mixed with an excipient. Molded tablets can be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

Examples of excipients that can be used in oral dosage forms of the invention include, but are not limited to, binders, fillers, disintegrants, and lubricants. Binders suitable for use in pharmaceutical compositions and dosage forms include, but are not limited to, corn starch, potato starch, or other starches, gelatin, natural and synthetic gums such as acacia, sodium alginate, alginic acid, other alginates, powdered tragacanth, guar gum, cellulose and its derivatives (*e.g.*, ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose), polyvinyl pyrrolidone, methyl cellulose, pre-gelatinized starch, hydroxypropyl methyl cellulose, (*e.g.*, Nos. 2208, 2906, 2910), microcrystalline cellulose, and mixtures thereof.

Suitable forms of microcrystalline cellulose include, but are not limited to, the materials sold as AVICEL-PH-101, AVICEL-PH-103 AVICEL RC-581, AVICEL-PH-105 (available from FMC Corporation, American Viscose Division, Avicel Sales, Marcus Hook, PA), and mixtures thereof. An specific binder is a mixture of microcrystalline cellulose and sodium carboxymethyl cellulose sold as AVICEL RC-581. Suitable anhydrous or low moisture excipients or additives include AVICEL-PH-103TM and Starch 1500 LM.

Examples of fillers suitable for use in the pharmaceutical compositions and dosage forms disclosed herein include, but are not limited to, talc, calcium carbonate (*e.g.*, granules or powder), microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof. The binder or filler in pharmaceutical compositions of the invention is typically present in from about 50 to about 99 weight percent of the pharmaceutical composition or dosage form.

Disintegrants are used in the compositions of the invention to provide tablets that disintegrate when exposed to an aqueous environment. Tablets that contain too much disintegrant may disintegrate in storage, while those that contain too little may not disintegrate at a desired rate or under the desired conditions. Thus, a sufficient amount of disintegrant that is neither too much nor too little to detrimentally alter the release of the active ingredients should be used to form solid oral dosage forms of the invention. The amount of disintegrant used varies based upon the type of formulation, and is readily discernible to those of ordinary skill in the art. Typical pharmaceutical compositions comprise from about 0.5 to about 15 weight percent of disintegrant, preferably from about 1 to about 5 weight percent of disintegrant.

Disintegrants that can be used in pharmaceutical compositions and dosage forms of the invention include, but are not limited to, agar-agar, alginic acid, calcium carbonate, microcrystalline cellulose, croscarmellose sodium, crospovidone, polacrillin potassium, sodium starch glycolate, potato or tapioca starch, other starches, pre-gelatinized starch, other starches, clays, other alginates, other celluloses, gums, and mixtures thereof.

Lubricants that can be used in pharmaceutical compositions and dosage forms of the invention include, but are not limited to, calcium stearate, magnesium stearate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, stearic acid, sodium lauryl sulfate, talc, hydrogenated vegetable oil (*e.g.*, peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil), zinc stearate, ethyl oleate, ethyl laureate, agar, and mixtures thereof. Additional lubricants include, for example, a syloid silica gel (AEROSIL200, manufactured by W.R. Grace Co. of Baltimore, MD), a coagulated aerosol of synthetic silica (marketed by Degussa Co. of Plano, TX), CAB-O-SIL (a pyrogenic silicon dioxide product sold by Cabot Co. of Boston, MA), and mixtures thereof. If used at all, lubricants are typically used in an amount of less than about 1 weight percent of the pharmaceutical compositions or dosage forms into which they are incorporated.

A preferred solid oral dosage form of the invention comprises a selective cytokine inhibitory drug of the invention, anhydrous lactose, microcrystalline cellulose, polyvinylpyrrolidone, stearic acid, colloidal anhydrous silica, and gelatin.

4.4.2 Delayed Release Dosage Forms

Active ingredients of the invention can be administered by controlled release means or by delivery devices that are well known to those of ordinary skill in the art. Examples include, but are not limited to, those described in U.S. Patent Nos.: 3,845,770; 3,916,899;

3,536,809; 3,598,123; and 4,008,719, 5,674,533, 5,059,595, 5,591,767, 5,120,548, 5,073,543, 5,639,476, 5,354,556, and 5,733,566, each of which is incorporated herein by reference. Such dosage forms can be used to provide slow or controlled-release of one or more active ingredients using, for example, hydropropylmethyl cellulose, other polymer
5 matrices, gels, permeable membranes, osmotic systems, multilayer coatings, microparticles, liposomes, microspheres, or a combination thereof to provide the desired release profile in varying proportions. Suitable controlled-release formulations known to those of ordinary skill in the art, including those described herein, can be readily selected for use with the active ingredients of the invention. The invention thus encompasses single unit dosage
10 forms suitable for oral administration such as, but not limited to, tablets, capsules, gelcaps, and caplets that are adapted for controlled-release.

All controlled-release pharmaceutical products have a common goal of improving drug therapy over that achieved by their non-controlled counterparts. Ideally, the use of an optimally designed controlled-release preparation in medical treatment is characterized by a
15 minimum of drug substance being employed to cure or control the condition in a minimum amount of time. Advantages of controlled-release formulations include extended activity of the drug, reduced dosage frequency, and increased patient compliance. In addition, controlled-release formulations can be used to affect the time of onset of action or other characteristics, such as blood levels of the drug, and can thus affect the occurrence of side
20 (*e.g.*, adverse) effects.

Most controlled-release formulations are designed to initially release an amount of drug (active ingredient) that promptly produces the desired therapeutic effect, and gradually and continually release of other amounts of drug to maintain this level of therapeutic or prophylactic effect over an extended period of time. In order to maintain this constant level
25 of drug in the body, the drug must be released from the dosage form at a rate that will replace the amount of drug being metabolized and excreted from the body. Controlled-release of an active ingredient can be stimulated by various conditions including, but not limited to, pH, temperature, enzymes, water, or other physiological conditions or compounds.

30 **4.4.3 Parenteral Dosage Forms**

Parenteral dosage forms can be administered to patients by various routes including, but not limited to, subcutaneous, intravenous (including bolus injection), intramuscular, and intraarterial. Because their administration typically bypasses patients' natural defenses against contaminants, parenteral dosage forms are preferably sterile or capable of being

sterilized prior to administration to a patient. Examples of parenteral dosage forms include, but are not limited to, solutions ready for injection, dry products ready to be dissolved or suspended in a pharmaceutically acceptable vehicle for injection, suspensions ready for injection, and emulsions.

5 Suitable vehicles that can be used to provide parenteral dosage forms of the invention are well known to those skilled in the art. Examples include, but are not limited to: Water for Injection USP; aqueous vehicles such as, but not limited to, Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, and Lactated Ringer's Injection; water-miscible vehicles such as, but not limited to, ethyl
10 alcohol, polyethylene glycol, and polypropylene glycol; and non-aqueous vehicles such as, but not limited to, corn oil, cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl myristate, and benzyl benzoate.

 Compounds that increase the solubility of one or more of the active ingredients disclosed herein can also be incorporated into the parenteral dosage forms of the invention.
15 For example, cyclodextrin and its derivatives can be used to increase the solubility of a selective cytokine inhibitory drug of the invention and its derivatives. *See, e.g.*, U.S. Patent No. 5,134,127, which is incorporated herein by reference.

4.4.4 Topical and Mucosal Dosage Forms

 Topical and mucosal dosage forms of the invention include, but are not limited to,
20 sprays, aerosols, solutions, emulsions, suspensions, eye drops or other ophthalmic preparations, or other forms known to one of skill in the art. *See, e.g.*, *Remington's Pharmaceutical Sciences*, 16th and 18th eds., Mack Publishing, Easton PA (1980 & 1990); and *Introduction to Pharmaceutical Dosage Forms*, 4th ed., Lea & Febiger, Philadelphia (1985). Dosage forms suitable for treating mucosal tissues within the oral cavity can be
25 formulated as mouthwashes or as oral gels.

 Suitable excipients (*e.g.*, carriers and diluents) and other materials that can be used to provide topical and mucosal dosage forms encompassed by this invention are well known to those skilled in the pharmaceutical arts, and depend on the particular tissue to which a given pharmaceutical composition or dosage form will be applied. With that fact in mind,
30 typical excipients include, but are not limited to, water, acetone, ethanol, ethylene glycol, propylene glycol, butane-1,3-diol, isopropyl myristate, isopropyl palmitate, mineral oil, and mixtures thereof to form solutions, emulsions or gels, which are non-toxic and pharmaceutically acceptable. Moisturizers or humectants can also be added to pharmaceutical compositions and dosage forms if desired. Examples of such additional

ingredients are well known in the art. *See, e.g., Remington's Pharmaceutical Sciences*, 16th and 18th eds., Mack Publishing, Easton PA (1980 & 1990).

The pH of a pharmaceutical composition or dosage form may also be adjusted to improve delivery of one or more active ingredients. Similarly, the polarity of a solvent carrier, its ionic strength, or tonicity can be adjusted to improve delivery. Compounds such as stearates can also be added to pharmaceutical compositions or dosage forms to advantageously alter the hydrophilicity or lipophilicity of one or more active ingredients so as to improve delivery. In this regard, stearates can serve as a lipid vehicle for the formulation, as an emulsifying agent or surfactant, and as a delivery-enhancing or penetration-enhancing agent. Different salts, hydrates or solvates of the active ingredients can be used to further adjust the properties of the resulting composition.

4.4.5 Kits

Typically, active ingredients of the invention are preferably not administered to a patient at the same time or by the same route of administration. This invention therefore encompasses kits which, when used by the medical practitioner, can simplify the administration of appropriate amounts of active ingredients to a patient.

A typical kit of the invention comprises a dosage form of a selective cytokine inhibitory drug of the invention, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, prodrug, or clathrate thereof. Kits encompassed by this invention can further comprise additional active ingredients such as oblimersen (Genasense[®]), melphalan, G-CSF, GM-CSF, EPO, topotecan, dacarbazine, irinotecan, taxotere, IFN, COX-2 inhibitor, pentoxifylline, ciprofloxacin, dexamethasone, IL2, IL8, IL18, Ara-C, vinorelbine, isotretinoin, 13 cis-retinoic acid, or a pharmacologically active mutant or derivative thereof, or a combination thereof. Examples of the additional active ingredients include, but are not limited to, those disclosed herein (*see, e.g.,* section 5.2).

Kits of the invention can further comprise devices that are used to administer the active ingredients. Examples of such devices include, but are not limited to, syringes, drip bags, patches, and inhalers.

Kits of the invention can further comprise cells or blood for transplantation as well as pharmaceutically acceptable vehicles that can be used to administer one or more active ingredients. For example, if an active ingredient is provided in a solid form that must be reconstituted for parenteral administration, the kit can comprise a sealed container of a suitable vehicle in which the active ingredient can be dissolved to form a particulate-free sterile solution that is suitable for parenteral administration. Examples of pharmaceutically

acceptable vehicles include, but are not limited to: Water for Injection USP; aqueous vehicles such as, but not limited to, Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, and Lactated Ringer's Injection; water-miscible vehicles such as, but not limited to, ethyl alcohol, polyethylene glycol, and polypropylene glycol; and non-aqueous vehicles such as, but not limited to, corn oil, cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl myristate, and benzyl benzoate.

5. EXAMPLES

Certain embodiments of the invention are illustrated by the following non-limiting examples.

5.1 MODULATION OF CYTOKINE PRODUCTION

A series of non-clinical pharmacology and toxicology studies have been performed to support the clinical evaluation of a selective cytokine inhibitory drug of the invention in human subjects. These studies were performed in accordance with internationally recognized guidelines for study design and in compliance with the requirements of Good Laboratory Practice (GLP), unless otherwise noted.

In a specific embodiment, the pharmacological properties of 3-(3,4-dimethoxy-phenyl)-3-(1-oxo-1,3-dihydro-isoindol-2-yl)-propionamide are characterized in *in vitro* studies. Studies examine the effects of the compound on the production of various cytokines. Inhibition of TNF- α production following LPS-stimulation of human PBMC and human whole blood by the compound is investigated *in vitro*. *In vitro* studies suggest a pharmacological activity profile for 3-(3,4-dimethoxy-phenyl)-3-(1-oxo-1,3-dihydro-isoindol-2-yl)-propionamide is five to fifty times more potent than thalidomide. The pharmacological effects of 3-(3,4-dimethoxy-phenyl)-3-(1-oxo-1,3-dihydro-isoindol-2-yl)-propionamide may derive from its action as an inhibitor of the generation of inflammatory cytokines.

5.2 INHIBITION OF MM CELL PROLIFERATION

The ability of a selective cytokine inhibitory drug to effect the proliferation of multiple myeloma (MM) cell lines is investigated in an *in vitro* study. Uptake [^3H]-thymidine by different MM cell lines (MM.1S, Hs Sultan, U266 and RPMI-8226) is measured as an indicator of cell proliferation. Cells are incubated in the presence of compound for 48 hours; [^3H]-thymidine is included for the last 8 hours of the incubation period. In a specific embodiment, 3-(3,4-dimethoxy-phenyl)-3-(1-oxo-1,3-dihydro-

isoindol-2-yl)-propionamide is added to MM.1S and Hs Sultan cells. The uptake [³H]-thymidine by different MM cell lines is measured.

5.3 IN VIVO LPS-INDUCED TNF- α PRODUCTION ASSAY

Male CD rats procured from Charles River Laboratories at seven weeks of age are allowed to acclimate for one week prior to use. A lateral tail vein is cannulated percutaneously with a 22-gage over-the-needle catheter under brief isoflurane anesthesia. Rats are administered a selective cytokine inhibitory drug of the invention either by intravenous injection via the tail vein catheter or oral gavage 15 to 180 min prior to injection of 0.05 mg/kg LPS (E. Coli 055:B5). Catheters are flushed with 2.5 mL/kg of normal injectable saline. Blood is collected via cardiac puncture 90 minutes after LPS challenge. Plasma is prepared using lithium heparin separation tubes and frozen at -80°C until analyzed. TNF- α levels are determined using a rat specific TNF- α ELISA kit (Busywork). The ED₅₀ values are calculated as the dose of the selective cytokine inhibitory drug of the invention at which the TNF- α production is reduced to 50% of the control value.

5.4 TOXICOLOGY STUDIES

The effects of 3-(3,4-dimethoxy-phenyl)-3-(1-oxo-1,3-dihydro-isoindol-2-yl)-propionamide on cardiovascular and respiratory function are investigated in anesthetized dogs. Two groups of Beagle dogs (2/sex/group) are used. One group receives three doses of vehicle only and the other receives three ascending doses of the compound (200, 400, and 800 mg/kg). In all cases, doses of the compound or vehicle are successively administered *via* infusion through the jugular vein separated by intervals of at least 30 minutes.

The cardiovascular and respiratory changes induced by 3-(3,4-dimethoxy-phenyl)-3-(1-oxo-1,3-dihydro-isoindol-2-yl)-propionamide are minimal at all doses when compared to the vehicle control group. The only statistically significant difference between the vehicle and treatment groups is a small increase in arterial blood pressure following administration of the low dose of 3-(3,4-dimethoxy-phenyl)-3-(1-oxo-1,3-dihydro-isoindol-2-yl)-propionamide. This effect lasts approximately 15 minutes and is not seen at higher doses. Deviations in femoral blood flow, respiratory parameters, and Qtc interval are common to both the control and treated groups and are not considered treatment-related.

5.5 CYCLING THERAPY IN PATIENTS

In a specific embodiment, a selective cytokine inhibitory drug of the invention are cyclically administered to patients with cancer. Cycling therapy involves the administration

of a first agent for a period of time, followed by a rest for a period of time and repeating this sequential administration. Cycling therapy can reduce the development of resistance to one or more of the therapies, avoid or reduce the side effects of one of the therapies, and/or improves the efficacy of the treatment.

5 In a specific embodiment, prophylactic or therapeutic agents are administered in a cycle of about four to six weeks, about once or twice every day. One cycle can comprise the administration of a therapeutic or prophylactic agent for three to four weeks and at least one week or two weeks of rest. The number of cycles administered is from about one to about 24 cycles, more typically from about two to about 16 cycles, and more typically from
10 about four to about eight cycles.

For example, in a cycle of four weeks, on day 1, the administration of 800 mg/d of 3-(3,4-dimethoxy-phenyl)-3-(1-oxo-1,3-dihydro-isoindol-2-yl)-propionamide is started. On day 22, the administration of the compound is stopped for a week of rest. On day 29, the administration of 800 mg/d of the compound is begun.

15 **5.6 CLINICAL STUDIES IN PATIENTS WITH RELAPSED MULTIPLE MYELOMA**

Patients with relapsed and refractory Dune-Salmon stage III multiple myeloma, who have either failed at least three previous regimens or presented with poor performance status, neutropenia or thrombocytopenia, are treated with up to four cycles of combination
20 melphalan (50 mg intravenously), a selective cytokine inhibitory drug of the invention (about 1 to 5,000 mg orally daily), and dexamethasone (40 mg/day orally on days 1 to 4) every four to six weeks. Maintenance treatment consisting of daily a selective cytokine inhibitory drug of the invention and monthly dexamethasone are continued until the disease progression. The therapy comprising the administration of a selective cytokine inhibitory
25 drug of the invention in combination with melphalan and dexamethasone is highly active and generally tolerated in heavily pretreated multiple myeloma patients whose prognosis is otherwise poor.

The embodiments of the invention described above are intended to be merely exemplary, and those skilled in the art will recognize, or will be able to ascertain using no
30 more than routine experimentation, numerous equivalents of specific compounds, materials, and procedures. All such equivalents are considered to be within the scope of the invention and are encompassed by the appended claims.

The embodiments of the invention described above are intended to be merely exemplary, and those skilled in the art will recognize, or will be able to ascertain using no more than routine experimentation, numerous equivalents of specific compounds, materials, and procedures. All such equivalents are considered to be within the scope
5 of the invention and are encompassed by the appended claims.

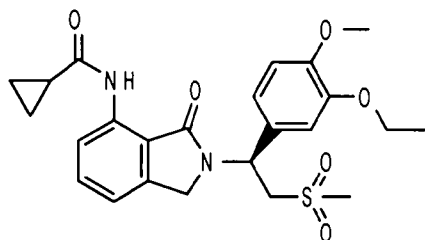
Throughout the description and the claims of this specification the word “comprise” and variations of the word, such as “comprising” and “comprises” is not intended to exclude other additives, components, integers or steps.

The discussion of documents, acts, materials, devices, articles and the like is
10 included in this specification solely for the purpose of providing a context for the present invention. It is not suggested or represented that any or all of these matters formed part of the prior art base or were common general knowledge in the field relevant to the present invention before the priority date of each claim of this application.

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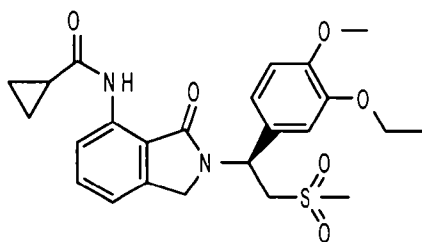
The Claims Defining The Invention Are As Follows:

1. A method of treating non-Hodgkin's lymphoma, which comprises administering to a patient having non-Hodgkin's lymphoma a therapeutically effective amount of cyclopropanecarboxylic acid {2-[1-(3-ethoxy-4-methoxy-phenyl)-2-methanesulfonyl-ethyl]-3-oxo-2,3-dihydro-1 *H*-isoindol-4-yl}-amide, which has the following structure:



or a pharmaceutically acceptable salt or solvate thereof.

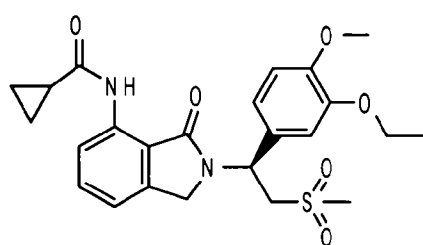
2. A method of treating non-Hodgkin's lymphoma, which comprises administering to a patient having non-Hodgkin's lymphoma a therapeutically effective amount of cyclopropanecarboxylic acid {2-[1-(3-ethoxy-4-methoxy-phenyl)-2-methanesulfonyl-ethyl]-3-oxo-2,3-dihydro-1 *H*-isoindol-4-yl}-amide, which has the following structure:



3. or a pharmaceutically acceptable salt or solvate thereof, and a therapeutically effective amount of a second active ingredient.

4. The method of claim 2, wherein the second active ingredient is dexamethasone.
5. The method of claim 1 or 2, wherein the compound is enantiomerically pure.
6. The method of any one of claims 1 to 4, wherein the compound is administered in an amount of from about 1 to about 5,000 mg per day.

6. The method of claim 5, wherein the compound is administered in an amount of about 10, 25, 50, 100, 200 or 300 mg per day.
7. The method of any one of claims 1 to 6, wherein the compound is orally administered.
- 5 8. The method of any one of claims 1 to 7, wherein the compound is administered in a capsule or tablet.
9. The method of claim 8, wherein the compound is administered in 50 mg or 100 mg of a capsule.
- 10 10. The method of any one of claims 1 to 9, wherein the lymphoma is relapsed, refractory or resistant to conventional therapy.
11. The method of any one of claims 1 to 10, wherein the compound is administered for 21 days followed by seven days rest in a 28 day cycle.
12. The method of claim 1 or 2, substantially as hereinbefore described and with reference to any of the Examples.
- 15 13. A pharmaceutical composition comprising cyclopropanecarboxylic acid {2-[1-(3-ethoxy-4-methoxy-phenyl)-2-methanesulfonyl-ethyl]-3-oxo-2,3-dihydro-1 *H*-isoindol-4-yl}-amide which has the following structure:



- 20 or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate or prodrug thereof, wherein the composition further comprises a second active ingredient.
14. The pharmaceutical composition of claim 13, wherein the second active ingredient is dexamethasone.
- 25 15. The pharmaceutical composition of claim 13 or 14 wherein the compound is enantiomerically pure.